The Art and Science of Infusion Nursing

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Neonatal Late-Onset Sepsis Following Peripherally Inserted Central Catheter Removal

Association With Antibiotic Use and Adverse Line Events

ABSTRACT

The objective of the study was to evaluate incidence of and risk factors for sepsis following peripherally inserted central catheter (PICC) removal. The retrospective cohort study looked at neonatal intensive care unit patients with PICC placement between February 2003 and June 2010 at a single medical center in the United States. Results showed that 14/216 patients (6.5%) had sepsis within 5 days of PICC removal. PICC removal because of adverse events was significantly associated with sepsis ($P = .017$). Antibiotic use before PICC removal did not have a significant impact on sepsis. The conclusions of the study are that removal of PICCs because of adverse events is significantly associated with late-onset neonatal sepsis and that antibiotic use at the time of PICC removal is not associated with a decline in sepsis rate.

Key words: adverse line event, catheter, neonatal sepsis, PICC

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Late-onset sepsis remains a significant source of morbidity and mortality in neonatal intensive care units (NICUs) despite considerable advances in critical care. Late-onset sepsis, defined as sepsis occurring 3 days or more after birth, is associated with intraventricular hemorrhage, increased hospital stay, and chronic lung disease, all of which contribute to complications in the care of neonates.[1,2] Several risk factors for late-onset sepsis have been identified, including low birth weight, patent ductus arteriosus, bronchopulmonary dysplasia, necrotizing enterocolitis, and younger gestational age.[1,2] Many studies also identify the presence and prolonged use of central venous catheters (CVCs) as a risk factor for late-onset sepsis in this patient population, which may provide an opportunity for interventions to reduce late-onset sepsis rates.[3-5]

Late-onset sepsis is commonly caused by *Staphylococcus aureus*, coagulase-negative staphylococci, gram-negative bacilli, and *Candida* species.[1,6] In the last decade, coagulase-negative staphylococci have been identified increasingly as a pathogen in late-onset sepsis.[1,6,7] This may be the result of the increased use of peripherally inserted central catheters (PICCs) and their association with coagulase-negative staphylococcal bloodstream infections.[5,7] PICCs have been shown to be an alternative to surgically placed catheters in neonates to address their needs for parenteral nutrition and intravenous medications.[8,9] In adults, both inpatient and outpatient PICCs have been reported to have much lower rates of bloodstream infections than surgically implanted cuffed and tunneled CVCs (2.4-3.5% vs 22.5, respectively).[10] Data for very low-birth-weight infants are less clear, although 1 study has shown a trend toward similar decreased infection rates with PICCs versus surgical catheters.[11] Several studies indicate that catheter-related infections may be reduced using prophylactic intravenous antibiotics or antibiotic locks, but this benefit may be outweighed by the risk of antibiotic resistance and, therefore, is not routinely recommended.[12-15]

A phenomenon of sepsis in the few days following PICC removal has been observed anecdotally and in scant literature. A single-center study reported an increase in sepsis events during the 72 hours following PICC removal.[16] There are conflicting data published regarding the benefit of prophylactic antibiotics at the time of PICC removal, with 2 studies at a single center demonstrating a decrease in late-onset sepsis following PICC removal with prophylactic antibiotics, but no benefit in another study.[16-18] This study was designed to evaluate the hypothesis that the rate of sepsis is increased in the 5 days following PICC removal and to analyze the use of a single dose of vancomycin or the presence of any other antibiotics at the time of PICC removal to decrease sepsis following PICC removal. The secondary aim was to identify any risk factors associated with sepsis following PICC removal. Identifying and understanding associated risk factors for PICC-associated sepsis is essential for devising evidence-based methods to decrease neonatal catheter-related infections and their related morbidities and mortality.

