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Catheter Duration & Risk of Central Line-Associated Bloodstream Infection in Neonates with PICCs

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Abstract

Objective—To determine whether the risk of central line-associated bloodstream infections (CLA-BSI) remained constant over the duration of peripherally inserted central venous catheters (PICC) in high risk neonates.

Patient and Methods—We performed a retrospective cohort study of NICU patients who had a PICC inserted between January 1, 2006 and December 31, 2008. A Poisson regression model with linear spline terms to model time since PICC insertion was used to evaluate potential changes in the risk of CLA-BSI while adjusting for other variables.

Results—683 neonates were eligible for analysis. There were 21 CLA-BSIs within a follow-up time of 10,470 catheter days. The incidence of PICC-associated CLA-BSI was 2.01 per thousand catheter days (95% CI=1.24, 3.06). The incidence rate of CLA-BSI increased by 14% per day during the first 18 days following PICC insertion (incidence rate ratio [IRR] 1.14; CI 1.04, 1.25). From days 19 through 35 after PICC insertion, the trend reversed (IRR 0.8; 95% CI 0.66, 0.96). From days 36 through 60 after PICC insertion, the incidence rate of CLA-BSI once again increased by 33% per day (IRR 1.33; 95% CI 1.12, 1.57). There was no statistically significant association between gestational age groups, birth weight groups, and chronological age groups with the risk of CLA-BSI.

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Conclusion—Our data suggest that catheter duration is an important risk factor for PICC associated CLA-BSI in the NICU. A significant daily increase in the risk of CLA-BSI after 35 days may warrant PICC replacement if intravascular access is necessary beyond that period.

Keywords

Peripheral catheterization; Infection; Catheter-Related; Neonatal Intensive Care Unit; Peripherally Inserted Central Venous Catheters

Introduction

Long term intravenous access is essential to provide nutrition, fluids, and medications to patients in the neonatal intensive care unit (NICU). Since the 1980s, peripherally inserted central venous catheters (PICC) have gained widespread popularity for facilitating vascular access.^{1, 2} PICC have the advantage of being placed at the bedside without general anesthesia and remaining in situ for days or weeks with minimal mechanical complications.²

PICCs comprise a large proportion of central lines inserted in NICU.² Central line-associated bloodstream infections (CLA-BSI) can complicate PICCs. An estimated 80,000 CLA-BSI occur in the United States every year.³ The attributable mortality of these CLA-BSIs remains unclear, but recent studies demonstrate a range from 4% to 20%.⁴ CLA-BSI extends patient length of stay by an average of 7 days, and the attributable cost is \$3,700 to \$29,000 per infection.⁵⁻¹⁰

PICCs were initially intended for short term vascular access, but these catheters can remain in place for prolonged periods of time.^{1, 11} Whether or not preventive replacement of PICCs at some point of time beyond seven days can reduce the risk of CLA-BSI is unknown. However, routine replacement of central catheters is resource intensive and associated with infectious and mechanical complications.¹² The objective of our study was to determine whether the risk of CLA-BSI remained constant over the PICC duration in high risk neonates. We hypothesized that the risk of CLA-BSI increases with the length of time a PICC remains in place, and that a threshold may exist beyond which the risks associated with retaining a catheter may outweigh the risks associated with replacing it.

Patients and Methods

Setting and Participants

We performed a retrospective cohort study of patients in the Neonatal Intensive Care Unit at The Johns Hopkins Hospital (JHH), an academic-affiliated tertiary care facility in Baltimore, Maryland (USA). The level four, 42-bed NICU admits approximately 720 patients per year, including those born at JHH and those transferred from outside hospitals. PICCs were placed by a designated team of trained nurses or physicians who followed a standard protocol outlining insertion and maintenance practices. Eligible patients had a PICC inserted in the JHH NICU between January 1, 2006 and December 31, 2008. For patients with multiple PICC lines placed during their NICU hospitalization, only the first PICC was included in the analysis. PICCs terminated the same day they were inserted and PICCs which were removed within 48 hours of NICU admission were excluded. This study was

approved by The Johns Hopkins University School of Medicine Institutional Review Board with a waiver of informed consent.

