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Original Article

Risk factors for persistent bacteremia in infants with catheter-related bloodstream infection due to coagulase-negative *Staphylococcus* in the neonatal intensive care unit

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ABSTRACT

Background: Coagulase-negative *Staphylococcus* (CoNS) is the predominant cause of catheter-related bloodstream infections (CRBSI). Infants in neonatal intensive care units (NICU) often suffer from CoNS CRBSI, which are often refractory to treatment.
Objectives: We sought to evaluate risk factors for developing persistent bacteremia due to CoNS CRBSI in infants, in order to identify those who require early aggressive management.
Methods: We conducted a retrospective case-control study of infants in the NICU who developed CRBSI due to CoNS. Patient demographics, condition and management of CRBSI were compared between those with persistent and non-persistent bacteremia. Furthermore, prognosis of infants in the NICU after CoNS CRBSI was evaluated.
Results: Seventy six episodes of CRBSI, including 17 persistent bacteremia and 59 non-persistent bacteremia, were analyzed. In univariate analyses, persistent bacteremia was significantly associated with corrected age equivalent to gestational age of 22–28 weeks at onset of CRBSI [Odds ratio (OR) = 4.33; $P = 0.04$], platelet count <100,000/μL (OR = 11.5; $P < 0.001$), use of vasopressor (OR = 5.38; $P = 0.003$), and delayed CVC removal (OR = 6.25; $P = 0.003$). In multivariate analysis, persistent bacteremia was significantly associated with platelet count <100,000/μL (OR = 7.80; $P = 0.007$), and delayed CVC removal (OR = 5.07; $P = 0.03$). Infants with persistent bacteremia tended to have a lower survival rate after CoNS CRBSI, however this was not statistically significant ($P = 0.21$).
Conclusions: Early CVC removal should be considered for the treatment of CRBSI due to CoNS in infants with platelet counts of less than 100,000/μL.

1. Introduction

Coagulase-negative *Staphylococcus* (CoNS) is a predominant organism that comprises the normal human skin flora. CoNS is also the predominant cause of catheter-related bloodstream infections (CRBSI) [1]. Infants in the neonatal intensive care unit (NICU) also often suffer from CRBSI due to CoNS [2,3].

Clinical practice guidelines by the Infectious Diseases Society of America (IDSA) generally recommends central venous catheter (CVC) removal to treat CRBSI [4]. However, for CRBSI due to CoNS, CVC removal is not considered essential. Management with appropriate antibiotics for 10–14 days in combination with antibiotic lock therapy is considered acceptable [4]. In fact, CVC retention has been reported not to have an impact on the resolution of CoNS CRBSI [5]. However, poor outcomes have also been reported [4], particularly in infants in the NICU who occasionally develop refractory bacteremia [3,6,7]. Strategies are needed to stratify patients into those who require early CVC removal versus those who can be treated conservatively.

In this study, we aimed to determine the risk factor for persistent bacteremia ≥3 days due to CoNS CRBSI in infants in the NICU to identify those who may require early CVC removal.

2. Patients and methods

2.1. Study design

We conducted a retrospective case-control study to evaluate risk factors for developing persistent bacteremia ≥3 days due to

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CoNS CRBSI in infants in the NICU at the National Center for Child Health and Development from January 2003 to April 2015.

The hospital microbiological database was screened to identify patients who had positive blood cultures for CoNS and clinical data was obtained from the electronic medical records. Inclusion criteria were; patients with CVC, who had at least one positive blood culture with signs of generalized infection and treated for CRBSI with antibiotics based on clinical judgment [8,9]. One set of blood culture consisted of both aerobic and anaerobic blood culture bottles. Isolation from either or both bottles was considered positive. Exclusion criteria consisted of patients who had a positive blood culture for *S. lugdunensis*, patients who had a positive blood culture for CoNS from one set of blood culture that was clinically judged as contamination and treated without antibiotics, and isolation of CoNS from only one out of two or more sets of blood cultures collected, or those who were judged to have an alternative focus of infection other than CRBSI. CoNS CRBSI was divided into two groups; persistent and non-persistent bacteremia. Persistent bacteremia was defined as isolation of CoNS from two or more consecutive blood cultures obtained at least three days apart [9]. Central line-associated bloodstream infection (CLABSI) were defined based on CDC criteria [10]; a laboratory-confirmed bloodstream infection where CVC was in place for >2 calendar days. Laboratory-confirmed bloodstream infection in this study met the following criteria; (1) patient has at least one of the following signs or symptoms: fever (>38.0 °C), hypothermia (<37 °C), apnea, or bradycardia, (2) signs and symptoms and positive laboratory results were not related to an infection at another site, and (3) detection of CoNS from two or more blood cultures drawn on separate occasions [10]. Bacteremia occurring within 30 days after treatment was defined as relapse. Bacteremia occurring more than 30 days after treatment was counted as a new episode of CRBSI.

