J Microbiol Immunol Infect
2005;38:283-288

Epidemiologic trends in nosocomial bacteremia in a neonatal intensive care unit

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Received: August 10, 2004 Revised: October 4, 2004 Accepted: December 4, 2004

The primary goal of this study was to analyze the epidemiologic features of nosocomial bloodstream infection (NBSI) in a neonatal intensive care unit over a 7-year period. All neonatal patients with NBSI treated from January 1997 to December 2003 were retrospectively analyzed. 232 NBSI episodes were diagnosed in 208 patients. The average NBSI patient-day rates were 4.69 and 2.59 per 1000 patient-days in 1997-1999 and 2000-2003, respectively. The average NBSI rates were 5.00 and 1.50 per 1000 patient days in neonates <1500 g and ≥1500 g, respectively. The proportion of Gram-positive organisms increased from 24% in 1997-2001 to 41% in 2002-2003, whereas the proportion of Gram-negative isolates decreased from 65% in 1997-2001 to 47% in 2002-2003. The implementation of measures for the prevention of nosocomial infection was associated with the reduction of NBSI rates. Low birth weight was demonstrated to be a significant risk factor for NBSI. The fact that Gram-positive organisms were isolated in increasing frequency may impact on the appropriate selection of empiric antimicrobial therapy for NBSI in the neonatal intensive care unit.

Key words: Bacteremia, cross infection, low birth weight infant, neonatal intensive care units, risk factors

Nosocomial infections are responsible for significant morbidity and late mortality among neonatal intensive care unit (NICU) patients, resulting in prolonged hospital stay and increased health care costs [1-7]. Multicenter and institutional surveillance data indicated that bloodstream infection was the most common nosocomial infection in NICUs [8,9].

The variability of endemic nosocomial infection rates among centers with similar patient populations suggests that the rigorous implementation of health care practice and the existence of predisposing factors will influence the nosocomial infection rates. Some reports demonstrated that through the improvement of health care practice, nosocomial infection rates would decrease [2,10]. Elucidation of epidemiologic risk factors and trends of nosocomial infection will help in the development of measures to control the occurrence of nosocomial infections in NICUs.

The NICU at China Medical University Hospital was founded in 1996. The primary goal of this study was to analyze the characteristics of nosocomial bloodstream infection (NBSI) over the 7 years after the foundation of the NICU.

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Materials and Methods

During the entire study period, the capacity of the China Medical University Hospital NICU was 30 beds. Patients who were admitted to the NICU were less than 1 month of age. All infants were admitted from the delivery room, baby room, or referred from other hospitals and obstetric clinics.

Microbiologic methods and definitions

When bacteremia was suspected, a blood sample was obtained and sent to the central laboratory to be cultured by a Bactec 9240 continuous monitoring blood culture system (Becton Dickinson, Sparks, MD, USA). If the blood culture was positive for bacteria, the pathogen was identified by biochemical methods [11]. NBSI was defined as 1 or more positive blood cultures obtained 48 h after admission to the NICU. If the same micro-organism was isolated from an infant on more than 1 occasion within a 7-day period, it was regarded as a single infection. The NBSI patient rate was expressed as the number of NBSIs per 100 patients, and the NBSI

patient-day rate was expressed as the number of NBSIs per 1000 patient-days.

Data collection

Patients with NBSI during the period from January 1997 to December 2003 were enrolled in this study. One nosocomial infection control practitioner was designated to assess the nosocomial infections in the NICU. Neonates were monitored for nosocomial infection and data were collected during the study period. The medical records were reviewed for clinical and demographic characteristics. Data on the registered nurse staff-to-patient ratio were obtained from the department of nursing. The diagnoses of each NICU patient were coded by the duty physician according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) criteria [12]. Patients were divided into 5 groups by birth weight as follows: group I, with birth weight <750 g and corresponding ICD-9-CM codes 765.01 and 765.02; group II, with birth weight between 750 and 999 g and corresponding ICD-9-CM code 765.03; group III, with birth weight between 1000 and 1249 g and corresponding ICD-9-CM code 765.14; group IV, with birth weight between 1250 and 1499 g and corresponding ICD-9-CM code 765.15. Infants with a birth weight ≥1500 g were assigned to group V. The patient data, including the ICD-9-CM codes, were recorded in the hospital computer system. Since this computer system was set-up in 1998, the data on annual patient-day stratified by each birth weight group were analyzed only for the period after that year.

Statistics

Relative risks (RRs) and their 95% confidence intervals were estimated in order to examine the association between birth weight and NBSI rates. The association between NBSI rates and yearly patient-days was calculated and a Spearman's correlation coefficient was determined. Proportions were compared by chi-squared test. A p value ≤0.05 was considered statistically significant. Data were analyzed by SAS software for Personal Computers (SAS Institute Inc., Cary, NC, USA).

