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Brief communication (Original)

Trends in neonatal sepsis in a neonatal intensive care unit in Thailand before and after construction of a new facility

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Background: Neonatal sepsis is a cause of mortality and long-term morbidity worldwide.

Objectives: To describe longitudinal trends in the cumulative incidence of early- and late-onset sepsis (EOS and LOS), mortality, and causative organisms in a Thai Hospital before and after construction of a new neonatal intensive care unit (NICU).

Methods: Review of NICU admissions with blood cultures positive for bacteria or fungi for the periods 1995 to 2002 (preconstruction) and 2004 to 2010 (postconstruction). Sepsis was categorized into EOS (within first 3 days of life) and LOS (after first 3 days of life).

Results: Of 5,570 admissions, 241 (4.3%) neonates with 276 episodes of sepsis were identified. There was no difference in the rate of sepsis overall ($P = 0.90$), LOS ($P = 0.30$), or sepsis-related mortality ($P = 0.61$) over the two periods, but the rate of EOS increased significantly from 0.34% to 0.81% ($P = 0.04$). Rates of *Klebsiella* species and *Escherichia coli* sepsis increased from 13.6% to 25.6% ($P = 0.01$) and from 5.3% to 12.2% ($P = 0.04$), respectively, while rates of *Staphylococcus aureus* sepsis decreased from 12.9% to 4.3% ($P < 0.007$). Sepsis-related mortality was 1.8%.

Conclusions: Although direct causality cannot be proven, the rate of EOS and the pattern of causative organisms changed following construction of the new NICU. Building a new unit does not necessarily result in a reduction in the rate of sepsis. This data may provide a baseline for implementing evidence-based infection control strategies to prevent/reduce sepsis and improve neonatal care.

Keywords: Early-onset sepsis, infant-newborn, late-onset sepsis, neonatal intensive care unit, sepsis.

Advances in perinatal and neonatal management have resulted in a significant reduction in neonatal mortality worldwide over the past 40 years [1]. Despite this reduction, neonatal sepsis continues to be a significant contributor to mortality and morbidity in both developed and developing countries [2] with a case-fatality rate ranging from 2% to 50% [3-6]. In addition to mortality, neonatal sepsis also contributes to prolonged hospital stay, increased health care costs, and adverse neurodevelopmental outcomes, particularly in infants with a very low birth weight [7, 8].

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Neonatal sepsis is categorized into early-onset sepsis (EOS), which occurs in the first 3 days of life, and late-onset sepsis (LOS), which occurs thereafter. In the USA, the overall cumulative incidence of EOS is from 0.8 to 1.0 cases per 1,000 live births [9] and the rate of LOS is 36% in preterm infants (22–28 weeks gestational age/401–1500 g birth weight) [10]. Similarly, two studies of groups of neonatal intensive care unit (NICUs) in developing countries including Malaysia, Thailand, China, and India, found the rate of EOS to be from 0.62 to 0.72 cases per 1,000 live births [11, 12]. However, these studies also found a rate of LOS ranging from 2.0 per 1,000 live births in Hong Kong to 22.0 per 1,000 live births in Thailand [11].

Long-term epidemiological data also document a substantial shift from EOS to LOS, and a change in

the causative organisms [4]. In the 1930s and 1940s, group A streptococcus infections were predominant across North America, while in the 1950s, nursery outbreaks of *Staphylococcus aureus* infection appeared in both North America and Europe. In the 1960s, *Escherichia coli* was the most common cause of bacterial sepsis, followed by group B streptococci in the 1970s [4]. Following implementation of the Center for Disease Control recommendations for prevention of perinatal group B streptococcal (GBS) disease [13], the rate of GBS-specific EOS has decreased to from 0.3 to 0.4 cases per 1,000 live births [9]. However, in the USA GBS infection remains a common cause of EOS [9], while *Staphylococcus epidermidis* remains the most common cause of LOS, especially in infants with a very low birth weight [14]. In developing countries, the rate of GBS-related sepsis remains low, while *Staphylococcus epidermidis* and gram-negative organisms such as *Klebsiella species* contribute most to LOS [11].

