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ORIGINAL ARTICLE

Risk factors of late-onset neonatal sepsis in Taiwan: A matched case-control study

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Background: Infants in a neonatal intensive care unit (NICU) have a higher incidence of bloodstream infections (BSIs) than any other pediatric or adult population. The predisposing factors have not been comprehensively evaluated in this population in Taiwan.
Methods: A retrospective matched case-control study was conducted in the NICUs of a teaching hospital in Taiwan. The case patients were identified from a staff-maintained electronic database containing the records of BSIs from July 2003 to June 2006. The case patients and the control patients (who did not develop BSI during their NICU stay) were 1:1 matched by birth weight, gestational age, gender, Apgar score, and date of birth.
Results: A total of 164 infants with culture-proven BSI were identified. Of these, 74 (45.1%) infants were female. The mean gestational age and birth weight were 30.7 ± 0.7 weeks and 1512 ± 804 g, respectively. The common etiologic pathogens included coagulase-negative staphylococci (28.7%), *Staphylococcus aureus* (16.5%), and *Klebsiella pneumoniae* (14.6%). Candida *spp.* accounted for 11 (6.7%) episodes. Two independent factors associated with BSIs in the neonates, as identified by multivariate analysis using conditional logistic regression,

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were the use of parenteral nutrition (matched odds ratio [mOR], 6.07; 95% confidence interval [CI], 1.14—32.32; $p = 0.034$) and intraventricular hemorrhage (mOR, 2.68; 95% CI, 1.20—5.99; $p = 0.017$).
Conclusion: Parenteral nutrition was a significant and independent risk of late-onset neonatal sepsis. This risk should be considered when implementing early parenteral nutrition in NICUs.

Introduction

Neonatal bloodstream infections (BSIs) are an important complication among premature infants in neonatal intensive care units (NICU) all over the world.[1] The invasive infections can lead to severe morbidities and mortality, prolong the length of hospitalization, and increase the cost of medical care. Managing neonatal BSIs is a challenge for physicians. In the past few decades, the mortality rate of late-onset sepsis has remained at a high level (5—15%) in most neonatal care facilities, despite with a declining trend.[2—6] The incidence of late-onset BSI on admission differs in infants at certain gestational ages, birth weights, gender, and conditions, and it is associated with various invasive procedures performed during intensive care.[3,7,8] To lessen the disease burden, it is essential to identify potential risk factors, followed by effective preventive or infection control measures.

In Taiwan, the incidence of neonatal late-onset BSIs ranged from 4% to 11.4% with a mortality rate of 7.2—20%.[7,9—11] The risk factors preceding BSIs were not comprehensively evaluated in this population. To identify the risk factors, we conducted a retrospective case-control study in the NICUs of a teaching hospital.

Materials and methods

Ethics statement

The study was approved by the institute review boards from Chang Gung Memorial Hospital (Taoyuan, Taiwan), which allowed the retrieval of patient lists from the electronic database and a retrospective review of the medical information. A waiver of consent was granted because of the retrospective nature of the project and the anonymous analysis of the data.

Study design

A retrospective matched case-control study was performed in the NICUs of Chang Gung Children's Hospital (CGCH) from July 1, 2003 to June 30, 2006. The CGCH is a 532-bed teaching hospital in northern Taiwan that provides primary to tertiary care for children younger than 18 years old. This hospital has three NICUs with a total of 98 beds. Since 1 July 2003, an electronic database was established to routinely collect the demographic data and information of several predefined major events that occurred in each neonate patient during her/his stay in the NICUs. The predefined major events included BSIs; any surgery; intraventricular hemorrhage; bronchopulmonary dysplasia; retinopathy of prematurity; necrotizing enterocolitis; and all positive culture results (i.e., blood culture, urine culture, sputum culture), irrespective of their clinical relevance. All discharge diagnoses were also collected. A well-trained nurse was responsible for gathering these data on the day of patient discharge by comprehensively reviewing the written and electronic medical records. During the study period, a list was retrieved from this database of the neonatal patients who fulfilled the criteria of late-onset culture-proven BSIs (discussed later). At a case-control ratio of 1:1, the case infants were matched to control infants (who never developed BSI during their stay in NICU) by birth weight (±250 g), gestational age (±2 weeks), gender, and date of birth (±1 month). The medical records of the case infants and the control infants were retrospectively reviewed. A standardized data collection form was used to collect the clinical information needed in this study. The data were digitized and cleaned before we proceeded with statistical analysis.

