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Changes in Epidemiology of Neonatal Sepsis according to Rapid Expansion of a Tertiary Neonatal Intensive Care Unit: Trends over 18 Years

3 차 신생아 집중치료실의 빠른 확장에 따른 신생아 패혈증의 역학 변화: 18 년 간의 추이

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by

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A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Pediatrics at Seoul National University College of Medicine

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Abstract

Changes in Epidemiology of Neonatal Sepsis according to Rapid Expansion of a Tertiary Neonatal Intensive Care Unit: Trends over 18 Years

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Objectives: We investigated changes in the admission patterns of neonatal intensive care units (NICU) and the epidemiology of neonatal sepsis following the rapid expansion and improvements in neonatal intensive care.

Methods: Data regarding the admission of neonates with culture-proven sepsis between 1996 and 2013 (period I: 1996-2005, period II: 2006-2013) were collected retrospectively.

Results: The admission of extremely low birth weight (ELBW) infants increased between periods I and II (11.1 vs. 28.7 infants per 1,000 live births, $P < 0.001$). The survival rate of the ELBW infants improved (57.5 vs. 80.1%, $P < 0.001$), and their duration of hospital stay increased (median days: 64 vs. 80, $P = 0.001$). The incidence of sepsis among all infants and ELBW infants increased (all infants, 5.9

vs. 12.7 cases per 1,000 live births; ELBW infants, 189.5 vs. 290.1 cases per 1,000 live births). In ELBW infants, the incidence of sepsis caused by coagulase-negative *Staphylococcus* (CONS), significantly increased during period II (8.8 vs. 25.4%, *P* = 0.039). By multivariate analysis, central vascular catheters and prolonged hospitalization were independently associated with increased sepsis rate, particularly CONS in ELBW infants.

Conclusions: The inborn admission rate for ELBW infants has increased significantly and is accompanied by improved survival and longer hospital stays. The incidence of neonatal sepsis, particularly in ELBW infants, has also increased, and CONS has emerged as a major pathogen. Our data suggested that central vascular catheters and prolonged hospitalization could be independent risk factors for the increased sepsis rate, particularly sepsis due to CONS.

keywords: Coagulase-negative *Staphylococci*; Epidemiology; Extremely low birth weight infant; Intensive care units, neonatal; Sepsis

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Introduction

Neonatal sepsis is a major concern and an important cause of morbidity and mortality in neonatal intensive care (1, 2). Infection control measures such as hand hygiene have been emphasized for the prevention of neonatal sepsis, and appropriate antibiotics usage strategies have been recommended according to each center's pathogenic epidemiology (3, 4). However, the patterns of the bacterial pathogens responsible for neonatal sepsis have changed with developments in intensive care units (5-7).

The preterm birth rate continues to increase in most developed countries. In the USA, the rate of preterm births increased by approximately 30% from 1981-2006 (8); in Europe, reported preterm rates are generally 5-9% (9-11). Recently, this trend has also been reported in many Asian countries. In China, the proportion of preterm births increased from 4.7 to 18.9% from 1987-2006 (12); in Taiwan, the preterm birth rate is 8.56%, and a 0.07% annual increase ($P < 0.001$) was observed from 2001-2009 (13). In South Korea, the preterm birth rate increased from 2.5 to 5.9% from 1995-2010 (14).

Under these circumstances, South Korea has experienced rapid expansion and development in neonatal intensive care over the past two decades, with increases in the number of tertiary neonatal intensive care units (NICUs) and improvements in survival outcomes that are comparable with those of the United States and Japan (15). Changes in the NICU population and

improvements in survival have been associated with the increased use of invasive medical devices, prolonged courses of antibiotics, and longer hospital stays, all of which can increase the chances of nosocomial infection (16-19). However, few reports have described the epidemiological changes in neonatal sepsis related to the rapid NICU expansion.

In this study, the trends in NICU patient population changes were reviewed, and possible changes in the epidemiology of neonatal sepsis over an 18-year period in a single representative tertiary NICU in South Korea are discussed.

