Incidence of Catheter-Related Bloodstream Infections in Neonates Following Removal of Peripherally Inserted Central Venous Catheters

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Objectives: Catheter-associated bloodstream infections are a significant source of morbidity and healthcare cost in the neonatal ICU. Previous studies examining the prevalence of bloodstream infections after removal of peripherally inserted central venous catheters in neonates are equivocal.


Measurements and Main Results: We evaluated the following outcomes: 1) bloodstream infections, 2) culture-negative sepsis, 3) number of sepsis evaluations, and 4) number of significant apnea/bradycardia events comparing odds ratios between 72 hours before and 72 hours after peripherally inserted central venous catheter removal. We analyzed a total of 1,002 peripherally inserted central venous catheters in 856 individual infants with a median (interquartile range) gestational age of 31 weeks (28–37 wk) and a median birth weight of 1,469 g (960–2,690 g). Comparing 72 hours before with 72 hours after peripherally inserted central venous catheter removal did not show a difference in the prevalence of bloodstream infections (9 vs 3, p = 0.08), prevalence of culture-negative sepsis (37 vs 40, p = 0.73), number of sepsis evaluations (p = 0.42), or number of apnea/bradycardia events (p = 0.32). However, in peripherally inserted central venous catheter not used for delivery of antibiotics, there was a 3.83-fold increase in odds for culture-negative sepsis following peripherally inserted central venous catheter removal (95% confidence interval, 1.48–10.5; p = 0.001). For infants less than 1,500 g birth weight (very low birth weight), odds for culture-negative sepsis increased to 6.3-fold following removal of peripherally inserted central venous catheters not used for antibiotic delivery (95% confidence interval, 1.78–26.86; p < 0.01).

Conclusions: Although these data do not support the routine use of antibiotics for sepsis prophylaxis prior to peripherally inserted central venous catheter removal, they suggests that very low birth weight infants not recently exposed to antibiotics are at increased odds for associated adverse events following discontinuation of their peripherally inserted central venous catheter. (Pediatr Crit Care Med 2013; 14:00–00)

Key Words: catheter-related infections; neonatal sepsis; percutaneously inserted central venous catheters; preterm infant; prophylaxis

Peripherally inserted central venous catheters (PICCs) are routinely used in neonatal ICUs (NICUs) for vascular access in neonates to allow delivery of total peripheral nutrition (TPN) and medication. At least 46% of very low birth weight (VLBW) infants receive a PICC during their NICU stay, and approximately 42% of low birth weight infants with a PICC in place longer than 22 days will have one or more events of PICC-associated late-onset sepsis (1). Consequences of late-onset sepsis include prolonged mechanical ventilation, prolonged hospitalization, increased risk of mortality, and higher prevalence of poor neurodevelopmental outcome (1, 2). Although quality improvement efforts have contributed to reduction in PICC-related bloodstream infections (BSI) in the NICU (3–5), measures to prevent infections potentially associated with removal of a PICC are controversial.

It has been hypothesized that catheter removal disrupts a biofilm that forms during the indwell period, thus causing an influx of bacteria into the patient’s bloodstream and...
predisposing the infant to sepsis (6). A small number of studies exist examining this theory within the NICU population with equivocal findings (7–9). Because data supporting the relationship between PICC removal and subsequent BSI in NICU patients remain in question, we conducted a large retrospective cohort study examining the prevalence of BSI following PICC removal in a large level IIIC NICU. However, treatment of definitive infections represents the minority of antibiotic use in the NICU population (10). Infants with clinical signs of infection (e.g., apnea and bradycardia [A/B] events) are frequently evaluated by invasive measures (e.g., phlebotomy, lumbar puncture) and exposed to broad-spectrum antibiotic treatment. We hypothesized that PICC removal results in BSI or culture-negative sepsis in the lowest birth weight category of premature infants with PICCs used for TPN over a prolonged period of time. Our objective was to test if PICC removal resulted in these clinically important outcomes and if so, which subgroup of infants would be at highest risk. We further evaluated if antibiotic exposure prior to pulling the PICC would prevent these PICC removal associated complications.