The rate of sepsis and causative organisms may differ in the same unit over time, from one unit to another, and between countries. In particular, there is a gap in the knowledge regarding long-term trends in neonatal sepsis in Thailand; knowledge that would be useful for planning infection control and prevention. Therefore, the objective of this study was to identify longitudinal trends in the rate of EOS, LOS, sepsis-related mortality, and causative organisms in Songklanagarind Hospital, Thailand, before and after construction of a new neonatal intensive care unit (NICU) facility in 2003. We hypothesized that the rate of sepsis would decrease after the construction of a new NICU with increased space and personnel.

Materials and methods

Study population and data collection

The study was approved by the Ethics Committee, Faculty of Medicine, Prince of Songkla University. In this retrospective study the health records of all infants with blood cultures positive for bacteria or fungi admitted to the NICU of Songklanagarind Hospital for the periods 1995 to 2002 (preconstruction) and 2004 to 2010 (postconstruction) were reviewed. Data from 2003 were excluded because the facility was being established. Songklanagarind Hospital is a tertiary-level perinatal center with approximately 3,000 live births per year. The unit also admits outborn infants from 14 provinces of Southern Thailand and from the hospital's outpatient clinic, and those who require surgical interventions.

Infants with a blood culture positive for bacteria or fungi were identified from a list generated by the microbiology department, which was cross-referenced with infant health records. Maternal and neonatal data were collected using a predesigned data collection form and entered into a database. Maternal data included any illness before and during pregnancy including infection, duration of rupture of membranes, and mode of delivery. Neonatal data collected included gestational age, birth weight, sex, Apgar scores at 1 and 5 minutes, inborn vs. outborn status (transferred from other hospitals/admitted from outpatient clinic), symptoms and signs of sepsis (temperature instability, respiratory distress, tachycardia [heart rate > 180 bpm] or bradycardia [heart rate < 100 bpm], apnea, and hypoglycemia [blood sugar level < 40 mg/dL] or hyperglycemia [blood sugar level > 140 mg/dL]), complete blood cell count, and blood culture. Cerebrospinal fluid and urine cultures were also performed for all infants with a blood culture positive for bacteria or fungi.

Outcomes measured

Sepsis was diagnosed if a blood culture yielded pathogens or a commensal species (bacteria and fungi normally present on skin and in intestinal flora), including staphylococcal species, gram-positive rods other than *Listeria* species, gram-negative cocci other than *Neisseria meningitidis* and *Neisseria gonorrhoeae*, and *Candida* species [4]. Sepsis attributed to a commensal species was diagnosed if the blood culture was positive for a commensal species and the following criteria were fulfilled when the culture was obtained: (1) presence of two or more of the following symptoms: apnea (cessation of breathing for >20 s or <20 s if also accompanied by bradycardia or cyanosis); bradycardia; rectal temperature >38°C (hyperthermia) or <36.5°C (hypothermia); hyperglycemia; or hypoglycemia; and (2) presence of a second blood culture positive for the same organism obtained within 24 hours of the first culture or the presence of a central access device before occurrence of symptoms [4]. Sepsis was further categorized as EOS or LOS.

Infants who were evaluated for EOS and LOS were managed as follows: for suspected EOS, infants were treated initially with ampicillin and gentamicin, and for suspected LOS, infants were initially treated with ceftazidime and amikacin. Further antibiotic therapy was based on the antibiotic susceptibility of

the isolated pathogens. Second or third line antibiotics used included a combination of cefoperazone with sulbactam or imipenem/meropenem or colistin.

Trends in the rates and patterns of EOS and LOS episodes, sepsis-related mortality and types of organisms were compared from 1995 to 2002 (preconstruction) and from 2004 to 2010 (postconstruction). Death was attributed to sepsis if a blood culture positive for bacteria or fungi was obtained within 7 days of death or there was clinical evidence of sepsis. The primary outcome was cumulative incidence of EOS and LOS over the two periods. Secondary outcomes included sepsis-related mortality and causative organisms.

Statistical analyses

The SAS statistical software package (version 9.2, SAS Institute, Cary, NC, USA) was used to develop a database of categorical and continuous variables. Demographic and clinical data were summarized with counts and percentages for categorical variables, means and standard deviations (SD) for normally distributed continuous variables, and medians with ranges for non-normally continuous variables. Binomial variables were analyzed using a χ^2 test and continuous variable comparisons using a Student *t* test. All tests were two-sided with a statistical significance of $P < 0.05$.