Data collection

As a part of a quality improvement initiative to reduce CLA-BSI in the JHH NICU, the Department of Hospital Epidemiology and Infection Control (HEIC) performs surveillance to monitor for the development of bacteremia in patients with indwelling catheters, using laboratory databases and an infection surveillance support system (Theradoc Inc., Salt Lake City, UT). Infection control practitioners prospectively identified CLA-BSI, using the existing Center for Disease Control and Prevention's National Healthcare Safety Network's (NHSN) definition for CLA-BSI.^{2, 13} Microorganisms causing CLA-BSI were isolated by means of routine blood cultures, and antibiotic susceptibility profiles were obtained from microbiology laboratory reports. Our research team was not involved in defining CLA-BSI. A list of all patients with CLA-BSI between January 1, 2006 and December 31, 2008 was obtained from HEIC. Patients with CLA-BSI attributed to a PICC were included. The JHH NICU documents intravascular access in the electronic medical record, including date of line insertion and date of line removal. Electronic medical records were queried to identify all patients with PICCs. Data on race, gender, date of birth, date of hospital admission, date of discharge, gestational age at birth, birth weight, date of blood culture, and organism cultured were extracted from hospital databases and medical records. Gestational age was categorized as less than 32 weeks and greater than or equal to 32 weeks. Birth weight was categorized as less than 1500 grams and greater than or equal to 1500 grams. Chronological age was grouped as less than or equal to seven days and greater than seven days.

Definitions

For the purpose of this study, PICC was defined as a peripherally inserted central venous catheter that terminates at or close to the heart or in one of the great vessels which is used for infusion, withdrawal of blood, or hemodynamic monitoring. The following were considered great vessels: aorta, pulmonary artery, superior vena cava, inferior vena cava, brachiocephalic or innominate veins, internal jugular veins, subclavian veins, external iliac veins, common femoral veins.^{2, 3, 14} A PICC-associated CLA-BSI was defined as a primary bloodstream infection in a patient admitted to the NICU for greater than 48 hours before the onset of infection that met the NHSN criteria for CLA-BSI.^{2, 5, 15} PICC follow-up time (or PICC duration) was defined as days from line insertion until either 1) date of CLA-BSI, 2) termination of the PICC, or 3) administrative censoring at discharge from NICU. Only the first CLA-BSI was included from a patient who had multiple CLA-BSI from the same PICC.

Statistical Analysis

Descriptive analyses were performed to characterize the patient population with reporting of median values and interquartile ranges. Risk of CLA-BSI over time was assessed by estimating a continuous hazard function, and by calculating incidence rates per 10 day intervals from PICC insertion. Both methods identified similar potential inflection points in the relative risk of CLA-BSI over time. After exploring the initial data, linear spline terms for modeling days since PICC insertion were introduced to evaluate nonlinear changes in the risk of CLA-BSI. We tested various cut-points around the spline terms to assess the

robustness of our findings. Independent predictors of CLA-BSI, including birth weight categories, gestational age categories and chronological age categories were assessed in univariate analysis using a Poisson regression model to estimate incidence rate ratios for CLA-BSI and then a multivariable regression model was constructed. Using the entire set of subjects, we initially fit a model with linear splines at 18, 35 and 55 days. However, only 16 patients had PICCs inserted for more than 60 days that resulted in an unstable estimate of the incidence rate ratio with a wide confidence interval for the period beyond 55 days. Therefore, our final analysis excluded these 16 patients with PICC duration beyond 60 days, using a best-fitting model with linear splines at 18 and 35 days. The final model was chosen on the basis of the Log Likelihood Ratio Test and Akaike's Information Criterion and confirmed by using Pearson's Goodness-of-Fit Test. A two-tailed p value of 0.05 was considered statistically significant. Data were maintained in Microsoft Access (2003, Bellevue, WA) and analyzed using Stata version 10.0 (Stata Corp., College Station, TX).