METHODS

Design, Methods, and Materials

A retrospective cohort study of patients with PICC placement between February 2003 and June 2010 was conducted at a single US Level III C NICU. The study was approved by the institutional review board. Neonatal nurse practitioners place all PICCs at the center. A prospective nurse practitioner log of PICC insertions in the NICU was used to identify patients. Only the first PICC insertion for each patient was counted in the very small number of patients who had multiple PICCs placed during their hospitalization, because repeated PICCs could place patients at additional unquantifiable risk and skew data analysis. The log included the catheter type, insertion date, indication for PICC placement, number of placement attempts, insertion site, reason for catheter removal, and any PICC complications. Multiple catheter brands were in use during the study period. The medical record was reviewed to obtain demographic information, common neonatal confounders, and sepsis risk factors. Antibiotic use in the 12 hours before PICC removal was recorded. Single doses of vancomycin ordered for prophylaxis were noted. All antibiotic use was at the discretion of the attending physician and included antibiotics used for prophylaxis and other indications, including completing treatment of other infections. Blood cultures performed around the time of PICC removal (48 hours before removal to 5 days after removal) were collected from the medical record to identify the frequency of sepsis in the 5 days following PICC removal, as well as to identify any catheter-related bloodstream infections that led to PICC removal. Previous studies on the rates of sepsis following PICC removal have reported on the rates of sepsis 48 to 72 hours after PICC removal.[16-18] The longer time frame of 5 days postremoval was chosen for this study to capture outliers that may present later following PICC removal with less aggressive infectious organisms, such as *Staphylococcus epidermidis*.[1,6]

Exclusion criteria included patients with a PICC in place less than 48 hours and those with a positive blood culture, surgical procedure, or an additional central catheter in place during the 48 hours before PICC removal. These patients were excluded because

it would be difficult to retrospectively associate any sepsis events with PICC removal in them rather than other causes of sepsis. In addition, patients who left the institution or who died with the PICC in place and patients with PICC-associated phlebitis were excluded. Patients with phlebitis were excluded because the nature of and circumstances surrounding the phlebitis were not documented and could have been infectious or mechanical in nature, which would have confounded the data.

Definitions

Sepsis was defined as 1 or more positive blood cultures, or as clinical sepsis as defined by the Centers for Disease Control and Prevention and the National Healthcare Safety Network before January 2010.[19] The definition of clinical sepsis has been used in other studies and states that the patient must have fever (>38°C, rectal or >36°C, axillary), hypothermia (<37°C, rectal or <35°C, axillary), apnea, or bradycardia; and no blood culture performed or a negative blood culture; and no apparent infection at another site, with a physician initiating treatment for presumed sepsis.[19-21] Patients with blood cultures positive for coagulase-negative staphylococci were considered to have sepsis if 2 positive cultures were drawn within 2 days of each other or 1 positive culture that was accompanied by an elevated C-reactive protein (>1) within 2 days of the blood culture, a definition outlined by the National Institute of Child Health and Human Development Research Network.[1]

Extraction of adverse PICC-related events from the medical record assumed accurate documentation of these events, which included catheter breakage, hole in catheter, PICC insertion site infection, catheter leakage, catheter loss, occlusion, and infiltration. Definitions for PICC adverse events could not be standardized because they were collected retrospectively and, therefore, were at the discretion of the nurse practitioner documenting their occurrence on the PICC data form or of the bedside nurse documenting their occurrence in the medical record.

Statistics

Descriptive statistics included medians, ranges for continuous variables, and frequencies and proportions for categorical variables. The association between categorical variables was examined using the Fisher exact test. Continuous distributions were compared between groups using the Wilcoxon rank sum test. Logistic regression was used to look at the association of risk factors with the outcome of sepsis adjusting for gestational age, and results were expressed as odds ratios with 95% confidence intervals. All tests were 2 sided and, with a $P < .05$, considered statistically significant. Data analysis used SAS software version 9.2 (SAS Institute).

RESULTS

Three hundred eighteen patient charts were reviewed, and 216 patients met inclusion criteria (Figure 1). Patient demographics were reviewed, including common NICU comorbidities (Table 1). The majority of PICC insertions were in the cephalic, greater saphenous, and basilic veins, with a median PICC duration of 14.0 days (range 2-81).

Fourteen patients (6.5%) had a sepsis event within 5 days of PICC removal (43% microbiologic, 57% clinical). Sepsis occurred a median of 1 day after PICC removal (range 0-5 days). Organisms identified included coagulase-negative staphylococci (66%), *Escherichia coli* (17%), and *S. aureus* (17%). There was no statistically significant difference in the median birth weight ($P = .23$), the median gestational age ($P = .44$), or the median number of catheter days ($P = .22$) in those who did and did not develop sepsis following PICC removal.