**METHODS**

We conducted a retrospective cohort study of all infants admitted to the Monroe Carell Jr Children’s Hospital at Vanderbilt NICU between 2007 and 2009 after approval by the Vanderbilt Institutional Review Board. We identified all infants with at least one PICC inserted during their hospital stay and reviewed their records. We generated a limited dataset with a priori defined outcomes, such as culture-negative (clinical) sepsis, sepsis evaluations, and significant monitor events. Charts could only be accessed once, and any patient identifiers had to be removed as soon as data collection was completed.

PICCs were included if placed during that infant’s NICU stay and removed before discharge or within 48 hours of patient transfer within the hospital. PICCs were excluded if a second central catheter was in place at time of removal. Multiple subsequent PICCs from a single subject were considered separate removal cases as long as they fulfilled the criteria above.

PICC placement in our NICU follows a standardized protocol as reported previously (11). Briefly, an individual specialized proceduralist inserted 95% of the study PICCs under maximum sterile barrier precautions (cap, mask, sterile gown, sterile gloves, and large sterile drape). As a member of the Tennessee Initiative for Perinatal Quality Care (http://tipqc.org/), we followed a central catheter insertion and maintenance bundle similar to the one suggested by Schulman et al (12). The bundle includes facilitation of adherence to hand hygiene practices, two staff member tubing changes, daily evaluation of the catheter entry site, consideration of PICC removal during daily rounds, root cause analysis of each central line-associated bloodstream infection, and regular audits for bundle adherence. All infants with an indwelling PICC received fluconazole prophylaxis for the first 6 weeks postpartum if they were less than 26 weeks’ gestation and/or less than 750 g at birth (11).

We defined PICC-associated BSI using the Centers for Disease Control and Prevention criteria, which require either a single positive blood culture for a recognized pathogen not related to infection at another site or two positive cultures for a common skin contaminant like coagulase-negative *Staphylococcus* species drawn at separate occasions plus clinical signs for infection, such as fever (> 38°C rectal), hypothermia (< 36°C rectal), apnea, or bradycardia (13). We defined culture-negative sepsis in cases of negative blood cultures but with laboratory values consistent with infection and subsequent antimicrobial treatment: C-reactive protein more than or equal to 10 mg/L, WBC count less than 5,000 cells/μL or more than 30,000 cells/μL, or absolute neutrophil count less than 1,750 cells/μL. Antibiotic delivery through PICC or lack thereof in the 72 hours prior to PICC removal was also recorded. We counted any IV administration of antibiotics as antimicrobial exposure independent of the number of doses. Our clinical protocol includes twice weekly fluconazole prophylaxis for the first 6 weeks postpartum for all infants with indwelling PICCs if they are less than 26 weeks’ gestation and/or less than 750 g at birth. Therefore, fungal infections are extremely rare in our NICU. Amphotericin B was included under “other antibiotics” but fluconazole and acyclovir were not. We compared total days of indwelling PICC and total days of TPN and lipids delivered through the PICC. In the 72 hours preceding and following PICC removal, we recorded the number of A/B events, number of new-onset BSIs, and culture-negative sepsis episodes. A/B events were included only if they required intervention by the care team. Demographic information collected for each infant included gestational age, birth weight, sex, race, and major diagnoses. Cases of culture-negative sepsis and BSI that were diagnosed in the 72 hours prior to PICC discontinuation and remained present within 72 hours after PICC removal were excluded. We analyzed only new-onset BSI and culture-negative sepsis episodes.

