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ORIGINAL ARTICLE

Increased frequency of peripheral venipunctures raises the risk of central-line associated bloodstream infection in neonates with peripherally inserted central venous catheters

Hao-Yuan Cheng [a], Chun-Yi Lu [a], Li-Min Huang [a], Ping-Ing Lee [a], Jong-Min Chen [b], Luan-Yin Chang [a,*]

[a] *Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan*
[b] *Department of Laboratory Medicine, National Taiwan University Hospital, Taiwan*

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peripherally inserted central venous catheter

Background/Purpose: Central-line associated bloodstream infection (CLA-BSI), which is mostly caused by coagulase-negative staphylococcus, is an important morbidity in neonatal intensive care units. Our study is aimed to identify the risk factors of CLA-BSI in neonates with peripherally inserted central venous catheters (PICCs).
Methods: A retrospective cohort study of neonatal intensive care unit patients with a PICC insertion between January 1, 2011 and December 31, 2012 was conducted. We performed univariate and multivariate analyses with a logistic regression model to investigate the risk factors and the association between increased frequency of peripheral venipunctures during PICC use and the risk of CLA-BSI while adjusting for other variables.
Results: There were 123 neonates included in our study. Thirteen CLA-BSIs were recorded within the follow-up period. The incidence of PICC-associated CLA-BSI was 4.99 per 1000 catheter-days. There was no statistically significant association between the risk of CLA-BSI and gestational age, birth weight, chronological age, or other comorbidities. However, the odds of CLS-BSI increased to 12 times if the patient received six or more venipunctures within the period without concurrent antibiotic use [odds ratio (OR), 11.94; $p < 0.001$]. The OR of CLA-BSIs increased by 16% per venipuncture during PICC use (OR, 1.14; $p = 0.003$).

* Corresponding author. Division of Pediatric Infectious Diseases, Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Number 8, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail addresses: ly7077@tpts6.seed.net.tw, lychang@ntu.edu.tw (L.-Y. Chang).

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Conclusion: During PICC use, increased frequency of venipunctures, especially when there was no concurrent antibiotic use, substantially raises the risk of CLA-BSI. By decreasing unnecessary venipunctures during PICC use, PICC-associated CLA-BSI and further morbidities and mortalities can be prevented.

Introduction

Hospital-acquired infections (HAIs), which usually result in the majority of the mortality and morbidities in the intensive care unit (ICU) setting, have been a serious problem for the health care of premature infants. In a survey conducted in the United States, HAIs occurred in about one-tenth of the patients in neonatal intensive care units (NICUs).[1,2] More than 50% of HAIs were bloodstream infections, especially central-line associated bloodstream infection (CLA-BSI).[1–3] The attributable mortality rate of CLA-BSIs in the ICUs ranged from 4% to 20%,[4] although the rate may be a little lower in the NICU,[5] but the consequent morbidities and prolonged duration of ICU admission still accounted for considerable medical costs.[4,6]

Although older children in the pediatric ICU may have other types of central lines, for example, double lumen catheter for renal replacement therapy or catheters for extracorporeal life support, peripherally inserted central catheter (PICC) accounts for the majority of central lines in the NICU because its placement is easier and it has fewer complications than a traditional central venous catheter.[7–10]

Many studies has tried to find the possible pathogenesis and the risk factors of CLA-BSI, but no consensus has been achieved.[11–17] Whereas some researchers argued whether low bodyweight (either at birth or at the time of catheter insertion) and the use of total parenteral nutrition contributed to CLA-BSI,[9,11,15,17] recent studies favored the prolonged duration of PICC use as the most important risk factor of acquiring CLA-BSIs.[13,18]

By contrast, about 70–90% of PICC-associated CLA-BSIs were caused by coagulase-negative staphylococci (CoNS).[11–13,19] Previous researchers considered that intraluminal colonization and increased frequency of hub manipulation might be the main pathogenesis of CLA-BSIs.[12,20] However, these studies had controversial findings to make a definite explanation, and their conclusion could not be applied completely to CLA-BSI in patients with PICCs. As a result, we designed this study to investigate the risk factors of PICC-associated CLA-BSIs.

