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ORIGINAL ARTICLE

Changing of bloodstream infections in a medical center neonatal intensive care unit

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Abstract *Background/Purpose:* Bloodstream infections (BSIs) are associated with high mortality and morbidity in neonatal intensive care units (NICUs). The epidemiology of these infections may change after the application of new infection control policies. The aims of this study are to reveal the changing epidemiology of BSIs in our NICU and inspect the effects of infection control efforts.

Methods: We reviewed and analyzed the clinical characteristics of culture-proven BSIs in our NICU from 2008 to 2013 and compared them with our two previously reported data (1992–2001 and 2002–2007).

Results: The mortality rate decreased from 16.3% in 1992–2001 to 5.6% in 2008–2013. In the recent study period, Gram-positive infections became predominant (58.0%). Coagulase-negative staphylococci remained the most commonly isolated organisms (26.0%). Group B *Streptococcus* (GBS) BSIs had the highest mortality rate (30.0%). Most GBS-infected infants' mother did not perform prenatal GBS screening. There was a decrease in the total fungal infection rate after fluconazole prophylaxis for very-low-birth-weight (VLBW) neonates, but the infections of fluconazole-resistant *Malassezia pachydermatis* increased. The incidence of central line-associated BSI increased to 10.6% in 2011. After restricting the catheter duration to <21 days, the incidence decreased to 4.2% in 2013.

Conclusion: Through the years, the overall mortality rate of BSIs in our NICU decreased. Maternal GBS screening is an important issue for avoiding early onset GBS mortality. Fungal

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infection rate decreased after antifungal prophylaxis policy for VLBW infants, but we should be aware of resistant strains. Restriction of the catheter duration may decrease the incidence of catheter-related BSI.

Introduction

Neonatal infection is a major cause of mortality and morbidity in newborns. Estimates suggest that >1.4 million neonatal deaths worldwide annually are due to invasive infections.[1] A systemic analysis of child mortality for 2010 with time trends since 2000 indicated that bloodstream infections (BSIs) are responsible for 13% of all neonatal mortality, and 42% of deaths in the 1st week of life.[2] Therefore, prevention and management of BSIs are very important to improve the outcomes of neonatal intensive care unit (NICU) patients. The epidemiology of BSIs in each NICU is different. Even in the same NICU, it will change over time. A BSI incidence rate of 3.01% with a density of 3.29 infections/1000 admission days in our NICU during 1992–2001 had been reported previously.[3] However, the incidence density changed to 2.78 infections/1000 admission days during 2002–2007 (unpublished report). In another northern Taiwan hospital, the reported incidence of BSI was 9.31% with an incidence density of 10.98 infections/1000 admission days during 1999–2001,[4] whereas the incidence rate was 4.06% in another hospital during 2001–2006.[5]

To decrease the burden of infections, several major infection control policies and procedures have been applied during the recent few years in our NICU, including maternal group B *Streptococcus* (GBS) screening plus intrapartum antibiotic prophylaxis, prophylactic fluconazole administration in very-low-birth-weight (VLBW) infants, restriction of peripherally inserted central catheter (PICC) duration to no longer than 21 days, etc. The aims of this study are to reveal the changing epidemiology of BSIs in our NICU and focus on the effects of the aforementioned infection control efforts.

Methods

Institute and ethics statement

This study was conducted in the NICU of a tertiary-level teaching hospital in northern Taiwan. The NICU has a total capacity of 23–33 beds, 348–896 hospitalized patients/year. This study and its protocol were approved by the Ethics Committee of MacKay Memorial Hospital, Taipei, Taiwan (Institutional Review Board number 14MMHIS 136).

Data collection and comparison

We collected the data from culture-proven BSI patients in NICU between January 2008 and December 2013, and compared these data with previously published (1992–2001)[3] and orally reported data (2002–2007). The data collected included patients' sex, gestational age, birth weight, symptoms/signs and the age of onset, pathogens, perinatal risk factors, underlying and associated conditions, maternal GBS screening, use of PICC, outcomes, etc.

