Epidemiology of Central Line—Associated Bloodstream Infections in the Pediatric Intensive Care Unit

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ORIGINAL ARTICLE

Epidemiology of Central Line–Associated Bloodstream Infections in the Pediatric Intensive Care Unit

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OBJECTIVE. Describe central line–associated bloodstream infection (CLA-BSI) epidemiology in pediatric intensive care units (PICUs).

DESIGN. Descriptive study (29 PICUs); cohort study (18 PICUs).

SETTING. PICUs in a national improvement collaborative.

PATIENTS/PARTICIPANTS. Patients admitted October 2006 to December 2007 with 1 or more central lines.

METHODS. CLA-BSIs were prospectively identified using the National Healthcare Safety Network definition and then readjudicated using the revised 2008 definition. Risk factors for CLA-BSI were examined using age-adjusted, time-varying Cox proportional hazards models.

RESULTS. In the descriptive study, the CLA-BSI incidence was 3.1/1,000 central line–days; readjudication with the revised definition resulted in a 17% decrease. In the cohort study, the readjudicated incidence was 2.0/1,000 central line–days. Ninety-nine percent of patients were CLA-BSI-free through day 7, after which the daily risk of CLA-BSI doubled to 0.27% per day. Compared with patients with respiratory diagnoses (most prevalent category), CLA-BSI risk was higher in patients with gastrointestinal diagnoses (hazard ratio [HR], 2.7 [95% confidence interval {CI}, 1.43–5.16]; $P < .002$) and oncologic diagnoses (HR, 2.6 [CI, 1.06–6.45]; $P = .037$). Among all patients, including those with more than 1 central line, CLA-BSI risk was lower among patients with a central line inserted in the jugular vein (HR, 0.43 [CI, 0.30–0.95]; $P < .03$).

CONCLUSIONS. The 2008 CLA-BSI definition change decreased the measured incidence. The daily CLA-BSI risk was very low in patients during the first 7 days of catheterization but doubled thereafter. The risk of CLA-BSI was lower in patients with lines inserted in the jugular vein and higher in patients with gastrointestinal and oncologic diagnoses. These patients are target populations for additional study and intervention.

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Central line–associated bloodstream infections (CLA-BSIs) in hospitalized adults and children are a significant source of morbidity, mortality, and increased healthcare costs.[1-12] During the past decade, the incidence of CLA-BSI, as reported by the National Healthcare Safety Network (NHSN) of the Centers for Disease Control and Prevention (CDC), has decreased by nearly one-third to 3.0 per 1,000 central line–days.[13-15] Nonetheless, a recent study estimates that 65%–70% of cases of CLA-BSI (in patients of all ages) may be preventable, with substantial reductions in mortality and healthcare costs.[16]

Previous epidemiologic studies suggest that children and adults share many similar risk factors for CLA-BSIs, although unique risks factors for children include underlying genetic syndromes, congenital malformations, and extracorporeal therapies.[7,17-19] Conversely, some risk factors in adults have not been supported in pediatric studies, such as femoral central lines being associated with a higher risk of CLA-BSI in adults but not in children.[17,18,20]

Since October 2006, the National Association of Children's Hospitals and Related Institutions (NACHRI) has supported a quality transformation collaborative to identify and test the impact of care practices designed to prevent CLA-BSIs in pediatric intensive care units (PICUs). During the first year of the project, the incidence of CLA-BSI in PICUs decreased by 43% (from 5.4 to 3.1 per 1,000 central line–days).[21] Additional analyses showed that this decrease was most strongly associated with implementation of a catheter care mainte-

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nance bundle. As preventable CLA-BSIs are eliminated through process improvements, patient-level and catheter-level risk factors may become more evident in aggregated residual cases.

We undertook this study to examine the epidemiology of CLA-BSIs in the NACHRI collaborative PICUs. We hypothesized that we would identify risk factors that could be used to guide additional prevention strategies. We also sought to characterize the impact of CDC/NHSN changes in the CLA-BSI definition on the incidence and pathogen profile of CLA-BSIs in the PICU setting.

METHODS

Study Design

The project had 2 components (Figure 1): first, a descriptive epidemiologic study of the incidence of CLA-BSI among patients, conducted in 29 PICUs that constituted the original members of the NACHRI collaborative; second, a cohort study of risk factors for CLA-BSI in patients with at least 1 central line in place during their PICU stay, conducted in a subset of 18 ICUs that also collected data on all PICU admissions and central lines, using the Virtual PICU Performance System (VPS).[22] The collaborative design, practice interventions, and effect of these interventions on the incidence of CLA-BSI have been reported previously.[21] The results presented in this analysis involve CLA-BSIs from October 2006 through December 2007, a period after these practice interventions had been implemented. Each PICU received institutional review board approval or exemption for this work, and the VPS research committee approved this research protocol.

