Optimizing Duration of Empiric Management of Suspected Central Line-Associated Bloodstream Infections in Pediatric Patients with Intestinal Failure

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Objectives To assess whether a 24-hour length of hospitalization and empiric antibiotic therapy to exclude central line-associated bloodstream infection (CLABSI) in children with intestinal failure is potentially as safe as 48 hours, which is the duration most commonly used but not evidence based.

Study design A prospective single-institution observational cohort study was conducted among pediatric patients with intestinal failure from July 1, 2015, through June 30, 2018, to identify episodes of suspected CLABSI. The primary end point was time from blood sampling to positive blood culture. Secondary end points included presenting symptoms, laboratory test results, responses to a parent/legal guardian-completed symptom survey, length of inpatient stay, costs, and charges.

Results Seventy-three patients with intestinal failure receiving nutritional support via central venous catheters enrolled; 35 were hospitalized with suspected CLABSI at least once during the study. There were 49 positive blood cultures confirming CLABSI in 128 episodes (38%). The median time from blood sampling to positive culture was 11.1 hours. The probability of a blood culture becoming positive after 24 hours was 2.3%. Elevated C-reactive protein and neutrophil predominance in white blood cell count were associated with positive blood cultures. Estimated cost savings by transitioning from a 48-hour to a 24-hour admission to rule-out CLABSI was $4639 per admission.

Conclusions A 24-hour duration of empiric management to exclude CLABSI may be appropriate for patients with negative blood cultures and no clinically concerning signs. A multi-institutional study would more robustly differentiate patients safe for discharge after 24 hours from those who warrant longer empiric treatment. *(J Pediatr 2020;227:69-76)*.

Parenteral nutrition (PN) is a critical treatment for pediatric patients with intestinal failure who are unable to absorb adequate nutrients enterally due to insufficient bowel length or function.[1] Patients who require long-term PN have an indwelling central venous catheter (CVC) for PN delivery. One risk of long-term PN use is the development of central line-associated bloodstream infection (CLABSI). Among patients with a long-term CVC there are 250 000-500 000 episodes of CLABSI per year and, among pediatric and adult patients with CVCs for PN, a range of 0.87-8.9 CLABSI episodes per 1000 catheter-days has been reported.[2-7]

There is a low threshold to admit and empirically treat patients with an indwelling CVC who present feeling or appearing unwell. These patients are empirically treated with antibiotics after blood is drawn for microbial culture to rule-out CLABSI. One commonly used policy has been to admit all such patients for empiric intravenous antibiotics and monitoring until 48 hours of blood culture data are obtained.[8] Specific factors that have been reported helpful in risk-stratifying patients with intestinal failure who present with concern for CLABSI include fever of greater than 38°C, elevated C-reactive protein, elevated percentage of neutrophils on the white blood cell count (WBC), alterations in bilirubin and albumin, and increased frequency of PN administration (more days per week).[2,8,9] Among those with suspected infection, blood cultures are negative in 30%-50% and in such cases patients are discharged having incurred risk of

CLABSI	Central line-associated bloodstream infection
CVC	Central venous catheter
LOS	Length of stay
PN	Parenteral nutrition
WBC	White blood cell count

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broad-spectrums antibiotics and exposure to the hospital environment.[10,11] There is a need to define strategies to minimize the duration of hospitalization and empiric treatment that ensure patient safety, decrease unnecessary antibiotic exposure, minimize exposure to hospital-acquired infections and financial burden, and compromise to quality of life. The aim of this study was to explore an optimal length of empiric inpatient management to exclude CLABSI in pediatric patients with intestinal failure, with the hypothesis that a 24-hour admission may be as safe and clinically appropriate as a 48-hour admission.

The cost of CLABSI care among patients with an indwelling CVC for any indication is $25 000-$56 000 per episode amounting up to $500 000 per 1000 catheter-days.[3,12,13] According to a retrospective analysis of Boston Children's Hospital's experience in 2012, the annual financial burden for CLABSI care among patients with intestinal failure was $1.7 million. among pediatric patients with intestinal failure with CLABSI the reported cost were $28 375 per hospitalization.[8,14] To improve understanding of the potential cost savings of transitioning from a 48-hour to a 24-hour hospitalization, costs at 24 hours after admission were compared with total hospitalization costs for patients who were discharged with a negative culture within 48 hours.

Methods

Survey on CLABSI Rule-out Practices

To assess the prevailing practices for hospitalization to exclude CLABSI, directors of 45 pediatric intestinal failure programs within the US were contacted via email with a link to complete a 5-question REDCap electronic survey regarding their institution's rule-out CLABSI practices. Study data were collected and managed using REDCap electronic data capture tool hosted at Boston Children's Hospital.[15,16]

Prospective Study

Approval was obtained from the Boston Children's Hospital Institutional Review Board, and written informed consent was obtained for all patients.

Patients

Patients enrolled during routine follow-up appointments at the Center for Advanced Intestinal Rehabilitation Program from June 1, 2015, to June 30, 2018, at Boston Children's Hospital. Inclusion criteria were age less than 18 years and the presence of any type of indwelling CVC for delivery of outpatient PN. Patients with a diagnosis of immunodeficiency or who were receiving immunosuppressive medications were excluded. The children of parents who signed consent to participate in the study were prospectively followed and each presentation to the emergency department, resulting in hospitalization with initiation of empiric CLABSI management during the study period was assessed for inclusion as a relevant episode. Only presentations to Boston Children's Hospital were included; presentations to outside hospitals were not captured. Presentations were excluded if patients had been discharged from the hospital within the 48 hours before presentation or if patients had undergone a surgical procedure within the previous 48 hours. Demographic and medical history data were recorded at the time of enrollment.