Definition

BSI was defined according to the surveillance guidelines published by the Taiwan Centers of Disease Control, which required a positive blood culture result with at least one of the following signs or symptoms: fever (anal body temperature $> 38^{\circ}C$), hypothermia (anal temperature $< 36^{\circ}C$), apnea, and bradycardia; and that the signs or symptoms and positive laboratory results were not related to a previous infection at another site. Patients were excluded if the blood culture results were caused by contamination, such as that caused by commensal organisms (e.g., a Gram-positive bacillus in a patient with a negative result in the second set of blood culture drawn before antibiotic agents were administered or in a patient who recovered without use of antibiotics or without clinical symptoms of infection).

For comparison with previous data, we defined patients with BSIs within the first 7 days of life as the early onset group and those afterward as the late-onset group,[6] although some investigators divided them at or before 72 hours of life.

Premature rupture of membranes was defined as rupture of membranes >24 hours prior to delivery. Maternal fever and chorioamnionitis were based on maternal hospital records. Prematurity was defined as gestational age <37 weeks. LBW infants were those with birth weight <2500 g, and VLBW babies were those with birth weight <1500 g. Other perinatal risk factors recorded included Apgar score <7 at 5 minutes of life, delay of initial crying, meconium aspiration syndrome, fetal distress, maternal eclampsia, hydramnios, cesarean section due to placenta previa, placenta abruption, etc.

BSI-related mortality was defined as death with positive blood culture and diagnosis of sepsis or septic shock in the same episode. If the death could be explained by other reason, it was not considered in this category.

A PICC-associated central line-associated BSI (CLA-BSI) was defined as a primary BSI in a patient admitted to the NICU for > 48 hours before the onset of infection and met the National Healthcare Safety Network (NHSN) criteria for CLA-BSI.[7]

Statistical analysis

Data were analyzed by Chi-square or Fisher's exact test for categorical variables, as appropriate. Univariate analyses

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were performed to evaluate the predictive effect of each factor. Continuous variables were compared using one-way analysis of variance. Statistical significance was defined as $p < 0.05$ (GraphPad Prism statistics software version 5.0; GraphPad Software, Inc., San Diego, CA, USA).

Results

BSIs during 2008–2013

A total of 166 BSI episodes involving 169 pathogens were identified in 144 patients. Eighteen patients had two or more septic episodes. The incidence of BSI was 5.2% (range 4.3–6.4% in each year) among all NICU admissions during the study period, or 3.6 infections/1000 admission days (range 2.56–4.38 infections/1000 admission days). The total NICU hospitalized patient density was 69.4 patients/1000 admission days (range 59.4–91.4 patients/1000 admission days). The lowest infection incidence was in 2010 and the highest was in 2011. The lowest hospitalized patient density was also in 2010 but the highest was in 2012 (Figure 1).

The demographic data of the patients are presented in Table 1. The male-to-female ratio was 0.8. The overall mean birth weight and gestational age were 1397 ± 914 g (range, 394–3980 g) and 30 ± 5 weeks (range, 22–41weeks). The majority of BSI episodes occurred in LBW (104 episodes, 72.2%) and premature (122 episodes, 84.7%) infants. The mean birth weight and gestational age were lower in the late-onset group. There was no significant difference in BSI incidence between term and premature babies in the early onset group, but BSIs occurred more frequently in VLBW (85.0%; $p < 0.0001$) and premature infants (92.9%; $p < 0.0001$) in the late-onset group. The major clinical presentations were cyanosis (55.6%), bradycardia (32.0%), apnea (26.6%), fever (7.6%), and lethargy (6.5%).