Materials and Methods

Study design and data collection

The data of all inborn infants admitted to the NICU of the Seoul National University Children's Hospital (SNUCH) between January 1, 1996, and December 31, 2013 were studied retrospectively. SNUCH is a 311-bed tertiary teaching facility in Seoul, Korea. The NICU is a level III, 42-bed unit with 500-600 admissions per year; it provides critical care for ill neonates. The study period was divided into the first 10 years (period I: 1996-2005) and the latter 8 years (period II: 2006-2013). During period II, the SNUCH NICU was expanded from 22 to 42 beds between 2006 and 2011. The medical records of all neonates with positive blood cultures who were admitted during period II were reviewed. The data were compared with period I data from a previously published survey (20). The study protocol was approved by the institutional review board (IRB) of the SNUH (IRB No. 1409-087-609).

Definition

The diagnosis of neonatal sepsis required isolation of the microorganism from a blood culture and at least one clinical sign or symptom. Coagulase-negative *Staphylococcus* (CONS) sepsis was defined using the modified specific criteria of the Centers for Disease Control and Prevention (21). Sepsis was classified as early onset (EOS, ≤ 4 days of life), late onset (LOS,

5-30 days of life) and late, late onset (LLOS, > 30 days of life) (22).

A sepsis-related death was defined when death occurred within 7 days of a positive blood culture or when clinical signs and symptoms were documented as the direct cause of death. Sepsis-related mortality (SRM) was defined as the proportion of sepsis-related deaths over the total number of sepsis episodes (22).

The presence of a central vascular catheter or a mechanical ventilator was only included in the study when the device was placed before the onset of sepsis and was in place at the time of the positive blood culture. Surgery as a potential risk factor for sepsis was included only when the procedure occurred ≤ 7 days before the onset of the positive blood culture (22).

Statistical analysis

The SPSS version 21.0 statistical software package (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Student's t-test was used to compare the continuous variables. Pearson's chi-square test or Fisher's exact test (both two-sided) were used to compare the categorical variables. $P < 0.05$ was considered statistically significant.

Results

Increased inborn admissions are accompanied by increased survival and longer hospital stays for extremely low birth weight (ELBW) infants

Table 1 shows the demographics of inborn admissions at the SNUCH NICU over an 18-year period. There were 13,742 live births during period I and 12,603 live births during period II. The total inborn admission rate at the NICU was 128.0 infants per 1,000 live births during period I and 215.8 infants per 1,000 live births during period II. The admission rate of ELBW infants (birth weight < 1,000 g) was 11.1 infants per 1,000 live births during period I and 28.7 infants per 1,000 live births during period II ($P < 0.001$).

In a subgroup of ELBW infants, the median gestational age (GA) was 26^{+5} weeks for period I and 26^{+4} weeks for period II. The median birth weight was 790 g for period I and 760 g for period II. There were no significant differences in GA, birth weight, percentage of males, percentage of cesarean sections and Apgar scores between the two periods. However, the overall survival rate was significantly higher for period II compared with period I (57.5% vs. 80.1%, $P < 0.001$), and the median duration of hospital stay was significantly longer for period II (64 vs. 80 days, $P = 0.001$).

Table 1. Changes in NICU population between periods I (1996-2005) and II (2006-2013).

	Period I	Period II
Total live births (n)	13,742	12,603
Total inborn admission in NICU (n)	1,760	2,720
Total inborn admission in NICU (/1,000 live births)	128	215.8
ELBW inborn admission in NICU (n)	153	362
ELBW inborn admission in NICU (/1,000 live births)*	11.1	28.7*
ELBW/total inborn admission in NICU (%)	8.7	13.3
Nurse-to-patient ratio	1:3.6	1:2.9-3.3
Distance between the patients (m)	1.5	1.8-2.6
Subgroup of ELBW infants		
GA (week), median (min, max)	26^{+5} (23^{+2}, 34^{+6})	26^{+4} (22^{+3}, 39^{+6})
Birth weight (g), median (min, max)	790 (340, 990)	760 (290, 990)
Male, n (%)	67 (43.7)	184 (50.8)
C/S, n (%)	109 (71.2)	248 (68.5)
1 min AS, median (min, max)	3 (0, 8)	3 (0, 8)
5 min AS, median (min, max)	6 (0, 9)	6 (0, 9)
Survival, n (%)*	88 (57.5)	290 (80.1)*
Hospital stay (days), median (min, max)†	64 (1, 275)	80 (1, 461)†