Definitions and Data Sources

In both the descriptive and cohort studies, CLA-BSI events were identified and central line–days were calculated prospectively at each site by trained, hospital-based, infection control professionals following NHSN methods.[23] Central lines were defined following NHSN definitions.[24] The NHSN definition for CLA-BSI in effect before 2008 was used to identify CLA-BSIs in all participating ICUs during the study period, with the following modifications: (1) only laboratory-confirmed primary bloodstream infections were included, (2) CLA-BSI date of onset was defined as the date of the first positive blood culture, and (3) BSIs identified in the first 48 hours of admission were excluded as present or incubating at admission. In 2008, the NHSN definition for CLA-BSI was revised, notably to require 2 positive cultures for organisms considered to be common skin contaminants.[15,24] To assess the effect of this change on CLA-BSI incidence, each site readjudicated all cases of CLA-BSI, using the revised 2008 definition.

In the descriptive study, patient demographics and isolate description were reported to an NACHRI-administered database for each CLA-BSI. Central line–days were reported in aggregate each month. In the cohort study, VPS was used to calculate central line–days and to collect demographics, patient origin/disposition, diagnoses, operative procedures, severity of illness, and mortality as well as catheter types, sites, number, and durations in situ. Severity of illness was measured with the pediatric index of mortality (PIM2).[25] For patients with more than 1 PICU stay, only the first stay was included. For patients with more than 1 CLA-BSI, only the first episode was included.

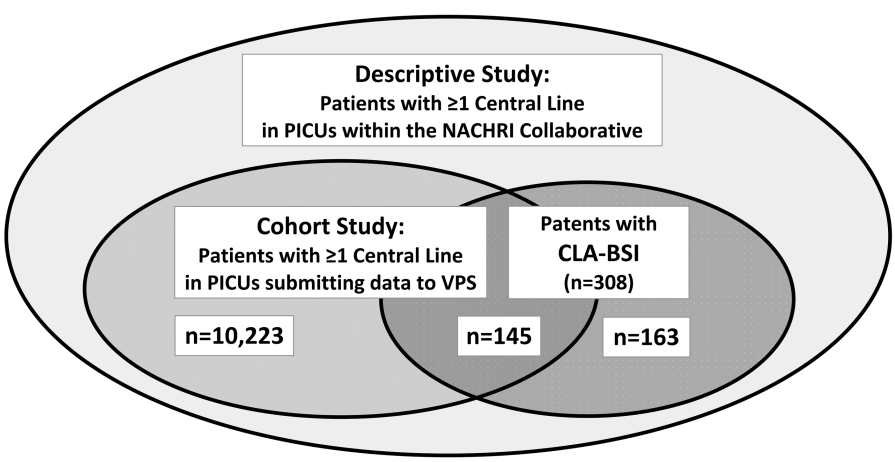

FIGURE 1. Study designs and data sources. The descriptive study describes the incidence of central line–associated bloodstream infection (CLA-BSI) in the 29 pediatric intensive care units (PICUs) in the National Association of Children's Hospitals and Related Institutions (NACHRI) collaborative. The cohort study was conducted in 18 ICUs in the NACHRI collaborative that utilize the Virtual PICU Performance System (VPS) to capture central line data on all patients admitted to the PICU. This cohort study examined risk factors for CLA-BSI in 145 patients with CLA-BSI and 10,223 patients without CLA-BSI.

Analysis

Descriptive statistics were used to characterize the collaborative PICUs and reported pathogens, using the pre-2008 and revised NHSN CLA-BSI criteria. In the cohort study, Kaplan-Meier survival estimates were derived and compared across catheter type, using log-rank tests. Demographics and catheter characteristics for patients with and without a CLA-BSI were compared, using Fisher's exact tests for categorical characteristics and rank-sum tests for continuous characteristics. Time-varying Cox proportional hazards models were applied to estimate the relative risk of CLA-BSI as a function of demographic and catheter characteristics. Time-varying characteristics included catheter number, location, and type. Because of the relatively small number of CLA-BSI events, several multivariable models were considered: a demographic model including age, predicted risk of mortality, gender, burn status, congenital heart disease, extracorporeal membrane oxygenation (ECMO), presence of arterial catheters, origin, and primary patient diagnosis; and 3 separate models assessing the risk of CLA-BSI as a function of catheter type, site, and number. The multivariable models included variables selected on the basis of scientific relevance, and all models included adjustment for age. The cohort study included all available subjects in the analysis with no a priori power calculations performed. The estimated power was high (>0.80) to detect significant differences across primary diagnostic categories and catheter sites/types; power was low (<0.50) to detect differences across patient origin and number of catheters.

RESULTS

Study Populations and Blood Culture Isolates

Characteristics of the 29 PICUs are shown in Table 1. Most were combined medical-surgical-cardiac units. Over 15 months, 377 CLA-BSIs occurred during 121,983 central line–days, for an incidence of 3.1/1,000 central line–days. Average CLA-BSI rates among PICUs ranged from 0.5 to 5.1/1,000 central line–days. Blood culture isolate information was provided for 371 (98.4%) of CLA-BSIs (Table 2). Among these, 110 (30%) were organisms consistent with common skin contaminants. Of these, 63 (57%) events did not satisfy the 2008 NHSN definition, all due to the absence of a second concordant isolate. Thus, 308 events satisfied the 2008 NHSN CLA-BSI definition for an incidence of 2.5/1,000 central line–days, a 17.0% decrease attributable to the application of the revised definition. CLA-BSIs satisfying the revised NHSN definition were used for all other analyses.

