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Major article

Case-control analysis of endemic *Acinetobacter baumannii* bacteremia in the neonatal intensive care unit

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Background: We aimed to characterize the clinical manifestations and outcomes of patients with *Acinetobacter baumannii* bacteremia in the neonatal intensive care unit (NICU).
Methods: All patients with *A baumannii* bacteremia in our NICU from 2004 to 2010 were reviewed. A matched case-control study was performed by comparing each case of *A baumannii* to 2 uninfected controls and all cases of *Escherichia coli* and *Klebsiella* bacteremia, respectively.
Results: Thirty-seven cases with *A baumannii* bacteremia were identified. Multidrug-resistant isolate was noted in only 2 cases (5.4%), and the overall mortality rate was 8.1%. Compared with matched, uninfected controls, infants with *A baumannii* were more likely to have had a central vascular catheter (CVC) ($P = .009$), use of total parenteral nutrition (TPN) ($P = .021$), longer duration of ventilator use ($P = .002$), and hospitalization ($P = .010$). Compared with *E coli* or *Klebsiella* bacteremia, infants with *A baumannii* bacteremia had lower birth weight (median of 1,090 g vs 1,300 g, $P = .044$) and a higher rate of CVC and TPN use (both $P < .001$) at the time of infection.
Conclusion: *A baumannii* bacteremia occurs endemically or sporadically in the NICU, primarily in low-birth-weight infants on TPN use and with CVC in situ. Although *A baumannii* does not often cause mortality, and multidrug-resistant *A baumannii* is uncommon, it contributes significantly to longer hospitalization.

Acinetobacter baumannii is a nonfermentative, gram-negative coccobacillus, which is increasingly found in the intensive care unit.[1,2] This microorganism has been one of the most important pathogens causing hospital-acquired infections for decades.[3,4] It contributes to 8% to 25% of all gram-negative bacillary (GNB) late-onset sepsis (LOS) in the neonatal intensive care unit (NICU).[5-7] In addition, *A baumannii* accounts for 4.6% of ventilator-associated pneumonia, 5.7% of catheter-related bloodstream infections (BSIs), and 4.3% of all BSIs.[8-10] *A baumannii* can possibly become highly resistant to all antibiotics,[11] which makes it deserve special attention and emphasis of infection control. Several recent reports have described the emergence or outbreak of multidrug-resistant (MDR) *A baumannii* in the NICU that is associated with higher morbidity or mortality.[3,12-14]

Recent studies focused on clinical features and successful control of MDR *A baumannii* outbreak[11-15]; however, non-MDR *A baumannii* is rarely investigated. In adult or surgical intensive care unit, an *A baumannii* outbreak has traditionally been linked to environmental sources, such as contaminated medical devices or prolonged mechanical ventilation,[16,17] but little relevant information was available in the NICU.[3] The purpose of this case-control analysis was to identify and compare cases of endemic *A baumannii* bacteremia in a NICU over a 7-year period with matched uninfected and other GNB-infected controls to identify risk factors, presenting signs and symptoms, and outcomes specific to *A baumannii* that may facilitate the diagnosis and development of interventions for the control of *A baumannii*.

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PATIENTS AND METHODS

Hospital characteristics and patients

Between January 2004 and December 2010, all neonates with at least 1 episode of *A baumannii* bacteremia during their hospitalization in the NICU of Chang Gung Memorial Hospital (CGMH) were identified from the electronic database. The NICU of CGMH is a tertiary-level medical center in northern Taiwan and contains a total of 49 beds equipped with mechanical ventilator and 28 beds with special care nurseries. This study was approved by the Institutional Review Board of CGMH.

Control case selection and matching criteria

To identify potential risk factors associated with acquisition of *A baumannii bacteremia*, 2 uninfected controls were selected and matched to each case of *A baumannii* bacteremia using birth weight (±100 g), gender, and gestational age (±1 week). Next, all cases of *E coli* and *Klebsiella* spp bacteremia during the same period—after excluding extended-spectrum β-lactamase-producing strain—were enrolled as the infected controls.

Date collection and analysis

Clinical information and microbiologic data were collected and included demographic characteristics, presence of central venous catheters (CVCs), invasive diagnostic and therapeutic procedures, total parenteral nutrition (TPN), mechanical ventilation, previous antibiotic exposure, and current usage.