A total of 47 patients received at least 1 antibiotic before PICC removal, with 2 patients developing

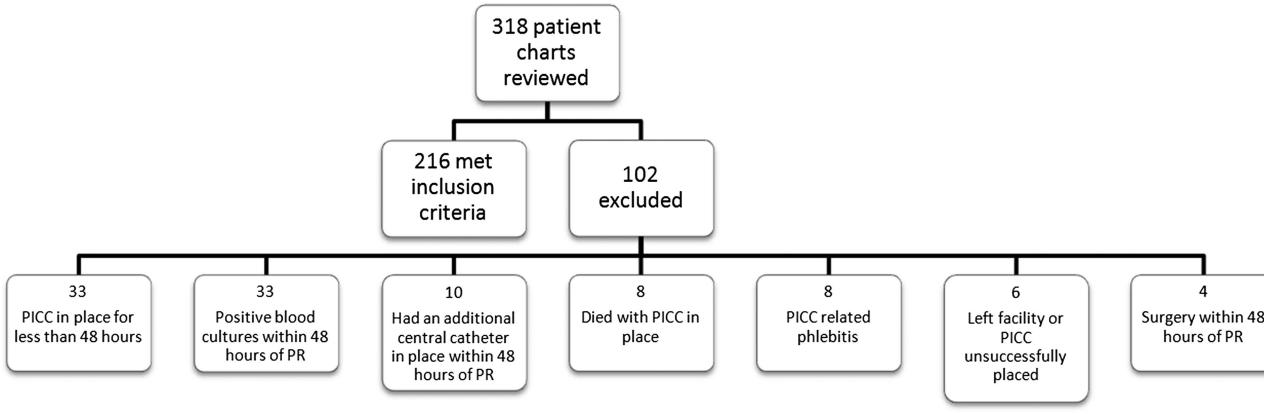

Figure 1 Patient study enrollment and reasons for exclusion. *Abbreviations: PICC, peripherally inserted central catheter; PR, PICC removal.*

TABLE 1

Overview of Patient Characteristics (N = 216)

Demographic	Value
Male gender	58.3%
Birth weight, median (range)	1119.5 grams (480-4255)
Gestational age, median (range)	29.0 weeks (22-42)
PICC days, median (range)	14.0 days (2-81)
Required mechanical ventilation	84.7%
Intraventricular hemorrhage	
Grade 1-2	19%
Grade 3-4	6.9%
Retinopathy of prematurity	22.9%
Patent ductus arteriosus	48.6%
Surfactant deficiency	71.8%
Steroid use	26.4%
Periventricular leukomalacia	3.2%
Bronchopulmonary dysplasia	31.5%

Abbreviation: PICC, peripherally inserted central catheter.

TABLE 2

Associations With Sepsis in the 5 Days Following PICC Removal

Associations With Sepsis Following PICC Removal	Odds Ratio	95% CI	*P*
Presence of at least 1 antibiotic at the time of PICC removal	0.6	0.1, 2.7	.74
Presence of vancomycin at the time of PICC removal	0.4	0.05, 3.2	.70
Adverse PICC event leading to PICC removal	3.9	1.3, 11.8	.017
Adjusted for birth weight, gestational age, and line days	3.5	1.1, 11.1	.03

Abbreviations: PICC, peripherally inserted central catheter; CI, confidence interval.

subsequent sepsis (4.2%). Thirty-three patients received vancomycin before PICC removal, either as a single dose for the presumptive purpose of sepsis prophylaxis or in combination with another antibiotic for prophylaxis or treatment of a previous infection. Of these, 1 patient developed sepsis despite the presence of vancomycin at the time of PICC removal (3%). However, neither the presence of at least 1 antibiotic nor specifically vancomycin at the time of PICC removal was statistically associated with a decrease in the rate of sepsis in the 5 days following PICC removal ($P = .74$ and $P = .70$, respectively; Table 2).

PICC removal as the result of adverse line events was significantly associated with the development of sepsis within 5 days after PICC removal ($P = .017$; Table 2). The total incidence of adverse catheter events was 22%—primarily infiltration, leakage, and occlusion. Fifty percent of sepsis cases in the 5 days following PICC removal were associated with an adverse catheter event, including 1 occlusion, 1 with leakage, 1 with breakage, and 4 with infiltration. Adjusting for catheter days, birth weight, and gestational age, adverse catheter events were an independent risk factor for sepsis after PICC removal ($P = .03$). After adjusting for these risk factors, the odds of developing sepsis in the 5 days following PICC removal associated with an adverse line event was 3.5 (95% CI,1.1-11.1).

