J Microbiol Immunol Infect 2010;43(5):407–415

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

Journal homepage: http://www.e-jmii.com

Original Article

Long-term Characteristics of Healthcare-associated Infections in a Neonatal Intensive Care Unit

Tzong-Shiann Ho[a,b], Shih-Min Wang[b], Yi-Hui Wu[c], Ching-Fen Shen[a], Yuh-Jyh Lin[a], Chyi-Her Lin[a], Ching-Chuan Liu[a,c]*

[a]Department of Pediatrics, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan.

[b]Department of Emergency Medicine, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan.

[c]Center for Infection Control, National Cheng Kung University Hospital, Tainan, Taiwan.

BACKGROUND/PURPOSE: Healthcare-associated infections in neonatal intensive care units (NICUs) are associated with a significant risk of morbidity and mortality. Knowledge regarding pathogens, primary sources of infection and antibiotic resistance in the NICU is essential for developing management strategies. This study aimed to analyze the long-term characteristics of healthcare-associated infections in a tertiary referral center in southern Taiwan.

METHODS: Infants < 30 days old, with positive blood, cerebrospinal fluid, urine or tissue fluid cultures during hospitalization in the NICU of National Cheng Kung University Hospital from July 1989 to June 2008 were included in the study.

RESULTS: In total, 1,417 organisms and episodes were identified during the study period. Gram-positive organisms, Gram-negative organisms and fungi constituted 923 (65.1%), 358 (25.3%) and 136 (9.6%) of the pathogens, respectively. Of the Gram-positive organisms, coagulase-negative *staphylococci* (51.5%), *Staphylococcus aureus* (34.8%) and *Enterococcus* spp. (6.1%) were the major pathogens; and 27% of *Staphylococcus aureus* isolates were oxacillin-resistant. For the Gram-negative organisms, *Klebsiella pneumoniae* (22%), *Pseudomonas aeruginosa* (21.8%), *Escherichia coli* (16.7%) and *Enterobacter cloacae* (16.7%) were dominant. Also, *Candida albicans* accounted for 50% of fungal infections. The most common source of infection was bloodstream infection (59.0%), and 5.6% of these were catheter-related. Skin and soft tissue infections were also frequent (26.3%).

*Corresponding author. Department of Pediatrics, National Cheng Kung University Medical College and Hospital, 138 Sheng-Li Road, Tainan 704, Taiwan.

E-mail: liucc@mail.ncku.edu.tw

Article History:
Received: Apr 30, 2009
Revised: Jun 26, 2009
Accepted: Aug 19, 2009

CONCLUSION: Bloodstream and skin/soft tissue infections caused by commensal species play an important role in healthcare-associated infections in the NICU. New measures should be developed in response to the changing patterns in the NICU.

KEYWORDS: bloodstream infection, *Candida albicans*, healthcare-associated infection, neonatal intensive care units, *Staphylococcus aureus*

Introduction

Nosocomial infections are associated with increased morbidity and mortality, prolonged hospitalization and increased healthcare costs.[1] It is estimated that there are more than 2,000,000 nosocomial infections in children and adults annually in the United States, resulting in extended lengths of hospital stay and treatment, and adding $17–29 billion to health care costs each year.[1–3] Among the causative pathogens, coagulase-negative *staphylococci* (CoNS), *Staphylococcus aureus*, *Enterococcus* spp., *Candida* spp. and *Enterobacter* spp. were the most frequently reported by the National Nosocomial Infection Surveillance System of the United States.[4] This surveillance system also provides evidence that the epidemiology of healthcare-associated infections in children differs from that in adults with regard to distribution by body sites and the pathogens involved.[5,6] Unlike other wards in the hospital, healthcare-associated infections in the neonatal intensive care units (NICUs) are unique in many aspects. The microbial causes of neonatal infection are age-dependent and unit-dependent, and the species distribution of the predominant nosocomial pathogens in a NICU depends on factors such as endemic microbial flora, clinical techniques and antibiotic stewardship policies.[7] Also, neonatal infections are still a challenge to the pediatrician, as clinical manifestations of the same pathogen can be quite different in different age groups. Bloodstream and skin/soft tissue infections caused by commensal species play important roles in nosocomial infections in the NICU, which poses difficulties in determining true pathogens from contaminants.[8] The distribution and antimicrobial susceptibility of pathogens causing healthcare-associated infections, namely their characteristics, vary considerably in different regions, over time and between hospitals. The availability of timely and accurate epidemiological information on healthcare-associated pathogens is essential for infection control and the appropriate selection of empiric antibiotics.[9] Previous studies in Taiwan also support the importance of nosocomial infection surveillance in managing the issue.[10–12]

In this study, we aimed to analyze the long-term characteristics of healthcare-associated infections, including the clinical features, pathogen distribution, antimicrobial susceptibility and yearly changes in a tertiary referring center in southern Taiwan.