NICU = Neonatal intensive care unit; ELBW = Extremely low birth weight;
GA = Gestational age; C/S = Cesarean section; AS = Apgar score
* *P*-value < 0.001; †*P*-value = 0.001

Increased sepsis during period II, particularly in ELBW infants

Of the total number of infants diagnosed with sepsis, 92 organisms were identified in 90 episodes of sepsis (including 2 cases of mixed infection) among 81 infants for period I, and 201 organisms were identified in 198 episodes of sepsis (including 3 cases of mixed infection) among 161 infants for period II (Table 2). The total sepsis rate was significantly higher among the infants from period II compared with those from period I (5.9 vs. 12.7 cases per 1,000 live births, $P < 0.001$). Among all of the infants with sepsis, the GA and birth weight were significantly lower during period II than during period I (median GA [weeks]: 29^{+1} vs. 27^{+3}, $P = 0.01$; birth weight [g]: 1,200 vs. 800, $P < 0.001$). The onset of sepsis was significantly later among the period II infants compared with the period I infants (median days: 17 [range of 1-116] vs. 20 [range of 1-167], $P = 0.028$). However, there was no significant difference in the survival rate between the two periods (77.8 vs. 80.1%, $P = 0.671$).

In subgroup analysis by birth weight, ELBW infants had the highest sepsis rate, with a significant increase during period II compared with period I (189.5 vs. 290.1 cases per 1,000 live births, $P = 0.018$). In the ELBW infants, the SRM decreased to a borderline-significant degree during period II. When the ELBW infants were divided into two groups by birth weight, the sepsis rate was higher among the infants with a birth weight < 750 g compared with those with a birth weight ≥ 750 g. Among the infants with a birth weight < 750 g, the sepsis rate was significantly higher during period

II than during period I (238.8 vs. 417.6 cases per 1,000 live births, P = 0.010). However, among infants with a birth weight ≥ 750 g, there was no significant difference in the sepsis rate between the two periods (151.2 vs. 177.1 cases per 1,000 live births, P = 0.594).

Table 2. Comparisons of sepsis rates and sepsis-related mortality by birth weight between periods I and II.

Birth weight (g)	Number of live births		Inborn cases of sepsis (Episodes)		Sepsis cases per 1,000 live births		*P*-value	SRM, n (%)		*P*-value
	P I	P II	P I	P II	P I	P II		P I	P II	
<1,000	153	362	29 (32)	105 (135)	189.5	290.1	0.018	7 (21.9)	14 (10.4)	0.078
<750	67	170	16 (18)	71 (93)	238.8	417.6	0.010	6 (33.3)	12 (12.9)	0.031
≥750	86	192	13 (14)	34 (42)	151.2	177.1	0.594	1 (7.1)	2 (4.8)	1.000
1,000-1,499	267	350	30 (33)	19 (19)	112.4	54.3	0.008	1 (3.0)	3 (15.8)	0.132
1,500-1,999	368	783	8 (9)	14 (16)	21.7	17.9	0.656	0 (0.0)	3 (18.8)	0.208
≥2,000	12,954	11,109	14 (16)	23 (28)	1.1	2.1	0.051	1 (6.3)	0 (0.0)	0.364
Total	13,742	12,604	81 (90)	161 (198)	5.9	12.7	< 0.001	9 (10.0)	20 (10.1)	0.979

SRM =Sepsis-related mortality

The changes in causative organisms among all sepsis cases, 1996-2013

Table 3 shows the percentage of causative organisms for all sepsis cases. During period I, the percentages of infants with sepsis for each onset time were as follows: 8.7% had EOS, 69.6% had LOS, and 21.7% had LLOS. During period II, the percentages of infants with sepsis for each onset time were as follows: 8.9% had EOS, 59.7% had LOS, and 31.3% had LLOS. Throughout the 18-year study, *S. aureus* was the most common causative organism of neonatal sepsis. Most of the *S. aureus* isolates (59/62) found during period II were methicillin resistant. Compared with period I, the incidence of sepsis caused by gram-positive bacteria (39.1 vs. 62.2%, $P < 0.001$), particularly by CONS (6.5 vs. 21.9%, $P = 0.001$), was significantly increased in period II. This pattern was observed in LOS and LLOS cases but not in EOS cases. The incidence of sepsis caused by fungus was lower for period II compared with period I (25.0 vs. 12.4%, $P = 0.007$), but this pattern was only observed in LLOS cases.