Results

In total, 5102 patients were admitted to the NICU from January 1997 to December 2003. The total number of patient-days was 64,607. During the study period, a total of 232 NBSI episodes occurred in 208 patients. Eighteen patients had 2 serial NBSI episodes during their hospitalizations. Three patients developed 3 serial NBSI episodes during their hospitalizations. Twenty four patients developed mixed NBSIs with 1 blood culture yielding 2 different pathogens. A total of 256 isolates was obtained.

Rates of nosocomial bloodstream infection

Of the 232 NBSIs, 54 occurred in 1997, 46 in 1998, 44 in 1999, 18 in 2000, 18 in 2001, 29 in 2002, and 23 in 2003 (Table 1). The infection patient rates were lowest in 2000 (2.32 per 100 patients) and highest in 1997 (6.55 per 100 patients). The infection patient-day rates were lowest in 2000 (1.96 per 1000 patient-days) and highest in 1998 (4.88 per 1000 patient-days). The average NBSI patient rate was 4.52 per 100 patients, while the average patient-day rate was 3.59 per 1000 patient-days. Of the 232 NBSIs, 109 occurred in girls and 123 in boys. The average registered nurse staff-to-patient ratio was 1.61, ranging from 1.35 to 1.92. No significant correlation existed between NBSI rates and nurse staff-to-patient ratio.

The average patient numbers per year were 829.0 and 660.5 in 1997-1999 and 2000-2003, respectively. The average duration of hospital stay per year was 10,225 and 8483 patient-days in 1997-1999 and 2000-2003, respectively. The average NBSI patient rates were 5.79 and 3.33 per 100 patients in 1997-1999 and 2000-2003, respectively. The average NBSI patient-day rates were 4.69 and 2.59 per 1000 patient-days in 1997-1999 and 2000-2003, respectively. The difference in NBSI

Table 1. Rates of nosocomial bloodstream infection (NBSI) in the neonatal intensive care unit, 1997-2003

	1997	1998	1999	2000	2001	2002	2003	Total
No. of admissions	824	804	859	776	564	721	581	5129
Duration of hospital stay (patient-days)	12,190	9417	9068	9177	7530	9338	7887	64,607
No. of NBSIs	54	46	44	18	18	29	23	232
Infection rate (%)	6.55	5.72	5.12	2.32	3.19	4.02	3.96	4.52
Infection patient-day rate (per 1000 patient days)	4.43	4.88	4.85	1.96	2.39	3.11	2.92	3.59
Registered nurse staff-to-patient ratio	1.35	1.56	1.63	1.54	1.92	1.61	1.85	1.61

Table 2. Rates of birth weight-specific nosocomial bloodstream infection (NBSI), 1998-2003[a]

Birth weight (g)	Infection episodes	No. of admitted patients	No. of admitted patient-days	NBSI patient rate (%)	NBSI patient-day rate (per 1000 patient-day)	RR	95% CI
<750	45	143	4106	31.47	10.96	7.29	4.72-11.26
750-999	66	220	9372	30.0	7.04	4.68	3.13-7.00
1000-1249	19	246	7867	7.72	2.42	1.61	0.92-2.79
1250-1499	9	291	6472	3.09	1.39	0.92	0.45-1.92
≥1500	37	3405	24,600	1.09	1.50	1.00	

Abbreviations: RR = risk reduction; CI = confidence interval

[a]Of the total of 178 episodes of NBSI between 1998 and 2003, 2 episodes without recorded birth body weight were excluded.

patient-day rates between the 2 periods was significant (95% confidence interval, 1.16-3.04; $p<0.05$).

Association between birth weight and infection rate

A total of 178 patients developed NBSIs from January 1998 to December 2003. Among these 178 patients, the birth weight of 2 patients was not available because of incomplete medical records. The NBSI patient rates and patient-day rates stratified by birth weight group are shown in Table 2. The average NBSI rates were 5.00 and 1.50 per 1000 patient-days in neonates <1500 g and those ≥1500 g, respectively. Rate ratio and confidence interval showed that birth weight was a significant risk factor for NBSI.