Presentations

Episodes of suspected CLABSI of enrolled patients from July 1, 2015, to June 30, 2018, were included in this study, with data accrual starting 1 month after enrollment began. Episodes in this study between July 1, 2015, and October 31, 2016 (72 total), were also included in a separate retrospective study assessing for factors at presentation that confer the greatest risk of CLABSI in the intestinal failure population.[17] For each suspected episode resulting in admission and initiation of empiric CLABSI management, times were recorded for presentation, blood sampling for laboratory tests, and blood cultures were obtained; initial dose of antibiotics (parenteral vancomycin and piperacillin/tazobactam by institutional practice); and hospital admission. Blood was drawn from the CVC for culture and measurement of complete blood count, general chemistries, serum hepatic enzymes, and C-reactive protein per institutional practice. Cultures were monitored and read continuously in the microbiology laboratory using a BACTEC system. Date from the most recent CVC placement or replacement was noted. Clinical data captured included vital signs, findings of clinical examination, and laboratory data. During each admission, the total number of antibiotic doses, blood culture data (time to positive blood culture and speciation where applicable), and date and time of hospital discharge were recorded. Distinction between positive blood cultures and potentially contaminated cultures was not made for this study because the institutional protocol is to treat all positive blood cultures as evidence of a CLABSI, including organisms and potentially representing contamination. Criteria for discharge at 48 hours were negative blood culture, afebrile and normal vital signs after initiation of antibiotics, no new or other non-CLABSI diagnosis requiring inpatient management, no problems with feeding tubes or ileostomies/colostomies requiring intervention or inpatient monitoring, and no social barriers to discharge (caretakers and home environment deemed safe and appropriate, rehabilitation or facility approval in place, insurance approvals in place). Assessment of time of clinical readiness for discharge clinically was not made prospectively.

Symptom Survey

At each admission, parents of enrolled patients or legal guardians were asked to complete a survey describing the signs and symptoms experienced by the patient at home before arriving at the emergency department. Additional survey questions queried routine CVC maintenance practices at home, including frequency of CVC dressing and cap changes and use of ethanol lock. Each survey was administered by a member of the study team using the REDCap electronic data capture interface.[15,16] For non-English-speaking parents or legal guardians an interpreter was used.

Financial Data for Each Hospitalization

Cost and charge data for each admission were obtained using the Pediatric Health Information System database. This administrative database is maintained by the Children's Hospital Association that compiles patient encounter information including diagnoses (according to the *International Classification of Diseases, Ninth and Tenth Revisions*), procedures, resource use, and billing activities from more than 52 children's hospitals. The Pediatric Health Information System utilizes hospital-specific cost-to-charge ratios, as reported by mandate to the Centers for Medicare and Medicaid Services, to estimate hospital costs from billed charges. For each admission in this study, billed charges as well as estimated costs (calculated using the cost-to-charge ratio specific for our institution) were extracted from the Pediatric Health Information System database.

Patients deemed safe for discharge by the inpatient treatment team within 48 hours of admission were the patients most likely to qualify for discharge at 24 hours if the practice shifted from a 48-hour to a 24-hour period of empiric therapy of suspected CLABSI. For these cases, potential cost savings to transition to a 24-hour admission were calculated as (total cost/length of stay [LOS]) × (LOS – 24 hours), where LOS was 24 hours or more.

Statistical Analyses

Data analysis and graphing were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina). Survey responses and baseline characteristics are presented as frequency and median (IQR), with 2-group comparisons made by Pearson chi-square test and Wilcoxon rank-sum test, respectively. When the expected cell count for Pearson χ^2 was less than 5 in any cell, the Fisher exact test was used. A 95% CI for the probability of a positive blood culture beyond 24 hours was determined by the method of Wilson.[18,19] The cumulative incidence of positive blood culture was estimated by the product-limit method and displayed with a Kaplan-Meier plot.

Independence was assumed between cultures taken from the same patient at different hospitalization episodes. Predictors of positive culture were determined assuming both independence and nonindependence to corroborate the suitability of the independence assumption. Results were consistent using both approaches; results assuming complete independence are shown. Potential risk factors for CLABSI were evaluated by comparing cases with negative blood culture at 48 hours (group A) to cases with positive blood culture within 24 hours (group B). Although there were only 3 cultures positive after 24 hours (group C), these were compared with group A to inform future research aimed to identify patients who should remain in hospital despite negative blood cultures at 24 hours. The frequency (%) is shown for each group and compared across groups by relative risk and 95% CI. Some frequency table cell values were zero, rendering the Wald 95% CI undefined; therefore, likelihood ratio 95% CIs are reported.[20]

Logistic regression with penalized maximum likelihood estimation was used to assess predictors, again assuming independence of presentations.[21] Laboratory measures were dichotomized as normal vs abnormal for ease of clinical interpretation.[22] Model fit was assessed by examining influence statistics, including plots of residuals and DFBETAs (the standardized difference in the parameter estimate due to deleting the observation). A general estimating equation with a logit link was used to corroborate predictors of positive culture assuming nonindependence between blood cultures from the same individual. Standard errors were calculated from a sandwich estimator based on a first-order autoregressive working covariance matrix that was selected by minimizing Akaike information criterion.[23] Results were consistent with those of ordinary logistic regression, and only the latter are presented.