Methods

Setting and patients

We conducted a retrospective cohort study of patients in the NICU at the National Taiwan University Hospital (NTUH), a tertiary-care facility in northern Taiwan. The NICU is a 25-bed ward admitting about 800–900 patients per year. Most patients in the NICU were born at the NTUH and admitted to the NICU soon after birth. The others were transferred to the NTUH from local obstetric clinics or other hospitals for more advanced medical care, for example, surgery for congenital heart disease.

In the NTUH NICU, a PICC would be inserted to deliver parenteral nutrition when a patient was not anticipated to have adequate oral intake at about 1 week after birth. PICCs were inserted by a skillful and experienced team, including pediatric residents and neonatologists, according to the standard protocol with sterile methods.

In this study, we included all the patients who received at least one PICC placement in the NTUH NICU between January 1, 2011 and December 31, 2012. The patients whose PICC insertion was performed at other hospitals prior to being transferred to NTUH were excluded because we could not confirm the medical records during the PICC use, and the setting and the catheter care routine were different outside the NTUH.

Data collection

The list of patients who had bloodstream infection that occurred in the NICU was obtained from the database of the central laboratory of NTUH. CLA-BSI was identified according to the surveillance definition of Centers for Disease Control and Prevention's National Healthcare Safety Network for CLA-BSI.[21,22]

The microorganism of CLA-BSI was cultured with standard laboratory methods at the central microbiology laboratory of NTUH, and the antibiotic susceptibility profiles were obtained from laboratory reports.

We reviewed all the medical charts of the eligible patients and conducted a thorough survey to record the data on sex, date of birth, gestational age at birth, birth bodyweight, and comorbidities during NICU admission. Data including the date of PICC insertion and removal, the site of PICC insertion, the date of antibiotic use and discontinuation, and the frequency of peripheral venipunctures patients received during PICC use were extracted from detailed medical records. Gestational age was categorized as $<$32 weeks or $\geq$32 weeks. Birth weight was categorized as $<$1500 g or $\geq$1500 g.[1,23] Chronological age was grouped as $\leq$7 days or $>$7 days. The PICC duration was divided into three groups — $\leq$10 days, 11–20 days, and $>$20 days — in univariate analysis, and the frequency of peripheral venipunctures was grouped as $<$6 times and $\geq$6 times.

Definition

In our study, a CLA-BSI was defined as a primary bloodstream infection in a patient that had a central line within the 48-hour period prior to the development of the

bloodstream infection and it was irrelevant to an infection at another site.[21,22] 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 and it was mainly used for infusion of intravenous drug or parenteral nutrition infusion. The PICCs in NTUH NICU were not used for blood sampling or hemodynamic monitoring.

PICC duration was defined as days from the insertion of the PICC until one of the following: (1) the date of positive blood culture regarded as a CLA-BSI; or (2) the date of PICC removal. We included all the episodes of PICC placement including those who had multiple PICC placements.

The frequency of venipunctures was calculated as the sum of (1) the number of times for peripheral venous catheter insertion, including failed and successful ones, and (2) the number of times for peripheral venipunctures for blood drawing, for example, drawing blood for checking of hemogram or culture from peripheral veins instead of a central venous catheter or an arterial catheter. Concurrent antibiotic use meant that the patient was under antibiotic treatment while the PICC was in place. The PICC duration without concurrent antibiotic use referred to the period the patient had a PICC in place without CLA-BSI and did not receive any antibiotics at the same time, for example, from the date the antibiotic was discontinued until the PICC was removed or the date of a positive blood culture for CLA-BSI.

Statistical analysis

We performed a descriptive analysis for the characteristic of the patient with PICCs. The incidence of PICC-associated CLA-BSI was measured as infection episodes per 1000 catheter-days. In the univariate analysis, Student's *t* test for continuous variables and Fisher's exact test for categorical variables were used to identify risk factors of PICC-associated CLA-BSI; then, we used a multivariable logistic regression model to find the most significant factors. A two-tailed $p < 0.05$ was considered statistically significant. Data were maintained in Microsoft Excel: Mac 2011 (Bellevue, WA, USA) and analyzed using Stata 12.0 (Stata Corp, College Station, TX, USA).