Definition of late-onset culture-proven BSIs in the neonates

The definition of late-onset neonatal BSI was adapted and modified from the 2008 criteria of the National Nosocomial Infection Surveillance System.[12] Neonatal late-onset culture-proven BSI was defined when a recognized pathogen was cultured from the blood of a patient older than 7 days and was unrelated to an infection at another body site (e.g., pneumonia with bacteremia). The BSIs of common skin contaminants (e.g., diphtheroids, *Bacillus*, *Propionibacterium*, coagulase-negative staphylococci, or micrococci) were identified if the organism was cultured from two or more blood cultures drawn on separate occasions or from at least one blood culture from a patient with an intravascular line and appropriate physician-instituted antimicrobial therapy, and if the patient had at least one of the following manifestations: fever (greater than 38°C), hypothermia (less than 37°C), apnea, or bradycardia. In our institute, the body temperature was measured by placing the thermometer under the back of the infants.

Assessment of risk factors

We assessed the exposure to potential risk factors for BSI. To avoid the influence of known general risks on the occurrence of BSI, univariate and multivariate analyses

were performed to control for factors such as gender, maturity, and health condition at birth. The case infants were assessed from their date of admission in the NICU to the first culture-proven BSI. For the control infants, the exposure to risk factors was determined from the date of admission to the NICU until the date of discharge or death.

The collected potential risk factors consisted of: (1) prenatal and maternal history such as toxemia, multiple gestation, intra-uterine growth retardation, and perinatal infections; (2) perinatal history such as premature rupture of membrane greater than 18 hours and delay in initial crying; (3) invasive procedures such as instrument insertion and its duration (e.g., placement of nasogastric tubes, endotracheal tubes, mechanical ventilation, peripherally inserted central catheters, chest tubes, blood transfusion or exchanged blood transfusion, and lumbar puncture); (4) the concomitant use of medications such as parenteral nutrition and intravenous lipid, antibiotics, and steroids; (5) comorbidities such as meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn (PPHN), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), inborn error of metabolism, and cardiac anomalies (except for patent ductus arteriosis, and secundum type of atrial septal defect).

Statistics

Each potential predictor was initially evaluated by univariate analysis. The categorical variables were compared with a χ^2 test or with the Fisher exact test, when appropriate. Differences among the numerical variables were analyzed using a two-sample *t* test. Potential individual risk factors at $p < 0.05$ were entered together into a set of final conditional logistic regression model (Proc PHREG; SAS version 9.1, SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a *p* value of <0.05.

Results

Demographics and clinical characteristics

During the study period, 164 case infants and 164 control infants were identified. Of the patients, 45.1% were female and the mean ± standard deviation of gestational age and birth weight was 31.1 ± 4.4 months and 1622 ± 835 g, respectively. Most (63.4%) patients were born in the hospital. The demographic data did not differ significantly for the case infants and the control infants (Table 1). The mean duration of the NICU stay before developing BSI was 30.7 ± 37.6 days for the case infants, which was similar to the mean duration of NICU stay for the control infants ($p = 0.684$). The prenatal and perinatal characteristics and illness severity of the two groups before admission were also similar in the rates of premature rupture of membrane, multiple gestation, intrauterine growth retardation, perinatal infections, and Apgar score at birth (Table 1). The maternal use of steroids was the only exception, which was more commonly identified in the case infants than in the control infants (35.3% vs. 21.3%, respectively; $p = 0.009$). The mortality rate was higher for the control infants than for the case patients (13.7% vs. 6.4%, respectively), but the difference was of borderline significance ($p = 0.053$).