Results

Cumulative incidence of sepsis and mortality

From 1995 to 2002, a total of 21,140 infants were born in Songklanagarind Hospital and 2,348 were admitted to the NICU. From 2004 to 2010, some 20,343 infants were born and 3,222 were admitted to the NICU. Of the total 5,570 admissions to NICU, 241 (4.3%) neonates with 276 episodes of sepsis were identified. **Table 1** shows the baseline characteristics of the study population during the two periods. Of the 241 infants with sepsis, 34 had EOS, while 207 had LOS. Among infants with LOS, 35 had a second episode of sepsis. The overall cumulative incidence of sepsis for inborn infants was 2.68 cases per 1,000 live births.

Over the two periods, the rate of EOS increased significantly from 0.34% (8/2,348) to 0.81% (26/3,222) ($P = 0.04$). The rates of all cases of sepsis (4.39% [103/2,348] vs. 4.28% [138/3,222], $P = 0.90$) and LOS (4.05% [95/2,348] vs. 3.48% [112/3,222], $P = 0.30$) were not significantly different between the two periods, neither was the rate of sepsis-related mortality (0.68% vs. 0.84%, $P = 0.61$).

Table 1. Baseline characteristics of the study population with blood culture positive for bacteria or fungi (241 infants)

Variables[a]	1995–2002 (n = 103)	2004–2010 (n = 138)
Gestational age (weeks)	35.0 (4.9)	34.9 (4.6)
Birth weight (g)	2,231 (960)	2,290 (971)
Very-low-birth weight (<1,500 g)	27 (26.2%)	37 (26.8%)
Sex (% male)	68 (66.0%)	78 (56.5%)
Small for gestational age	19 (18.4%)	11 (8.0%)*
Apgar score at 1 minute	7 (0–9)	8 (1–10)
Apgar score at 5 minutes	9 (0–10)	9 (1–10)
Mode of delivery		
Vaginal delivery	62 (60.2%)	76 (55.1%)
Cesarean section	38 (36.9%)	59 (42.8%)
Instrumentation	3 (2.9%)	3 (2.2%)
Prolonged rupture of membrane (>18 hours)	3 (2.9%)	12 (8.7%)
Status of admission		
Inborn	48 (46.6%)	63 (45.7%)
Outborn	50 (48.5%)	71 (51.4%)
Outpatient	5 (4.9%)	4 (2.9%)

[a]Results are presented as mean (SD), median (range) and number (%) as appropriate. *$P < 0.05$

Types of causative organisms

A total of 296 organisms were isolated from the 241 infants with a blood culture positive for bacteria or fungi (**Table 2**). In infants with EOS, 50.0% of the organisms cultured over the total study period were gram-positive and 47.2% were gram-negative. The most common gram-positive organisms were *Staphylococcus epidermidis* followed by *Enterococcus* species and *Staphylococcus aureus*. Only one newborn had GBS sepsis and was outborn. *Klebsiella species* and *E. coli* were the most common gram-negative organisms isolated, followed by *Acinetobacter baumannii* and *Enterobacter* species.

In infants with LOS, 28.8% of the organisms cultured were gram-positive and 58.1% were gram-negative. The predominant gram-positive organism cultured included *Staphylococcus epidermidis* followed by *Staphylococcus aureus* and *Enterococcus* species, while the most common gram-negative organisms cultured were *Klebsiella* species followed by *Acinetobacter* species and *E. coli*. In LOS, 13.1% of organisms cultured were fungi while this rate was only 2.8% for EOS.

Longitudinal changes in rates of causative organisms

Comparison between the two periods showed that the percentage of all cases of sepsis caused by *Klebsiella* species and *Escherichia coli* increased from 13.6% to 25.6% ($P = 0.01$) and from 5.3% to 12.2% ($P = 0.04$), respectively, while the percentage of sepsis from *Staphylococcus aureus* decreased from 12.9% to 4.3% ($P < 0.007$) (**Table 2**). Comparing infants with EOS and LOS, the rates of infection with *Klebsiella* species increased and *Staphylococcus aureus* decreased only in infants with LOS from 13.1% to 28.3% ($P = 0.003$) and from 13.1% to 5.1% ($P = 0.023$), respectively. No significant differences were noted for the rates of any other organisms.