Methods

Patients and setting

Infants < 30 days old, with positive blood, cerebrospinal fluid, urine or tissue fluid cultures during hospitalization at the NICU in National Cheng Kung University Hospital from July 1989 to June 2008 were enrolled. National Cheng Kung University Hospital is a teaching hospital that provides tertiary care in southern Taiwan and has a 16-bed level-III NICU. This NICU offers care to critically ill newborns, extremely-low-birthweight premature infants, neonates requiring pre- or postoperative management, and those who have congenital anomalies that require close observation or intervention. The antimicrobial hand washing solutions used are 4% chlorhexidine (Hibiscrub) and 70% alcohol. Visitors are restricted to two per bed and required to wash their hands and wear masks. Universal fluconazole prophylaxis for extremely-low-birthweight infants started in May 2002.[13] Bacterial cultures are obtained routinely from patients with poor activity, respiratory symptoms (apnea, bradycardia, cyanosis, hypoxemia, and respiratory distress), gastrointestinal symptoms (feeding

intolerance, abdominal distention), fever (≥38°C) or hypothermia (≤35°C). At least one blood sample for culture is obtained whenever infection is suspected, and before empirical antibiotic treatment (ampicillin/sulbactam and amikacin) is started.

Definitions and microbiological analysis

A healthcare-associated infection is defined as an infection not present or incubating at the time of NICU admission.[14] Bloodstream infection must meet at least one of the following criteria: (1) the patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured is not related to an infection at another site; or (2) the patient has at least one of the following signs or symptoms: fever, hypothermia, apnea or bradycardia, and the symptoms/signs are not related to an infection at another site. Common skin contaminants such as diphtheroids (*Corynebacterium* spp.), *Bacillus* (not *B. anthracis*) spp., *Propionibacterium* spp., CoNS (including *S. epidermidis*), viridans group *Streptococci*, *Aerococcus* spp., and *Micrococcus* spp. are considered pathogens if positive from two or more blood cultures drawn on separate occasions. All blood cultures are processed by the clinical microbiology laboratory using the Bactec 9240 system (Becton, Dickson and Company, NJ, USA). Skin/soft tissue infections must meet at least one of the following criteria: (1) the patient has purulent drainage, pustules, vesicles, or boils; or (2) the patient has at least two of the following signs or symptoms with no other recognized cause: pain or tenderness, localized swelling, redness or heat, and at least one of the following: (i) organisms cultured from aspirate or drainage from affected site, and if organisms are normal skin flora [i.e. diphtheroids (*Corynebacterium* spp.), *Bacillus* (not *B. anthracis*) spp., *Propionibacterium* spp., CoNS (including *S. epidermidis*), viridans group *Streptococci*, *Aerococcus* spp., or *Micrococcus* spp.], they must be a pure culture; (ii) organisms cultured from blood. Antimicrobial susceptibility testing is determined using the disk diffusion technique, in accordance with the criteria established by the Clinical and Laboratory Standards Institute.[15] A nosocomial infection surveillance system has been maintained by the Center for Infection Control of the hospital since 1989. The incidence density of healthcare-associated infections was calculated as the number of episodes divided by the number of patient-days at risk.

Statistical analysis

The significance of differences in proportions was determined by a two-tailed χ^2 test, and a p value <0.05 was considered to be statistically significant. All the calculations were performed using SPSS version 15 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of healthcare-associated infections

In total, 1,417 isolates were identified from July 1989 to June 2008. The annual average NICU stay was 6,333 patient-days, ranging from 9,255 patient-days in 1995 to 4,696 in 2004. The average infection density was 9.4 per 1,000 patient-days. The infection densities were lowest in 2008 (3.9 per 1,000 patient-days) and highest in 1995 (17.3 per 1,000 patient-days). The most common source of infection was bloodstream infection (59.0%) and 5.6% of these were catheter-related. The average incidence of healthcare-associated bloodstream infection was 5.4, ranging from 1.5 (1989) to 9.4 (1995) per 1,000 patient-days (Figure 1). Furthermore, skin and soft tissue infections were also frequent (26.3%). Pneumonia accounted for 4.1% of the healthcare-associated infections (Table 1).