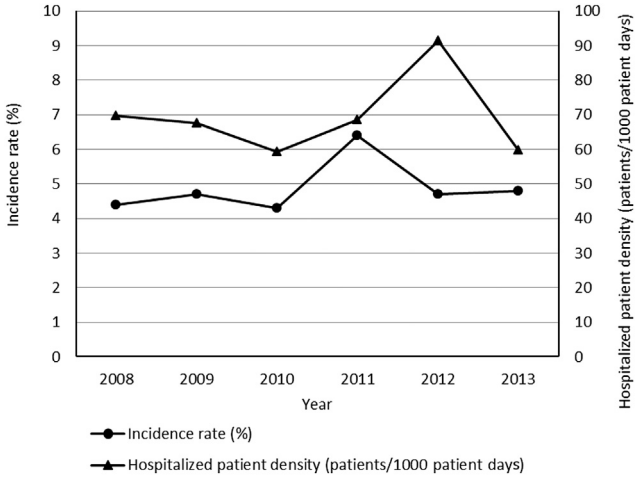

Figure 1. Incidence of bloodstream infection and total hospitalized patient density in neonatal intensive care unit (NICU) from 2008 to 2013. Closed circles represent infection incidence rate (%) and closed triangles represent the total hospitalized patient density (patients/1000 admission days) of the NICU.

Table 1 Demographics of infants with early onset and late-onset neonatal bloodstream infections.

	Early onset (n = 31)	Late onset (n = 113)	Total (n = 144)
Sex			
Male:Female	1.4	0.7	0.8
Male	18 (58.1)	45 (39.8)	63 (43.7)
Female	13 (41.9)	68 (60.2)	81 (56.2)
Gestational age (wk)			
Mean	33 ± 6	29 ± 4	30 ± 5
<37	17 (54.8)	105 (92.9)	122 (84.7)
≥37	14 (45.2)	8 (7.1)	22 (15.3)
Birth weight (g)			
Mean	2299 ± 1154	1150 ± 651	1397 ± 914
<1500	8 (25.8)	96 (85.0)	104 (72.2)
≥1500	23 (74.2)	17 (15.0)	40 (27.8)
Mortality	7 (22.6)	1 (0.9)	8 (5.6)

Data are presented as n (%) or mean ± SD.

Compared with Gram-negative pathogens (n = 56, 33.1%), there were more Gram-positive (n = 98, 58.0%) pathogens isolated (Table 2). The most commonly isolated pathogen was coagulase-negative staphylococci (CoNS; 44 episodes, 26.0%). *Escherichia coli* (15 episodes, 8.9%), *Staphylococcus aureus* (14 episodes, 8.3%), *Acinetobacter baumannii* (14 episodes, 8.3%), and *Klebsiella pneumoniae* (13 episodes, 7.7%) were the other dominant pathogens. Among the 10 GBS (*Streptococcus agalactiae*) infected infants, infants mother did not receive GBS screening in nine cases, and gestational age was less than suggested screening time in two of these nine cases. In other words, the GBS infection of seven infants could have been prevented if they had proper screening. The most frequently encountered pathogens in the early onset group were *E. coli* (9 episodes, 28.1%) and GBS (9 episodes, 28.1%). CoNS and Enterobacteriaceae, including *A. baumannii* and *K. pneumoniae*, were the most common pathogens in the late-onset group.

Fungal infection accounted for 8.9% of septic episodes, all in the late-onset group. The most common fungal pathogen isolated was *Candida parapsilosis* (7 episodes, 46.7%). Seven fungal infections, all caused by *Candida* species, were detected in 2009, so prophylactic fluconazole treatment in VLBW neonates was started since then. This treatment was initiated only for those with gestational age <28 weeks or birth weight <1000 g and was continued for up to 6 weeks or until full feeding was achieved without intravenous lines. In 2010, there was not any fungal infection. However, fluconazole-resistant *Malassezia pachydermatis* and *C. parapsilosis* infections appeared in 2011 (Figure 2).

No significant difference of perinatal risk factors was found between the early onset and late-onset groups. The underlying and associated conditions of the patients are presented in Table 3. Bronchopulmonary dysplasia, catheter usage, operation, pneumonia, respiratory distress syndrome, and total parental nutrition were more frequent in the late-onset group. High-grade intracranial hemorrhage occurred more frequently in the early onset group.

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Table 2 Pathogens of early onset and late-onset neonatal bloodstream infections.