The types of causative organisms based on the status of admission (inborn, outborn and admitted from hospital outpatient clinic) are presented in **Table 3**. Comparison between 2004 to 2010 and 1995 to 2002 shows a decrease in *Staphylococcus aureus* and an increase in *E. coli* sepsis in inborn infants, and an increase in *Klebsiella species* sepsis in outborn infants.

Table 2. Trends in causative organisms in early-onset, late-onset, and overall sepsis during the two periods (296 organisms)

	Early-onset sepsis, n (%)		Late-onset sepsis, n (%)		All sepsis cases, n (%)	
	1995–2002	**2004–2010**	**1995–2002**	**2004–2010**	**1995–2002**	**2004–2010**
Total number of organisms	**10**	**26**	**122**	**138**	**132**	**164**
Gram-positive organisms	**3 (30.0)**	**15 (57.7)**	**44 (36.1)**	**31 (22.5)***	**47 (35.6)**	**46 (28.0)**
Staphylococcus epidermidis	0	8 (30.8)	19 (15.6)	13 (9.4)	19 (14.4)	21 (12.8)
Staphylococcus aureus	1 (10.0)	0	16 (13.1)	7 (5.1)*	17 (12.9)	7 (4.3)*
Enterococcus species	1 (10.0)	3 (11.5)	5 (4.1)	8 (5.8)	6 (4.5)	11 (6.7)
Group B streptococci	1 (10.0)	0	0	0	1 (0.8)	0
Other gram positive	0	4 (15.4)	4 (3.3)	3 (2.2)	4 (3.0)	7 (4.3)
Gram-negative organisms	**6 (60.0)**	**11 (42.3)**	**62 (50.8)**	**89 (64.5)***	**68 (51.5)**	**100 (61.0)**
Klebsiella species	2 (20.0)	3 (11.5)	16 (13.1)	39 (28.3)*	18 (13.6)	42 (25.6)*
Acinetobacter species	1 (10.0)	2 (7.7)	16 (13.1)	16 (11.6)	17 (12.9)	18 (11.0)
Escherichia coli	0	5 (19.2)	7 (5.7)	15 (10.9)	7 (5.3)	20 (12.2)*
Enterobacter species	1 (10.0)	0	7 (5.7)	4 (2.9)	8 (6.1)	4 (2.4)
Pseudomonads	0	0	4 (3.3)	4 (2.9)	4 (3.0)	4 (2.4)
Other gram negative rods	2 (20.0)	1 (3.8)	12 (9.8)	11 (8.0)	14 (10.6)	12 (7.3)
Fungi	**1 (10.0)**	**0**	**16 (13.1)**	**18 (13.0)**	**17 (12.9)**	**18 (11.0)**
Candida parapsilosis	0	0	9 (7.4)	8 (5.8)	9 (6.8)	8 (4.9)
Candida albicans	1 (10.0)	0	3 (2.5)	8 (5.8)	4 (3.0)	8 (4.9)
Other fungi	0	0	4 (3.3)	2 (1.4)	4 (3.0)	2 (1.2)

*$P < 0.05$ for the two periods

Table 3. Trends in causative organisms in early-onset, late-onset and overall sepsis during the two periods based on status of admission (inborn, transferred and outpatient infant) during the two periods (296 organisms)