Table 1 Demographics, maternal comorbidities, perinatal characteristics, and outcome of the case infants and the control infants

	Case infants ($N = 164$)	Control infants ($N = 164$)	*p*
Gestational age (wk)	30.7 ± 4.2	31.5 ± 4.5	0.333
Birth weight (g)	1512 ± 804	1705 ± 850	0.052
Patient source			0.119
Inborn (%)	69.6	58.6	
Other hospitals (%)	25.6	37.0	
ER or clinic (%)	4.8	4.3	
Duration of risk exposure[a]	30.7 ± 37.6	28.5 ± 60.0	0.684
PROM > 18 h (%)	24.2	23.2	0.840
Apgar scores at 5 min	7.5 ± 1.9	7.9 ± 1.8	0.052
Multiple gestation (%)	24	20.6	0.496
IUGR (%)	8	5.6	0.425
Perinatal infection (%)	6.4	3.75	0.304
Use of steroids (%)	35.3	21.25	0.009
Mortality (%)	6.4	13.7	0.053

[a] The value indicates the duration of patients at risk of bloodstream infections. For the case infants, this is the period of time before they developed a bloodstream infection; for the control infants, this is the duration of the whole NICU stay.
ER = emergency room; IUGR = intrauterine growth retardation; PROM = premature rupture of membranes.

Table 2 Bacterial species identified in 164 neonatal patients who had a bloodstream infection in a Taiwanese teaching hospital during July 2003—June 2006

Species	No. of episodes	%
Coagulase-negative staphylococci	47	28.7
Klebsiella pneumoniae	24	14.6
Methicillin-resistant *Staphylococcus aureus*	21	12.8
Escherichia coli	12	7.3
Enterobacter cloacae	12	7.3
Acinetobacter baumannii	11	6.7
Candida albicans	8	4.9
Enterobacter aerogenes	7	4.2
Methicillin-sensitive *Staphylococcus aureus*	6	3.7
Enterococcus faecalis	4	2.4
Klebsiella oxytoca	4	2.4
Candida parapsilosis	3	1.8
Pseudomonas aeruginosa	2	1.2
Hanfnia alvei	2	1.2
Viridans streptococcus	1	0.6
Total	164	100

Etiologic pathogens

Among the 164 culture-proven BSIs, 79 (48.2%) episodes were caused by Gram-positive organisms; 74 (45.1%) episodes, by Gram-negative organisms; and 11 (6.7%) episodes, by *Candida* spp. (Table 2). The most common pathogen was coagulase-negative staphylococci (28.7%), followed by *Klebsiella pneumonia* (14.6%), and methicillin-resistant *Staphylococcus aureus* (12.8%).

Univariate analysis of risk factors associated with BSIs

In univariate analysis, an increased incidence of BSIs was associated with the placement of a variety of instruments or catheters such as nasogastric tubes ($p = 0.003$), tracheal intubation ($p < 0.001$), and percutaneously inserted central catheters ($p < 0.001$) (Table 3). Infants also had higher risk of BSIs if they received parenteral nutrition ($p < 0.001$) or intrafat ($p < 0.001$), or if they developed RDS ($p = 0.009$) or intraventricular hemorrhage (IVH) ($p = 0.013$). The following factors were not associated with BSIs: transfusion, antimicrobial treatment, use of steroids, and the presence of other comorbidities (e.g., MAS, NEC, and cardiac anomalies).

Multivariate analysis of factors associated with BSIs

The multivariate analysis using conditional logistic regression identified parenteral nutrition (matched odds ratio [mOR], 6.07; 95% confidence interval [CI], 1.14—32.32; $p = 0.034$) and IVH (mOR, 2.68; 95% CI, 1.20—5.99; $p = 0.017$) as two significant factors that were independently associated with BSIs. Prenatal use of steroids was associated with a 1.82-fold increased risk of BSIs, although this had no statistical significance (95% CI, 0.98-3.40; $p = 0.059$).