Continuous variables were summarized using means, medians, and interquartile ranges (IQRs), and categorical variables were summarized using percentages. Every study subject had their PICC removed as condition for inclusion in the study; therefore, we compared the odds of an event in the 72 hours before PICC removal with the odds of an event in the 72 hours after a PICC removal, using McNemar’s test for paired data. Each PICC placement was treated as an independent event and served as its own control. To compare risk factors that vary across subjects, separate multivariable logistic regression models were fit to estimate the associations of culture-negative sepsis, BSI, A/B events and sepsis evaluations after PICC removal with birth weight, gestational age, PICC duration, TPN duration, and duration of lipids. Each model controlled for the potential confounding effects of gender, race, and the presence of the outcome prior to PICC removal. We report the complete set of analyses performed, including subgroups examined, and thus make no formal adjustments for multiple comparisons. Subgroups were defined prior to conducting the data analysis.
RESULTS
A total of 1,002 PICCs from 856 infants met criteria for our study and were evaluated for BSI and other adverse events in the 72 hours preceding and following PICC removal. Indications for PICC removal were as follows: achievement of full feeds (73.2%), completion of therapy (typically antimicrobials) (18.6%), PICC malfunction (5.2%), and PICC-associated infection (3%). Median gestational age was 31 weeks (IQR, 28, 37 wk) and median birth weight was 1,469 g (IQR, 960, 2,690 g). Average PICC duration was 17.3 days, with TPN and lipids being infused on average 14.2 and 12.4 days, respectively. A total of 362 PICCs were infused with antibiotics during the 72 hours preceding PICC removal, with 165 of those being infused with vancomycin. Table 1 shows the patient demographics for the three antibiotic groups (vancomycin, other antibiotics, and no antibiotics). Among PICCs without reported BSI prior to discontinuation, new-onset BSI was documented in three cases within 72 hours after removal (Table 2). All three new BSI events following PICC removal occurred in VLBW infants who had PICCs for reasons other than antibiotic delivery.

For the entire study population, PICC removal did not increase odds of BSI (odds ratio [OR] = 0.33 [95% confidence interval (CI), 0.07–1.3]; p = 0.08) or culture-negative sepsis (OR = 1.08 [95% CI, 0.68–1.7]; p = 0.73). In fact, we found decreased odds of sepsis evaluations (OR = 0.73 [95% CI, 0.55–0.95]; p = 0.02) and A/B events (OR = 0.73 [95% CI, 0.54–0.98]; p = 0.03) after PICC discontinuation. However after conducting subgroup analysis based on delivery of vancomycin (n = 165), any other antibiotic (n = 197), or no antibiotic (n = 640) in the 72 hours preceding PICC removal, we documented a 3.83-fold increased odds of culture-negative sepsis following PICC removal in PICCs not used for delivery of antibiotics (95% CI, 1.48–10.5; p = 0.001) (Fig. 1). This was the case even though these patients were more mature and exhibited a lower number of prematurity-associated complications compared with the vancomycin group (Table 1). Likewise, there was a 1.68-fold increased odds of sepsis evaluation following removal of PICC in infants whose PICCs were not used for antibiotic delivery (95% CI, 1.11–2.52; p < 0.01). An increase in odds of sepsis evaluation was not observed in the other two groups (Fig. 2). Odds of A/B events following PICC removal were reduced in PICCs used for vancomycin delivery (OR = 0.46 [95% CI, 0.21–0.98]; p = 0.03) but not in PICCs used for other antibiotics (OR = 0.68 [95% CI, 0.32–1.45]; p = 0.29) or no antibiotic administration (OR = 0.83 [95% CI, 0.58–1.19]; p = 0.29).