LOS, total costs and billed charges, and estimated cost savings are summarized with range, mean ± SD, median (IQR), and total summation over all admissions.

Results

Survey of "Rule-Out CLABSI" Practices

Thirty of the 45 programs surveyed responded (67%) and 18 programs (60%) reported having an established institutional protocol for managing suspected CLABSI. A 48-hour empiric LOS was used by 26 programs (87%), 2 programs (7%) reported using more than 48 hours and 2 programs (7%) reported using less than 48 hours LOS for rule-out CLABSI (**Table I**; available at www.jpeds.com).

Patient Characteristics

Of 73 patients enrolled in the study, 38 (52%) did not have a rule-out CLABSI episode during the study period, and 35 (48%) had at least 1. There were no differences between the 35 patients who presented at least once with suspected CLABSI and the 38 who did not (**Table II**). Forty-nine of the enrolled patients (67%) carried a single diagnosis resulting in intestinal failure, and 24 patients carried multiple diagnoses contributing to intestinal failure (**Table III**; available at www.jpeds.com).

There were 128 episodes of hospitalization for suspected CLABSI among 35 patients; 23 (66%) presented more than once with suspected CLABSI (range, 2-12 presentations; median, 5 presentations). Twenty patients (57%) had at least 1 positive blood culture (**Table IV**; available at www.jpeds.com).

Outcomes

There were 49 positive blood cultures among 128 suspected episodes (38%) confirming CLABSI among children hospitalized for suspected CLABSI. Among the 73 enrollees there were 48 826 catheter-days, for a CLABSI rate of 1.00 per 1000 catheter-days (95% CI, 0.72-1.28). Forty-six of 49 positive blood cultures became positive within 24 hours (median time to positivity, 11.1 hours; range, 5.5-23.9 hours). Three

Table II. Demographic data and baseline characteristics of 73 children with intestinal failure and a CVC for nutritional support

Characteristics	All patients (n = 73)	Presented with suspected CLABSI		*P* value*
		No (n = 38)	Yes (n = 35)	
Female sex	33 (45)	18 (47)	15 (43)	.70
Age at initial presentation, years	2.9 (0.9-7.2)	3.3 (1.5-7.6)	2.8 (0.6-7.1)	.25
History of CLABSI	57 (78)	30 (79)	27 (77)	.85
Surgical history				
Feeding gastrostomy tube	66 (90)	33 (87)	33 (94)	.43
Ileostomy or colostomy	19 (26)	7 (18)	12 (34)	.12
Small bowel resection	59 (81)	31 (82)	28 (80)	.86
Residual bowel length, n = 51	30.0 (21.0-54.0)	35.0 (21.0-67.0)	28.5 (15.0-47.0)	.27
Indication for PN/CVC†				
Gastroschisis	20 (27)	10 (26)	10 (29)	.83
Intestinal atresia	18 (25)	10 (26)	8 (23)	.73
Midgut volvulus	17 (23)	9 (24)	8 (23)	.93
Necrotizing enterocolitis	12 (16)	5 (13)	7 (20)	.43
Pseudo-obstruction	9 (12)	5 (13)	4 (11)	>.95
Hirschsprung disease	5 (7)	1 (3)	4 (11)	.19
Omphalocele	3 (4)	1 (3)	2 (6)	.60
Microvillus inclusion disorder	2 (3)	1 (3)	1 (3)	>.95
Other malabsorptive disorder	1 (1)	1 (3)	0 (0)	>.95
Traumatic resection	1 (1)	0 (0)	1 (3)	.48
Other	10 (14)	5 (13)	5 (14)	>.95
CVC type				.70
Indwelling tunneled catheter	65 (89)	35 (92)	30 (86)	
Peripherally inserted central catheter	6 (8)	2 (5)	4 (11)	
Port, subcutaneously implanted	2 (3)	1 (3)	1 (3)	
Time with central venous access, months	25.0 (8.0-70.0)	28.5 (12.0-65.0)	15.0 (6.0-74.0)	.20
Type of lipid emulsion				.37
Pure soybean oil	38 (52)	17 (45)	21 (60)	
Pure fish oil	31 (42)	19 (50)	12 (34)	
Soybean/MCT/olive/fish oil	4 (6)	2 (5)	2 (6)	

MCT, medium chain triglycerides.
Values are number (%) or median (IQR).
**P* value from Wilcoxon rank-sum, Pearson χ^2, or Fisher exact test.
†Not mutually exclusive.

positive blood cultures became positive beyond 24 hours but within 48 hours (Table V). The probability of a positive blood culture beyond 24 hours was 2.3% (Figure 1). No blood culture became positive beyond 48 hours. All culture data were finalized by 6 days after sampling and submission to the microbiology laboratory. The most common groups of organisms isolated were *Staphylococcus species* (any species, 40% of organisms isolated), *Escherichia coli* (22%), and *Klebsiella pneumoniae* (17%) (Table VI; available at www.jpeds.com).

The 3 blood cultures that became positive beyond 24 hours were each positive for a single organism. These were *Citrobacter freundii* in the culture that became positive at 27 hours, methicillin-resistant *S aureus* that became positive at 28 hours, and *Moraxella osloensis* that became positive at 47 hours. All 3 of these cases occurred in patients who used ethanol locks as outpatients; however, the timing of the last ethanol lock exposure before admission to the hospital was unknown.