During period I, there were 6 (66.7%) fatal cases of sepsis caused by gram-negative bacteria, whereas there was only 1 (11.1%) death from methicillin-resistant *Staphylococcus epidermidis* (MRSE). During period II, there were 10 (50.0%) fatal cases of sepsis caused by gram-negative bacteria, 4 (20.0%) deaths from methicillin-resistant *Staphylococcus aureus* (MRSA), and 2 (10.0%) deaths from MRSE.

Table 3. Comparison of causative organisms in total sepsis cases of NICU between periods I and II.

Causative organisms	Sepsis onset time											
	EOS, n (%)			LOS, n (%)			LLOS, n (%)			Total, n (%)		
	P I	P II	*P*-value	P I	P II	*P*-value	P I	P II	*P*-value	P I	P II	*P*-value
G(+) bacteria	5 (62.5)	10(55.6)	1.000	24 (37.5)	72 (60.0)	0.004	7 (35.0)	43 (68.3)	0.008	36 (39.1)	125 (62.2)	< 0.001
S. aureus	1 (12.5)	3* (16.7)	1.000	15 (23.4)	40§ (33.3)	0.163	6 (30.0)	19*(30.2)	0.989	22 (23.9)	62 (30.8)	0.223
CONS	1† (12.5)	4* (22.2)	1.000	4‡ (6.3)	24 (20.0)	0.017	1 (5.0)	16* (25.4)	0.049	6 (6.5)	44 (21.9)	0.001
GBS	0 (0.0)	1 (5.6)	1.000	0 (0.0)	2 (1.7)	0.544	0 (0.0)	6 (9.5)	0.328	0 (0.0)	9 (4.5)	0.061
Enterococcus species	2† (25.0)	1 (5.6)	0.215	3 (4.7)	5§ (4.2)	1.000	0 (0.0)	1 (1.6)	1.000	5 (5.4)	7 (3.5)	0.434
Others	1 (12.5)	1 (5.6)	0.529	2 (3.1)	1 (0.8)	0.278	0 (0.0)	1 (1.6)	1.000	3 (3.3)	3 (1.5)	0.382
G(-) bacteria	2 (25.0)	8 (44.4)	0.420	23 (35.9)	28 (23.3)	0.069	8 (40.0)	15 (23.8)	0.159	33 (35.9)	51 (25.4)	0.065
E. coli	1 (12.5)	2 (11.1)	1.000	4 (6.3)	2 (1.7)	0.185	1 (5.0)	1 (1.6)	0.426	6 (6.5)	5 (2.5)	0.092
K. pneumoniae	0 (0.0)	1 (5.6)	1.000	8 (12.5)	10 (8.3)	0.365	5 (25.0)	10 (15.9)	0.355	13 (14.1)	21 (10.4)	0.361
Enterobacter species	1 (12.5)	2 (11.1)	1.000	2 (3.1)	5 (4.2)	1.000	1 (5.0)	2 (3.2)	0.568	4 (4.3)	9 (4.5)	1.000
Acinetobacter species	0 (0.0)	0 (0.0)	.	6 (9.4)	5 (4.2)	0.156	0 (0.0)	1 (1.6)	1.000	6 (6.5)	6 (3.0)	0.156
P. aeruginosa	0 (0.0)	2 (11.1)	1.000	1 (1.6)	0 (0.0)	0.348	0 (0.0)	0 (0.0)	.	1 (1.1)	2 (1.0)	1.000
S. marcescens	0 (0.0)	1 (5.6)	1.000	0 (0.0)	0 (0.0)	.	0 (0.0)	1 (1.6)	1.000	0 (0.0)	2 (1.0)	1.000
Others	0 (0.0)	0 (0.0)	.	2 (3.1)	6 (5.0)	0.716	1 (5.0)	0 (0.0)	0.241	3 (3.3)	6 (3.0)	1.000
Fungus	1 (12.5)	0 (0.0)	0.308	17 (26.6)	20 (16.7)	0.111	5 (25.0)	5 (7.9)	0.041	23 (25.0)	25 (12.4)	0.007
Candida species	1 (12.5)	0 (0.0)	0.308	17‡ (26.6)	20 (16.7)	0.111	3 (15.0)	5 (7.9)	0.392	21 (22.8)	25 (12.4)	0.023
Others	0 (0.0)	0 (0.0)	.	0 (0.0)	0 (0.0)	.	2 (10.0)	0 (0.0)	0.056	2 (2.2)	0 (0.0)	0.098
Total	8 (100.0)	18 (100.0)		64 (100.0)	120 (100.0)		20 (100.0)	63 (100.0)		92 (100.0)	201 (100.0)	