Across all subjects, each decrease in gestational age by 1 week was associated with a 1.11-fold increase (95% CI, 1.04–1.18) in the odds of culture-negative sepsis, a 1.14-fold increase (95% CI, 1.10–1.19) in the odds of sepsis evaluation, and a 1.30-fold increase (95% CI, 1.25–1.36) in A/B events following PICC removal. Similarly, each decrease in birth weight of 100 g was associated with a 1.06-fold increase (95% CI, 1.02–1.1) in culture-negative sepsis, a 1.06-fold increase (95% CI, 1.04–1.08) in the odds of sepsis evaluation was not observed in the other two groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vancomycin (n = 165)</th>
<th>Other Antibiotics (n = 197)</th>
<th>No Antibiotics (n = 640)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, wk (median, IQR)</td>
<td>29 (26, 35)</td>
<td>36 (28, 38)</td>
<td>31 (28, 36)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Birth weight, g (median, IQR)</td>
<td>1,232 (860, 2,318)</td>
<td>2,610 (1,380, 3,220)</td>
<td>1,390 (945, 2,338)</td>
<td>&lt;0.001</td>
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<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>111 (68)</td>
<td>142 (72)</td>
<td>448 (70)</td>
<td>0.63</td>
</tr>
<tr>
<td>Black</td>
<td>29 (18)</td>
<td>34 (17)</td>
<td>123 (19)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>24 (15)</td>
<td>21 (11)</td>
<td>68 (11)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>73 (44)</td>
<td>68 (35)</td>
<td>315 (49)</td>
<td>0.001</td>
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<tr>
<td>Primary diagnoses, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary disease</td>
<td>95 (58)</td>
<td>110 (56)</td>
<td>277 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>46 (28)</td>
<td>39 (20)</td>
<td>153 (24)</td>
<td>0.2</td>
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<tr>
<td>Congenital heart disease</td>
<td>20 (12)</td>
<td>15 (8)</td>
<td>51 (8)</td>
<td>0.2</td>
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<tr>
<td>Medical necrotizing enterocolitis</td>
<td>14 (8)</td>
<td>8 (4)</td>
<td>62 (10)</td>
<td>0.05</td>
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<tr>
<td>Multiple congenital anomalies</td>
<td>28 (17)</td>
<td>35 (18)</td>
<td>57 (9)</td>
<td>0.001</td>
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<tr>
<td>Liver disease</td>
<td>24 (15)</td>
<td>20 (10)</td>
<td>54 (8)</td>
<td>0.06</td>
</tr>
<tr>
<td>PDA—medically treated</td>
<td>23 (14)</td>
<td>11 (6)</td>
<td>60 (9)</td>
<td>0.05</td>
</tr>
<tr>
<td>PDA—surgically treated</td>
<td>31 (19)</td>
<td>8 (4)</td>
<td>44 (7)</td>
<td>0.001</td>
</tr>
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</table>

IQR = interquartile range, PDA = patent ductus arteriosus.
*Kruskal-Wallis test was used for continuous variables and Pearson chi-square test for categorical variables. A small p value means that at least one of the groups differs from the other(s).
in sepsis evaluation, and a 1.16-fold increase (95% CI, 1.13–1.2) in A/B events in the 72 hours following PICC removal. In a subanalysis based on birth weight, we found that VLBW infants (< 1,500 g birth weight, n = 502) had 2.07-fold (95% CI, 1.08–4.01) increased odds of culture-negative sepsis following PICC removal, whereas those weighing more than or equal to 1,500 g (n = 488) had reduced odds of culture-negative sepsis (OR = 0.43 [95% CI, 0.18–0.98]) (Fig. 3). Furthermore, within VLBWs, odds increased to 6.3-fold (95% CI, 1.78–26.9) for culture-negative sepsis following removal of PICCs not used for antibiotic delivery, whereas removal of PICCs used for vancomycin delivery did not increase the odds of culture-negative sepsis (OR = 0.82 [95% CI, 0.31–2.12]).

Each additional day in PICC duration was associated with increased odds of culture-negative sepsis, sepsis evaluation, and A/B events (OR = 1.03 [95% CI, 1.01–1.05]; OR = 1.02 [95% CI, 1.01–1.04]; OR = 1.03 [95% CI, 1.02–1.04], respectively) but not BSI (OR = 0.97 [95% CI, 0.87–1.09]). In infants without signs of culture-negative sepsis 72 hours prior to PICC removal, the risk of developing post-PICC removal culture-negative sepsis increased as duration of PICC increased beyond approximately 10 days (Fig. 4). Similarly, in the 72 hours following PICC removal, each

