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Major article

Neonatal gram-negative bacillary late-onset sepsis: A case-control-control study on a prospectively collected database of 5,233 admissions

Ming-Horng Tsai MD [a,b,c,1], I. Hsyuan Wu MD [b,d,1], Chiang-Wen Lee MD [c,e], Shih-Ming Chu MD [b,d], Reyin Lien MD [b,d], Hsuan-Rong Huang MD [b,d], Ming-Chou Chiang MD [b,d], Ren-Huei Fu MD, PhD [b,d], Jen-Fu Hsu MD [b,d,**], Yhu-Chering Huang MD, PhD [b,f,*]

[a] Division of Neonatology and Pediatric Hematology/Oncology, Department of Pediatrics, Chang Gung Memorial Hospital, Yunlin, Taiwan
[b] College of Medicine, Chang Gung University, Taoyuan, Taiwan
[c] Department of Nursing, Division of Basic Medical Sciences and Chronic Diseases and Health Promotion Research Center, Chang Gung University of Science and Technology, Chia-Yi, Taiwan
[d] Division of Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[e] Research Center for Industry of Human Ecology, Chang Gung University of Science and Technology, Taoyuan, Taiwan
[f] Division of Pediatric Infectious Disease, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan

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Background: Gram-negative bacillary (GNB) bloodstream infections account for 20%-30% of neonatal late-onset sepsis (LOS). We aimed to identify the incidence, clinical characteristics, and risk factors for adverse outcomes in neonates with GNB LOS.

Methods: All patients with GNB LOS admitted to the neonatal intensive care units (NICUs) of a university-affiliated teaching hospital in Taiwan from January 1, 2004-December 31, 2011, were enrolled. A case-control-control study was performed to evaluate risk factors for acquisition of neonatal GNB LOS.

Results: Of the 5,010 neonates, 290 (5.8%) had a total of 346 episodes of GNB LOS (36.7% of total LOS), with an incidence rate of 13.6 per 10,000 neonate hospital days. The overall mortality rate was 17.6% (51/290), and the sepsis attributable mortality rate was 9.8% (34/346 episodes). After multivariate logistic regression analysis, neonates with prolonged use of total parenteral nutrition (adjusted odds ratio [OR] = 1.53; 95% confidence interval [CI], 1.02-2.29; $P = .041$) were independently associated with acquisition of GNB LOS. The independent predictors of in-hospital mortality were *Pseudomonas aeruginosa* etiology (OR = 11.45; 95% CI, 2.83-46.24) and underlying secondary pulmonary hypertension (OR = 18.02; 95% CI, 3.28-98.89), renal disease (OR = 17.16; 95% CI, 2.96-99.38), and neuromuscular comorbidities (OR = 2.72; 95% CI, 1.06-7.00).

Conclusion: Given the higher illness severity and sepsis-attributable mortality rate of neonatal GNB LOS in the NICU, strategies to reduce the incidence need to be addressed urgently.

Late-onset sepsis (LOS) is associated with significant morbidity and mortality in the neonatal intensive care unit (NICU), especially among very low birth weight (VLBW; birth weight [BW] ≤1500 g) or extremely preterm infants.[1,2] Despite expanded availability of broadly active antibiotics and improved neonatal care, approximately 30%-40% of VLBW and 15% of late-preterm neonates suffer from LOS,[3-5] with mortality rates ranged from 10%-30%.[5-7] Although

* Address correspondence to Yhu-Chering Huang, MD, PhD, Division of Pediatric Infection Disease and Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital, 5, Fu-Shing St, Kwei-Shan, Taoyuan 333, Taiwan.
** Address correspondence to Jen-Fu Hsu, MD, PhD, Division of Pediatric Infection Disease and Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital, 5, Fu-Shing St, Kwei-Shan, Taoyuan 333, Taiwan.
E-mail addresses: ychuang@adm.cgmh.org.tw (Y.-C. Huang), jeff0724@gmail.com (J.-F. Hsu).

Conflicts of Interest: None to report.

[1] Contributed equally to this article.

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Table 1
Rates and incidence rates of neonates with GNB-LOS versus birth weight and gestational age, Chang Gung Memorial Hospital, January 1, 2004-December 31, 2011

Birth weight (g)	Total population number*	Neonates with GNB-LOS, n (%)	Incidence rates† (10,000/neonate hospital days)	Gestational age (wk)	Total population number*	Neonates with GNB-LOS, n (%)	Incidence rates† (10,000/neonate hospital days)
≤500	8	2 (25.0)	19.3	≤24	111	21 (18.9)	28.3
501-750	209	36 (17.2)	24.2	25-26	272	32 (11.8)	18.4
751-1,000	372	50 (13.4)	21.9	27-28	386	60 (15.5)	10.4
1,001-1,250	445	47 (10.6)	7.6	29-30	510	37 (7.3)	6.3
1,251-1,500	488	35 (7.2)	6.3	31-32	816	36 (4.4)	14.6
1,501-2,000	1,082	46 (4.3)	15.9	33-34	918	28 (3.1)	13.8
2,001-2,500	902	27 (3.0)	19.9	35-36	766	24 (3.1)	20.6
2,501-3,500	1,286	39 (3.0)	21.9	37-40	1,182	49 (4.1)	32.1
>3,500	218	8 (3.7)	21.4	>40	49	3 (6.1)	16.5
Total	5,010	290 (5.8)	13.6	Total	5,010	290 (5.8)	13.6