Gram-positive organisms, Gram-negative organisms and fungi constituted 923 (65.1%), 358 (25.3%) and 136 (9.6%) of the pathogens, respectively. Of the Gram-positive organisms, CoNS (57.1%), *S. aureus* (34.8%) and *Enterococcus* spp. (6.1%) were the major pathogens. As for the Gram-negative organisms, *Klebsiella pneumoniae* (22.1%), *Pseudomonas aeruginosa* (21.8%), *Escherichia coli* (16.8%) and *Enterobacter cloacae* (16.8%) dominated. *Candida albicans* accounted for 52.9% of the fungal infections (Table 2).

Changing patterns of pathogens

For comparison, the study was divided into two periods: 1989–1998 and 1999–2008. The dominant pathogens responsible for healthcare-associated infections changed over the years. Gram-positive bacteria were still the leading causes of infection, but *S. aureus* took the place of CoNS during 1999–2008. *Enterococcus* spp. infections increased compared with the period 1989–1998 ($p=0.02$). The proportion of Gram-negative pathogens decreased from 28.3% in 1989–1998 to 21.3% in 1999–2008 ($p<0.01$). The percentage of *P. aeruginosa* and *E. cloacae* decreased

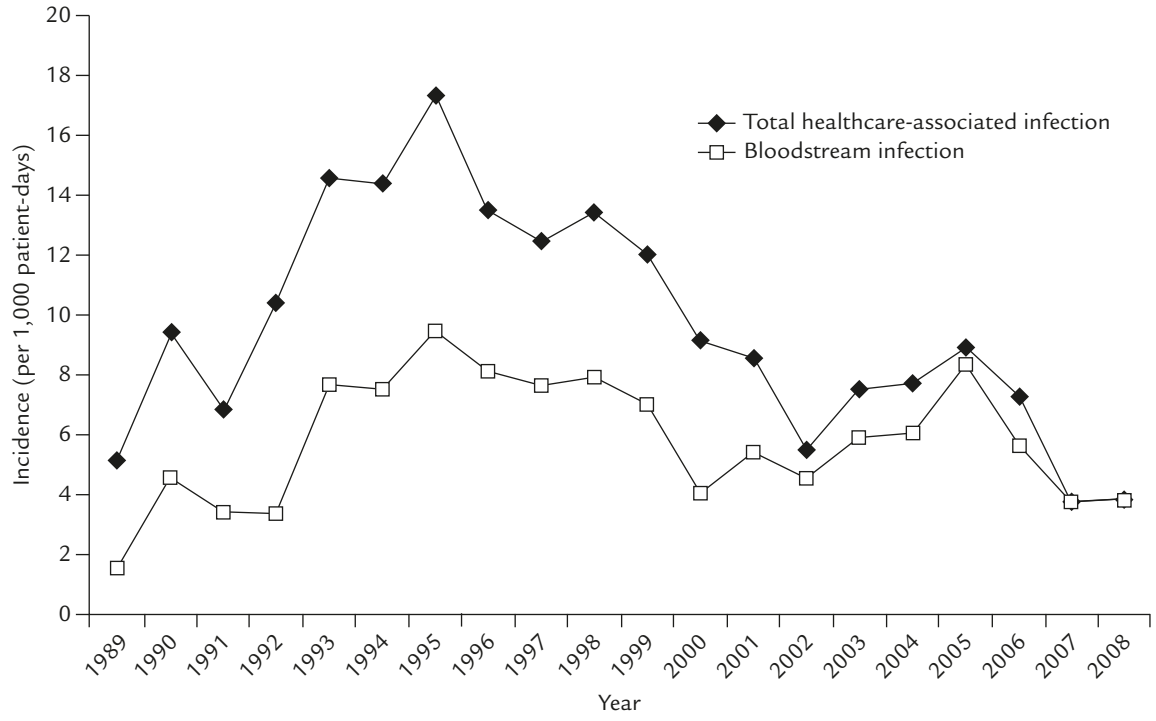

Figure 1. Incidence of total healthcare-associated infection and bloodstream infections in neonatal intensive care units from 1989 to 2008.