Factors at presentation that were associated with positive blood cultures included fever, presence of a gastrostomy tube, predominance of neutrophils (>70%) on the WBC regardless of WBC, elevated C-reactive protein, and elevated aspartate aminotransferase (Table V). When included in a single model assuming independence among 128 blood cultures, the presence of a gastrostomy feeding tube was not statistically significant and the remaining 4 factors were independently associated with a positive blood culture ($P < .04$). Similar results were obtained when adjusted for within-patient correlation in a general estimating equation model (data not shown). Symptoms to localize infection were assessed, including dyspnea, abdominal tenderness, and erythema around the CVC site; however, the prevalence of these findings at presentation was low (0%-11%) and none was an independent risk factor for CLABSI. Having received antibiotics chronically to manage bacterial overgrowth of the gastrointestinal tract did not seem to affect the risk of CLABSI in patients when accounting for within-patient correlation across repeated presentations (data not shown). Among the 49 cases with positive blood cultures, 41 (84%) occurred in patients who used ethanol locks. The median time to positive blood culture in patients who used ethanol locks was 13.1 hours (95% CI, 10.5-15.6 hours) compared with 9.9 hours (95% CI, 6.2-16.3 hours) in cases with patients who did not use ethanol locks. Comparing these groups, the *P* value was 0.28 by log-rank test.

There were 45 patients (35%) with no CLABSI identified who met the criteria for discharge within 48 hours, 34 patients (27%) with no CLABSI identified remained inpatient

Table V. History and laboratory variables at the time of suspected CLABSI presentation (n = 128)

Variables	A Negative culture at 48 h (n = 79)	B Positive culture at 0-24 h (n = 46)	C Positive culture at 24-48 h (n = 3)	Relative risk (95% CI)* B:A (n = 125)	Relative risk (95% CI)* C:A (n = 82)
Presenting complaint					
Fever at home	50 (63%)	33 (72%)	2 (67%)	1.13 (0.87-1.45)	1.05 (0.25-1.68)
Fever at presentation	24 (30%)	28 (61%)	0 (0%)	2.00 (1.34-3.06)	0.00 (0.00-1.62)
GI symptoms	49 (62%)	27 (59%)	1 (33%)	0.95 (0.69-1.26)	0.54 (0.04-1.40)
Lethargy/AMS	27 (34%)	20 (43%)	1 (33%)	1.27 (0.80-1.99)	0.98 (0.07-2.72)
Past surgical history					
Gastrostomy tube	73 (92%)	46 (100%)	3 (100%)	1.08 (1.02-1.17)	1.08 (0.57-1.17)
Ileostomy/colostomy at time of presentation	29 (37%)	11 (24%)	0 (0%)	0.65 (0.34-1.13)	0.00 (0.00-1.33)
Use of ethanol lock	55 (70%)	38 (83%)	3 (100%)	1.19 (0.96-1.45)	1.44 (0.75-1.70)
Laboratory findings					
Abnormal WBC	26 (33%)	17 (37%)	0 (0%)	1.12 (0.67-1.82)	0.00 (0.00-1.49)
Abnormal %PMN	24 (30%)	29 (63%)	1 (33%)	2.08 (1.40-3.16)	1.10 (0.07-3.10)
Abnormal Platelets	28 (35%)	21 (46%)	2 (67%)	1.29 (0.82-1.98)	1.88 (0.44-3.33)
Abnormal CRP†	35 (45%)	35 (78%)	1 (33%)	1.73 (1.30-2.35)	0.74 (0.05-2.00)
Abnormal glucose	16 (20%)	16 (35%)	0 (0%)	1.72 (0.94-3.14)	0.00 (0.00-2.50)
Abnormal albumin†	42 (55%)	19 (41%)	1 (33%)	0.75 (0.48-1.09)	0.60 (0.04-1.59)
Abnormal AST†	28 (37%)	26 (57%)	1 (33%)	1.51 (1.02-2.25)	0.89 (0.06-2.47)
Abnormal ALT†	33 (45%)	28 (61%)	1 (33%)	1.37 (0.96-1.94)	0.75 (0.05-2.02)
Abnormal total bilirubin†	13 (17%)	9 (20%)	0 (0%)	1.13 (0.50-2.41)	0.00 (0.00-2.97)
Abnormal direct bilirubin†	8 (11%)	11 (24%)	0 (0%)	2.24 (0.98-5.41)	0.00 (0.00-5.14)
Abnormal alkaline phosphatase†	14 (18%)	7 (15%)	0 (0%)	0.83 (0.33-1.83)	0.00 (0.00-2.78)

ALT, alanine aminotransferase; *AMS*, acute mental status change; *GI*, gastrointestinal; *%PMN*, percentage of neutrophils; *WBC*, white blood count.
*Shown are likelihood ratio 95% CI.
†Reduced sample size owing to unknown values for CRP (column A, n = 78; column B, n = 45), albumin (column A, n = 76), aspartate aminotransferase (column A, n = 75), ALT (column A, n = 74), total and direct bilirubin (column A, n = 75), and alkaline phosphatase (column A, n = 76).

for a non-CLABSI reason, and 49 patients (38%) had culture-confirmed CLABSI. Costs were highest for the 49 CLABSI cases ($2 526 197 total), followed by the 34 non-CLABSI cases who remained inpatient for care of medical issues unrelated to CLABSI ($547 645) and then by other 45 cases ($375 300).

