ORIGINAL ARTICLE INFECTIOUS DISEASES

Predictors of clinical and microbiological treatment failure in neonatal bloodstream infections

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Abstract

This study aimed to identify independent predictors of clinical and microbiological treatment failure and develop a predictive model for neonates with bloodstream infection (BSI). This study included 1087 episodes of BSIs in 793 neonates in a tertiary-level neonatal intensive care unit of northern Taiwan between 2004 and 2012. Patient demographics, underlying chronic comorbidities, clinical features, antimicrobial treatment and microbiological characteristics were evaluated. The presence of underlying congenital anomalies (odds ratio [OR] 2.12, 95% confidence interval [CI] 1.09 to 4.10) and pulmonary hypertension (OR 3.63, 95% CI 1.70 to 7.74), infections caused by multidrug-resistant gram-negative bacteria (OR 2.89, 95% CI 1.23 to 6.79), group B *Streptococcus* (OR 3.15, 95% CI 1.33 to 7.46), and fungi (OR 4.13, 95% CI 2.02 to 8.46), a Neonatal Therapeutic Intervention Scoring System score of $\geq$ 23 (OR 6.96, 95% CI 2.55 to 28.58), inappropriate antibiotics (OR 2.13, 95% CI 1.41 to 3.23), and concomitant meningitis (OR 4.25, 95% CI 2.08 to 8.69) and ventilator-associated pneumonia (OR 2.73, 95% CI 1.22 to 6.13) were identified as independent risk factors for 28-day treatment failure in neonatal BSI. A risk score model was created by adding the points for each independent risk factor, and had a c-statistic of 0.83. Patients with risk scores of 0, 4, 8, 12 and 15 had estimated 28-day treatment failure rates of approximately 3.5%, 17.0%, 53.5%, 86.6% and 95.9%, respectively. This predictive model, calculated after documentation of a BSI, reflects a spectrum of BSI severity and was associated with subsequent treatment failure through illness severity score and case mix variables. This simple score could prove useful in clinical and research settings, and practical in estimating the prognosis.

Keywords: 28-day mortality, Antibiotic resistance, late-onset sepsis, mortality, risk factors
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Introduction

Neonatal bloodstream infections (BSIs) are significantly associated with an increased morbidity and mortality in neonatal intensive care units (NICUs) [1–3]. The reported mortality rate of neonatal BSI ranges from 7.2% to 17.8% [2,4,5] despite the fact that broad-spectrum antibiotics are administrated on time. In recent years, antimicrobial-resistant bacteria have become an increasing problem in the NICU [6–8], and are associated with a significantly higher risk of infectious complications and in-hospital mortality. There is also growing evidence that infection with some organisms, such as methicillin-resistant *Staphylococcus aureus* or *Pseudomonas*, with an increased antimicrobial MIC that is still within the susceptible range may be associated with increased rates of treatment failure [9,10].

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Given the emerging information regarding the outcomes of antimicrobial therapy for neonatal BSIs, a comprehensive evaluation of the patients, pathogens, treatment characteristics, and underlying comorbidities is necessary to determine which factors or combinations of factors are most predictive of the outcomes and whether any treatment strategies can improve the outcomes. Traditionally, studies evaluating neonatal BSIs have often focused on very low birth weight (VLBW, birth weight $\leq$ 1500 g) infants [5,11–14] and lacked one or more of the aforementioned factors. In addition, previous studies used early mortality [11,12] or last positive blood culture before death [13] for analysis, whereas some important outcome parameters, such as infectious complications and recurrence, were often ignored [11–14]. The aim of the present study was to determine the clinical and microbiological outcomes of neonatal BSIs, identify independent predictors of treatment failure, and develop a scoring model with which to estimate the prognosis.

Patients and methods

Study setting, design, and population

This retrospective cohort study was conducted in the NICU of Chang Gung Memorial Hospital, a university-affiliated teaching hospital and referral centre in Northern Taiwan with an annual admission of 1700 neonates. This NICU contains three units, and has a total capacity of 47 beds with mechanical ventilators and 58 beds with special nurseries. All infants < 34 to 35 weeks' completed gestation, with a birth weight < 2 kg or > 5 kg, or with any clinical signs of respiratory distress or cardiovascular, gastrointestinal, or neurologic problems requiring surgical or intensive treatment were eligible for admission in our NICU. We retrospectively screened for neonates with BSIs hospitalized in the NICU between July 2004 and June 2012. All episodes of BSI were considered as an independent event, but the subsequent episode of a BSI that occurred < 1 month after the previous one was excluded from the analysis. Infants without detailed medical records and those who were transferred to other hospitals before the outcomes could be assessed were excluded from analysis. This study was approved by the institutional review board of Chang Gung Memorial Hospital, with a waiver of informed consent because all patient records/information was anonymized and de-identified before analysis.

Demographic characteristics were obtained from a prospectively collected database in our NICU [2,6]. We reviewed the patients' medical records and collected detailed information of each BSI as follows: the antimicrobial treatment data, additional interventions (surgery, invasive intubation, use of central venous catheters or total parenteral nutrition), and response to treatment. The severity of illness was scored using the Neonatal Therapeutic Intervention Scoring System (NTISS) [15], with variables taken at the first 48 hours after onset of the BSI episode.

Definitions

An episode of BSI was defined according to clinical and microbiological criteria, which considered any bacteria isolated from at least one blood culture and not pertaining to the saprophytic skin flora as significant. Growth of *Corynebacterium*, *Propionibacterium*, *Penicillium*, or *Diphtheroids* in the blood cultures was considered contaminant and excluded. For coagulase-negative staphylococci (CoNS) BSI, the diagnosis required clinical signs of sepsis, a blood culture positive for CoNS, and intravenous antibacterial therapy for at least 5 days after performing the blood culture, or until death [2,12,13]. Early-onset and late-onset sepsis were defined as clinical sepsis and a positive blood culture obtained within and after 3 days of life [2,3,16], respectively.

Blood cultures were requested at the discretion of the attending physician and processed using the Bactec 9240 culture system. Identification of all causative microorganisms was performed using standard microbiological methods. Antibiotic susceptibility patterns were determined according to methods recommended by the National Committee for Clinical Laboratory Standards Institute (CLSI) for disk diffusion method, and categorical assignment was performed using CLSI breakpoints [17]. Extended-spectrum β-lactamase–producing gram-negative bacteraemia and multidrug-resistant gram-negative bacteraemia were defined according to CLSI guidelines and previous publications, respectively [6,17–19]. Polymicrobial BSIs were defined as more than 1 μg identified from a single set of blood cultures [20]. The first-line antibiotics in our NICU were ampicillin plus gentamicin and oxacillin or vancomycin plus gentamicin or cefotaxime for early-onset sepsis and late-onset sepsis, respectively. Empirical antibiotic therapy was considered inappropriate if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganisms within 24 hours of blood culture collection.

All comorbidities of prematurity, including respiratory distress syndrome (RDS), intraventricular haemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis (NEC) were based on the latest updated diagnostic criteria in the standard textbook of neonatology [21]. All concurrent infectious focus, including NEC, ventilator associated pneumonia (VAP), catheter-related BSIs or meningitis were also recorded and based on the strict diagnostic criteria of Centers for Disease Control and Prevention and previous official publications [22–24].

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