Distribution of pathogens in nosocomial bloodstream infections

In total, 256 pathogens were isolated from the 232 infection episodes. The distribution of pathogens associated with NBSI is shown in Table 3. The most common organism associated with NBSI was *Staphylococcus aureus* (46 isolates, 17.97%), followed by *Acinetobacter baumannii* (39 isolates, 15.23%), *Pseudomonas aeruginosa* (21 isolates, 8.2%), *Klebsiella pneumoniae* (20 isolates, 7.81%), and *Candida albicans* (19 isolates, 7.42%). Of the 19 patients with NBSI caused by *C. albicans*, 3 received total parenteral nutrition support prior to the occurrence of NBSI. Five isolates of coagulase-negative staphylococci (CoNS)

Table 3. Distribution of pathogens associated with nosocomial bloodstream infection, 1997-2003

Pathogen	1997	1998	1999	2000	2001	2002	2003	Total isolates
Gram-positive organisms								
Staphylococcus aureus	13	7	6	0	3	9	8	46
Enterococcus spp.	0	2	2	1	1	4	2	12
CoNS	3	2	0	0	0	0	0	5
Group B *Staphylococcus*	2	2	0	0	0	0	0	4
Other Gram-positive organisms[a]	1	2	0	0	0	1	0	4
Gram-negative organisms								
Acinetobacter baumannii	2	7	16	5	0	6	3	39
Klebsiella pneumoniae	5	6	4	0	0	3	2	20
Escherichia coli	4	7	2	1	2	1	0	17
Pseudomonas aeruginosa	3	3	5	5	3	0	2	21
Serratia marcescens	3	7	3	0	0	0	0	13
Enterobacter cloacae	6	0	3	0	1	2	0	12
Stenotrophomonas maltophilia	0	1	5	0	0	1	0	7
Burkholderia cepacia	0	0	1	1	4	4	2	12
Other Gram-negative organisms[b]	6	6	0	0	1	2	0	15
Fungus								
Candida albicans	6	2	1	4	2	0	4	19
Other species[c]	2	1	1	2	1	1	2	10
Total of isolates	56	55	49	19	18	34	25	256

Abbreviation: CoNS = coagulase-negative staphylococci

[a]Including viridans streptococci, *Micrococcus lylae.*

[b]Including *Proteus mirabilis, Moraxella osloensis, Alcaligenes xylosoxicans, Chryseobacterium indologenes,* etc.

[c]Including *Candida parapsilosis, Candida utilis.*

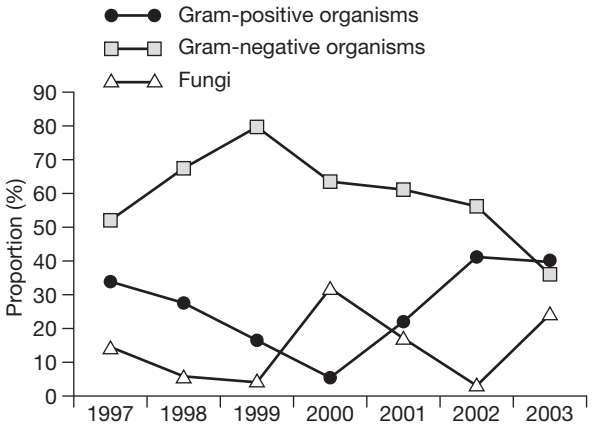

Fig. 1. Gram-positive and Gram-negative organisms associated with nosocomial bloodstream infection, 1997-2003.

were discovered (1.95%). Among these 5 isolates, 4 were *Staphylococcus epidermidis*, 1 was *Staphylococcus haemolyticus*. Gram-negative organisms comprised most of the isolates during the study period except in 2003; in that year, the proportion of Gram-positive organisms (10 isolates, 40.0%) exceeded that of Gram-negative organisms (9 isolates, 36.0%) [Fig. 1]. The proportion of Gram-positive organisms increased from 24% in 1997-2001 to 41% in 2002-2003, whereas the proportion of Gram-negative isolates decreased from 65% in 1997-2001 to 47% in 2002-2003. The difference in the distribution of Gram-positive and Gram-negative organisms between the 2 periods was significant (p=0.031).

Discussion

This study found a significant decline of NBSI patient-day rates from 4.69 per 1000 patient-days in 1997-1999 to 2.59 per 1000 patient-days in 2000-2003. After the foundation of the NICU, the prevalence of nosocomial infections, especially NBSIs, resulted in high morbidity and mortality among neonates. In 1999, additional measures were taken to prevent nosocomial infections, including increased emphasis on hand washing, caring for skin meticulously, minimizing venipuncture, reducing the duration of mechanical ventilation, reducing hyperalimentation days and promoting early enteral nutrition. This study demonstrated that the implementation of these measures resulted in a decline in NBSI rates. Our results are compatible with those of Kurlat et al, and indicate that development and implementation of aseptic guidelines in a NICU can reduce rates of nosocomial infection [13].

Understaffing and heavy staff workloads were associated with increased risks of acquiring nosocomial infections [14-16]. In this study, the NBSI rates were not found to be associated with the registered nurse staff-to-patient ratio. However, the level of expertise and the experience of registered nurse staff were not taken into account in this study. The use of relatively junior staff and extra nurse staff was associated with the spread of methicillin-resistant *S. aureus* (MRSA) in a NICU [17]. In the early years after the foundation of the NICU, the newly recruited nurse staff were not very experienced in the health care of neonates and some breaks in aseptic practice occurred. However, the relationship of nurse staff experience levels to the high NBSI rates in 1997-1999 needs further evaluation.