Results

Between 1st January 2006 and 31st December 2008, 719 neonates had 953 PICCs inserted in the JHH NICU. Fourteen PICCs were excluded from the analysis because their insertion and termination dates were the same (indicating failed insertion). Six PICCs were excluded because the lines were discontinued within 48 hours from date of hospital admission, and 16 PICCs were excluded because they were maintained beyond 60 days (as described in methods). Six hundred and eighty three neonates were eligible for analysis. The median gestational age at birth was 31 weeks (Inter-Quartile Range [IQR] = 27-37 weeks) [see Table 1]. The median birth weight was 1610 grams (IQR=978-2720 grams), and the median age at time of PICC insertion was 5 days (IQR=2-8 days). There were similar percentages of Caucasian (46%) and African American (43.6%) patients. In the cohort, 51% of neonates were less than 32 weeks gestational age at birth, and 46.6% had birth weights less than 1500 grams. At the time of PICC insertion, 71.6% of the neonates were less than or equal to 7 days old. Total follow-up time was 10,470 catheter days with a median of 12 catheter days (IQR=6-21 catheter days) per patient.

There were 21 CLA-BSIs from the 683 PICCs (3.1%). Of the 21 patients with CLA-BSI, 61.9% were males, 76.2% had birth weight <1500 g, 80.9% had a gestational age less than 32 wk, and 61.9% were less than or equal to seven days old. Median time from line insertion to infection was 18 days (IQR=9-22 days). The incidence of PICC-associated CLA-BSI over the three year period was 2.01 per thousand catheter days (95%CI: 1.24, 3.06). Among the CLA-BSIs, the most common organism identified was coagulase negative staphylococcus ($n=7$, 32%) [see Table 2]. Coagulase negative staphylococcus was the dominant infection (55.6%) within the first two weeks, while Gram-negative bacteria were dominant pathogens (58.3%) after the first two weeks.

To evaluate the association between PICC duration and incidence of CLA-BSI, we categorized events into 10-day time intervals [see Table 3]. The CLA-BSI incidence rate per 10-day intervals from the time of PICC insertion demonstrated a bimodal increase in risk over time. Using Poisson regression [see Table 4], during the first 18 days following PICC insertion, the incidence rate of CLA-BSI increased by 14% per day (incidence rate ratio

[IRR] = 1.14; 95% CI: 1.04, 1.25). From days 19 through 35 after PICC insertion, the trend reversed (IRR= 0.8; 95% CI: 0.66, 0.96). From days 36 through 60 after PICC insertion, the incidence rate of CLA-BSI once again increased by 33% per day (IRR= 1.33; 95% CI: 1.12, 1.57). In univariate and multivariable regression analysis, there were no significant associations between gestational age groups, birth weight groups, or chronological age groups with the risk of CLA-BSI.

Discussion

CLA-BSIs are a common cause of morbidity and mortality among neonates. While many studies have assessed risk factors for CLA-BSI in neonates, this is the largest study examining the duration of PICC as a risk factor of CLA-BSI among NICU patients. PICCs are often used for extended durations due to perceived threat of complications from replacement.¹² However our data suggest that in our population, beyond 35 days, the daily risk of CLA-BSI increases by a substantial 33% per day. This substantial daily increase in risk of CLA-BSI may warrant reconsideration of catheter replacement as a strategy for CLA-BSI prevention.

Several factors have been shown to contribute to the pathogenesis of nosocomial CLA-BSI. Host-related risk factors include age, immunologic immaturity, and severity of underlying disease.¹⁶ Environmental and catheter-related risk factors, many of which are preventable include prolonged catheterization, poor aseptic insertion technique, emergent catheter placement, size of catheter, number of lumens, type of catheter material, location of catheter, frequency of catheter manipulations, type of insertion, site dressing, and frequency of system entry.^{5, 8} Current CLA-BSI prevention strategies recommend best practices to reduce CLA-BSI infection including hand hygiene, maximal barrier precaution, chlorhexidine skin antisepsis, optimal catheter site selection, and daily review of need for a central line with prompt removal of unnecessary line.^{8, 17-19}