	Inborn infant, n (%)		Outborn infant, n (%)		Outpatient infant, n (%)	
	1995–2002	2004–2010	1995–2002	2004–2010	1995–2002	2004–2010
Total number of organisms	**58**	**72**	**69**	**88**	**5**	**4**
Gram-positive organisms	**22 (37.9)**	**20 (27.8)**	**22 (31.9)**	**24 (27.3)**	**3 (60.0)**	**2 (50.0)**
Staphylococcus epidermidis	8 (13.8)	9 (12.5)	10 (14.5)	12 (13.6)	1 (20.0)	0
Staphylococcus aureus	9 (15.5)	2 (2.8)*	7 (10.1)	4 (4.5)	1 (20.0)	1 (25.0)
Enterococcus species	3 (5.2)	5 (6.9)	3 (4.3)	5 (5.7)	0	1 (25.0)
Group B streptococci	0	0	1 (1.4)	0	0	0
Other gram positive	2 (3.4)	4 (5.6)	1 (1.4)	3 (3.4)	1 (20.0)	0
Gram-negative organisms	**30 (51.7)**	**43 (59.7)**	**36 (52.2)**	**55 (62.5)**	**2 (40.0)**	**2 (50.0)**
Klebsiella species	10 (17.2)	18 (25.0)	8 (11.6)	24 (27.3)*	0	0
Acinetobacter species	5 (8.6)	8 (11.1)	12 (17.4)	10 (11.4)	0	0
Escherichia coli	1 (1.7)	9 (12.5)*	5 (7.2)	10 (11.4)	1 (20.0)	1 (25.0)
Enterobacter species	5 (8.6)	3 (4.2)	3 (4.3)	1 (1.1)	0	0
Pseudomonads	2 (3.4)	2 (2.8)	2 (2.9)	2 (2.3)	0	0
Other gram-negative rods	7 (12.1)	3 (4.2)	6 (8.7)	8 (9.1)	1 (20.0)	1 (25.0)
Fungi	**6 (10.3)**	**9 (12.5)**	**11 (15.9)**	**9 (10.2)**	**0**	**0**
Candida parapsilosis	3 (5.2)	4 (5.6)	6 (8.7)	4 (4.5)	0	0
Candida albicans	1 (1.7)	4 (5.6)	3 (4.3)	4 (4.5)	0	0
Other fungi	2 (3.4)	1 (1.4)	2 (2.9)	1 (1.1)	0	0

*$P < 0.05$ for the two periods

Discussion

This study describes the longitudinal trends and pattern of neonatal sepsis before and after the 2003 construction of a new NICU facility in Songklanagarind Hospital in Thailand. No difference in the rate of overall sepsis and LOS was noted over the two periods. However, an increase in the rate of EOS was observed. *Staphylococcus epidermidis* remained the most common gram-positive organism responsible for EOS, while a reduction in *Staphylococcus aureus* sepsis was noted. By contrast with reports from Western countries [4, 15], despite the lack of universal screening of pregnant women for GBS infection in Thailand, GBS-related sepsis was only noted in one infant. In terms of gram-negative organisms, sepsis secondary to infection with *Klebsiella* species and *Escherichia coli* increased significantly over time.

By comparison with the old NICU, the new larger facility had 15 beds instead of 10 and the number of staff increased with the addition of another neonatologist, two to four pediatric residents per year, and two neonatal fellows. The nurse-to-patient ratio changed from 1:2 to 1:1 for critically ill patients and was 1:2 for more stable infants. Furthermore, the number of incubators and sinks for hand washing was increased and antiseptic hand hygiene solutions were made available at each bedside. Even though the unit does not have a dedicated infection control practitioner or specific infection control education program, anecdotal reports suggest there was increased awareness of infection control practices including hand hygiene. However, the perceived improvements in care provision and attention to hand hygiene did not result in a decreased rate of sepsis in the new NICU.

There are several potential factors that can explain this finding. The long length of the comparison period before and after the construction of the unit. Even though the newly built physical environment may initially have had a strong influence on the performance of healthcare workers in terms of compliance with evidence-based practices including hand hygiene and other infection control practices, over time the compliance may have decreased and therefore influenced the rate of sepsis. There was no designated infection control practitioner to monitor hand hygiene compliance and other infection control practices in the unit. More babies were admitted in the postconstruction phase, which could have resulted in overcrowding and impacted on the workload of health care professionals leading to poor compliance with infection control practices. Other factors that

could influence the rate of sepsis include the need for central catheters including peripheral intravenous catheters, multiple skin breaks, and prolonged use of antibiotics. However, no data regarding these influences were collected and therefore we cannot attribute our results to any of these factors.