Table 1. Characteristics of healthcare-associated infections in neonatal intensive care units

Site of infection	*n* (%)
Bloodstream	836 (59.0)
Skin and soft tissue	372 (26.3)
Pneumonia	58 (4.1)
Surgical wound	39 (2.8)
Urinary tract	29 (2.0)
Meningitis	20 (1.4)
Others	63 (4.4)
Total	1,417 (100)

($p<0.01$), while *K. pneumoniae* ($p=0.38$) and *E. coli* ($p=0.53$) remained unchanged. *A. baumannii* was the only Gram-negative pathogen to increase from 1999–2008 (Table 2).

Fungal infections increased during 1999–2008 and *Candida* spp. accounted for 86.3% (63/73) of these. Except for *C. albicans* (58.7%, 37/63 of candidal infections), infections caused by non-*albicans Candida* spp. mainly emerged after 2000 (Table 2 and Figure 2). The non-*albicans* species seen in 1999–2008 were *C. parapsilosis* (57.7%), *C. tropicalis* (23.1%), *C. lusitaniae* (15.4%) and *C. glabrata* (3.8%). The average rate of non-*albicans* candidal infections increased after fluconazole prophylaxis (0.75 *vs.* 7.93 per 1,000 patient-days; $p=0.043$). However, the average rate of *Candida albicans* infection did not change significantly (5.72 *vs.* 7.13 per 1,000 patient-days; $p=0.893$).

Trends of antimicrobial susceptibility

To explore the recent trends in antimicrobial resistance of the above leading pathogens, the antimicrobial susceptibility patterns of these isolates from 2000–2008 were analyzed. The majority (97.4%) of CoNS isolates were resistant to oxacillin, but only 5.7% of isolates were resistant to ampicillin/sulbactam. No vancomycin-resistant CoNS were detected. Oxacillin-resistance was observed in 91.8% of *S. aureus* isolates; however, all *S. aureus* remained sensitive to vancomycin and the incidence of oxacillin-resistant *S. aureus* decreased after 2001 (Figure 3). Two thirds of the *S. aureus* isolates were resistant to sulfamethoxazole/trimethoprim. Only two (6.6%) of the *Enterococcus* isolates were resistant to ampicillin. No vancomycin-resistant *Enterococcus* was found during this period (Table 3).

Table 2. Microorganism distribution of healthcare-associated infections in neonatal intensive care unit[a]

Pathogen	1989–2008	1989–1998	1999–2008	*p*
Total	1,417 (100)	794 (100)	623 (100)	
Gram-positive organisms[b]	923 (65.1)	506 (63.7)	417 (66.9)	0.21
Coagulase-negative *staphylococci*	527/923 (57.1)	348/506 (68.8)	179/417 (42.9)	<0.01
Staphylococcus aureus	321/923 (34.8)	117/506 (23.1)	204/417 (48.9)	<0.01
Enterococcus spp.	56/923 (6.1)	23/506 (4.5)	33/417 (7.9)	0.02
Others	19/923 (2.1)	18/506 (3.6)	1/417 (0.2)	<0.01
Gram-negative organisms[b]	358 (25.3)	225 (28.3)	133 (21.3)	<0.01
Klebsiella pneumoniae	79/358 (22.1)	48/225 (21.3)	31/133 (23.3)	0.38
Pseudomonas aeruginosa	78/358 (21.8)	60/225 (26.7)	18/133 (13.5)	<0.01
Escherichia coli	60/358 (16.8)	36/225 (16.0)	24/133 (18.0)	0.53
Enterobacter cloacae	60/358 (16.8)	46/225 (20.4)	14/133 (10.5)	<0.01
Acinetobacter baumanii	38/358 (10.6)	13/225 (5.7)	25/133 (18.8)	<0.01
Serratia marcescens	9/358 (2.5)	4/225 (1.8)	5/133 (3.8)	0.48
Others	34/358 (9.5)	18/225 (8.0)	16/133 (12.0)	0.71
Fungi[b]	136 (9.6)	63 (7.9)	73 (11.7)	0.02
Candida albicans	72/136 (52.9)	35/63 (55.6)	37/73 (50.7)	0.19
Non-*albicans Candida*	26/136 (19.1)	0/63 (0)	26/73 (35.6)	<0.01
Others	38/136 (27.9)	28/63 (44.4)	10/73 (13.7)	0.02

[a]Data presented as number of positive cases/number of cases in the corresponding subgroup (%); [b]data presented as number of positive cases/total number of cases.