Pathogen	Early onset (n = 32)				Late onset (n = 137)				Total	%	Mortality rate %
	Total	%	Death	%	Total	%	Death	%			
Gram-positive bacteria	20	62.5	4	20.0	78	56.9	0	—	98	58.0	4.1
Coagulase-negative *Staphylococcus*	3	9.4	1	33.3	41	29.9	0	—	44	26.0	2.3
Staphylococcus aureus	0	—	0	—	14	10.2	0	—	14	8.3	0.0
Group B *Streptococcus*	9	28.1	3	33.3	1	0.7	0	—	10	5.9	30.0
Other Gram-positive organisms	8	25.0	0	—	22	16.1	0	—	30	17.8	0.0
Gram-negative bacteria	12	37.5	3	25.0	44	32.1	1	2.3	56	33.1	7.1
Escherichia coli	9	28.1	3	33.3	6	4.4	0	—	15	8.9	20.0
Acinetobacter baumannii	1	3.1	0	—	13	9.5	0	—	14	8.3	0.0
Klebsiella pneumoniae	0	—	0	—	13	9.5	1	7.7	13	7.7	7.7
Pseudomonas aeruginosa	0	—	0	—	5	3.6	0	—	5	3.0	0.0
Other Gram-negative organisms	2	6.3	0	—	7	5.1	0	—	9	5.3	0.0
Fungi	0	—	0	—	15	10.9	0	—	15	8.9	0.0
Candida parapsilosis	0	—	0	—	7	5.1	0	—	7	4.1	0.0
Malassezia pachydermatis	0	—	0	—	4	2.9	0	—	4	2.4	0.0
Candida albicans	0	—	0	—	2	1.5	0	—	2	1.2	0.0
Other fungi	0	—	0	—	2	1.5	0	—	2	1.2	0.0

Twenty patients had associated pneumonia and seven patients had necrotizing enterocolitis, all in the late-onset group. Associated meningitis was found in five patients who were all in the early onset group, with three of these cases being caused by GBS infection.

During the study period, 1235 PICCs were inserted with 93 BSIs. Twelve neonates had concomitant other site infections that were excluded according to the NHSN criteria. A total of 81 PICCs were associated with CLA-BSI (6.6%). Median time from line insertion to infection was 18 days (interquartile range, 11—25 days, range, 4—35 days). Among the CLA-BSIs, the most common organism identified was CoNS (26 episodes, 32.0%). The incidence of PICC-related CLA-BSI increased from 3.3% to 10.6% between 2010 and 2011. After restricting the catheter duration to <21 days, the incidence of PICC-related CLA-BSI decreased gradually to 8.4% in 2012, then to 4.2% in 2013 (Figure 3).

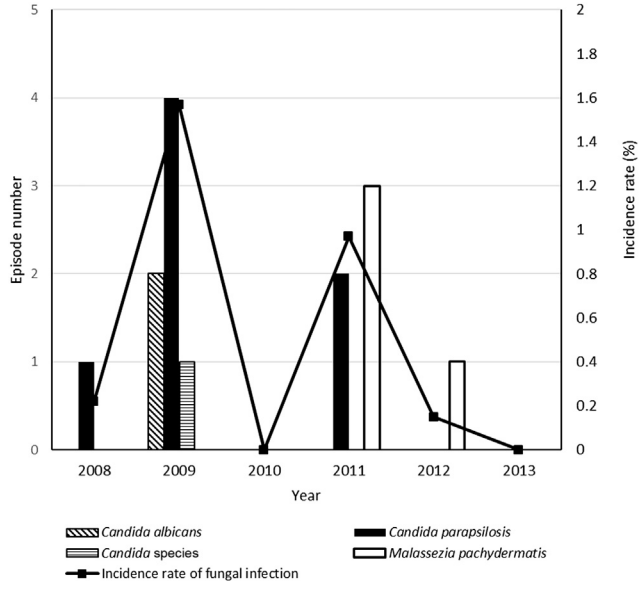

Figure 2. Numbers of fungal bloodstream infections and the fungal infection incidence from 2008 to 2013. Fluconazole prophylaxis in very-low-birth-weight neonates was administered after the surge of fungal infections in 2009. There was no fungal infection in 2010, but five fluconazole-resistant fungi were isolated in 2011, and one in 2012.