Rates and causative pathogens of neonatal sepsis can vary within the same unit, among units, and across countries [11, 12, 16, 17]. The rates of sepsis in this study are comparable to those in units in Taiwan that reported rates ranging from 3% to 4% [18, 19], but lower compared with data from other countries such as the Philippines, The Netherlands, and Nigeria, where sepsis rates have been reported to range from 15.1% to 19.6% [20-22]. Furthermore, at 2.68 cases per 1,000 live births, the rate of sepsis for inborn infants was lower than that reported in other countries including Korea (5.9 cases per 1,000 live births) [23], the USA (6.1 cases per 1,000 live births) [4], and India (14.8 cases per 1,000 live births) [24]. However, it is important to recognize that the study population was of higher gestational age and birth weight (about 25%–30% were of very-low-birth weight infants), which could account for the lower rate of sepsis.

The implications of *Staphylococcus epidermidis*, *Klebsiella* species, and *E. coli* as the main causative organisms for sepsis in the Songklanagarind Hospital NICU, with only rare cases of GBS-related sepsis, is consistent with studies in other developing countries [25]. The finding that rates of infection with *Klebsiella* species and *E. coli* increased over the two periods, while *Staphylococcus aureus* rates decreased suggests an alteration in the predominant modes of transmission of infection. Infants on ventilators, with prolonged use of intravenous catheters or central lines, and those requiring surgery are more likely to be exposed to *Klebsiella* species [26-28]. However, data on patient characteristics and care practices are not available to provide an explanation for the change in rates of *Klebsiella* species.

We observed an increase in the cumulative incidence of EOS attributed mainly to *Staphylococcus epidermidis*. This was surprising because *Staphylococcus epidermidis* is a primary pathogens isolated in LOS rather than EOS and is usually seen between postnatal days 7 and 14, coinciding with the use of interventions such as intravascular catheters and mechanical ventilators. However, because *Staphylococcus epidermidis* is a component of normal skin flora it can contaminate blood cultures that are drawn peripherally or though venous catheters [29, 30]. In this study sepsis was attributed to a commensal species if the infant was symptomatic at the time blood for culture was obtained and later found to be positive for a commensal species.

A major strength of this study is that it covers long periods before and after construction of the new facility. However, there are several limitations including the use of data from a single center, the retrospective nature of the study, and the limited clinical data available to correlate the maternal and neonatal characteristics of infants with the type of sepsis and causative organisms isolated. There are no data regarding care practices including the antibiotics used and the pattern antibiotic resistance over time. On-going surveillance to monitor the rate of sepsis and describe the type of organisms along with their antibiotic susceptibility profile is important to monitor the impact of preventive strategies to reduce neonatal sepsis.

Conclusion

Although there was no difference in the overall rate of sepsis and LOS in Songklanagarind Hospital, Thailand, the rate of EOS was higher in the postconstruction period. *Klebsiella* species continue to be a major contributor to sepsis and are on the rise. Building a new unit does not necessarily result in a reduction in the rate of sepsis. Surveillance of sepsis rates and common etiological organisms is crucial for implementing evidence-based infection control strategies to prevent/reduce sepsis and improve neonatal care.

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References

1. Rajaratnam JK, Marcus JR, Flaxman AD, Wang H, Levin-Rector A, Dwyer L, et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970–2010: a systematic analysis of progress towards