Many recent studies recognize catheter duration as a risk factor for CLA-BSI^{5, 7, 20-23}; however, evidence for prevention of CLA-BSI through routine replacement of catheters is lacking.^{16, 24-26} Previous studies that considered catheter duration as a risk factor for CLA-BSI treated time as a categorical variable to assess risk over the duration of the catheter.²⁶⁻²⁹ Arbitrary cut points set at three to seven days following catheter insertion²⁶⁻³⁰, small sample sizes of 160-234 patients^{26, 28, 29}, and a focus on central catheters in general and not exclusively on PICCs has limited assessment of prolonged catheter duration as a risk factor for CLA-BSI. A study by Stenzel and colleagues used survival analysis techniques to demonstrate no relationship between duration of catheterization and the daily probability of developing an infection.³¹ Alternatively, our study treated time as a continuous variable to track the incidence of CLA-BSI over time and determine the continuous hazard of developing a CLA-BSI. This approach enabled us to demonstrate that the risk of CLA-BSI did not remain constant over the duration of PICC catheterization in high-risk neonates. In fact, beyond 35 days, there was a substantial and sustained daily increase in risk of CLA-BSI by 33% per day. Due to statistical constraints, we excluded patients with catheters in place for greater than 60 days; however, the incidence rate of CLA-BSI in these 16 patients beyond 60 days was 3.54/1000 catheter days, higher than any time intervals before 35 days.

Overall, our data suggest that preventive catheter replacement beyond 35 days would offer maximum reduction in PICC-associated BSI, but further studies are needed to identify an acceptable threshold for catheter replacement beyond which absolute risk reduction outweighs costs associated with catheter replacement.

However, preventive replacement of PICCs cannot be entertained without first recognizing the risks of catheter replacement and subsequent infection from a new catheter. Risks associated with catheter replacement include procedural costs including pain as well as risk of mechanical and subsequent infectious complications. In our original cohort, one hundred and forty-four patients had a second PICC line placed. Over the 2,812 catheter days of follow-up time, there was only one CLA-BSI which occurred 45 days following PICC insertion (incidence rate 0.36 per thousand catheter days, 95% CI: 0.01-1.98) [data not shown]. This suggests that the CLA-BSI incidence rate from second PICCs was lower than that from first PICCs. Thus, a formal study and assessment of the cost-benefit of preventive replacement of PICCs in this population is warranted.

Our findings concur with previous studies demonstrating that in the NICU population most CLA-BSIs are caused by commensal skin flora such as coagulase-negative staphylococci.^{3, 16} Some studies have found birth weight³, gestational age⁸, and chronological age^{6, 32} to be risk factors for CLA-BSI. However, in our study these factors did not have a significant effect on CLA-BSI. This may be explained by the fact that we only included first PICCs, 72% of which were placed within seven days of birth. Premature as well as low birth weight infants will usually have more catheter days (i.e. exposure time) because they remain in the NICU for longer periods of time. Increased exposure may in turn place them at higher risk of CLA-BSI, and most studies do not adjust for exposure time when assessing risk factors for CLA-BSI. Therefore, exposure time may modify the effect of these other factors on CLA-BSI and warrants further investigation.

Several limitations should be considered when interpreting our data. Because our NICU has a low CLA-BSI incidence, we conducted the study on a large cohort of patients over a three year period. Despite this large cohort and long observation period, we only captured 21 events. Yet, this study remains the largest study to our knowledge in the NICU population with such stringent eligibility criteria, and our PICC-associated CLA-BSI rate (2.0 cases per 1000 catheter days) was similar to that previously reported (1.7-2.3 cases per 1,000 catheter days).¹ Second, JHH has an active hospital epidemiology and infection control and prevention program and we were unable to adjust for changes in infection prevention measures that may have happened over the three years. Still, we did not find a significant change in trend of CLA-BSI rates over the three years of the study (data not shown). Third, our study investigated PICC-associated BSI at a single institution and findings may not be generalizable to other NICUs. Fourth, we recognize the potential impact of excluding patients whose catheters remained in place for more than 60 days. This strategy omits time at-risk (catheter days) within 60 days for these patients which may overestimate infection rates, particularly in later intervals with smaller numbers of catheter days. However, we found insignificant differences in incidence rate ratios if these at-risk catheter days were included in the analysis (data not shown). Finally, our institution uses NHSN definitions for CLA-BSI surveillance which changed in 2008. Some of the CLA-BSIs detected prior to

2008 may not conform to the current definition. However, because this definition change mostly affected CLA-BSI caused by common skin contaminants which were more prevalent in CLA-BSI occurring within 14 days of catheter insertion, it would not likely have impacted our findings of increasing risk beyond 35 days.