Results

Cases

There were 123 neonates with 129 PICCs inserted from January 1, 2011 to December 31, 2012. Four PICCs were excluded. Three patients had irreversible end-stage disease and the patients' parents decided to let these three babies receive only palliative care. They died while their PICCs were not removed. We excluded these patients because the patients may have undiscovered PICC-related infection. We also excluded another patient, who had bloodstream infection but the isolated pathogen, *Enterobacter aerogenes*, was considered to have originated from the gastrointestinal tract rather than from the skin. Overall, a total of 125 PICCs were considered eligible for further analysis.

Demography and incidence of CLA-BSI

Among the 125 PICCs, there were 13 CLA-BSIs that occurred (10.4%). The incidence rate of PICC-associated CLA-BSI was 4.99 infections per 1000 catheter-days. Eleven of the 13 CLA-BSI were caused by CoNS, whereas the other two were caused by *Candida glabrata*.

The mean gestational age at birth was 28.7 ± 0.3 weeks (Table 1). The mean birth weight was 1102.9 ± 49.0 g, and the mean chronological age at PICC insertion was 7.5 ± 0.9

Table 1 Characteristics of patients with PICCs

	Total	No CLA-BSI	CLA-BSI	*p*
Patient number	125	112	13	
Gestational week[a]	28.7 ± 0.3	27.7 ± 1.2	28.8 ± 0.4	0.34
Birth bodyweight (g)[a]	1102.9 ± 49.0	1070.7 ± 183.3	1106.6 ± 50.7	0.82
Chronological age at PICC insertion (d)[a]	7.5 ± 0.9	7.4 ± 1.0	8.6 ± 3.2	0.69
ICU duration at PICC insertion (d)	7.6 ± 0.9	7.6 ± 1.0	7.5 ± 2.2	0.95
Cormobidities (*n*)				
Lung diseases[a]	79 (63)	70 (62)	9 (69)	0.72
GI diseases[b]	16 (13)	13 (12)	3 (23)	0.24
CHD[c]	66 (53)	56 (50)	10 (77)	0.07
CNS diseases[d]	24 (19)	19 (17)	5 (39)	0.06
Hydrops fetalis	4 (3)	4 (3)	0 (0)	0.49
Renal failure	8 (6)	7 (6)	1 (7)	0.84

[a] Lung diseases, included respiratory distress syndrome, bronchopulmonary dysplasia, chylothorax and other diseases that may impair lung function.
[b] GI diseases: gastrointestinal diseases, included intestinal perforation, necrotizing enterocolitis and other conditions that may cause functional disorder of the gastrointestinal tract or prolong the use of parenteral nutrition.
[c] CHD: congenital heart diseases, included patent ductus arteriosus, ventricular septal defect or other congenital cardiac anomalies.
[d] CNS diseases: central nervous system diseases, included intracranial hemorrhage, intraventricular hemorrhage, epilepsy or other CNS disorders.
Data are presented as mean ± SE or *n* (%).
CLA-BSI = central-line associated bloodstream infection; ICU = intensive care unit; PICC = peripherally inserted central venous catheter.

days. The gestational age and bodyweight at birth, chronological age, and bodyweight at the time of PICC insertion were all similar between those with or without CLA-BSI.

As for comorbidities, we did not find any significant association between CLA-BSI and comorbidities. The exceptions were congenital heart disease and central nervous system (CNS) diseases, which accounted for higher percentages in the CLA-BSI group (77% and 39%, respectively).

The mean PICC duration was 20.8 ± 1.2 days. Eight of 13 (62%) CLA-BSIs in patients with PICCs occurred between the 11th day and the 20th day after the PICC insertion. The PICC duration for those had CLA-BSIs was 19.2 ± 3.0 days, which was not significantly longer than the duration for those without CLA-BSI (21.0 ± 1.3 days, $p = 0.63$; Fig. 1). If we excluded the periods with concurrent antibiotics use, the PICC duration without concurrent antibiotics remained similar (12.5 days in CLA-BSI group vs. 11.4 days in non-CLA-BSI group; $p = 0.65$; Fig. 1). The total frequencies of peripheral venipunctures received in both groups were similar (18.5 times vs. 14.1 times, respectively; $p = 0.31$), but the patients with a PICC-associated CLA-BSI received double venipunctures than those without CLS-BSI within the periods without concurrent antibiotic use (11.4 times vs. 5.3 times, respectively; $p < 0.001$; Fig. 2.)