Discussion

Central venous catheter insertion and its duration of use were the main risk factors of nosocomial BSI in premature neonates.[3,4,8,13—15] In the current study, a central venous catheter (CVC) inserted at a peripheral site was more frequently used in the septic infants than in the control infants (81.6% vs. 53.1%, respectively; $p < 0.001$). However, this significance disappeared after adjusting for other potential risk factors and controlling for gender, maturity, and the health status of the neonate at birth ($p = 0.579$) (Table 4). This finding suggested that the use of CVC did not substantially increase the incidence of BSI when the premature infants were of similar demographics and similar health condition at birth.

The administration of parenteral nutrition was associated with approximately 6-fold greater risk of BSI. The risk factor has also been identified in several previous reports. Sohn et al[4] reported a 5.7-fold relative risk in infants receiving parenteral nutrition. Kawagoe et al[8] demonstrated a 4.0-fold higher risk of nosocomial infections in neonates on parenteral nutrition. Parenteral nutrition has been extensively used to maintain the nutritional condition of critically ill neonates that are intolerable to or in advancing on gastrointestinal feeding. Several plausible theories have been suggested to explain the relationship between parenteral nutrition and neonatal BSI. For instance, an elemental diet and parenteral nutrition may

Table 3 Univariate analysis of procedures and comorbidities associated with neonatal sepsis

	Case infants ($N = 164$)	Control infants ($N = 164$)	p
Procedures			
Placement of NG tube (%)	96.8	86.6	0.003
Duration (d)	30.1 ± 28.9	32.2 ± 28.1	0.558
Intubation (%)	78.4	56.1	<0.001
Duration (d)	22.2 ± 24.4	17.2 ± 21.1	0.127
PICC line placement (%)	81.6	53.1	<0.001
Duration (d)	27.7 ± 28.4	23.8 ± 17.1	0.241
Lumbar puncture (%)	6.4	11.0	0.216
Chest tube placement (%)	19.2	16.5	0.641
Duration (d)	4.5 ± 4.4	7.2 ± 18.7	0.483
RBC transfusion (%)	65.6	59.8	0.329
PLT transfusion (%)	21.6	15.4	0.216
Parenteral nutrition (%)	88.8	56.7	<0.001
Duration (d)	23.4 ± 23.7	21.6 ± 17.8	0.537
Intravenous lipid (%)	84.8	54.3	<0.001
Duration (d)	23.0 ± 24.1	20.9 ± 17.3	0.483
Use of extended spectrum beta-lactam antibiotics (%)[a]	38.4	40.2	0.821
Use of carbapenem (%)	6.1	7.3	0.826
Use of steroids (%)	14.4	14.2	0.571
Exchange blood therapy (%)	4.0	1.96	0.474
Comorbidity			
MAS (%)	1.6	0.61	0.580
PPHN (%)	2.4	0	1.000
RDS (%)	59.2	43.6	0.009
IVH (%)	21.6	10.5	0.013
Grade III or IV IVH (%)	5.5	4.3	0.799
NEC (%)	4.0	4.3	1.000
Use of surfactant (%)	81.3	80	1.000
IEM (%)	1.6	0	0.188
Cardiac anomaly (%)	5.6	4.97	1.000

[a] The extended spectrum beta-lactams included cefotaxime, ceftazidime, ceftriaxone, cefepime, flomoxef, piperacillin, and piperacillin/tazobactam.

IEM = inborn errors of metabolism; IVH = intraventricular hemorrhage; MAS = meconium aspiration syndrome; NEC = necrotizing enterocolitis; PICC = peripherally inserted central catheter; PLT = platelet; PPHN = persistent pulmonary hypertension; RBC = red blood cell; RDS = respiratory distress syndrome.

Table 4 Multivariate analysis of risk factors associated with neonatal sepsis by using conditional logistic regression in a matched case-control study

Predictors	mOR	95% CI	*p*
Prenatal use of steroids (%)	1.82	0.98—3.40	0.059
Placement of NG tube (%)	1.09	0.26—4.59	0.906
Intubation (%)	1.49	0.66—3.35	0.335
PICC line placement (%)	1.28	0.54—3.05	0.579
Parenteral nutrition (%)	6.07	1.14—32.32	0.034
Intrafat (%)	0.77	0.16—3.68	0.747
RDS	0.87	0.41—1.85	0.709
IVH (%)	2.68	1.20—5.99	0.017