Time to First Event and Mortality

In the cohort study, there were 10,368 patient admissions, 145 CLA-BSIs, and 71,212 central line–days for a CLA-BSI incidence of 2.0/1,000 central line–days. Time-to-event analyses demonstrated that 99.0% of patients remained CLA-BSI-free through day 7, with an average daily risk of CLA-BSI of 0.14% during the first week. After day 7, the average daily risk of CLA-BSI doubled to 0.27% and remained steady through day 100 (Figure 2, *left*). Patients with 1 central line in place during their PICU stay (in whom CLA-BSIs could be associated with specific catheters) comprised 75% of the cohort, but only 39% of CLA-BSI cases occurred in these patients. Among these patients, no significant differences in the estimated survival functions existed between conventional/short-term catheters, tunneled/long-term catheters, and peripherally inserted central catheters (Figure 2, *right*). Given the small number of CLA-BSI events beyond 21 days in this subsample, diverging trends for different central line types in Figure 2 were not statistically significant.

TABLE 1. Characteristics of the 29 Pediatric Intensive Care Units (PICUs) in the National Association of Children's Hospitals and Related Institutions Collaborative

Characteristic	% ($n = 29$)
Type of ICU	
General medical-surgical and cardiac	62
General medical-surgical	31
Cardiac	7
No. of beds	
10–16	41
17–27	45
28–36	14
Mean PICU length of stay, days	
2.7–4.5	48
4.6–6.3	41
6.4–9.6	10
Services provided by ICU	
Level 1 traumas	66
Solid organ transplants	86
Bone marrow transplants	72
Extracorporeal membrane oxygenation	90

All-cause mortality for patients with CLA-BSI was 15% ($n = 21$) compared with 7% ($n = 708$) among patients with no CLA-BSI ($P < .002$). Survivors and nonsurvivors were similar in age and weight but significantly different on most other patient characteristics. Mortality was significantly higher for the following patient variables: ECMO, trauma, noncardiac, noncancer, nonoperative, transfers from other facilities, greater central line–day exposure, and number of catheters. Deaths among patients with CLA-BSI were too infrequent or temporally distant to analyze independent risk factors or quantify attributable mortality.

Risk Factors

Characteristics of patients and central lines in the cohort study are summarized in Table 3. In the adjusted analysis, younger age and higher PIM2 scores were not associated with a higher risk of CLA-BSI. The risk of CLA-BSI was significantly different across primary diagnosis categories ($P < .004$). Relative to the referent group, patients had a higher risk of CLA-BSI for primary diagnoses of gastrointestinal dis-

TABLE 2. Central Line–Associated Bloodstream Infection Blood Culture Isolates in 29 Pediatric Intensive Care Units

	Pre-2008 NHSN definition		Revised NHSN definition[a]	
	%	*n*	%	*n*
All central line infections	100.0	371	100.0	308
1 organism	91.9	341	90.9	280
2 organisms	7.3	27	8.1	25
3 organisms	0.8	3	1.0	3
No pathogen info (excluded below)	...	6	...	6
Gram-positive cocci	55.2	223	46.6	158
Staphylococcus	34.9	141	24.2	82
Coagulase (−)[b]	28.7	116	16.8	57
aureus	4.2	17	5.0	17
aureus, MRSA	2.0	8	2.4	8
Enterococcus	17.1	69	20.4	69
faecalis	10.4	42	12.4	42
faecium	4.5	18	5.3	18
faecalis/faecium, VRE	1.2	5	1.5	5
Species NOS	1.0	4	1.0	4
Streptococcus species[b]	2.2	9	2.1	7
Gram-negative bacilli	29.7	120	35.40	120
Enterobacter	9.9	40	11.8	40
cloacae	6.7	27	8.0	27
aerogenes	2.2	9	2.7	9
Species NOS	1.0	4	1.2	4
Klebsiella	7.7	31	9.1	31
pneumonia	6.2	25	7.4	25
oxytoca or *ozaenae*	1.6	6	2.0	6
Pseudomonas	3.5	14	4.1	14
aeruginosa	3.0	12	3.5	12
Species NOS	0.5	2	0.6	2
Serratia marcescens	3.2	13	3.8	13
Stenotrophomonas maltophilia	2.0	8	2.4	8
Escherichia coli	1.7	7	2.1	7
Acinetobacter species NOS	0.5	2	0.6	2
Bacteroides species NOS	0.5	2	0.6	2
Citrobacter freundii	0.5	2	0.6	2
Alcaligenes xylosoxidans	0.3	1	0.3	1
Fungal	13.4	54	15.9	54
Candida	12.6	51	15.0	51
parapsilosis	6.2	25	7.4	25
albicans	5.5	22	6.5	22
tropicalis	1.0	4	1.2	4
Yeast NOS	0.8	3	1.0	3
Gram-positive bacilli	2.7	11	2.1	7
Bacillus cereus[b]	1.2	5	0.9	3
Lactobacillus species NOS	1.0	4	1.2	4
Corynebacterium species NOS[b]	0.5	2	0.0	0

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus*; NHSN, National Healthcare Safety Network; NOS, not otherwise specified; VRE, vancomycin-resistant *Enterococcus*.