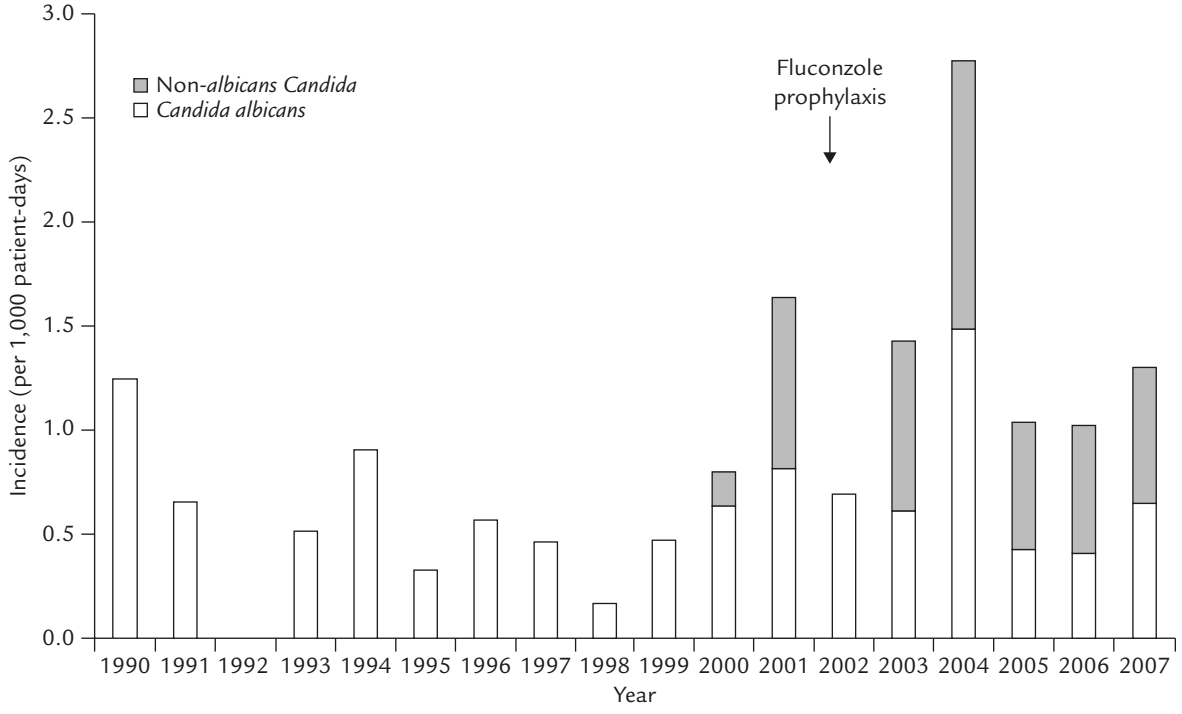

Figure 2. Changing pattern of healthcare-associated candidal infections in neonatal intensive care unit, 1990–2007.

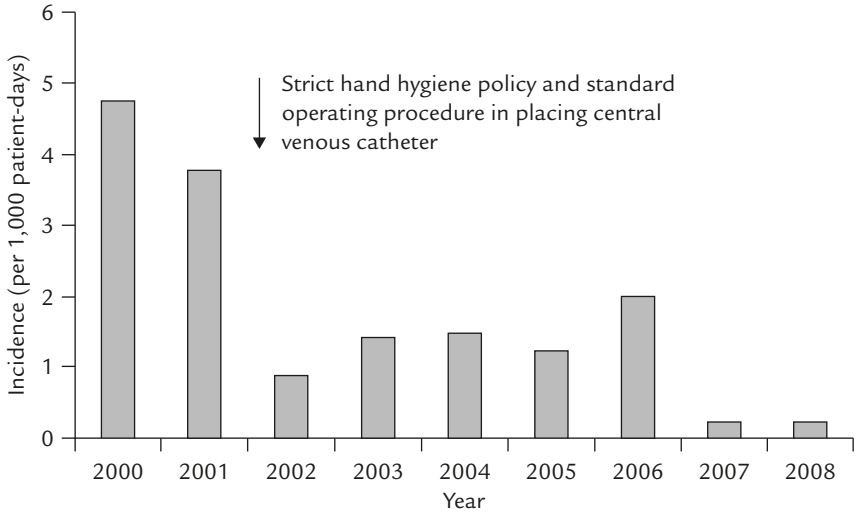

Figure 3. Yearly trends of healthcare-associated oxacillin-resistant *Staphylococcus aureus* infections in neonatal intensive care units from 2000 to 2008.