DISCUSSION

Late-onset sepsis in neonates is a significant source of morbidity and mortality. The use of PICCs, although necessary to provide lifesaving nutrition and medications, contributes to the risk of late-onset sepsis as a nidus for infection. Removal of PICCs was shown in van den Hoogen and colleagues'[16] study to increase the risk for late-onset sepsis. Although our study design did not allow for a direct comparison of baseline sepsis rates and the rate of sepsis following PICC removal, the overall incidence of sepsis in the 5 days following PICC removal was low, with only 6 culture-positive episodes of sepsis and 8 additional episodes of clinical sepsis for a total percentage of 6.5% in our cohort. This is lower than published baseline rates of late-onset sepsis in neonates (7.1%-36%).[1,2,6,7] Additionally, we observed no benefit from antibiotics given before PICC removal. This finding must be interpreted with caution given the retrospective nature of this study and the variability in antibiotic-prescribing practices applied by the attending physicians caring for this cohort of patients. Given the rare occurrence of sepsis following PICC removal and the significant risk of antibiotic side effects or the development of antibiotic resistance, antibiotic prophylaxis at the time of PICC removal cannot be routinely recommended without larger studies. It is reasonable to recommend heightened awareness for clinical signs of sepsis in the days following any procedure, including PICC removal, while larger-scale studies are performed to determine if PICC removal can be definitively identified as a risk factor for late-onset neonatal sepsis.

Removal of PICCs because of noninfectious adverse events in our study, including catheter breakage, leaking, infiltration, or occlusion, was significantly associated with late-onset sepsis in the 5 days following PICC removal. This is consistent with previous studies showing an increase in sepsis in catheters that remain in situ after amelioration of adverse catheter events, such as catheter breakage followed by repair, or malposition followed by guide wire exchange.[22,23] However, this is the first time, to our knowledge, that adverse catheter events have been identified as an independent risk factor for subsequent late-onset sepsis in neonates after PICCs were removed.

This study is limited by its retrospective design, which makes it difficult to establish a control group to compare infection rates and directly evaluate the impact of interventions, such as prophylactic antibiotics. The data on PICC placement and any subsequent complications were collected in a prospective manner by the neonatal nurse practitioner at the time of PICC insertion, somewhat limiting the bias that can be present in retrospective analyses. This was also a relatively small cohort from a single center, potentially limiting its broader applicability. Specifically, this study was not powered to address the secondary aim of evaluating the impact of antibiotics on the rates of sepsis following PICC removal, limiting the applicability of those findings. No alternative method was used to cross-check for any missed PICC placements, but it is unlikely that a significant number of PICC placements were unreported because the placement and logging of PICCs were done exclusively by a single hospital group. By broadening the study period to include patients with sepsis up to 5 days beyond PICC removal, rather than 48 to 72 hours as previously studied, we could have overreported the rates of sepsis following PICC removal by including patients with sepsis attributable to other causes rather than PICC removal. However, given the low rates of sepsis identified in this patient series, this appears not to have been a significant confounder.

PICCs removed for phlebitis were excluded because the cause of phlebitis can be varied, including mechanical, chemical, or infectious, and is inconsistently defined on the basis of those possible causes in the literature.[5,21,24,25] We did not want to confound our data on sepsis events occurring after PICC removal with phlebitis that was potentially infectious in nature, given that the designation of phlebitis relied on provider reports in the medical record and could not be standardized in this retrospective study. We also did not include exit site infections as an adverse event in our analysis because of the difficulty in retrospectively assessing exit site infection versus phlebitis based on the limited data available. There were only 8 episodes of phlebitis that were excluded, and although these may have added to the adverse event-related data, it is likely that this number would not influence the outcome that adverse PICC events are associated with increased sepsis events after PICC removal.

On the basis of the results of our study, heightened awareness for sepsis in the days following PICC removal in patients who experience adverse catheter events is warranted. It is particularly important to consider clinical signs of sepsis in neonates, such as increased oxygen need, apnea and bradycardia, temperature instability, and feeding intolerance, among other issues that may present independent of positive blood culture results in these patients, given the larger number of neonates in our cohort presenting with clinical rather than microbiologic sepsis. At this time, there is not sufficient evidence to support routine antibiotic prophylaxis at the time of PICC removal, given the relative rarity of this occurrence and the risks of widespread antibiotic use. Further study is needed to guide the development of optimal insertion and daily catheter care practices to prevent adverse catheter events in neonates with PICCs, reducing late-onset sepsis.

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