Millennium Development Goal 4. Lancet. 2010; 375: 1988-2008.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2095-128.
3. Nizet V, Klein JO. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA, editors. Infectious diseases of the fetus and new born infant. 7th ed. Philadelphia: Elsevier Saunders; 2011. p. 222-75.
4. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. Pediatrics. 2005; 116:595-602.
5. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am. 2013; 60:367-89.
6. Morioka I, Morikawa S, Miwa A, Minami H, Yoshii K, Kugo M, et al. Culture-proven neonatal sepsis in Japanese neonatal care units in 2006-2008. Neonatology. 2012; 102:75-80.
7. Polin RA, Denson S, Brady MT; Committee on Fetus and Newborn; Committee on Infectious Diseases. Epidemiology and diagnosis of health care-associated infections in the NICU. Pediatrics. 2012; 129:e1104-9.
8. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet. 2012; 379:445-52.
9. Mukhopadhyay S, Puopolo KM. Risk assessment in neonatal early onset sepsis. Semin Perinatol. 2012; 36: 408-15.
10. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010; 126:443-56.
11. Al-Taiar A, Hammoud MS, Cuiqing L, Lee JK, Lui KM, Nakwan N, et al. Neonatal infections in China, Malaysia, Hong Kong and Thailand. Arch Dis Child Fetal Neonatal Ed. 2013; 98:F249-55.
12. Tiskumara R, Fakharee SH, Liu CQ, Nuntnarumit P, Lui KM, Hammoud M, et al. Neonatal infections in Asia. Arch Dis Child Fetal Neonatal Ed. 2009; 94: F144-8.
13. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010; 59:1-36.
14. Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotten CM, et al. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. J Pediatr. 2013; 162:1120-4.e1.
15. Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B streptococcal and *E. coli* disease continues. Pediatrics. 2011; 127:817-26.
16. Osrin D, Vergnano S, Costello A. Serious bacterial infections in newborn infants in developing countries. Curr Opin Infect Dis. 2004; 17:217-24.
17. Janjindamai W, Srithaveesinsup Y, Chanwitan P. Neonatal septicemia in Songklanagarind Hospital. Songkla Med J. 1998; 16:9-18.
18. 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.
19. Wu JH, Chen CY, Tsao PN, Hsieh WS, Chou HC. Neonatal sepsis: a 6-year analysis in a neonatal care unit in Taiwan. Pediatr Neonatol. 2009; 50:88-95.
20. Gill CJ, Mantaring JB, Macleod WB, Mendoza M, Mendoza S, Huskins WC, et al. Impact of enhanced infection control at 2 neonatal intensive care units in the Philippines. Clin Infect Dis. 2009; 48:13-21.
21. Ogunlesi TA, Ogunfowora OB, Osinupebi O, Olanrewaju DM. Changing trends in newborn sepsis in Sagamu, Nigeria: bacterial aetiology, risk factors and antibiotic susceptibility. J Paediatr Child Health. 2011; 47:5-11.
22. van den Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, Krediet TG. Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. Neonatology. 2010; 97:22-8.
23. Shim GH, Kim SD, Kim HS, Kim ES, Lee HJ, Lee JA, et al. Trends in epidemiology of neonatal sepsis in a tertiary center in Korea: a 26-year longitudinal analysis, 1980-2005. J Korean Med Sci. 2011; 26:284-9.
24. Viswanathan R, Singh AK, Mukherjee S, Mukherjee R, Das P, Basu S. Aetiology and antimicrobial resistance of neonatal sepsis at a tertiary care centre in eastern India: a 3 year study. Indian J Pediatr. 2011; 78:409-12.
25. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. Arch Dis Child Fetal Neonatal Ed. 2005; 90:F220-4.
26. Hocevar SN, Edwards JR, Horan TC, Morrell GC, Iwamoto M, Lessa FC. Device-associated infections among neonatal intensive care unit patients: incidence and associated pathogens reported to the National

Healthcare Safety Network, 2006–2008. Infect Control Hosp Epidemiol. 2012; 33:1200-6.
27. Larson EL, Cimiotti JP, Haas J, Nesin M, Allen A, Della-Latta P, et al. Gram-negative bacilli associated with catheter-associated and non-catheter-associated bloodstream infections and hand carriage by healthcare workers in neonatal intensive care units. Pediatr Crit Care Med. 2005; 6:457-61.
28. Parm U, Metsvaht T, Sepp E, Ilmoja ML, Pisarev H, Pauskar M, et al. Risk factors associated with gut and nasopharyngeal colonization by common Gram-negative species and yeasts in neonatal intensive care units patients. Early Hum Dev. 2011; 87:391-9.
29. Jean-Baptiste N, Benjamin DK, Jr., Cohen-Wolkowiez M, Fowler VG, Jr., Laughon M, Clark RH, et al. Coagulase-negative staphylococcal infections in the neonatal intensive care unit. Infect Control Hosp Epidemiol. 2011; 32:679-86.
30. Thylefors JD, Harbarth S, Pittet D. Increasing bacteremia due to coagulase-negative staphylococci: fiction or reality? Infect Control Hosp Epidemiol. 1998; 19:581-9.