GNB-LOS, gram-negative bacillary late-onset sepsis.
*Only infants who survived after 3 full days of life were enrolled.
†Infants followed to discharge or death.

gram-positive flora remain the most common cause of neonatal LOS,[8,9] there has been an increasing concern regarding gram-negative bacillary (GNB) LOS, not only because of the more severe illness and higher rate of mortality caused by gram-negative pathogens,[10,11] but also the increasing incidence in recent decades.[10,12]

Established risk factors for GNB LOS include central venous catheterization duration of >10 days, gastrointestinal tract pathology, H2-blocker/proton-pump inhibitor use, or long-term use of total parenteral nutrition (TPN).[13-15] However, most studies focused on VLBW or extremely premature infants, whereas high-risk late-preterm or term-born neonates were often ignored.[1,11,13,16] Besides, previous studies regarding neonatal GNB LOS were limited by small sample size,[12-15] inadequate detailed data, or lack of controls for comparisons.[10,12,17,18] Few data exist regarding risk factors of mortality for neonates with GNB LOS, and less is known about infectious complications of neonatal GNB LOS. Therefore, we conducted a large cohort-based, case-control-control analysis to delineate the epidemiology, clinical characteristics, and risk factors for adverse outcome in neonates with GNB LOS.

MATERIALS AND METHODS

Study population and design

This study was conducted in the NICU of Chang Gung Memorial Hospital (CGMH), which provides care from primary to tertiary levels in a university-affiliated teaching hospital in Northern Taiwan. The NICU of the CGMH includes 3 units and has a total capacity of 49 beds equipped with mechanical ventilators and 28 beds with special care nurseries. We made use of the prospectively collected neonatal database of our NICU, which have been kept by research nurses for >10 years.[5,19] Between January 2004 and December 2011, all neonates with at least 1 episode of GNB LOS during hospitalization were enrolled for analyses. There was no difference in infection control practices throughout this study period.

To identify the clinical characteristics of GNB LOS and the risk factors for its acquisition, a case-control-control study design was applied. All neonates with LOS caused by gram-positive pathogens during the same period constituted the first control group for comparisons. For a neonate with both gram-negative and gram-positive LOS, this subject is enrolled in both the case and control groups, respectively. The second controls were uninfected subjects and chosen from the base population: 1 control patient per case patient was chosen from those who were admitted within half a month before or after the case patient in the same unit and had a hospital stay longer than the age at onset of GNB LOS in the case patient.

Table 2
Demographic characteristics of 290 neonates with a total of 346 episodes of GNB-LOS

Demographic characteristics	Values
Birth weight (g)	1,288.0 (922.0-2020.0)
Gestational age (wk)	30.0 (27.0-34.3)
Sex	
Male	149 (51.4)
Female	141 (48.6)
Pathogens (total of 346 episodes)	346 (100)
Klebsiella pneumoniae	80 (23.1)
K oxytoca	35 (10.1)
Escherichia coli	74 (21.4)
Enterobacter cloacae	26 (7.5)
Ent aerogenes	17 (4.9)
Pseudomonas aeruginosa	16 (4.6)
Acinetobacter baumannii	41 (11.8)
Serratia marcescens	11 (3.2)
Others*	12 (3.7)
Polymicrobial late-onset sepsis	34 (9.8)
Age at onset of GNB-LOS (d)	30.0 (16.0-60.0)
Sequences of GNB-LOS during hospitalization	
1 episode	246 (71.1)
2 episodes	66 (19.1)
>2 episodes	34 (9.8)

NOTE. Values are n (%) or median (interquartile range).
GNB-LOS, gram-negative bacillary late-onset sepsis.
*Including *Citrobacter freundii* (n = 3), *Stenotrophomonas maltophilia* (n = 3), *Hafnia alvei* (n = 2), *Neisseria meningitidis* (n = 2), *Chryseobacterium meningoseptium* (n = 1), and *Flavobacterium* (n = 1).

Ethics

The study used routinely collected clinical data in an anonymized format. This study was approved by the Institutional Review Board of CGMH. The chair of the institutional review board informed us that this study did not require individual patient consent.

Data collection

Medical records were reviewed to characterize all detailed courses of every episode of gram-negative and gram-positive LOS, including the clinical manifestations, progression of septic symptoms, concurrent infectious focus, treatment, and outcomes. Severity of illness was evaluated at the most severe period during the course of LOS using the Neonatal Therapeutic Intervention Scoring System (NTISS).[20] For identifying risk factors of