EOS = Early onset sepsis; LOS = Late onset sepsis; LLOS = Late, late onset sepsis; CONS = Coagulase-negative *Staphylococcus*; GBS = Group B *Streptococcus*

* Mixed infection: Methicillin-resistant *S. aureus* (MRSA) + CONS; †Mixed infection: CONS + *Enterococcus faecalis*; ‡Mixed infection: CONS + *Candida albicans*; § Mixed infection: MRSA + *Enterococcus faecalis*

The changes in causative organisms among ELBW infants, 1996-2013

During period I, the percentages of infants with sepsis for each onset time were as follows: 9.1% had EOS, 72.7% had LOS and 21.2% had LLOS. During period II, the percentages of infants with sepsis for each onset time were as follows: 8.7% had EOS, 62.3% had LOS and 29.0% had LLOS. *S. aureus* was the most common causative organism of neonatal sepsis in period I (Table 4). However, in period II, *S. aureus* and CONS were present in similar proportions. Compared with period I, the incidence of sepsis caused by gram-positive bacteria (44.1 vs. 61.6%, $P = 0.064$) was increased in period II with borderline significance. The incidence of sepsis caused by CONS increased significantly between periods I and II for the total group of infants with sepsis (8.8 vs. 25.4%, $P = 0.039$). There was no significant difference in the incidence of sepsis caused by gram-negative bacteria and fungus.

Table 5 shows the clinical characteristics of the ELBW infants diagnosed with neonatal sepsis. The gestational age (26^{+4} vs. 25^{+4} weeks, $P = 0.088$) and birth weight (737 vs. 680 g, $P = 0.055$) were lower for the period II infants, although the difference was only borderline significant. More of the ELBW infants from period II had indwelling central vascular catheters at the time of infection (52.9 vs. 86.2%, $P < 0.001$) and required mechanical ventilation (26.5 vs. 65.2%, $P < 0.001$). The ELBW infants from period II had longer hospital stays (71 vs. 97 days, $P = 0.053$) and a higher overall survival rate (51.7 vs. 80.0%, $P = 0.002$) compared with the period I infants.

Multivariate analysis showed that central vascular catheters (odds ratio [OR] 4.100, 95% confidence interval [CI] 1.557-10.799; $P = 0.004$) and duration of hospitalization (OR 1.009, 95% CI 1.000-1.019; $P = 0.047$) were independently associated with increased neonatal sepsis, particularly CONS, in ELBW infants (Table 6).

Table 4. Comparison of causative organisms in ELBW infants between periods I and II.