One study found that nosocomial infection rate was most strongly correlated with patient density [16], while others correlated staphylococcal outbreaks with overcrowding [14,17,18]. Overcrowding may also contribute to the outbreak of *Enterobacter cloacae* infection [19]. Although there are only limited data to support the role of overcrowding in nosocomial infection, possible explanations for the relationship may be poor aseptic practice associated with increased workload and inadequate sterilization of devices. In this study, we found a moderate association between annual patient-day numbers and NBSI patient-day rates (Spearman's correlation coefficient=0.54). Although the decline in patients admitted and patient-day numbers may have partly contributed to the decline in the NBSI rates in this study, this relationship was not significant (p=0.22).

During the early years of the study period (1997-2002), Gram-negative organisms were the predominant isolates. However, the proportion of Gram-positive organisms exceeded that of Gram-negative organisms in 2003. This change in proportion was significant over the study period. A cyclic pattern of pathogen distribution in hospitals has been described [20]. Gram-positive organisms and Gram-negative organisms were shown to have alternated in predominance in a previous report [20]. In this study, the trend of epidemiologic change was toward a decline in the prevalence of Gram-negative organisms. An outbreak of *A. baumannii* infection occurred in 1999. Fifteen of the 20 *K. pneumoniae* isolates emerged between 1997 and 1999. Thirteen of the 17 *Escherichia coli* isolates and all 13 isolates of *Serratia marcescens* were also identified during the same period. Of the 7 *Stenotrophomonas maltophilia* isolates, 5 were found

in 1999. Changes in pathogen distribution have also been reported to be associated with antimicrobial resistance patterns of pathogenic organisms [21]. Judicious use of antibiotics will help to prevent the occurrence of drug-resistant organisms.

The NBSI rates increased from 2.15 per 1000 patient-days in 2000-2001 to 3.02 per 1000 patient-days in 2002-2003. Gram-positive organisms contributed partly to the increase of NBSI rates. There was an outbreak of enterococci infection in December 2002, with 3 episodes of enterococci bacteremia occurring in that month. Seventeen episodes of NBSI caused by *S. aureus* occurred in 2002-2003, whereas only 3 occurred in 2000-2001. Nineteen of the 20 isolates of *S. aureus* were resistant to methicillin and susceptible to vancomycin (data not shown). The epidemiologic transition to Gram-positive organisms, especially MRSA and enterococci, as the predominant pathogens could impact the appropriate choice of antimicrobials for the empiric treatment of nosocomial infections in the NICU.

Low birth weight was demonstrated to be a significant risk factor for nosocomial infection [9,21-24]. Its causes included premature immune systems of low birth weight neonates, dependence on invasive intervention therapies, and extended exposure to broad-spectrum antimicrobials in low birth weight neonates [25,26]. A different method of assessment of NBSI in low birth weight neonates was used in this study. The birth weights and the corresponding ICD-9-CM codes of each NICU patient were obtained from computerized records, and the NBSI rates with birth weight were stratified with each birth weight group. Neonates with birth weight <750 g had the highest possibility of acquiring NBSI (10.96 per 1000 patient-days), whereas those with birth weight between 1250 g and 1499 g had the lowest rate (1.39 per 1000 patient-days). Patients with birth weight <1500 g had a higher NBSI rates than those with birth weight ≥1500 g (5.00 vs 1.50 per 1000 patient-days). The results were similar to other studies [27,28].

There was a limitation in this study. We regarded CoNS to be a contaminant. Once CoNS was isolated, the species was not identified, and the antimicrobial susceptibility test of that isolate was not performed. No specific antimicrobial therapy was administered to patients infected with these organisms. Only when symptoms and signs of infection persisted and CoNS were cultured in serial blood samples was it regarded as pathogenic. During the study period, only 1.95% of isolates (5/256) were CoNS. By contrast, CoNS accounted for 51% of pathogens of nosocomial infections in an NICU in 1 prior study [23]. Other reports have also described that CoNS were the most prevalent organisms in nosocomial infections in the NICU [21,27]. Whether CoNS is a true pathogen in NICU nosocomial infection or simply a contaminant organism continues to be a subject for debate [29-32]. The clinical significance of CoNS in NBSI in this study was not clearly determined.

In conclusion, there was a reduction in NBSI rates in our NICU between 1997-1999 and 2000-2003. The implementation of measures for prevention of nosocomial infection contributed to this reduction. Low birth weight was demonstrated to be a significant risk factor for NBSI in the NICU. There has been a recent transition to Gram-positive organisms as the predominant pathogens of NBSI in our NICU. Such change of epidemiologic features could impact the appropriate choice of antimicrobials as empiric therapy for NBSI.

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