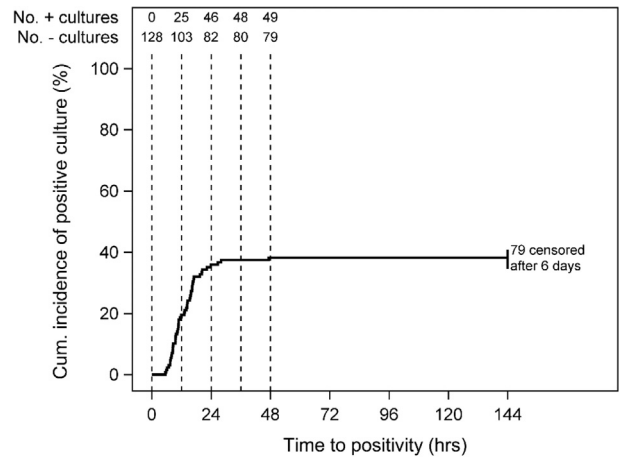

Figure 1. Time to culture positivity. Shown is the cumulative incidence of positive culture for 128 presentations for CLABSI rule-out (49 positive cultures; 38%). Three (2%) cultures became positive beyond 24 hours (26.7, 28.0, and 47.3 hours). Among 46 cultures turning positive within 24 hours, the median time to positivity was 11.1 hours (range, 5.5-23.9 hours). The probability of a positive blood culture beyond 24 hours was 0.023 (95% CI, 0.008-0.067).

Per-person hospital costs among patients with negative blood cultures were significantly increased for those who stayed beyond 48 hours (mean $7432 vs $14 312 per hospitalization). For patients without CLABSI who were discharged without need for additional medical care (ie, those safe to discharge within 48 hours), the cost savings to shift the standard of care to a 24-hour hospital stay (assuming these patients would meet the criteria for discharge at 24 hours) was estimated to be $4639 per hospitalization ($204 109 total over the study period) (**Table VII**; available at www.jpeds.com). LOS data for each case are depicted in **Figure 2**, showing the distribution of LOS among admissions broken down by presence or absence of CLABSI.

Discussion

The overall aim was to achieve a safe balance between the risks of CLABSI in outpatients with intestinal failure and the risks associated with exposure to antibiotics and inpatient days for patients without CLABSI.[24-26]

No blood culture became positive beyond 48 hours, suggesting that the current common practice of a 48-hour empiric approach to exclude CLABSI is safe regarding avoidance of missed CLABSI diagnoses. However, most positive blood cultures became positive within 24 hours and only 1 blood culture became positive beyond 30 hours. This finding suggests that the majority of patients admitted to exclude CLABSI might be safely discharged after 1 day. Elevated C-reactive protein and predominance of neutrophils in the WBC were associated with positive blood cultures, consistent

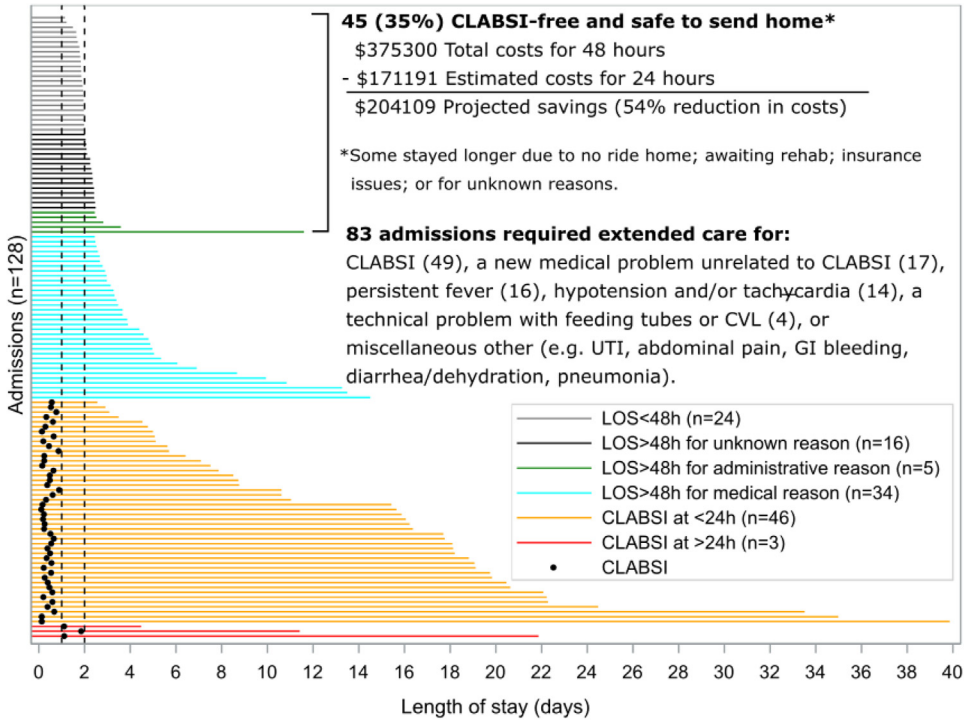

Figure 2. LOS data. Shown is the LOS for each CLABSI rule-out admission. These are separated into groups, denoted by the color of the data bar, according to whether or not blood cultures were positive, LOS, and reason for LOS according to the key in the bottom right.

with prior findings.[7] Other factors associated with positive blood cultures within 24 hours of admission included the presence of a fever at presentation and abnormal serum aspartate aminotransferase level. Although this information may aide risk stratification, there are likely other factors not defined by this study that may inform the appropriate duration of empiric management.