[a] The revised NHSN definition required 2 positive blood cultures for organisms considered common skin contaminants.

[b] Organisms considered to be common skin contaminants in the revised NHSN definition.

ease (hazard ratio [HR], 2.7; $P < .002$), oncology (HR, 2.6; $P < .036$), and other (HR, 3.0; $P < .001$). Specific diagnostic subcategories are outlined in Table 4.

The number or types of central lines were not significantly associated with CLA-BSI (Table 3), although compared with all other sites, the risk of CLA-BSI was lower for catheters in a jugular vein (HR, 0.43; $P < .015$). Because of complexities in associating CLA-BSIs with a specific catheter when multiple lines are present, the 70% of patients with only 1 central line were analyzed, and no significant associations with specific catheter sites or types emerged (Table 5).

DISCUSSION

This cohort study of CLA-BSI is the largest of its kind in the PICU setting and was conducted in the context of standardized and reliably performed best practices for both central line insertion and maintenance care. The change in the NHSN CLA-BSI definition had a modest impact on the incidence of infection, and the distribution of pathogens was most affected by reducing events caused by coagulase negative *Staphylococci*. The risk of CLA-BSI was low during the first week of central line catheterization but doubled thereafter. This later period is more relatable to daily maintenance practices of catheters rather than insertion-related practices, which have been identified drivers of adult CLA-BSI.[26,27] The risk of CLA-BSI was higher in primary gastrointestinal (GI) and oncologic diagnoses. Additionally, a lower risk of CLA-BSI was observed in patients with central lines in the jugular vein. This contrasts somewhat with the adult pattern of increased risk associated with femoral placement and decreased risk associated with the subclavian site.[17,18,20] While deaths were too infrequent and temporally distant from CLA-BSI events to analyze robustly, the twofold higher all-cause mortality rate in patients with CLA-BSI—in spite of similar predicted risk of mortality on admission—affirms meaningful attributable mortality.

The increased per diem risk of CLA-BSI after a week of catheterization is consistent with previous findings in adults.[28] This finding emphasizes the importance of continually reassessing the need for central access and promptly removing unnecessary catheters, particularly during the second week of catheterization and thereafter. This intervention is included in CLA-BSI prevention bundles with established effectiveness and is recommended by current prevention guidelines.[21,27,29] However, the appropriate use of central lines in critically ill patients requiring prolonged central access is less clear. Previous research in adults has not demonstrated that scheduled replacement of nontunneled, nonimplanted catheters is associated with a reduction in CLA-BSI risk, and current prevention guidelines recommend against this practice.[29-31] Data from this report are consistent with this recommendation insofar as they reflect a small cumulative risk of CLA-BSI during the first week of catheterization, regardless of catheter type. Given the lower risk of CLA-BSI with short-term jugular