Risk factors of CLA-BSI

In the univariate analysis, no association between gestational age, birth weight, chronological age at PICC insertion, and CLA-BSI was found (Table 2). However, patients who received six or more venipunctures within the periods without concurrent antibiotic use had almost 12 times the odds than that of those who received less than six venipunctures (odds ratio 11.94; $p < 0.001$). Here, we chose six venipunctures as a cutoff value because the mean number of venipunctures within the periods without concurrent antibiotic use in patients without CLA-BSI was 5.3. We also used four or five venipunctures as the cutoff, and the results were similar (odds ratio 12.0 and 7.9, respectively; both $p < 0.001$).

As for multivariate logistic regression model, we analyzed possible risk factors including gestational age, birth weight, PICC duration without concurrent antibiotic use, frequency of venipunctures during PICC use without concurrent antibiotics, congenital heart disease, and CNS disease. After adjusting all confounding factors, the only significant risk factor was the frequency of venipunctures during the periods of PICC use without concurrent antibiotics (Table 3). For every one more venipuncture a patient received, the odds of acquiring a CLA-BSI increased by 16% (odds ratio, 1.16; $p = 0.003$).

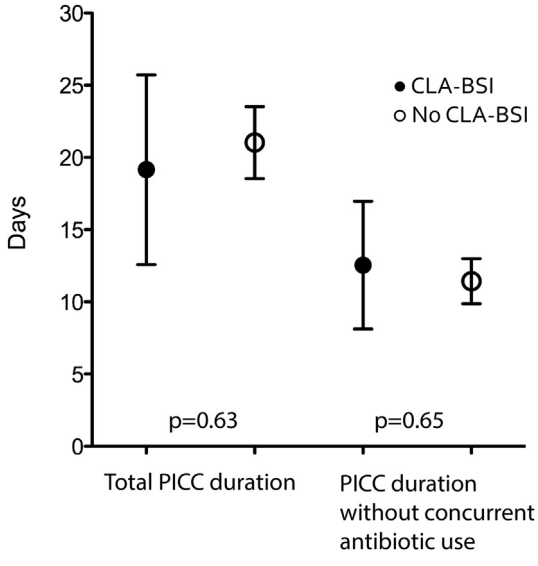

Figure 1. Mean PICC duration during PICC use in NICU patients with and without CLA-BSI. The I bar represents the 95% confidence interval. CLA-BSI = central-line associated bloodstream infection; NICU = neonatal intensive care unit; PICC = peripherally inserted central venous catheter.

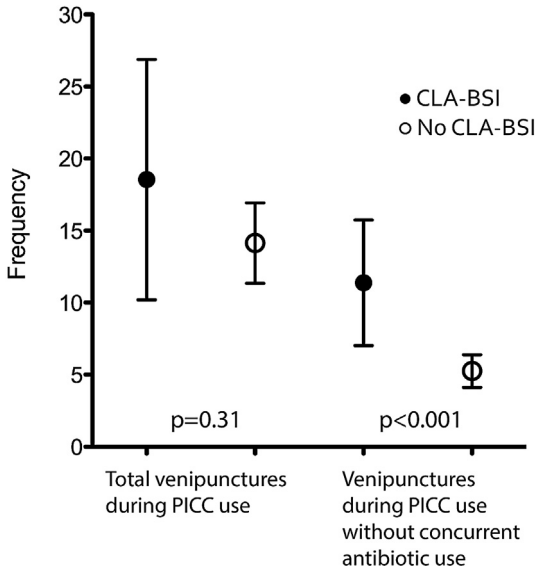

Figure 2. Mean frequency of venipunctures during PICC use in NICU patients with and without CLA-BSIs. The I bar represents the 95% confidence interval. CLA-BSI = central-line associated bloodstream infection; NICU = neonatal intensive care unit; PICC = peripherally inserted central venous catheter.