Table 3. Selected antimicrobial susceptibility patterns from tested isolates of healthcare-associated infections in NICU, 2000–2008

Microorganism	Antimicrobial	Isolates (*n*)	Resistance, *n* (%)
Coagulase-negative *staphylococci*	Oxacillin	156	152 (97.4)
	Vancomycin		0 (0)
	Ampicillin/sulbactam		9 (5.8)
Staphylococcus aureus	Oxacillin	97	89 (91.8)
	Vancomycin		0 (0)
	Sulfamethoxazole/trimethoprim		67 (69.1)
Enterococcus sp.	Ampicillin	30	2 (6.7)
	Vancomycin		0 (0)
Klebsiella pneumoniae	Third-generation cephalosporins	25	5 (20.0)[a]
Pseudomonas aeruginosa	Carbapenems	15	0 (0)
	Ceftazidime		1 (6.7)
	Quinolones		0 (0)
Escherichia coli	Third-generation cephalosporins	20	1 (5.0)
Enterobacter cloacae	Gentamicin	22	12 (54.5)
	Amikacin		5 (22.7)
Acinetobacter baumanii	Carbapenems	10	2 (20.0)
	Ampicillin/sulbactam		2 (20.0)

[a]Including four with extended-spectrum β lactamases.

One fifth (5/25) of the *K. pneumoniae* isolates were resistant to third-generation cephalosporins (i.e. ceftriaxone, cefotaxime), including four (16%, all isolated from bloodstream) with extended-spectrum β-lactamases. Moreover, most of the *E. coli* isolates (95.0%) were susceptible to third-generation cephalosporins. All the *P. aeruginosa* isolates were susceptible to carbapenems and quinolones. Moreover, 54.5% of the *E. cloacae* isolates showed resistance to gentamicin, but were less resistant (22.7%) to amikacin, both common empiric regimens in the NICU. Eighty percent of isolated *A. baumannii* were susceptible to ampicillin/sulbactam, whereas two carbapenem-resistant *A. baumannii* (20.0%) isolates were identified (Table 3).

Discussion

Neonatal infections are an important cause of mortality and morbidity worldwide. In the World Health Organization 2000–2003 report, neonatal sepsis and pneumonia were responsible for about 1.6 million deaths each year, mainly in resource-poor countries.[16] However, most of these serious neonatal infections in Taiwan and developed countries occurred in hospitals, and especially in the NICU. Knowledge regarding the distribution of infection and pathogens is crucial due to the advances in medical technologies and subsequently longer hospital stays.

The infection densities in the NICU changed over time. The first peak was around 1995 and might reflect increased hospitalization after the commencement of national health insurance. Similar findings were reported in a previous study in Taiwan.[17] In 2002, our institute instigated a strict hand-hygiene policy and standard operating procedures for placing central venous catheters; these might be the reasons for the decrease in healthcare-associated infections other than bloodstream infections, from 2002 to 2008.

In the current study, bloodstream infections served as the single most important type of infection because of their frequency (59%) and potential life-threatening consequences. Most episodes of nosocomial infection in the NICU are associated with indwelling vascular catheters.[18,19] Administration of lipids, low birthweight, respiratory disease, catheter hub colonization, blood sampling from central venous catheters and use of H2 blockers are also associated with bloodstream infections.[20]

S. aureus is the most common pathogen causing pustulosis and cellulitis in neonates. The presence of virulence factors such as the Panton-Valentine leukocidin are thought to contribute to the pathogen's ability to cause skin and soft tissue infections.[21] The underdeveloped epidermis and frequent breeches in skin integrity due to intravenous catheters, blood draws and heel sticks place preterm neonates at risk of infection.[22] With advances in our NICU, the survival rates, hospital stay and number of invasive procedures have increased. This might be part of the reason why *S. aureus* became the dominant Gram-positive pathogen during the last decade.