To evaluate risk factors for persistent bacteremia, the following variables were analyzed: demographic characteristics (age, sex, gestational age, corrected gestational age, birth weight, body weight at CRBSI, and underlying disease), patient condition (white blood cell count, C-reactive protein, platelet count, serum lactate, device, surgical history, initiation or increased demand for vasopressors, isolation of two or more species from the blood, coexisting infection, site of CVC insertion, duration of CVC retention) and management of CRBSI (empiric therapy and CVC removal). Delayed CVC removal was defined as CVC removal after more than one day after positive blood culture, including those that were treated without CVC removal. Additional analysis of the risk factors for developing persistent bacteremia was performed in a subset of patients who were diagnosed with two sets of blood cultures, given some uncertainty in the diagnosis of patients diagnosed with one set of blood culture.

Furthermore, prognosis of infants in the NICU after CoNS CRBSI was evaluated. The prognosis of patients with persistent bacteremia was compared against those with non-persistent bacteremia using, death within 30 days, death within three months and death directly related with CoNS CRBSI, as endpoints.

This study was approved by the ethics committees of National Center for Child Health and Development.

2.2. Microbiological assessment

Blood culture was performed using the BacT/Alert 3D™ (SYSMEX bioMérieux Co. Ltd., Tokyo, Japan) automated continuous monitoring system.

CoNS was identified by automated microbiology system BD Phoenix™ 100 (Becton, Dickenson and Company Japan, Tokyo, Japan). Gram positive cocci that were coagulase negative and were not speciated beyond the genus *Staphylococcus* spp. were considered CoNS. Antibiotic susceptibility testing was performed according to Clinical and Laboratory Standards Institute M02-A11, M07-A9 and M100-S24 reference methods.

2.3. Statistical analysis

Data was analyzed using SPSS Statistics 22.0 software (SPSS, Chicago, IL, USA). We compared factors associated with persistent and non-persistent bacteremia using chi-square test or Fisher's exact test, Mann–Whitney *U* test, and multivariate logistic regression analysis. For multivariate analysis, univariate factors with $P < 0.1$ were entered into a logistic regression model. Kaplan–Meier analysis and Log-rank test was used to analyze the overall survival rate of infants after CoNS CRBSI. *P* values less than 0.05 were considered statistically significant.

3. Results

During the study period, 6135 sets of blood cultures were obtained, 559 sets were positive and the remaining 5576 sets were negative. CoNS were detected from 253 sets of blood cultures. Sixty-eight of these were excluded: *S. lugdunensis* was isolated from 2 sets, 63 sets were clinically judged as contamination, and three sets from two infants were excluded due to diagnosis of an alternative site of infection other than CRBSI, which included, ventriculo-peritoneal shunt infection and early onset sepsis (same CoNS was isolated from the mother's amniotic fluid). We analyzed 185 sets from 76 episodes of CRBSI, including 17 with persistent bacteremia and 59 with non-persistent bacteremia (Fig. 1). All infants with persistent bacteremia and 17 of 59 infants with non-persistent bacteremia were met CLABSI criteria. Of the 59 episodes of non-persistent bacteremia, blood culture taken in 26 infants within three days of the first positive blood culture and were negative. In the remaining 33 infants, subsequent blood cultures were not collected due to clinical improvement.

In univariate analysis, persistent bacteremia was significantly associated with, corrected age at CRBSI, corresponding to 22–28 weeks of gestation [Odds ratio (OR) = 4.33; 95% confidence interval (CI) 1.09–17.25; $P = 0.04$], platelet count <100,000/μL (OR = 11.50; 95% CI 3.20–41.30; $P < 0.001$), use of vasopressor (OR = 5.38; 95% CI 1.70–17.06; $P = 0.003$), and delayed CVC removal (OR = 6.25; 95% CI 1.91–20.50; $P = 0.003$) (Tables 1 and 2). Median platelet count before development of bacteremia was 160×10^9/L [interquartile range (IQR) 114–370 $\times$ 10^9/L] in persistent bacteremia and 270×10^9/L (IQR 140–372 $\times$ 10^9/L) in non-persistent bacteremia, which was not statistically different by the Mann–Whitney *U* test ($P = 0.32$). However, median platelet count at the onset of CRBSI was significantly decreased in persistent bacteremia [76×10^9/L (IQR 36–90 $\times$ 10^9/L)] compared with non-persistent bacteremia [179×10^9/L (IQR 110–302 $\times$ 10^9/L)] ($P = 0.01$).

In multivariate analysis, persistent bacteremia was significantly associated with platelet count of <100,000/μL (OR = 7.80; 95% CI 1.78–34.28; $P = 0.007$), and delayed CVC removal (OR = 5.07; 95% CI 1.21–21.31; $P = 0.03$) (Table 3).

In 34 CRBSI infants meeting CLABSI criteria, only platelet count <100,000/μL was statistically associated with persistent bacteremia in univariate (OR = 7.80; 95% CI 1.69–36.06; $P = 0.006$) and multivariate analysis (OR = 6.08; 95% CI 1.10–33.52; $P = 0.04$) (Supplementary Tables 1–3).

Infants with persistent bacteremia tended to have a lower survival rate after CoNS CRBSI, but this difference was not statistically significant ($P = 0.21$) (Fig. 2). Two infants were died during treatment of persistent bacteremia (Table 4). None of the patients relapsed during this study period.

CoNS species and methicillin-resistant *Staphylococcus* (MRS) isolated from blood culture is shown in Table 5. All CoNS isolated