Discussion

The incidence of PICC-associated CLA-BSI, 4.99 per 1000 catheter-days, was still low in our medical care setting compared to that reported in previous studies in different medical settings, but the PICC duration in our study was longer.[11,13,14,18] A possible explanation is that PICCs in the NTUH NICU were only used for infusion of intravenous drugs or parenteral nutrition and were not used for hemodynamic monitoring or blood sampling. This practice reduced the chance to manipulate the catheter hub and thus decreased the chance of microorganism invasion.

The onset time of CLA-BSI in patients with PICCs in this study was similar to that in previous studies, that is, the risk was highest during the 11th day to the 20th day after PICC insertion.[13,14] Theoretically, if PICC duration was really an important risk factor, the risk of CLA-BSI should increase

Table 2 Risk factors of CLA-BSIs in NICU patients with PICCs

	PICC infection	No PICC infection	OR	95% CI	*p*
Gestational age					
<32 wk	11	90	1		
≥32 wk	2	22	0.74	0.15–3.63	0.71
Birth bodyweight					
<1500 g	11	96	1		
≥1500 g	2	16	1.09	0.22–5.42	0.92
Chronological age at PICC insertion					
>7 d	9	88	1		
≤7 d	4	24	1.62	0.46–5.80	0.45
PICC site					
Upper limbs	10	91	1		
Lower limbs	3	21	1.3	0.33–5.17	0.71
Total duration of PICC insertion					
≤10 d	2	26	1		
11–20 d	8	30	3.47	0.65–18.6	0.12
>20 d	3	56	0.70	0.11–4.48	0.70
Total venipunctures during PICC insertion					
Mean ± SE	18.5 ± 3.8	14.1 ± 1.4			0.31
<15	7	72	1		
≥15	6	40	1.54	0.48–4.94	0.46
Venipunctures during PICC insertion without concurrent antibiotic use					
Mean ± SE	11.4 ± 2.0	5.25 ± 0.6			0.0009*
<6	2	73	1.00		
≥6	11	39	11.94	1.99–53.25	0.0006*

CLA-BSI = central-line associated bloodstream infection; NICU = neonatal intensive care unit; OR = odds ratio; PICC = peripherally inserted central venous catheter; SE = standard error.

proportionally with the prolonged PICC duration. Nevertheless, the findings of previous studies and our research showed that the incidence beyond the 20th day did not keep increasing. This trend implied that longer PICC duration might not completely explain a CLA-BSI.

By contrast, the single lumen design of PICC makes it more likely to be used for continuous infusion rather than for blood sampling. This preference suggests that the source of CoNS in PICC infection comes more possibly from the skin or mucosa than from the catheter hub. This theory could be further supported by the observation that CoNS, as a member of commensal skin flora, was the most common pathogen isolated in PICC-associated CLA-BSI.[14,18,23]

As a result, we designed this study, and our hypothesis was that the prolonged duration resulted in increased frequency of peripheral venipunctures. With the increased frequency of peripheral venipunctures, the possibility of transient bacteremia increased and it was more likely to cause bacteria colonization on PICC and subsequent CLA-BSI. That is to say, it is the increased frequency of venipunctures that raises the risk of CLA-BSI rather than prolonged PICC duration. Therefore, we calculated the frequency of venipunctures during PICC usage, especially when there was no concurrent antibiotic use, because concurrent antibiotics decreased the possibility for bacteria circulating in the blood to colonize on the catheter.

Interestingly, although the total venipunctures in both groups were similar, we found that the frequency of venipunctures, when there was no concurrent antibiotic use, increased significantly in those with CLA-BSI (11.4 times vs. 5.6 times, respectively). The risk for CLA-BSI in those with six or more venipunctures also increased to almost 12 times.