<table>
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<tr>
<th>Variables</th>
<th>All Subjects (n = 1,002)</th>
<th>Vancomycin (n = 165)</th>
<th>Other Antibiotics (n = 197)</th>
<th>No Antibiotics (n = 640)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of culture-negative sepsis before/after PICC removal</td>
<td>37/40</td>
<td>20/12</td>
<td>11/5</td>
<td>6/23</td>
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<tr>
<td>Number of BSI before/after PICC removal</td>
<td>9/3</td>
<td>8/0</td>
<td>1/0</td>
<td>0/3</td>
</tr>
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<td>Type and number of species identified before/after PICC removal in BSI</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td><em>Candida parapsilosis</em></td>
<td>1/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcus</em></td>
<td>6/0</td>
<td>6/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td><em>Enterobacter</em> species</td>
<td>1/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td><em>Enterococcus</em> species</td>
<td>0/1</td>
<td>0/0</td>
<td>0/0</td>
<td>0/1</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>1/0</td>
<td>0/0</td>
<td>1/0</td>
<td>0/0</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>0/2</td>
<td>0/0</td>
<td>0/0</td>
<td>0/2</td>
</tr>
</tbody>
</table>

PICC = peripherally inserted central venous catheter, BSI = blood stream infection. Cases of culture-negative sepsis (n = 10) and BSI (n = 3) that were diagnosed in the 72 hr prior to PICC discontinuation and remained present within 72 hr after PICC removal were not included.

**Figure 1.** Odds of culture-negative sepsis following peripherally inserted central venous catheter (PICC) removal. We used McNemar’s test to compare odds ratios between 72 hr before and 72 hr after PICC removal for all infants and infants exposed or not exposed to vancomycin or other antibiotics. Compared with all other groups, infants without exposure to antibiotics within 72 hr prior to PICC removal had 3.83-fold increased odds of culture-negative sepsis following PICC removal (95% CI, 1.48–10.5; p = 0.001). Vanc = vancomycin, Abx = antibiotics, *p* value of 0.001. The diamonds are the odds ratio estimate and the lines are the 95% confidence interval.

**Figure 2.** Odds of sepsis evaluations following peripherally inserted central venous catheter (PICC) removal. Using McNemar’s test to compare odds ratios between 72 hr before and 72 hr after PICC removal, we detected a 1.68-fold increased odds of sepsis evaluation following PICC removal in infants whose PICCs were not used for antibiotic delivery (95% CI, 1.11–2.52; p < 0.01). Vanc = vancomycin, Abx = antibiotics, *p* value of less than 0.001, #p value of less than 0.01, ##p value of less than 0.05. The diamonds are the odds ratio estimate and the lines are the 95% confidence interval.
additional day in TPN or lipid duration also increased the odds of culture-negative sepsis (OR = 1.03 [95% CI, 1.01–1.05]), sepsis evaluation (OR = 1.02 [95% CI, 1.01–1.04]), and A/B events (OR = 1.03 [95% CI, 1.02–1.04]) but not BSI (OR = 1.0 [95% CI, 0.92–1.09]).

**DISCUSSION**

Here, we report the largest retrospective cohort study on the prevalence of BSI and other associated morbidities after PICC removal. Despite 1,002 PICCs studied, we documented only three new-onset BSI within 72 hours following PICC discontinuation (0.3%), which does not support routine use of antimicrobial prophylaxis prior to pulling a PICC. These data are in stark contrast to the study reported by Hemels et al (9), who reported a BSI rate of over 11% within 48 hours of PICC removal in their institution; however, their BSI criteria were less stringent (9). One explanation for the much lower BSI rate in this study may have been the long-standing implementation of CLABSI prevention bundles in our institution, which have been shown to reliably decrease CLABSI rates (3, 14, 15).

Because early removal of a PICC that is no longer essential is included in our maintenance bundle, we sought to determine if this maneuver itself increases the odds for CLABSI, and if so in which population and under which circumstances. Our goal was to include credible data for discussion in future CLABSI reduction initiatives.