Conclusion

PICCs remain an essential component of NICU care and CLA-BSI is a serious complication. Our data suggest that catheter duration is an important risk factor for PICC associated CLA-BSI in the NICU. A significant daily increase in the risk of CLA-BSI may warrant replacement of PICCs if intravascular access is necessary beyond 35 days. Future studies should determine the cost-benefit of preventive catheter replacement in the NICU and evaluate if these findings are generalizable to other populations and other catheter types.

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Abbreviations

CLA-BSI	Central line- associated bloodstream infection
PICC	Peripherally inserted central venous catheter
NICU	Neonatal intensive care unit
IRR	Incidence rate ratio
JHH	Johns Hopkins Hospital
NHSN	National Healthcare Safety Network
IQR	Inter-Quartile Range

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TABLE 1

Characteristics of Neonates with Peripherally Inserted Central Venous Catheters

Variable	
Age at line insertion, median (IQR), days	5 (2-8)
Birth weight, median (IQR), grams	1610 (978-2720)
Gestational age at birth, median (IQR), weeks	31 (27-37)
Race, n (%)	
Caucasian	314 (46.0)
African American	298 (43.6)
Hispanics	34 (5.0)
Others	37 (5.4)
Gender, n (%)	
Male	385 (56.4)
Female	298 (43.6)
Year of study, n (%)	
2006	213 (31.2)
2007	259 (37.9)
2008	211 (30.9)
Total neonates	683

Results reported as Median (IQR) unless specified

IQR= Interquartile Range; n = number

TABLE 2

Pathogens Causing Central Line-Associated Blood Stream Infection in Neonates with Peripherally Inserted Central Catheters

	n (%)
Coagulase negative staphylococci species	7 (33.3)
Staphylococcus aureus	2 (9.5)
Coagulase negative staphylococcus species, Enterococcus faecalis	1 (4.8)
Enterococcus faecalis	2 (9.5)
Enterobacter cloacae	2 (9.5)
Klebsiella species	1 (4.8)
Klebsiella oxytoca	1 (4.8)
Enterobacter aerogenes	1 (4.8)
Pseudomonas aeruginosa	1 (4.8)
Escherichia coli	1 (4.8)
Rhodotorula species	1 (4.8)
Candida parapsilosis	1 (4.8)

n = number

TABLE 3

Incidence Rate of Central Line-Associated Blood Stream Infection over 10 day Time Intervals since Peripherally Inserted Central Catheter Insertion

	Day 1-10	Day 11-20	Day 21-30	Day 31-40	Day 41-50	Day 51-60
Number of events	6	8	4	0	1	2
Number of catheters ^a	315	192	85	50	25	16
Number of catheter days ^b	5563	2883	1480	810	437	257
Incidence rate per 1,000 catheter days	1.08	2.77	2.7	0	2.29	7.78

^a Number of catheters at the end of the time bin

^b Catheter days from catheters extending beyond 60 days included

Table 4

Risk Factors for Central Line-Associated Blood Stream Infection in Neonatal Intensive Care Unit patients with Peripherally Inserted Central Catheters

	Univariate			Multivariable		
	IRR ^a	95% CI	P	IRR	95% CI	P
Gestational age category						
<32 weeks	1.00			1.00		
32 weeks	0.40	0.14, 1.19	0.10	0.50	0.08, 3.18	0.46
Birth weight category						
<1500 grams	1.00			1.00		
1500 grams	0.45	0.16, 1.22	0.12	0.94	0.17, 5.18	0.94
Chronological age						
7 days	1.00			1.00		
> 7 days	1.44	0.59, 3.46	0.42	1.34	0.56, 3.25	0.51
Days since PICC Insertion						
< 19 days	1.15 ^b	1.05, 1.26	<0.01	1.14	1.04, 1.25	<0.01
19-35 days	0.80 ^b	0.67, 0.96	0.02	0.80	0.66, 0.96	0.02
After 35 days	1.32 ^b	1.12, 1.55	<0.01	1.33	1.12, 1.57	<0.01

IRR - Incidence Rate Ratio; CI – Confidence interval; PICC- peripherally inserted central catheters

^aCalculated using Poisson regression

^bIRR represents change in incidence rate per day within each time interval