Published data show that increased costs are associated with methicillin-resistant *S. aureus* (MRSA) compared with no infection or with methicillin-sensitive *S. aureus*.[23] Besides hand-hygiene, the isolation and cohorting of MRSA-colonized infants, and regular neonatal surveillance cultures were recommended.[24] Many NICU are routinely using mupirocin to eradicate endemic MRSA. Lower eradication rates have been observed in infants who are nasotracheally intubated or using nasal continuous positive airway pressure.[22,25] The declining incidence of oxacillin-resistant *S. aureus* seen in the current study might be related to changes in strict aseptic technique and hand washing policy (Figure 3), but the significance of this needs to be clarified.

CoNS is one of the most common healthcare-associated pathogens in NICUs. Levels of transplacental anti-CoNS immunoglobulin and complement correlate with gestational age, and this relative deficiency in preterm infants might contribute to their suboptimal opsonization and impaired bacterial killing of CoNS.[26] In comparison with previous studies, CoNS is the predominant source of infection in NICU in the United States and Asian countries,[27,28] which is quite different from the community-acquired setting. Gram-negative pathogens were responsible for most community-acquired neonatal infections and *E. coli* and *Klebsiella* species are the cause of nearly half of all infections in most regions of the world.[29] *A. baumannii*, classically described as nosocomial pathogens in adults, is also responsible for infections in neonates hospitalized in ICUs, causing pneumonia. It is a ubiquitous microorganism implicated in a number of outbreaks in ICUs.[30] Most of these outbreaks have been traced to environmental sources, such as mechanical ventilation equipment and air conditioners.[31] Although no pan-drug resistant *A. baumannii* was isolated, two carbapenem-resistant strains appeared in recent years, and this trend should be closely monitored.

C*andida* infections are a common cause of late-onset sepsis in the NICU and are associated with significant mortality and neurodevelopmental impairment. Non-*albicans Candida* spp. became more frequent after 2000; a similar trend was reported earlier in Taiwan.[32] One of the most important developments in managing candidal infection in the NICU is the use of prophylactic fluconazole in very-low-birthweight infants to prevent invasive candidiasis. The rationale for this strategy is to prevent fungal colonization in high-risk infants and reduce the invasiveness of the disease.[33] Previous studies demonstrate a reduction

of disease invasiveness, but no difference in mortality.[14,33] The major concerns regarding fluconazole prophylaxis include the risk of selecting fluconazole resistant fungi, short- and long-term safety and cost.[34] Whether the emergence of non-albicans *Candida* resulted from the use of prophylactic fluconazole is an important issue and demands further research.

In conclusion, bloodstream and skin/soft tissue infections caused by commensal species play important roles in healthcare-associated infections in the NICU. An increased incidence of *S. aureus* and *A. baumannii* infection and a decreased number of CoNS infections were observed. Non-*albicans Candida* spp. also become more frequent during 1999–2008. These changing patterns of isolated pathogens and antibiotic susceptibilities suggest that the use of empirical antibiotics for healthcare-associated infection in NICU needs constant review.