Causative organisms	Sepsis onset time											
	EOS, n (%)			LOS, n (%)			LLOS, n (%)			Total, n (%)		
	P I	P II	*P*-value	P I	P II	*P*-value	P I	P II	*P*-value	P I	P II	*P*-value
G(+) bacteria	2 (66.7)	8 (66.7)	1.000	9 (37.5)	50 (58.1)	0.073	4 (57.1)	27 (67.5)	0.676	15 (44.1)	85 (61.6)	0.064
S. aureus	0 (0.0)	2* (16.7)	1.000	5 (20.8)	25‡ (29.1)	0.423	4 (57.1)	9* (22.5)	0.080	9 (26.5)	36 (26.1)	0.964
CONS	1 (33.3)	4* (33.3)	1.000	2† (8.3)	19 (22.1)	0.154	0 (0.0)	12* (30.0)	0.166	3 (8.8)	35 (25.4)	0.039
GBS	0 (0.0)	1 (8.3)	1.000	0 (0.0)	2 (2.3)	1.000	0 (0.0)	5 (12.5)	1.000	0 (0.0)	8 (5.8)	0.359
Enterococcus species	1 (33.3)	1 (8.3)	0.371	2 (8.3)	4‡ (4.7)	0.610	0 (0.0)	1 (2.5)	1.000	3 (8.8)	6 (4.3)	0.383
G(-) bacteria	0 (0.0)	4 (33.3)	0.516	9 (37.5)	16 (18.6)	0.051	2 (28.6)	10 (25.0)	1.000	11 (32.4)	30 (21.7)	0.193
E. coli	0 (0.0)	0 (0.0)	.	1 (4.2)	0 (0.0)	0.218	0 (0.0)	1 (2.5)	1.000	1 (2.9)	1 (0.7)	0.357
K. pneumoniae	0 (0.0)	1 (8.3)	1.000	2 (8.3)	7 (8.1)	1.000	1 (14.3)	7 (17.5)	1.000	3 (8.8)	15 (10.9)	1.000
Enterobacter species	0 (0.0)	1 (8.3)	1.000	1 (4.2)	2 (2.3)	0.526	1 (14.3)	1 (2.5)	0.278	2 (5.9)	4 (2.9)	0.339
Acinetobacter species	0 (0.0)	0 (0.0)	.	5 (20.8)	3 (3.5)	0.012	0 (0.0)	0 (0.0)	.	5 (14.7)	3 (2.2)	0.008
P. aeruginosa	0 (0.0)	2 (16.7)	1.000	0 (0.0)	0 (0.0)	.	0 (0.0)	0 (0.0)	.	0 (0.0)	2 (1.4)	1.000
S. marcescens	0 (0.0)	0 (0.0)	.	0 (0.0)	0 (0.0)	.	0 (0.0)	1 (2.5)	1.000	0 (0.0)	1 (0.7)	1.000
Others	0 (0.0)	0 (0.0)	.	0 (0.0)	4 (4.7)	0.575	0 (0.0)	0 (0.0)	.	0 (0.0)	4 (2.9)	0.586
Fungus	1 (33.3)	0 (0.0)	0.200	6 (25.0)	20 (23.3)	0.859	1 (14.3)	3 (7.5)	0.488	8 (23.5)	23 (16.7)	0.351
Candida species	1 (33.3)	0 (0.0)	0.200	6† (25.0)	20 (23.3)	0.859	0 (0.0)	3 (7.5)	1.000	7 (20.6)	23 (16.7)	0.589
Others	0 (0.0)	0 (0.0)	.	0 (0.0)	0 (0.0)	.	1 (14.3)	0 (0.0)	0.149	1 (2.9)	0 (0.0)	0.198
Total	3 (100.0)	12 (100.0)		24 (100.0)	86 (100.0)		7 (100.0)	40 (100.0)		33 (100.0)	138 (100.0)	

EOS = Early onset sepsis; LOS = Late onset sepsis; LLOS = Late, late onset sepsis; CONS = Coagulase-negative *Staphylococcus*; GBS = Group B *Streptococcus*

* Mixed infection: Methicillin-resistant *S. aureus* (MRSA) + CONS; †Mixed infection: CONS + *Candida albicans*; ‡Mixed infection: MRSA + *Enterococcus faecalis*

Table 5. Clinical characteristics of ELBW infants diagnosed with neonatal sepsis.

Clinical characteristics	Period I	Period II	*P*-value
GA (week), median (min, max)	26^{+4} (24^{+1}, 31^{+2})	25^{+4} (23^{+1}, 34^{+2})	0.088
Birth weight (g), median (min, max)	737 (500, 990)	680 (390, 980)	0.055
Male, n (%)	13 (44.8)	54 (51.4)	0.529
C/S, n (%)	17 (58.6)	65 (61.9)	0.748
Central vascular catheters, n (%)	18 (52.9)	119 (86.2)	< 0.001
Surgery, n (%)	1 (2.9)	16 (11.6)	0.200
Mechanical ventilation, n (%)	9 (26.5)	90 (65.2)	< 0.001
> 1 episodes of sepsis, n (%)	3 (10.3)	23 (21.9)	0.195
Days to onset of sepsis, median (min, max)	16.5 (2, 67)	18.5 (1, 135)	0.081
Hospital stay (days), median (min, max)	71 (13, 275)	97 (2, 1761)	0.053
Survival, n (%)	15 (51.7)	84 (80.0)	0.002

GA = Gestational age; C/S = Cesarean section

Table 6. Multivariate logistic regression analysis of the independent risk factors of increased neonatal sepsis in ELBW infants.