A protective effect of antibiotic exposure at the time of PICC removal was reported by van den Hoogen et al (8), who detected a seven-fold lower prevalence of sepsis among infants who received antibiotics at the time of PICC removal. This is in contrast to the much smaller study reported by Brooker and Keenan (7), where infusing any antibiotics in the 72 hours preceding PICC removal was not associated with less sepsis evaluations after PICC discontinuation. A recent prospective randomized trial from Hemels et al (9) concluded that administration of cefazolin 1 hour before and 12 hours after catheter removal significantly reduced the rate of sepsis associated with PICC removal. However, in this European study, Coagulase-negative *Staphylococcus* was universally sensitive to first-generation cephalosporins, and therefore, its applicability to regions with different antibiotic susceptibility is limited. Although prophylactic vancomycin appears to be effective in preventing catheter-related sepsis in preterm neonates (6, 16), its routine use in this population is not recommended (17).

We identified nine cases of BSI in the 72 hours prior to PICC removal; three-fold more than occurred in the 72 hours following PICC discontinuation. We did not record specific reasons for pulling the PICC, but the higher number of BSI prior to PICC removal may indicate that BSI was the basis for PICC discontinuation. All three new cases of BSI following PICC removal occurred in VLBW infants who had PICCs in place for reasons other than antibiotic administration.

Infants at highest risk for culture-negative sepsis were VLBW infants with PICC dwell time more than 21 days and lack of antibiotic exposure within 72 hours of PICC removal (> 6.3-fold increase in odds). In addition to culture-negative sepsis, lack of antibiotic exposure, decreasing birth weight, decreasing gestational age, increasing PICC dwell time, and increasing duration of TPN and/or IV lipids were independent risk factors for sepsis evaluation and increase in A/B events after PICC removal. Decreasing birth weight and gestational age as well as increasing duration of PICC dwell time and time on TPN/lipids are considered risk factors for late-onset sepsis in NICU patients (1).
However, the duration of PICC dwell time as an independent risk factor for CLABSI has been controversial (18–20). Although these data support increasing risk of PICC-associated morbidity with longer dwell time (18), we focused our investigation on PICC removal. Therefore, our study cannot be directly compared with those addressing overall CLABSI rates.

We do not know why decreasing gestational age and decreasing birth weight were associated with higher odds for adverse events following removal of a PICC not used for antibiotics. We speculate that a possible inflammatory reaction to very low colony count bacteremia, not detected in standard blood cultures, or material dislodged from the catheter tip is more evident in VLBW infants, similar to what has been observed following bacterial antigen exposure in association with routine immunizations (21–23).

One limitation of our study is the definition of culture-negative sepsis. We included WBC counts indices, which despite their almost uniform use have reportedly low diagnostic accuracy (24). Other limitations include the retrospective design in a single level III NICU and the low number of documented BSI. Only a multicenter prospective randomized placebo-controlled trial evaluating the effect of antibiotic prophylaxis on the risk of subsequent BSI after PICC removal in NICU patients could provide conclusive evidence. This study is difficult to perform given the low baseline risk for BSI within 72 hours of PICC removal (0.3%). However, whether our results can be extrapolated to NICUs with higher rates of BSI following PICC removal remains speculative.

Strengths of this study comprise placement and maintenance of almost all PICCs by a single specialized proceduralist, the large cohort of patients, and the a priori inclusion of culture-negative sepsis, sepsis evaluations, and significant A/B episodes to allow capture of all real and potential PICC removal-related events. We feel that the typical limitations of multiple subgroup analysis are not applicable to our study because we defined these subgroups prior to conducting the data analysis to evaluate if anecdotaly reported adverse events are in fact associated with pulling the PICC.

In conclusion, we identified a subgroup of NICU patients that are at increased risk for adverse events following PICC removal. All new-onset BSI cases occurred in VLBW infants not exposed to antibiotics prior to pulling the PICC. Although the number of BSI cases was too low to recommend universal antimicrobial prophylaxis, the same patient population had statistically significant increased odds of culture-negative sepsis and sepsis evaluations. Although most of these events are of limited clinical significance, they often result in phlebotomy and prolonged antibiotic exposure, both of which have been associated with short- and long-term morbidity (25, 26). Therefore, it seems reasonable, in our opinion, to propose a single-dose antibiotic prophylaxis trial for VLBW infants not exposed to antibiotics prior to pulling the PICC and with PICC dwell time more than 21 days.

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REFERENCES