Definitions

LOS was defined as positive microbial growth in ≥ 1 culture of blood samples obtained after 72 hours of life with accompanying clinical signs of sepsis. Recurrent bacteremia was defined as any new episode of documented BSI by the same or different pathogens occurring at least 2 weeks after the initial episode, a period during which blood cultures were negative. Prolonged intubation was defined as the need for mechanical ventilation for more than 14 days prior to infection. Prolonged hospitalization was defined as an infant who stayed in the NICU after the postconceptional age of 42 weeks. Cholestasis was defined according to the definition of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.[18,19] Death was considered attributable to sepsis if it occurred within 7 days of the positive blood culture or if clinical signs and symptoms of sepsis were documented in the medical record as the direct cause of death. All comorbidities of prematurity, including respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis were based on the latest updated diagnostic criteria in the standard textbook of neonatology.[20]

In our NICU, all blood cultures were assessed using the Bactec 9240 system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD), and antibiotic susceptibility patterns were tested using disk diffusion methods on Mueller-Hinton agar plates, using calibrated inoculum of the isolates based on the McFarland standard.[21,22] MDR *A baumannii* was defined when the isolate was resistant to 3 of the following 4 antibiotics: ceftazidime, ciprofloxacin, gentamicin, and imipenem.

Statistical analysis

Continuous variables were summarized using means and standard deviations if normally distributed and median and ranges if not normally distributed. Student *t* test and the Mann-Whitney test were used to compare continuous variables and the χ^2 test or Fisher exact test was used to compare categorical variables. All *P* values were 2 tailed, and *P* values $< .05$ were considered to be statistically significant. Dichotomous variables were analyzed using odds ratio and bivariate logistic regression analysis. Despite the relatively small sample size and risk of model breakdown, independent covariates with a *P* value of $< .10$ as identified by bivariate analysis were subjected to multivariate logistic regression analysis. Statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient characteristics

Thirty-seven cases of *A baumannii* bacteremia were identified in neonates hospitalized in the NICU of CGMH between January 2004 and December 2010. Infants with *A baumannii* bacteremia had median gestational age and birth weight of 28 weeks and 1,090 g, respectively. During the same period, a total of 137 neonates who experienced *Escherichia coli* or *Klebsiella* bacteremia, after excluding extended-spectrum β-lactamase-producing bacteria, was identified as the control group. The uninfected controls consisted of 74 neonates. The demographic characteristics of cases and selected controls are summarized in Table 1.

Organism characteristics and antibiotic susceptibility patterns of A baumannii

Of all episodes, 19 cases occurred endemically into 4 major outbreaks (defined as significantly more episodes within a short period when compared with a 6-month interval by χ^2 test), and others occurred sporadically over this 7-year period (Fig 1). Only 2 isolates were MDR strain, and none of the others were resistant to gentamicin or third-generation cephalosporins. Most cases (35/37, 94.6%) were on TPN and/or intralipids nutritional support and with a CVC in situ, and 81.1% (30/37) were under ventilator support at the time of infection.

Comparison of cases of A baumannii *and uninfected controls*

The overall mortality was significantly higher among infected patients (8.1% vs 0%, respectively, $P = .014$, Table 1). Patients with *A baumannii* were more likely to have longer duration of ventilator use and hospitalization ($P = .002$ and $P = .010$, respectively). None of perinatal risk factors, bronchopulmonary dysplasia, intraventricular hemorrhage, or necrotizing enterocolitis were found to be associated with acquisition of *A baumannii* bacteremia. Although neonates with *A baumannii* were comparable with the uninfected controls with regard to the day of first attempt at feeding, they used significantly longer duration of TPN and/or intralipids and thus much later reached full feeding amount (both $P < .001$).

The bivariate logistic regression analysis (Table 2) revealed that patients with *A baumannii* were more likely to have an indwelling CVC (OR, 11.22; 95% CI: 1.43-88.21, $P = .021$), use of TPN and/or intralipids (OR, 9.27; 95% CI: 1.17-73.40, $P = .035$), use of high frequency oscillatory ventilator after birth (OR, 3.11; 95% CI: 1.14-8.44, $P = .026$), prolonged intubation (OR, 2.59; 95% CI: 1.12-5.97, $P = .025$), and cholestasis (OR, 6.35; 95% CI: 2.47-16.30, $P < .001$). Multivariate logistic regression confirmed cholestasis as the only significant independent risk factor for *A baumannii* bacteremia (OR, 4.50; 95% CI: 1.61-12.54, $P = .004$).