CI = confidence interval; IVH = intraventricular hemorrhage; mOR = matched odds ratio; NG = nasogastric; PICC = peripherally inserted central catheter; RDS = respiratory distress syndrome.

impair the intestinal mucosal barrier and result in bacterial translocation.[16] Longterm parenteral nutrition utilization would also impair host defense mechanisms and bactericidal activity.[17] In recent years, experts have nevertheless proposed commencing early post-natal parenteral nutrition within 24 hours of birth for increasing positive nitrogen balance, caloric intake and weight gain.[18—20] Because of the strong association of parenteral nutrition and bacteremia, we speculate the practice may increase the risk of BSIs. This iatrogenic complication should be taken into consideration when implementing this practice into the routine care of preterm neonates.

Intraventricular hemorrhage (IVH) was another factor independently associated with BSI in the current study. It is possible that IVH may not be a risk factor preceding BSI; it may instead be a consequence of BSI. Sepsis concomitant with other factors (e.g., low birth weight, young gestational age, mechanical ventilation, and hypotension) is known to significantly increase the risk of IVH in preterm newborns.[21] This finding corroborates the need for early and frequent evaluation of the brain of preterm neonates with sepsis.

The prenatal use of steroids was not statistically significant in the analysis of risk factors of neonatal BSI, although we did find a trend toward a higher incidence of BSIs in infants exposed to steroid treatment before birth. Steroid treatment is often used prenatally to accelerate lung maturation in preterm infants and it is able to decrease neonatal morbidities and mortality.[22,23] Potential adverse consequences nevertheless were also reported, which included increased incidence of neonatal and maternal infections, especially among patients who received multiple courses of prenatal steroids.[23] The potential harm of the steroid administration should be considered in the prenatal care of mothers at risk of premature birth.

In this study, the mortality rate was 6.4% for the case infants, which was lower than the rate for the control infants (13.7%), and was of borderline significance ($p = 0.053$). This finding was unexpected and should be interpreted with caution. The observation may result from a possible selection bias, which was caused by the nonrandom method of selecting the control infants. The study was not designed to address the impact of infection on the outcome, and potential outcome-related factors were not controlled in the comparison. It was not adequate to draw any conclusion regarding to the impact of BSI on the outcome of NICU patients in the current study.

There were several limitations in this study. First, this was a single center study and the identified factors of BSI may not be generalized to other institutions. The sample size was relatively small and some potential risk factors may not have been readily identified. However, the risks that are already identified should remain significant and should not be severely affected by the sample size. Second, coagulase-negative staphylococci were the most common organisms accounting for neonatal sepsis in our NICU—this was consistent with previous reports.[4,5,9,24] It was difficult to clarify the clinical relevance of the normal skin flora when the organisms were isolated from blood cultures in NICU settings.[25] Although strict criteria were applied to define the neonatal BSI by the skin flora, we were unable to completely rule out the possibility that some case patients infected with coagulase-negative staphylococci may actually not have true infections. Third, the control infants were not randomly selected, which may have led to a selection bias and possibly affected the significance of the risk factors.

The methods to prevent neonatal BSI include improved handwashing, aseptic manipulation, ameliorated feeding strategies, care bundles against common nosocomial infections (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]), nasal screening of resistant strains, and interventions such as prophylactic antibiotics.[26] Data from the current study highlighted the importance of re-evaluating the indication, administration, and preparation of parenteral nutrition. Every attempt should be applied to minimize the duration of parenteral nutrition and encourage early enteral feeding.

In conclusion, we demonstrated that—after controlling for gender, birth weight and Apgar scores, the administration of parenteral nutrition, and possibly the prenatal use of steroids remained significant predictors of neonatal BSIs. The identified factors can be generalized to the preterm neonates, regardless of their demographic characteristics.

The recognition of risk factors should help in developing a preventive strategy against BSIs and would ultimately promote the quality of care for preterm infants. The findings should also help reshape the policy and practice in NICUs regarding the timing of parenteral nutrition and may reduce the burden of BSIs in neonates.

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