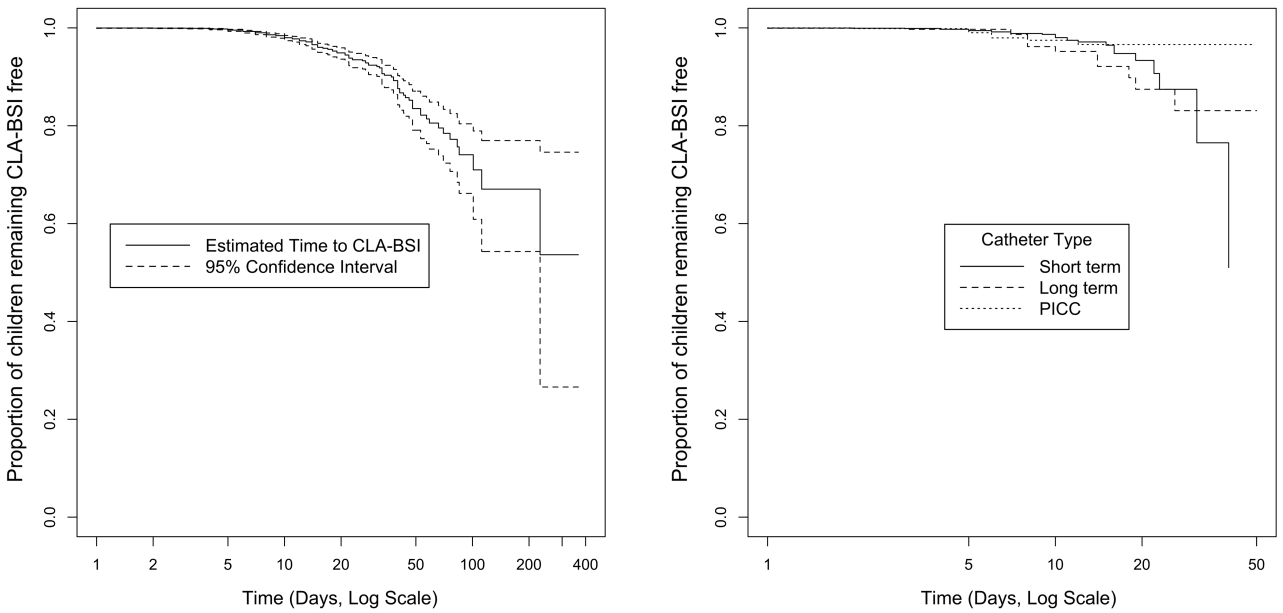

FIGURE 2. Proportion of subjects remaining central line–associated bloodstream infection (CLA-BSI)–free as a function of time. The left panel includes all subjects and central line types (n = 10,368); the right panel includes only the subset of patients with a single central line, divided by selected catheter type (n = 7,513). PICC, peripherally inserted central catheter.

catheters, if the need for central access is expected to be prolonged beyond the first week, the risk of CLA-BSI may be reduced by selecting or re-siting temporary catheters to this location. However, the risks and costs of an additional line insertion procedure must be weighed appropriately, and the efficacy of such an approach should be studied prospectively. Studies in adults have shown that avoidance of the femoral site of insertion is associated with lower CLA-BSI rates, and this practice is recommended strongly by current prevention guidelines.[20,27] Older studies in children did not observe significant differences between central lines inserted in the femoral vein versus other sites, and current guidelines make no recommendation regarding the preferred site of insertion in pediatric patients.[29,32] The findings of this study indicate that in the current era, it may be appropriate to reevaluate the preferred site of insertion for short-term central lines in pediatric patients.

The increased risk for CLA-BSI observed among patients with a primary GI diagnosis, combined with the revised pathogen profile showing a majority of gut flora, is intriguing. Several potential explanations exist for this finding. GI patients may be more likely to receive therapies that increase CLA-BSI risk, such as parenteral nutrition or blood product transfusions.[33] Malnutrition has also been implicated as a risk factor for nosocomial BSIs.[34] Some GI patients may be more prone to chronic diarrhea, which can increase fecal soilage in a patient's immediate environment and increase the risk of contamination of the central line and attached access points. Bacterial translocation across the intestinal mucosa may also be more frequent in these patients, as with direct bloodstream entrainment from GI bleeding, dysmotility, or atrophic bowel due to protracted non per os status. Bacterial translocation is not uncommon in critically ill patients, but reliable methods for distinguishing it from CLA-BSI are not available.[35] These latter arguments of soilage and translocation are somewhat refuted by the relatively similar proportion of gut flora comprising CLA-BSIs both within and outside the GI diagnostic group. A better understanding of what is driving the increased risk of CLA-BSI in children with GI diagnoses would help guide potential future interventions, such as control of bacterial overgrowth through probiotics/antibiotics or protocols to mitigate unnecessary exposure to parenteral nutrition and blood products.

The observed increase in CLA-BSI risk for oncology patients in the PICU has a number of intuitive pathophysiologic explanations. Historically reported rates in pediatric oncology inpatients have generally been similar to or higher than PICU rates in the same period.[14,36-38] Further, central line utilization and manipulation in the critically ill child with cancer are likely greater compared with oncology wards. Immunocompromised children are presumably more susceptible to typical pathogens as well as to less virulent isolates that immune competent hosts might spontaneously clear (eg, *Staphylococcus epidemidis*) and may be less tolerant of microcontamination that an immune competent host could effectively mitigate. Further, translocation from mucositis or other occult sources of bacteremia may be more persistent in an immunocompromised patient and attributed by default to a central line when using the surveillance definition for CLA-BSI.

National CLA-BSI rates in the PICU are a third of what

TABLE 3. Characteristics of Patients and Central Lines in the Cohort Study (18 Pediatric Intensive Care Units)