Table 3 Logistic regression models for risk factors of CLA-BSI in NICU patients with PICCs

	OR	95% CI	*p*
Gestational age ≥32 wk	1.5	0.14–15.47	0.74
Birth bodyweight ≥1500 g	1.47	0.15–14.28	0.74
Duration of PICC use without concurrent antibiotic use (d)	0.94[a]	0.85–1.03	0.17
Venipunctures during PICC use without concurrent antibiotic use (times)	1.16[a]	1.05–1.26	0.003
Congenital heart disease	3.17	0.73–13.87	0.13
CNS disease	3.53	0.92–13.56	0.07

[a] OR represents the change in odds ratio per day or times.
CI = confidence interval; CLA-BSI = central-line associated bloodstream infection; CNS = central nervous system; NICU = neonatal intensive care unit; OR = odds ratio; PICC = peripherally inserted central venous catheter.

This finding supported our hypothesis and might also explain why some patients with much longer PICC indwelling did not acquire a CLA-BSI because they usually received prolonged antibiotic treatment at the same time and actually had less venipunctures within the PICC duration without concurrent antibiotic use. The most common concurrent antibiotic regimens during PICC use in our study were vancomycin plus ceftazidime, ampicillin plus cefotaxime, and ampicillin plus gentamicin. In total, of the 13 CLA-BSI cases, there was only one patient receiving concurrent antibacterial antibiotics while he acquired *Candida glabrata* CLA-BSI. The other CLA-BSI case caused by *Candida glabrata* did not receive any antibiotics at the same time. Whether the concurrent antibiotic use increases fungal CLA-BSI is difficult to confirm because of the low incidence of fungal CLA-BSI. However, our findings would favor the avoidance of unnecessary venipunctures rather than the increase of concurrent antibiotic use to prevent a PICC-associated CLA-BSI. Prolonged concurrent antibiotic use with increased frequency of venipunctures may raise the risk of CLA-BSIs caused by resistant strains or fungus in the long run.

We also analyzed other risk factors of CLA-BSI in patients with PICCs. Most of them, for example, gestational age, birth bodyweight, or chronological age at PICC insertion, did not significantly correlate to CLS-BSI. Although these factors had been claimed to associate with CLS-BSI,[9,11,15] further studies did not show lower birth weight or smaller gestational age to be the consistent risk factor of CLA-BSI in patients with PICCs.[13,14,18] Our study was consistent with this controversy.

In addition, our study revealed there were more patients with CLA-BSIs having congenital heart diseases or CNS diseases. The most common congenital heart disease was Patent ductus arteriosus, whereas the most common CNS disease was intraventricular hemorrhage. This observation also supported our hypothesis because a Patent ductus arteriosus might cause a right-to-left shunt, which helped the circulating microorganism in the blood to escape from the filtration of pulmonary circulation and allowed the transient bacteremia to persist longer in systemic circulation. Unstable hemodynamics also increased the risk of intraventricular hemorrhage.

The major indications of peripheral venipunctures in our study included intravenous drug infusion, inotropics, blood transfusion, and calcium or albumin supplement. Most of them can be avoided, for example, by using the oral form of drugs instead of using intravenous forms. Our findings supported the recommendation of declining unnecessary intravenous catheter insertion and blood sampling. By reducing unnecessary peripheral venipunctures, doctors are able to substantially reduce the chances of PICC-associated CLA-BSI.

There are several limitations in our study. First, our study was a retrospective study and depended on medical records to calculate the frequency of venipunctures, and this might be underestimated if the medical staff did not record the frequency of venipunctures correctly. This situation occurred most possibly when a patient received too many venipunctures at the same time. Second, we did not perform further laboratory tests, for example, genetic typing, to identify if the microorganism isolated from blood was the same as that on the skin flora. Third, the sample size of our cohort and the case number of CLA-BSI in patients with PICCs were not very large. However, the results of our study were still statistically significant. Finally, our study can only explain those CLA-BSIs caused by commensal skin flora, which accounted for about 70% to 90% of all-cause CLA-BSIs.[11,12]

In conclusion, our study demonstrates the association of peripheral venipunctures and CLA-BSIs in patients with PICCs. The findings of our study contribute not only to clarify the possible pathogenesis and the origin of microorganism of CLA-BSI but also to help develop preventive measures against HAIs in the NICU.

Conflicts of interest

All authors declared no conflicts of interest.

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