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Original Article

Risk factors and molecular epidemiology of *Acinetobacter baumannii* bacteremia in neonates

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Sequence type;
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Abstract *Background: Acinetobacter baumannii* infections in neonates are not uncommon but rarely studied.
Methods: Clinical and molecular epidemiology of 40 patients with *A. baumannii* bacteremia in the neonatal intensive care units (NICUs) of a medical center from 2004 to 2014 was analyzed.
Results: Multi-drug resistance was found in only 3 isolates (7.5%). Sequence types (STs) of *A. baumannii* defined by multilocus sequencing typing were diverse, and 72.4% identified isolates belonged to novel STs. Majority of the isolates were susceptible to antibiotics tested. Among the 3 imipenem-resistant *A. baumannii* (IRAB) isolates, 2 (66.7%) belonged to ST684, a novel ST. All of the 3 isolates were susceptible to tigecycline and colistin. The predominant mechanism of imipenem resistance in these neonatal isolates is IS*Aba1-bla*$_{\text{OXA-80}}$, which has never been reported in Asia before. Most infected newborns were premature (95%), with very low birth weight (70% < 1500 g), prolonged intubation, usage of percutaneous central venous catheter (65%) and long-term usage of total parenteral nutrition or intravenous lipid (95%). IRAB infection, inappropriate initial therapy, 1-minute Apgar score and early onset infection within the first 10 days of life were found to correlate with mortality by log-rank test. Prior use of imipenem for at least 5 days and use of high frequency oscillation ventilation (HFOV) were statistically significant risk factors for acquiring IRAB infections.

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Conclusions: To reduce mortality of IRAB infection, it is crucial to consider giving effective agents, such as colistin, in 2 days for high risk neonates who has been given imipenem or used HFOV.
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Introduction

In the neonatal intensive care unit (NICU), *Acinetobacter baumannii* contributes to 0.2—6.9% of all bacteremia,[1,2] and 8%—25% of all late onset sepsis caused by Gram-negative bacilli.[3,4] Bacteremia caused by imipenem-resistant *A. baumannii* (IRAB) has been associated with a higher mortality (46.0%) than bacteremia by imipenem-susceptible *A. baumannii* (ISAB) (28.3%) and other diagnoses of *A. baumannii* infection.[5] The mortality rate of neonates due to IRAB sepsis was 20.34% (12/59) at a medical center in central Taiwan.[6] In our previous study in adult patients, imipenem-resistant *A. baumannii* complex bacteremia showed a high mortality (69.9%), and was associated with prior use of broad-spectrum antibiotics for more than 5 days for treating ventilator-associated pneumonia before the occurrence of bacteremia.[7] However, there are few studies surveying risk factors of acquiring IRAB in neonates and we did not know how to prevent these fatal infections in newborns.

The predominant resistance mechanism to imipenem in *A. baumannii* isolates from adult patients from 1993 to 2007 in Taiwan was IS*Aba1*—$bla_{\text{OXA-51-like}}$.[8] Since 2006, Tn*2006* (IS*Aba1*—$bla_{\text{OXA-23}}$—IS*Aba1*) has been increasingly found in the clinical *A. baumannii* isolates and can be easily selected by antibiotic pressure from the use of imipenem or extended-spectrum cephalosporins.[8] However, imipenem resistance mechanisms in *A. baumannii* isolates from newborns and risk factors of IRAB remain unknown.

Multilocus sequence typing (MLST), a widely used technique for bacterial typing, was proven to provide unambiguous typing data for long-term and global *A. baumannii* epidemiological surveillance.[9] However, there is no published MLST data in clinical neonate *A. baumannii* isolates in Taiwan.

By comparing clinical presentations and molecular epidemiology of neonatal IRAB infections with those of ISAB infections, our aim was to identify risk factors of acquiring IRAB infections and those of mortality that may facilitate the interventions for the control of neonatal *A. baumannii* infections and thus improve their outcome.

Materials and methods

Study subjects and inclusion criteria

This study was approved by the Institutional Review Board (100-3592B). Charts were reviewed for NICU patients who were treated in Chang Gung Memorial Hospital (CGMH) from 2004 to 2014 and had ≥1 positive blood culture for *A. baumannii*, with symptoms and signs of infection. For patients with multiple episodes, only the first episode was included. Patients with incomplete medical records or with polymicrobial infections were excluded. The NICUs of CGMH, a tertiary medical center in northern Taiwan, contains a total of 47 beds with mechanical ventilator and 54 beds with special care nurseries.

Date collection and analysis

Clinical data including demographic characteristics, perinatal findings, presence of central venous catheters (CVCs), peripheral central venous catheters (PCVCs), umbilical vein catheters, history of surgery, total parenteral nutrition (TPN) and/or intravenous lipid usage, mechanical ventilation including nasal continuous positive airway pressure (NCPAP) and high frequency oscillation (HFO), previous antibiotic exposure duration, adequate prompt antibiotic treatment, and initial blood testing for white blood cell count and C-reactive protein, were collected and analyzed.

Definitions

Premature rupture of membranes (PROM) in pregnancy refers to rupture of membranes of the amniotic sac and chorion >18 h prior to the onset of labor, whereas preterm PROM refers to rupture of the membranes with a gestation of <37 weeks, >18 h prior to the onset of labor. Ventilator use was defined as ever having used a ventilator with intermittent mandatory ventilation, HFO and NCPAP mode. The usage of CVCs (central venous catheters) was defined as ever having used a peripheral CVC (PCVC), femoral CVC, or umbilical vein catheter. Apgar scores and chorioamnionitis were based on the latest updated diagnostic criteria in the standard textbook of neonatology.[10] Mortality was defined as infection-attributable death, wherein the criteria of death were met before the symptoms and signs of bacteremia were resolved and with at least a blood culture positive for *A. baumannii*.[11] Considering "time at risk" for acquiring resistance under antimicrobial selective pressure, prior exposure to antimicrobial agents was defined as at least 5 days of therapy during the 14 days before the isolation of *A. baumannii*.[7,8,12] Appropriate antimicrobial therapy was defined as administering patients with at least one antimicrobial agent, except aminoglycoside, susceptible in vitro, within 2 days after bacteremia onset.[11,13] Culture detecting time was the interval (days) from culture sampling to reporting.

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