There were 3 patients with positive blood cultures beyond 24 hours. None of these patients had a fever at the time of presentation, and 61% of patients with positive blood cultures within 24 hours were febrile at presentation. Two of the 3 patients had fevers (38.2°C and 40.6°C) and the third patient had a mildly elevated temperature (37.4°C) over the first 24 hours of hospitalization, after antibiotics were initiated. By clinical standards, these patients would not have met temperature criteria for discharge at 24 hours if that were the usual practice. Other common factors among these 3 patients were the presence of a gastrostomy tube and use of ethanol locks. The majority of enrolled patients had a gastrostomy tube, reflecting the usual practice of providing enteral feedings to prevent intestinal villus atrophy and promote intestinal adaptation.[27] Thus, the effect of a gastrostomy tube on the relative risk of CLABSI at or beyond 24 hours was not significant. Daily use of ethanol locks with 2-4 hours of dwell time per day was recommended for the majority of intestinal failure patients. Our hypothesis was that failure to comply with ethanol lock use may increase CLABSI risk. Alternatively, ethanol lock use may have been more commonly initiated in patients with a higher risk of CLABSI or prior CLABSI episodes with the current indwelling catheter. Although insufficient power to assess the significance of this finding, adherence to ethanol lock usage seemed to trend toward increasing CLABSI risk and delays in culture positivity.

There were several limitations of this study. Most notable is the small sample size, with 128 presentations among 35 patients, and 49 positive blood cultures confirming CLABSI among 20 patients. With only 3 blood cultures that became positive beyond 24 hours and a 2.3% likelihood of positive blood cultures beyond 24 hours, this finding may not be representative over a longer duration or of a larger group of patients with intestinal failure. Any true differences between the 3 cases in which cultures became positive beyond 24 hours and the cases with cultures positive within 24 hours would likely not be identified because of small sample size. Alternatively, isolates could have been contaminants (as shown in **Table V**). Although this study did include an assessment of how patients failed to meet the criteria for discharge at 48 hours when inpatient stay was longer than 48 hours, there was not a formal assessment of clinical readiness for discharge at 24 hours using the criteria for discharge at 48 hours. This specific information would be useful in determining the likely usefulness of a 24-hour period of hospitalization and empiric therapy to rule out CLABSI. A larger scale or multi-institutional collaboration would be important to provide more highly powered data

to further inform the safety of adopting a 24-hour rule-out CLABSI protocol and to more robustly study the factors that in this study trended toward protecting from or exacerbating the risk of CLABSI and delaying time to positive blood cultures. Additionally, this study did not capture presentations of enrolled patients to other hospitals to exclude CLABSI.

It is known that size of an inoculum is an important predictor of time to positive blood culture.[28,29] Patient age and size impact blood volume, which in turn can impact number of bacteria or yeasts inoculated and may affect time to positive blood cultures. This circumstance is mitigated somewhat by sampling through the CVC. The patient population in this study was young, with a median age of 2.9 years. Among the 3 blood cultures that were positive after 24 hours of incubation the patient ages were 2, 3, and 14 years. Based on this low number and wide age range of patients with positive cultures beyond 24 hours, no conclusion can be drawn regarding the impact of patient age on density of bacteremia and time to positive blood cultures. However, given that our patient population was young, we urge caution in applying these data to older children and adults.

CVC salvage generally is attempted in pediatric patients with intestinal failure with CLABSI. Fungemia and hemodynamic instability are indications for CVC removal, and persistently positive blood cultures while receiving appropriate antibiotics usually also prompt CVC removal. It is, therefore, plausible that a previously infected CVC or a CVC that has been in place for an extended duration may have biofilms that could increase reinfection rates or contain biologically static organisms that could prolong time to positive blood culture. In this study, there were 4 repeat episodes within 30 days, 2 of which yielded cultures positive for the same organism as the prior episode. These were consecutive episodes in the same patient 25 and 30 days after the prior episode, with blood cultures positive for methicillin-resistant *S aureus* in both instances; cultures became positive within 24 hours in these recurrent episodes. In 1 of the 4 cases, a patient presented with an *E coli* CLABSI 8 days after a presentation in which blood culture was negative. In the fourth case, a patient presented with an *Enterobacter cloacae* CLABSI 28 days after presenting with a *K pneumoniae* CLABSI. Cultures for these 2 cases were positive within 24 hours. Based on our data, which collected CVC type and location at each presentation, all 4 of these 30-day recurrences were in the setting of the same catheter type in the same location. However, a limitation in interpreting this as unchanged CVCs is that instances of rewiring CVCs in the same location with the same catheter type could not be detected through our study design. This study design flaw will need to be rectified for future study of this patient.

Only 48% of enrolled patients were ever investigated for CLABSI during the 3-year study period. This may be due to patients presenting to other hospitals for suspected CLABSI or parents observing their child at home rather than bringing them to the emergency department upon development of fever. Although there were no significant differences identified between patients who presented at least once with suspected CLABSI and those who did not, there may be important differences in outpatient care or patient characteristics that affect this variable. Prior studies in patients with intestinal failure have demonstrated the usefulness of ethanol locks in preventing CLABSI.[30,31] Although there were no significant differences in ethanol lock use between patients with positive and negative cultures in this study, the data do not include patients who did not have episodes of suspected CLABSI. Inpatient measures to minimize CLABSI in patients with intestinal failure also have been reported, some of which could potentially be adapted for outpatients.[32-35]

It is notable that there were several patients with multiple admissions to exclude CLABSI, 1 patient having 12 episodes. This patient had 11 episodes of confirmed CLABSI. On analysis with and without this patient, there were no significant differences in time to positive blood culture, nor were there differences in factors associated with increased risk of CLABSI. Thus, there did not seem to be bias in the data based on the results for this single patient. Among patients who had suspected CLABSI more than once, there did not seem to be a pattern of rapidly recurrent CLABSIs. Among patients with 2 suspected CLABSI presentations within 30 days, only 1 patient had blood cultures positive for the same organism.