	Unadjusted analysis			Adjusted analysis		
Variables	BSI, % (n = 145)	No BSI, % (n = 10,223)	P	HR	95% CI	P
Patient						
Continuous						
Age, median, years	0.75	2.4	<.001	0.97	0.94–1.00	.076
Weight, median, kg	7.0	12.5	<.001			
PIM2 risk of mortality	3.0	1.5	.078	1.02	0.89–1.16	.825
Categorical						
Sex, male	53.8	54.3	.933	0.92	0.66–1.28	.627
Primary diagnostic category (all together)			<.004			<.001
Respiratory	20.0	16.1		Ref.		
Cardiovascular	23.4	35.3		0.80	0.45–1.43	.445
Gastrointestinal	10.3	5.3		2.72	1.43–5.16	.002
Infectious	6.9	5.4		1.94	0.93–4.05	.077
Trauma/injury/poisoning	3.4	5.3		1.06	0.37–3.07	.911
Neurologic	5.5	8.3		1.11	0.50–2.48	.791
Oncologic	4.1	5.4		2.61	1.06–6.45	.037
Other	26.2	19.0		2.96	1.81–4.85	<.001
Specific diagnoses, interventions, contexts						
Death	14.5	6.9	.002			
Extracorporeal membrane oxygenation	7.6	1.7	<.001	1.00	0.52–1.94	.998
Any operations	66.9	59.1	.061	0.94	0.63–1.38	.735
Congenital heart disease	21.4	19.4	.527	1.00	0.62–1.61	.992
Burn	1.4	0.3	.073	2.70	0.58–12.64	.207
Cancer	4.1	5.4	.708			
Trauma	2.9	4.7	.417			
Postoperative <24 h from ICU admission	58.6	57.5	.866			
Interinstitutional transfer (any unit type)	19.3	18.1	.665			
Patient origin at admission (type of unit)			<.001			
Emergency department	24.8	25.3		Ref.		
Operative/perioperative units	31.7	46.7		1.38	0.84–2.25	.201
General/intermediate care	29.7	18.4		0.94	0.59–1.49	.788
ICU	11.7	6.9		0.90	0.49–1.66	.743
Other	2.1	2.7		0.55	0.17–1.82	.330
Central line						
Catheter site						
Femoral	46.9	28.6	<.001	1.00	0.61–1.50	.840
Neck (internal or external jugular)	19.3	26.5	.057	0.43	0.22–0.85	.015
Subclavian	28.3	21.2	.041	1.02	0.56–1.73	.951
Peripheral	32.4	20.3	<.001	0.75	0.46–1.22	.249
Umbilical	11.7	4.9	<.001	0.52	0.16–1.69	.278
Remainder (irregular/unspecified site)	44.8	26.3	<.001	1.29	0.83–2.01	.260
Central line type						
Short term (percutaneous)	75.2	72.3	.513	0.75	0.45–1.24	.257
Long term (tunneled/subcutaneous)	33.8	17.3	<.001	1.46	0.87–2.44	.148
Peripherally inserted	32.4	20.3	<.001	0.76	0.45–1.27	.293
Hemodialysis	9.7	3.6	<.001	1.42	0.73–2.78	.304
Extracorporeal membrane oxygenation	7.6	1.7	<.001	0.31	0.04–2.26	.249
Pulmonary artery	0.7	0.6	.595	1.46	0.20–10.49	.708
No. of central lines			<.001			
1	38.6	74.6		Ref.		
2	23.4	16.5		0.71	0.46–1.11	.136
3 or more	37.9	8.9		0.98	0.51–1.88	.952

NOTE. BSI, bloodstream infection; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; PIM2, pediatric index of mortality; Ref., referent group.

TABLE 4. Proportion of Specific Diagnoses Comprising Primary Diagnostic Categories with Increased Risk of Central Line–Associated Bloodstream Infection in the Cohort Study (18 Pediatric Intensive Care Units)

Diagnosis	HR	*P*	%
Gastrointestinal	2.7	.002	
Gastrointestinal bleed			12
Chronic liver failure			10
Acute liver failure			10
Gastroesophageal reflux			6
Esophageal disease			6
Each of remaining diagnoses			<5
Oncologic	2.6	.037	
Leukemia			22
Brain neoplasm			17
Neuroblastoma			5
Each of remaining diagnoses			<5
Other	3.0	.001	
Symptoms not otherwise specified			25
Orthopedic			19
Renal/genitourinary			19
Genetic/metabolic			17
Each of remaining diagnoses			<5

NOTE. HR, hazard ratio.

they were a decade ago, and rigorous implementation of pediatric-specific central line care bundles reduces CLA-BSI rates dramatically.[13,14,21,39] This rate reduction has occurred without meaningfully adjusting catheter types or insertion sites and without notable changes in patient demographics, suggesting that the most important risk factors for CLA-BSI in the PICU have been (and still may be) catheter care practices and the healthcare systems that promote or inhibit adherence to best practice. The extensive literature seeking patient-level or catheter-level risk factors for nosocomial infections may reflect a form of omitted variable bias, where biology and technology are assumed to be the main drivers, instead of the interactions of biology and technology with complex systems and human factors.[40] It may become more constructive to consider CLA-BSI risk factors in terms of the subtle ways that certain types of patients or technology alter the way care is delivered. For instance, the GI patient with diarrhea may increase diaper care and hand contamination, amplifying defects in hand hygiene practices. Such phenomena could be identified through subgroup analyses aimed at finding discrepant adherence to recommended practices in patients with identified risk factors. Because most CLA-BSI risk factors cited here and in the literature may not be modifiable (eg, diagnosis) or may be so only in certain circumstances (eg, dialysis catheter site), it is perhaps fortunate that the largest driver of PICU CLA-BSIs has been something that is modifiable—namely, how central lines are managed.