Table 3 Underlying and associated conditions of early-onset and late-onset neonatal bloodstream infections.

Underlying and associated conditions	Early onset (n = 31)	Late onset (n = 113)	Total (n = 144)	p*
Bronchopulmonary dysplasia	2	54	56	<0.0001
Catheter insertion[a]	2	103	105	<0.0001
Congenital heart disease	1	5	6	0.617
Intraventricular hemorrhage Grade III—IV	3	4	7	<0.0001
Mechanical ventilation	30	100	130	0.3
Meningitis	5	0	5	0.0004
Necrotizing enterocolitis	0	7	7	0.171
Operation	3	43	46	0.002
Pneumonia	0	20	20	0.0074
Respiratory distress syndrome	14	88	102	0.001
Total parental nutrition	7	106	113	<0.0001

[a] Catheter included peripherally inserted central catheter, BROVIAC catheter, and umbilical venous catheter.
*p value was calculated by Fisher's's exact test.

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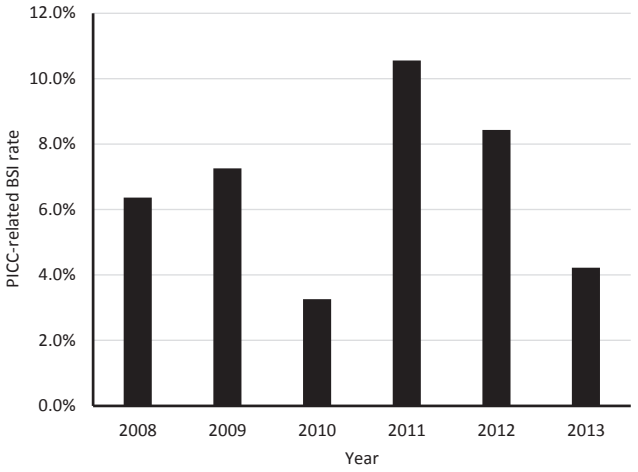

Figure 3. Change in the peripherally inserted central catheter-associated bloodstream infection rates during the period from 2008 to 2013. BSI = bloodstream infection; PICC = peripherally inserted central catheter.

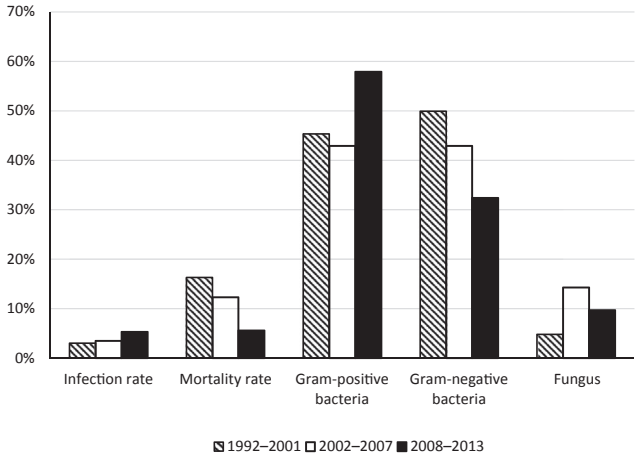

Figure 4. Three periods, 1992—2001, 2002—2007, and 2008—2013, were separated based on previously published, oral presented data, and this study. Infection rate, mortality rate, and pathogen distribution of neonatal intensive care unit bloodstream infections in these three periods are shown.

