ORIGINAL ARTICLE 10.1111/1469-0691.12661

Recurrent late-onset sepsis in the neonatal intensive care unit: incidence, clinical characteristics and risk factors

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Abstract

We aimed to characterize the incidence, clinical features, risk factors and outcomes of recurrent late-onset sepsis (LOS) in the neonatal intensive care unit (NICU). All neonates with LOS from the NICU of a tertiary-level teaching hospital in northern Taiwan between 2004 and 2011 were enrolled for analyses. A case-control study was performed to determine risk factors for recurrence. Of 713 neonates with LOS, 150 (21.0%) experienced recurrence and 48 (6.7%) had >1 recurrences; *c.* two-thirds of recurrent LOS occurred in infants with birth weight (BW) ≦ 1500 g or gestational age (GA) ≦ 30 weeks. The recurrent LOS episodes were significantly more severe and had a higher sepsis-attributable mortality rate than the first episodes. The overall in-hospital mortality rate was 30.7% for neonates with recurrent LOS and 7.8% for those with single LOS (odds ratio (OR), 5.22; 95% CI, 3.28–8.30). When both BW and GA were controlled, neonates with recurrent LOS had a significantly prolonged hospitalization compared with the controls (median 109 vs. 84 days, $p < 0.001$). After multivariate logistic regression, longer duration of total parenteral nutrition (TPN; OR, 1.30; 95% CI, 1.10–1.52 for every 10-day increment), presence of congenital anomalies (OR, 2.64; 95% CI, 1.10–6.35) and neurological co-morbidities (OR, 4.14; 95% CI, 1.14–15.10) were identified as the independent risk factors for LOS recurrence. We concluded that *c.* one-fifth of neonates with LOS had recurrence, which significantly resulted in prolonged hospitalization and increased mortality. Longer TPN administration, presence of congenital anomalies and neurological co-morbidities are independently associated with recurrent LOS.

Keywords: Antibiotic resistance, bacteraemia, late-onset sepsis, recurrence, risk factor
Original Submission: 11 November 2013; **Accepted:** 28 April 2014
Editor; D. Raoult
Article published online: 2 May 2014
Clin Microbiol Infect

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Dr Ming-Horng Tsai wrote the first draft of the manuscript and no honorarium, grant or other form of payment was given to anyone to produce the manuscript.

Introduction

Although advances in perinatal resuscitation and neonatal care have led to improved survival of high-risk neonates in the neonatal intensive care unit (NICU), late-onset sepsis (LOS) remains an important cause of morbidity and mortality [1–3]. A significant percentage of neonates experience one or more episodes of blood culture-proven LOS during their

hospitalization [2,4,5], and there have been a number of studies focused on the epidemiology, microbiology, clinical characteristics, risk factors and outcomes of LOS [1–7]. Recent studies extended the long-term outcome investigation and found that LOS is highly associated with poor neurodevelopmental delay and growth impairment during early childhood [8,9].

However, most neonatal LOS studies ignored an important outcome of LOS, the repeated episode(s), and only the first episode for each infant was retrieved for analysis [1,3,6,10–12]. Recurrent LOS deserves greater awareness because most neonates survive the primary infection and those who potentially experience a repeated episode may have a prolonged hospital stay and higher mortality rate. Recurrent bacteraemia has been concluded to be an independent risk factor for mortality [13], and risk factors for recurrence were identified in several studies [13–16]. In the neonatal setting, 23.7–28% of very low birth weight (VLBW; birth weight < 1500 g) infants were reported to have recurrent LOS [4,5], but the clinical impact and risk factors for recurrence are still unknown. We therefore conducted this study in order to determine the incidence, clinical characteristics, risk factors and outcomes of recurrent LOS in the NICU.

Patients and Methods

Study population

Through our database search, all neonates admitted to the NICU of Chang Gung Memorial Hospital (CGMH) between January 2004 and December 2011 were enrolled for analysis if they had one or more episodes of LOS. This database was managed by the trained research nurses, who entered the detailed data regarding the hospitalized infants, including maternal demographics, pregnancy, delivery information and the hospital course of the infants, from birth/admission to discharge/death from the year 2003. This study was approved by the institutional review board of Chang Gung Memorial Hospital (CGMH).

Definition

Late-onset sepsis was defined as a positive blood culture obtained after 72 h of life in the presence of clinical septic symptoms and intent to treat with antibiotics for 5 days or more. Blood cultures positive for the microorganisms, including *Bacillus*, *Corynebacterium*, *Propionibacterium*, *Penicillium* and *Diphtheroids* were considered to be contaminants and excluded from analysis. Records of patients with blood culture positive for coagulase-negative staphylococci (CoNS) were reviewed, and the strict criteria from the Centers for Disease Control and Prevention for CoNS LOS were applied [5,17,18]. The presence of clinical septic symptoms required at least two of the following: fever or hypothermia, hyper- or hypoglycaemia, apnoea or tachypnoea, frequent desaturation with increased requirement of ventilator support, bradycardia and/or cyanosis, feeding intolerance, abdominal distension, seizure, decreased activity, skin mottling and hypotension. If the same pathogen was identified after 14 days of appropriate antibiotic therapy or after 7 days of appropriate antibiotic therapy and at least one negative blood culture, or if a different pathogen was identified from a subsequent culture 7 days after the first one, it was considered as a recurrent episode of LOS [4,5]. If more than one microorganism was identified from a single set of blood cultures or from different sets within a 48-h period, it was defined as a polymicrobial LOS episode [19,20].

All co-morbidities of prematurity, including respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and periventricular leukomalacia (PVL), were based on the latest updated diagnostic criteria in the standard textbook of neonatology [21]. Severity of illness was evaluated at the most severe period during the course of each LOS episode by two investigators (S-MC and J-FH) using the neonatal therapeutic intervention scoring system (NTISS) [22]. For patients who died during hospitalization, the cause of death was recorded according to the clinician's presumption, and mortality was considered attributable to the episode of LOS if the patient died within 7 days of the onset of LOS or in the presence of persisting clinical sepsis or bacteraemia; otherwise death was considered unrelated to the episode of LOS.

Statistical methods

All episodes of LOS were considered independently. Statistical significance for unadjusted comparisons between the first episode of LOS and recurrent episodes of LOS was determined by the chi-squared or Fisher exact test for categorical data, and the Student's *t*-test or the Wilcoxon/Mann–Whitney test for continuous variables. Tests were two-sided and a p value <0.05 was considered significant.

To assess risk factors for the development of recurrence, we conducted a matched case-control study by selecting one control with single LOS for each case with recurrent LOS. This control was matched to each case using birth weight (BW; $\pm$100 g) and gestational age (GA; $\pm$1 week). The association between the different variables analysed and recurrence was estimated by calculating the odds ratio (OR) for the univariate analysis. Finally, a multivariate logistic regression model consisting of those variables that were significantly associated with recurrence at a p value of <0.05 by univariate analysis was