There are several limitations to this study. The CDC/NHSN definition for CLA-BSI changed in January 2008, making the 2006–2007 pathogen profile outdated for current practice. We have addressed this issue by retrospectively applying the new definition. Specific catheter types were aggregated into categories that could have washed-out opposing signals (eg, long-term catheters included both tunneled and implanted devices). The data analyzed in this study did not contain detailed information on time-varying patient care practices (eg, parenteral nutrition, lipid solutions, blood products); consequently, we were unable to assess the effect of these factors on the risk of CLA-BSI. The CLA-BSI definition has limitations in both specificity (eg, inclusive of gut translocation) and exposure adjustment (eg, a central line–day may be exposure to more than 1 central line) and is limited in attribution to a specific central line type or site when there are multiple central lines (especially for patients that almost always have coexisting catheters, such as with ECMO and continuous renal replacement therapy). There is also evidence that variability in surveillance practices and interpretation of the CDC/NHSN definition affects reported rates, with more aggressive surveillance being associated with higher rates.[41] While sites participating in this study received standardized instructions on the application of the CDC/NHSN definition, we did not evaluate the reliability or validity of the application of the definition.

In summary, the microbiology of CLA-BSIs in this national PICU quality improvement collaborative mirrors profiles historically reported. The 2008 CDC definition change for CLA-BSI reduced the rate by 17% and altered the organism profile, principally by reducing the percent of CLA-BSI caused by coagulase negative *Staphylococci*. The risk of CLA-BSI is very low during the first week of catheterization but doubles there-

TABLE 5. Characteristics of Central Lines in Patients with Only 1 Central Line at the Time of Central Line–Associated Bloodstream Infection (CLA-BSI) in the Cohort Study (18 Pediatric Intensive Care Units)

	Unadjusted analysis			Adjusted analysis		
Central line category	CLA-BSI rate	Lines, %	Line days, %	HR	95% CI	*P*
Short term						
Femoral vein insertion site	9.5	22	26	Ref.		
Subclavian vein insertion site	7.7	19	18	1.14	0.53–2.45	.746
Internal/external jugular vein site	2.8	24	19	0.54	0.20–1.49	.236
Peripherally inserted	7.9	15	17	0.79	0.35–1.82	.582
Long term (tunneled/subcutaneous)	11.7	17	17	1.49	0.71–3.13	.289

NOTE. CI, confidence interval; HR, hazard ratio; Ref., referent group.

after. Although not sufficient to support definitive practice recommendations, the results of this study support selection of the jugular vein as the insertion site for short-term central lines, particularly if the dwell time is expected to exceed a week. The increased risk of CLA-BSI in patients with GI and oncologic diagnoses warrants further study to better understand the nature of these risks and potential additional prevention strategies. The complex interplay of patient factors, catheter variables, and unit practices may obscure other significant factors important in understanding how to eradicate pediatric CLA-BSI. This report of significant associations with CLA-BSI should not overshadow the substantial decline in nationally pooled CLA-BSI rates over the past decade, a fact that suggests that processes relating to the insertion and maintenance of central lines have been the most significant source of modifiable risk for CLA-BSI heretofore and may remain so.

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REFERENCES

1. Richards MJ, Edwards JR, Culver DH, Gaynes RP, National Nosocomial Infections Surveillance System. Nosocomial infections in pediatric intensive care units in the United States. *Pediatrics* 1999;103:e39.
2. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;132:391–402.
3. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;271:1598–1601.
4. Urrea M, Pons M, Serra M, Latorre C, Palomeque A. Prospective incidence study of nosocomial infections in a pediatric intensive care unit. *Pediatr Infect Dis J* 2003;22:490–494.
5. Yogaraj JS, Elward AM, Fraser VJ. Rate, risk factors, and outcomes of nosocomial primary bloodstream infection in pediatric intensive care unit patients. *Pediatrics* 2002;110:481–485.
6. Grohskopf LA, Sinkowitz-Cochran RL, Garrett DO, et al. A national point-prevalence survey of pediatric intensive care unit–acquired infections in the United States. *J Pediatr* 2002; 140:432–438.
7. Odetola FO, Moler FW, Dechert RE, VanDerElzen K, Chenoweth C. Nosocomial catheter-related bloodstream infections in a pediatric intensive care unit: risk and rates associated with various intravascular technologies. *Pediatr Crit Care Med* 2003;4: 432–436.
8. Wisplinghoff H, Seifert H, Tallent SM, Bischoff T, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in pediatric patients in United States hospitals: epidemiology, clinical features and susceptibilities. *Pediatr Infect Dis J* 2003;22:686–691.
9. Aly H, Herson V, Duncan A, et al. Is bloodstream infection preventable among premature infants? a tale of two cities. *Pediatrics* 2005;115:1513–1518.
10. Elward AM, Hollenbeak CS, Warren DK, Fraser VJ. Attributable cost of nosocomial primary bloodstream infection in pediatric intensive care unit patients. *Pediatrics* 2005;115:868–872.
11. Costello JM, Morrow DF, Graham DA, Potter-Bynoe G, Sandora TJ, Laussen PC. Systematic intervention to reduce central line–associated bloodstream infection rates in a pediatric cardiac intensive care unit. *Pediatrics* 2008;121:915–923.
12. Nowak JE, Brilli RJ, Lake MR, et al. Reducing catheter-associated bloodstream infections in the pediatric intensive care unit: business case for quality improvement. *Pediatr Crit Care Med* 2010; 11:579–587.
13. Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control* 2009;37: 783–805.
14. National Nosocomial Infections Surveillance (NNIS) system report, data summary from October 1986-April 1998, issued June 1998. *Am J Infect Control* 1998;26:522–533.
15. Centers for Disease Control and Prevention. Vital signs: central line–associated blood stream infections—United States, 2001, 2008, and 2009. *MMWR Morb Mortal Wkly Rep* 2011;60: 243–248.
16. Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. *Infect Control Hosp Epidemiol* 2011;32:101–114.
17. Elward AM, Fraser VJ. Risk factors for nosocomial primary bloodstream infection in pediatric intensive care unit patients: a 2-year prospective cohort study. *Infect Control Hosp Epidemiol* 2006;27:553–560.
18. Kritchevsky SB, Braun BI, Kusek L, et al. The impact of hospital practice on central venous catheter associated bloodstream infection rates at the patient and unit level: a multicenter study. *Am J Med Qual* 2008;23:24–38.
19. Almuneef MA, Memish ZA, Balkhy HH, Hijazi O, Cunningham G, Francis C. Rate, risk factors and outcomes of catheter-related bloodstream infection in a paediatric intensive care unit in Saudi Arabia. *J Hosp Infect* 2006;62:207–213.
20. Safdar N, Kluger DM, Maki DG. A review of risk factors for catheter-related bloodstream infection caused by percutaneously inserted, noncuffed central venous catheters: implications for preventive strategies. *Medicine (Baltimore)* 2002;81:466–479.
21. Miller MR, Griswold M, Harris JM II, et al. Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. *Pediatrics* 2010;125:206–213.
22. VPS. *Virtual PICU Performance System.* Alexandria, VA: VPS, 2011. https://portal.myvps.org/Default.aspx.
23. Centers for Disease Control and Prevention. *Central Line–Associated Bloodstream Infection (CLABSI) Event: Guidelines and Procedures for Monitoring CLABSI.* National Healthcare Safety