Eight deaths were BSI related. The overall BSI-related mortality rate was 5.6%. Seven deaths occurred in the early onset group (87.5%). Significantly higher mortality rate was found in the early onset group in comparison with the late-onset group (22.6% vs. 0.9%, $p < 0.0001$). The BSI-related mortality rate in VLBW infants was only 1.9%, and in gestational age groups <28 weeks it was 3.5%. Mortality was significantly higher in the "birth weight >1500 g" ($p = 0.006$) and "term infant" groups ($p = 0.0193$). GBS had the highest mortality rate (30.0%), followed by *E. coli* (20.0%) and *K. pneumoniae* (7.7%). Three early onset BSI-related deaths were caused by GBS, and two of them had associated meningitis. Two neonates' mother did not receive GBS screening and one infant's mother had a negative GBS screening result. Three infants' BSI-related mortality was caused by *E. coli*. They all developed symptoms/signs within the 1st day of life and deteriorated quickly. A 3-day-old newborn who had CoNS isolated from blood died suddenly, due to the colonization of maternal GBS; besides, this infant's mother did not receive prophylaxis treatment. The only BSI-related death in the late-onset group was a hydrops fetalis baby who died on the 54th day due to *K. pneumoniae*—extended-spectrum beta-lactamase infection.

Comparison of 2008—2013 BSIs with infections in 1992—2001 and 2002—2007

In these three periods, the trends revealed that the infection rate increased from 3.0% to 5.3%, but the mortality rate decreased from 16.3% to 5.6% (Figure 4). However, continuous variables through the years had no statistical significance. The predominance of pathogens changed from being Gram-negative bacteria to Gram-positive bacteria. Fungal infection ratio increased from 4.8% to 14.3% and decreased to 9.7% in the latest period.

Among BSIs, the ratio of VLBW infants changed from 54.4% to 84.3%, and then to 72.2%. Late-onset infections had a higher ratio of VLBW infants in all the three periods. *Pseudomonas aeruginosa* had the highest mortality rate in the first two periods (55.0% and 52.2%) but only five patients had this pathogen isolated in the last period and all of them survived. The underlying and associated conditions for early and late-onset infections were similar through the periods.

Discussion

The epidemiology of each NICU is different and each unit should know its own trend. In Taiwan, the BSI-related mortality rate was 7.2—20.0% in previous reports.[3—5,8,9] Compared with Taiwan's previous reports and our previous data, the overall BSI mortality rate during 2008—2013 in our NICU was better (5.6%) and BSI-related mortality was hardly found in the late-onset group (0.9%). However, we observed a high rate of BSI-related mortality in the early onset group (22.6%). Because mortality occurred most in the early onset group, statistical association was found in the term and >1500 g birth-weight infants. Quick and fulminate course of infection in the early onset group may be the reason why patients in this group did not respond to antibiotic therapy. Nonetheless, some neonatal deaths due to GBS infection in the early onset group might have been avoided had their mothers undergone maternal GBS screening and received intrapartum antibiotic prophylaxis.

Our hospital started to promote the policy of maternal GBS screening and intrapartum antibiotic prophylaxis in 2004. The screening rate and intrapartum antibiotic prophylaxis rate increased gradually during the years since. The incidence of GBS BSI has been found to be decreasing in our previous report.[10] Because many of our patients were referred from other hospitals or clinics without prenatal examination in our hospital, nine infants without maternal screening still suffered GBS BSIs during 2008—2013 in our NICU. A nationwide maternal GBS screening program was started in 2012 in Taiwan. We hope that neonatal GBS infection will become even less in the coming years.

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Nonetheless, one of our patients who died from GBS infection had negative maternal GBS screening. Therefore, precise screening procedure and careful interpretation of the result are important.

The lowest infection incidence (4.3%) was found in 2010. The patient-admission day (5858) was lowest that year, as was the total hospitalized patient density (59.4 patients/1000 admission days). The patient-admission day increased to 7527 and patient density increased to 68.6 patients/1000 admission days the following year, and the infection incidence went up to 6.4%. Avoidance of overcrowding may be related to the infection rate.

The ratio of preterm and VLBW infants in the late-onset group is rather high. Preterm and VLBW infants often require aggressive interventions, such as mechanical ventilator, intravascular catheterization, parenteral nutrition supplement, and prolonged length of hospitalization.[11,12] Late-onset infection is associated with all these managements. Although the ratio of these more vulnerable patients remained high, better outcome was found through the years. It indicates progression in patient care ability for the high-risk babies.