Opportunities may exist to safely decrease LOS (and therefore costs and charges) among those with negative blood cultures who remain inpatients beyond 48 hours. Although some of these patients remain inpatients beyond 48 hours for medical reasons unrelated to exclusion of CLABSI, others remain as inpatients for nonmedical reasons, and these patients may represent opportunities to decrease inpatient LOS. Furthermore, there is widely variable LOS among patients with confirmed CLABSI. This may in part reflect the wide range of disease severity. Most patients with positive blood cultures remained inpatients for the duration of their antibiotic course. Certain patients were discharged and completed antibiotics as an outpatient.

There are insufficient data from this study alone to conclude that a 24-hour period of empiric management is safe for all patients with intestinal failure to exclude CLABSI. Although most patients may have been safely discharged at 24 hours, more work is needed to identify factors related to delayed time to positivity and whether these factors can aid in differentiating patients who can safely be discharged at 24 hours from those who require a longer LOS and empiric therapy. Attaining such information likely would require a multi-institutional collaborative study. ■

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Table I. Survey of CLABSI rule-out practices among intestinal failure programs in the US (n = 30)

1. How would you describe your program's management of patients on home PN with suspected CLABSI?
   18 (60%) There is a specific protocol for managing these patients.
   12 (40%) There is no specific protocol for managing these patients, but there is general agreement among attending physicians on the management of these patients.
   0 (0%) There is no specific protocol for managing these patients and management varies widely among attending physicians.
2. At your hospital(s), what is the predominant routine practice for ruling out CLABSI in patients on home PN?
   19 (63%) Patients are always admitted to the hospital.
   10 (33%) Patients are usually admitted to the hospital.
   1 (3%) Patients are usually not admitted to the hospital.
   0 (0%) Patients are never admitted to the hospital.
   0 (0%) There is no predominant practice; management varies widely depending on the patient and/or attending physician.
3. At your hospital(s), what is the usual length of admission to rule out CLABSI in patients on home PN?
   2 (7%) <48 hours.
   26 (87%) 48 hours.
   2 (7%) >48 hours.
   0 (0%) There is no single predominant length of admission; it varies widely.
   0 (0%) Not applicable; patients are not usually admitted at all.
4. At your hospital(s), what laboratories are routinely measured in patients on home PN with suspected CLABSI? (check all that apply)
   30 (100%) Blood cultures
   30 (100%) CBC with or without differential
   24 (80%) Blood chemistry*
   19 (63%) LFTs†
   13 (43%) C-reactive protein
   0 (0%) Coagulation panel‡
5. Of the list below, what are the 3 signs/symptoms felt to be most important in determining likelihood of CLABSI in patients on home PN at your hospital(s)? (Please check 3)
   30 (100%) Fever
   17 (57%) Leukocytosis
   12 (40%) Fatigue/lethargy/decreased activity
   9 (30%) Tachycardia
   7 (23%) Thrombocytopenia
   6 (20%) Elevated CRP
   3 (10%) Elevated LFTs
   3 (10%) Leukopenia
   1 (3%) Changes in ostomy output
   1 (3%) Respiratory distress
   1 (3%) Vomiting
   0 (0%) Decreased appetite
   0 (0%) Electrolyte derangements
   0 (0%) Abdominal tenderness or distention

CBC, complete blood count; *CRP*, C-reactive protein; *LFT*, liver function test.
*At least 1 of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, or glucose.
†At least 1 of alanine aminotransferase, aspartate aminotransferase, direct/total bilirubin, alkaline phosphatase, total protein, or albumin.
‡At least 1 of prothrombin time, partial thromboplastin time, international normalized ratio, or fibrinogen.

Table III. Intestinal failure diagnosis (73 patients [rows] with 98 diagnoses [columns])

Rows, no. (% of patients)	Gastroschisis	Intestinal atresia	Midgut volvulus	NEC	Pseudo-obstruction	Hirschsprung disease	Omphalocele	Microvillus inclusion disease	Other malabsorption disorder	Traumatic resection	Other*
9 (12)	○	○	●	○	○	○	○	○	○	○	○
9 (12)	○	○	○	●	○	○	○	○	○	○	○
8 (11)	●	●	○	○	○	○	○	○	○	○	○
7 (10)	○	○	○	○	●	○	○	○	○	○	○
6 (8)	●	○	●	○	○	○	○	○	○	○	○
6 (8)	○	●	○	○	○	○	○	○	○	○	○
6 (8)	○	○	○	○	○	○	○	○	○	○	●
4 (5)	○	○	○	○	○	●	○	○	○	○	○
3 (4)	●	○	○	○	○	○	○	○	○	○	○
2 (3)	○	○	○	○	○	○	○	●	○	○	○
1 (1)	●	○	○	●	○	○	○	○	○	○	○
1 (1)	●	○	○	○	●	○	○	○	○	○	○
1 (1)	●	●	●	○	○	○	○	○	○	○	○
1 (1)	○	●	○	●	○	○	○	○	○	○	○
1 (1)	○	●	○	○	○	○	○	○	○	○	●
1 (1)	○	●	○	○	○	○	●	○	○	○	○
1 (1)	○	○	●	○	○	●	○	○	○	○	○
1 (1)	○	○	○	●	○	○	○	○	○	○	●
1 (1)	○	○	○	○	●	○	○	○	○	○	●
1 (1)	○	○	○	○	○	○	●	○	○	○	○
1 (1)	○	○	○	○	○	○	●	○	○	○	●
1 (1)	○	○	○	○	○	○	○	○	●	○	○
1 (1)	○	○	○	○	○	○	○	○	○	●	○
Column, No. (% of diagnoses)	20 (20)	18 (18)	17 (17)	12 (12)	9 (9)	5 (5)	3 (3)	2 (2)	1 (1)	1 (1)	10 (10)