Network (NHSN) manual. Atlanta, GA: NHSN, 2010. http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf.
24. Centers for Disease Control and Prevention. *Catheter-Associated Bloodstream Infection Definitions*. National Healthcare Safety Network (NHSN) manual. Atlanta, GA: NHSN, 2008. http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf.
25. Garcia PC, Piva JP. Pediatric Index of Mortality 2 (PIM2)—a prognostic tool for developing countries: easy, efficient, and free! *Pediatr Crit Care Med* 2007;8:77–78.
26. Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med* 2004;32:2014–2020.
27. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355:2725–2732.
28. Ullman RF, Gurevich I, Schoch PE, Cunha BA. Colonization and bacteremia related to duration of triple-lumen intravascular catheter placement. *Am J Infect Control* 1990;18:201–207.
29. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011;52:e162–e193.
30. Eyer S, Brummitt C, Crossley K, Siegel R, Cerra F. Catheter-related sepsis: prospective, randomized study of three methods of long-term catheter maintenance. *Crit Care Med* 1990;18:1073–1079.
31. Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med* 1992;327:1062–1068.
32. Stenzel JP, Green TP, Fuhrman BP, Carlson PE, Marchessault RP. Percutaneous central venous catheterization in a pediatric intensive care unit: a survival analysis of complications. *Crit Care Med* 1989;17:984–988.
33. Wylie MC, Graham DA, Potter-Bynoe G, et al. Risk factors for central line–associated bloodstream infection in pediatric intensive care units. *Infect Control Hosp Epidemiol* 2010;31:1049–1056.
34. Al-Rawajfah OM, Stetzer F, Hewitt JB. Incidence of and risk factors for nosocomial bloodstream infections in adults in the United States, 2003. *Infect Control Hosp Epidemiol* 2009;30:1036–1044.
35. Wiest R, Rath HC. Gastrointestinal disorders of the critically ill: bacterial translocation in the gut. *Best Pract Res Clin Gastroenterol* 2003;17:397–425.
36. Allen RC, Holdsworth MT, Johnson CA, et al. Risk determinants for catheter-associated blood stream infections in children and young adults with cancer. *Pediatr Blood Cancer* 2008;51:53–58.
37. Simon A, Fleischhack G, Hasan C, Bode U, Engelhart S, Kramer MH. Surveillance for nosocomial and central line–related infections among pediatric hematology-oncology patients. *Infect Control Hosp Epidemiol* 2000;21:592–596.
38. Edwards JR, Peterson KD, Andrus ML, et al. National Healthcare Safety Network (NHSN) report, data summary for 2006, issued June 2007. *Am J Infect Control* 2007;35:290–301.
39. Jeffries HE, Mason W, Brewer M, et al. Prevention of central venous catheter–associated bloodstream infections in pediatric intensive care units: a performance improvement collaborative. *Infect Control Hosp Epidemiol* 2009;30:645–651.
40. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008:128–147.
41. Niedner MF. The harder you look, the more you find: catheter-associated bloodstream infection surveillance variability. *Am J Infect Control* 2010;38:585–595.