GBS and *E. coli* are still the most frequently isolated pathogens in the early onset group, which was the case in previous studies as well.[3,4] By contrast, GBS is hardly found in late-onset infection cases. *S. aureus* has been reported as the most common nosocomial pathogen in another Taiwan hospital,[9] similar to our NICU, during 2002—2007. CoNS was the most commonly isolated pathogen during the 1992—2001 and 2008—2013 periods in our NICU, similar to other reports from Taiwan.[3,4,12] Because of the high proportion of CoNS infection, Gram-positive organisms were the dominant pathogens in our NICU. CoNS BSI may be related to prolonged central line catheter use.

Catheter duration is an important risk factor for PICC-associated CLA-BSI in the NICU. In a previous study, the duration of silastic deep lines was correlated with the incidence of BSI, and the authors concluded 21 days as the critical point beyond which the risk of BSI becomes significant.[13] We found a surge of PICC-associated CLA-BSI cases in 2011, so we restricted the duration to $<$21 days since then and subsequently the results improved. Although hospitalized patient density increased to 91.4 patients/1000 admission days in 2012 (Chinese dragon year), the infection incidence rate still dropped. Because the median time from line insertion to infection is 18 days in this study, we will closely follow the infection condition to adjust our policy accordingly.

Multiple factors can influence the infection control results. A multifaceted infection control program has been proved to be effective in reducing the CLA-BSI rate among neonates.[14] Care bundle, a novel line procedure to reduce the rate of CLA-BSI, is introduced to the intensive care units or even general wards recently.[15] Our NICU has started to use this program to reduce the burden of CLA-BSI since 2014.

Fungal infections occur mostly in premature infants with gestational age $<$28 weeks. Critically, ill neonates are at an increased risk of infection because of their developmentally immature immune systems, the increased permeability of their skin and mucosal barriers, and the long-term need for central vascular access, parenteral nutrition, broad-spectrum antibiotics, postnatal steroids, and mechanical ventilation.[16] This high-risk population could benefit greatly from effective prophylactic measures. The outcome of our fungal infection patients between 2008 and 2013 is rather good without related mortality. We started prophylactic fluconazole in 2009 after a surge of fungal infection in VLBW infants. Fluconazole-sensitive *Candida* infection disappeared but *M. pachydermatis* infections occurred. There are several reports of *M. pachydermatis* fungemia in preterm/LBW neonates who received total parenteral nutrition through central venous catheter.[17—19] Most strains of *M. pachydermatis* exhibit reduced susceptibility to fluconazole and flucytosine and are health care related.[20—22] *C. parapsilosis* also exhibits reduced susceptibility to fluconazole, and was found before and after the application of fluconazole prophylaxis policy. Antifungal prophylaxis has contributed to the decline in the incidence of invasive candidiasis among premature infants[23] and we recommend it; however, we need to be aware of the possibility of increasing resistant strains.

Some limitations of the study should be considered. First, it is restricted to a single medical center and uses a retrospective review method. The case number is relatively small and some potential risk factors may not have been readily identified. Thus, the statistical analysis may not have sufficient power to draw definitive conclusions. However, we have carefully collected and analyzed the data, which reveal some significant information and trends in NICU BSIs. Second, it is hard to distinguish the true pathogen from the normal skin flora isolated from blood cultures in NICU even strict criteria are applied.

In conclusion, through the years, the overall mortality rate of BSI in our NICU has had a decreasing trend. However, at present, Gram-positive pathogens have become predominant. Maternal GBS screening and intrapartum antibiotic prophylaxis are important, so neonatal death can be prevented in most cases. Fungal infection number decreases after applying antifungal prophylaxis policy for VLBW infants, but we should be aware of resistant strains. Restriction of the catheter duration may decrease the incidence of catheter-related BSI.

Conflicts of interest

All authors declare that they have no conflicts of interest associated with the materials discussed in the article.

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