References

1. Payne NR, Carpenter JH, Badger GJ, Horbar JD, Rogowski J. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. *Pediatrics* 2004;114:348–55.
2. Wenzel RP, Edmond MB. Team-based prevention of catheter-related infections. *N Engl J Med* 2006;355:2781–3.
3. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birthweight infants with neonatal infection. *JAMA* 2004;292:2357–65.
4. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990–May 1999, issued June 1999. *Am J Infect Control* 1999;27:520–32.
5. National Nosocomial Infections Surveillance (NNIS) System report, data summary from October 1986–April 1998, issued June 1998. *Am J Infect Control* 1998;26:522–33.
6. Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infections Surveillance System. *Pediatrics* 1996;98:357–61.
7. Gray JW. Surveillance of infection in neonatal intensive care units. *Early Hum Dev* 2007;83:157–63.
8. van der Zwet WC, Kaiser AM, van Elburg RM, Berkhof J, Fetter WP, Parlevliet GA, et al. Nosocomial infections in a Dutch neonatal intensive care unit: surveillance study with definitions for infection specifically adapted for neonates. *J Hosp Infect* 2005;61:300–11.
9. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. *Arch Dis Child* 2005;90:F220–4.
10. Su BH, Hsieh HY, Chiu HY, Lin HC, Lin HC. Nosocomial infection in a neonatal intensive care unit: a prospective study in Taiwan. *Am J Infect Control* 2007;35:190–5.
11. Wei SH, Chiu HH, Hung KC, Wang JH, Su BH, Lin HC, et al. Epidemiologic trends in nosocomial bacteremia in a neonatal intensive care unit. *J Microbiol Immunol Infect* 2005;38:283–8.
12. Jiang JH, Chiu NC, Huang FY, Kao HA, Hsu CH, Hung HY, et al. Neonatal sepsis in the neonatal intensive care unit: characteristics of early versus late onset. *J Microbiol Immunol Infect* 2004; 37:301–6.
13. Tsai CH, Lin YJ, Liu CC, Yang Kao YH, Lin CH. Effects of fluconazole prophylaxis against systemic fungal infection in extremely-low-birth-weight infants. *Clinical Neonatology* 2005;12:6–12.
14. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;16:128–40.
15. National Committee for Clinical Laboratory Standards, 2000. *Performance Standards for Antimicrobial Disk Susceptibility Test: Approved Standard 7th edition M2-A7*. Villanova, PA, USA.
16. Posfay-Barbe KM, Zerr DM, Pittet D. Infection control in paediatrics. *Lancet Infect Dis* 2008;8:19–31.
17. Lin IJ, Chen CH, Chen PY, Wang TM, Chi CS. Nosocomial infection in a neonatal intensive care unit—from a viewpoint of national health insurance. *Acta Paediatr Taiwan* 2000;41:123–8.
18. Brodie SB, Sands KE, Gray JE, Parker RA, Goldmann DA, Davis RB, et al. Occurrence of nosocomial bloodstream infections in six neonatal intensive care units. *Pediatr Infect Dis J* 2000;19:56–65.
19. Stoll BJ, Hansen N. Infections in VLBW infants: studies from the NICHD Neonatal Research Network. *Semin Perinatol* 2003;27: 293–301.
20. Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med* 1990;323:301–8.
21. Saiman L, O'Keefe M, Graham PL 3rd, Wu F, Said-Salim B, Kreiswirth B, et al. Hospital transmission of community-acquired methicillin-resistant *Staphylococcus aureus* among postpartum women. *Clin Infect Dis* 2003;37:1313–9.
22. Carey AJ, Saiman L, Polin RA. Hospital-acquired infections in the NICU: epidemiology for the new millennium. *Clin Perinatol* 2008;35:223–49.
23. Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost-benefit analysis in an intensive care unit. *JAMA* 1999;282:1745–51.
24. Gerber SI, Jones RC, Scott MV, Price JS, Dworkin MS, Filippell MB, et al. Management of outbreaks of methicillin-resistant *Staphylococcus aureus* infection in the neonatal intensive care unit: a consensus statement. *Infect Control Hosp Epidemiol* 2006;27:139–45.
25. Hitomi S, Kubota M, Mori N, Baba S, Yano H, Okuzumi K, et al. Control of a methicillin-resistant *Staphylococcus aureus* outbreak

in a neonatal intensive care unit by unselective use of nasal mupirocin ointment. *J Hosp Infect* 2000;46:123–9.

26. Strunk T, Richmond P, Simmer K, Currie A, Levy O, Burgner D. Neonatal immune responses to coagulase-negative staphylococci. *Curr Opin Infect Dis* 2007;20:370–5.
27. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002;110:285–91.
28. Tiskumara R, Fakharee SH, Liu CQ, Nuntnarumit P, Lui KM, Hammoud M, et al. Neonatal infections in Asia. *Arch Dis Child* 2009;94:F144–8.
29. Zaidi AK, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries. *Pediatr Infect Dis J* 2009;28:S10–8.
30. Huang YC, Su LH, Wu TL, Leu HS, Hsieh WS, Chang TM, et al. Outbreak of *Acinetobacter baumannii* bacteremia in a neonatal intensive care unit: clinical implications and genotyping analysis. *Pediatr Infect Dis J* 2002;21:1105–9.
31. Villegas MV, Hartstein AI. *Acinetobacter* outbreaks, 1977–2000. *Infect Control Hosp Epidemiol* 2003;24:284–95.
32. Huang YC, Lin TY, Lien RI, Chou YH, Kuo CY, Yang PH, et al. Candidaemia in special care nurseries: comparison of *albicans* and *parapsilosis* infection. *J Infect* 2000;40:171–5.
33. Manzoni P, Stolfi I, Pugni L, Decembrino L, Magnani C, Vetrano G, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N Engl J Med* 2007;356:2483–95.
34. Long SS, Stevenson DK. Reducing Candida infections during neonatal intensive care: management choices, infection control, and fluconazole prophylaxis. *J Pediatr* 2005;147:135–41.