Key: ●, present; ○, absent *NEC*, necrotizing enterocolitis

*One each of iatrogenic injury, MELAS (Mitochondrial disorder), malrotation, suspected intrauterine volvulus, meconium pseudocyst, megacystic microcolon, multiple intestinal strictures, OEIS syndrome, chronic lung disease with failure to thrive, feeding intolerance, vanishing gastroschisis.

Table IV. Per-patient account of episodes of suspected CLABSI

Characteristics	Value (% of patients presenting)
Patients presenting with suspected CLABSI	35
No. of presentations per patient	
1	12 (34)
2	5 (14)
3	3 (9)
4	1 (3)
5	4 (11)
6	4 (11)
7	3 (9)
8	2 (6)
12	1 (3)
Median (IQR)	3 (1-6)
Number of positive blood culture episodes per patient	
0	15 (43)
1	13 (37)
>1	7 (20)
Median (IQR)	1 (1-4)

Table VI. Pathogens isolated in positive blood cultures (49 patients [rows] with 60 pathogens [columns])

Rows, No. (%) of patients	*E coli*	*S non-aureus*	*K pneumoniae*	Methicillin-sensitive *S aureus*	Methicillin-resistant *S aureus*	Other bacterial species*	*Candida* species	*Streptococcus* species	Vancomycin-sensitive *Enterococcus* species
8 (16)	●	○	○	○	○	○	○	○	○
8 (16)	○	●	○	○	○	○	○	○	○
8 (16)	○	○	●	○	○	○	○	○	○
5 (10)	○	○	○	○	●	○	○	○	○
5 (10)	○	○	○	○	○	●	○	○	○
4 (8)	○	○	○	●	○	○	○	○	○
3 (6)	○	○	○	○	○	○	●	○	○
2 (4)	●	○	●	○	○	○	○	○	○
1 (2)	●	○	○	○	○	○	○	○	●
1 (2)	●	○	○	●	○	○	○	●	○
1 (2)	●	●	○	○	○	○	○	○	○
1 (2)	○	○	○	○	○	○	○	●	○
1 (2)	○	●	○	●	○	○	○	○	●
1 (2)	○	●	○	●	●	○	○	○	○
Column, No. (%) of pathogens	13 (22)	11 (18)	10 (17)	7 (12)	6 (10)	6 (10)	3 (5)	2 (3)	2 (3)

Key: ●, present; ○, absent.
Species not isolated: vancomycin-resistant *Enterococcus* species; *Pseudomonas* species; *Serratia* species; *Acinetobacter* species; non-*Candida* yeast species.
*Other bacterial species included *Proteus mirabilis* + *Leuconostoc* species (n = 1); *Bacillus* species (n = 1); *Citrobacter freundii* (n = 1); *Enterobacter cloacae* (n = 1); and *Moraxella osloensis* (n = 1).

Table VII. Hours from admission until discharge, total costs, and billed charges among 35 patients admitted for suspected CLABSI

Variables	No.	Range	Mean ± SD	Median (Q1-Q3)	Total*
Overall	128				
Hours from admission until discharge		27-957	183 ± 187	88 (56-262)	23 380
Total costs (RCC based)		$3741-$258 544	$28 042 ± $33 896	$13 459 ($8596-$37 012)	$3 449 142
Billed charges		$6766-471 549	$43 995 ± 56 534	$21 189 ($14 019-$58 388)	$5 411 328
No CLABSI: safe for discharge within 2 calendar days†	45				
Hours from admission until discharge		27-278	55 ± 35	47 (45-57)	2458
Total costs (RCC based)		$3741-$33 720	$8530 ± 4230	$7805 ($7071-$9167)	$375 300
Billed charges		$6766-$49 814	$14 173 ± 6364	$12 846 ($11 534-$14 884)	$623 632
Estimated cost savings‡		$658-$30 813	$4639 ± 4283	$4093 ($3446-$4645)	$204 109
No CLABSI: retained for other medical reasons	34				
Hours from admission until discharge		59-348	125 ± 82	90 (71-128)	4233
Total costs (RCC based)		$8263-$51 436	$17 114 ± 10 292	$13 690 ($10 430-$17 927)	$547 645
Billed charges		$13 910-$81 104	$26 726 ± 15 325	$21 508 ($16 797-$28 947)	$855 243
CLABSI admissions	49				
Hours from admission until discharge		62-957	341 ± 209	376 (154-459)	16 688
Total costs (RCC based)		$10 110-$258 544	$53 749 ± 42 855	$48 835 ($22 463-$69 552)	$2 526 197
Billed charges		$15 153-$471 549	$83 669 ± 74 927	$70 233 ($35 337-$104 940)	$3 932 453

RCC, related clinical costs.
There were 128 admissions for rule-out CLABSI, ranging from 1-12 per patient (median, 3 [IQR, 1-6]).
*Summation over all admissions.
†Some patients stayed longer owing to lack of a ride home; awaiting rehabilitation; or insurance issues.
‡Estimated cost savings calculated for each admission as (total cost/LOS) × (LOS − 24).