Variables	Odds ratio	95% CI	*P*-value
GA	0.971	0.941-1.002	0.066
Birth weight	0.675	0.021-21.377	0.824
Central vascular catheters	4.100	1.557-10.799	0.004
Mechanical ventilation	2.544	0.964-6.713	0.059
Hospital stay (days)	1.009	1.000-1.019	0.047

GA = Gestational age; CI = Confidence interval

Discussion

In the present study, *S. aureus* was the major pathogen responsible for neonatal sepsis throughout the study period, and CONS emerged as a causative organism during period II. Furthermore, the rate of neonatal sepsis increased with no changes in the SRM.

The SNUCH NICU is a representative tertiary referral unit in Korea. This unit has experienced dramatic changes in both the quality and quantity of care, with rapid expansion from 22 to 42 beds during period II. The structural factors of the NICU (overcrowding, nurse-to-patient ratio) can affect the neonatal sepsis rate (23, 24). In our unit, the nurse-to-patient ratio decreased (1:3.6 vs. 1:2.9-3.3) and the distance between the patients increased (1.5 m vs. 1.8-2.6 m) between the two periods. Therefore, these environmental and manpower factors were changed in favor of infection control.

The total inborn NICU admission rate per 1,000 live births and the ELBW infant admission rate both increased from period I to period II. Although the median GA and birth weights of the ELBW infants did not differ between the two study periods, the survival rate and length of hospital stay for this population increased dramatically. These trends are similar with national epidemiological data (14). Increased preterm birth rate is associated with many factors such as high maternal age, maternal obesity, smoking,

prenatal infection, and multiple pregnancy according to development of assisted reproductive technology. In our hospital, the multiple pregnancies were significantly increased for period II compared with period I (twin: 4.8% vs. 17.8%, $P < 0.001$; triplet: 0.1% vs. 1.3%, $P < 0.001$). This could be an important risk factor for increased preterm birth rate.

In our study, the total neonatal sepsis rate increased significantly between the two study periods, from 5.9 cases per 1,000 live births in period I to 12.7 cases per 1,000 live births in period II, and this increase was accompanied by a dramatic increase in the ELBW infant admission rate. The number of ELBW infants admitted to the NICU could contribute to the burden of neonatal sepsis, despite policies that prevent infection (22), because these infants have many risk factors for sepsis such as impaired innate immune function, the prolonged hospitalization they require, the need for invasive procedures and devices, a lack of enteral feeding, and the utilization of broad spectrum antibiotics (3, 25). Furthermore, the more premature ELBW infants are at an increased risk of sepsis, as shown in Table 2. Therefore, the incidence rates should be considered within the context of each unit's patient characteristics, such as the admission rate of ELBW infants. The incidence of sepsis found in our study seemed higher than that reported in the literature (2.8 to 8.1 cases per 1,000 live births) (22, 26-28). Bizzarro et al. reported an inborn sepsis rate of 7.1 cases per 1,000 live births (22), however, the inborn admission rate of ELBW infants was 14-15 infants per

1,000 live births, which was only approximately half the rate for our unit.

In the most recent published survey from our unit, the presence of *S. aureus* increased significantly between 1980 and 2005 (20). We conducted the prevention measures during period II. Surveillance cultures were performed for all neonates admitted to the NICU. Infants who were colonized or infected with MRSA were isolated, and standard contact precautions were utilized (hand hygiene, gowns and gloves). Decolonization treatments were conducted using mupirocin ointment and 0.4% chlorhexidine bathing. In the previous studies, the prevalence of MRSA colonization and MRSA infection significantly decreased following the use of prevention measures such as alcohol-based hand rub and gloves (29, 30). However, in our unit, the incidence of MRSA sepsis has not decreased (unpublished data), and MRSA remains a primary cause of neonatal sepsis. These results might be influenced by the expansion of the NICU. The effects of isolation, contact precautions and decolonization treatments should be evaluated in further studies.

The majority of neonatal sepsis cases occurred after 4 days of life. Moreover, the presence of gram-positive bacteria, particularly CONS, increased significantly between the two study periods for the LOS and LLOS cases. This trend was also observed in the ELBW group. Most of the CONS isolates were MRSE. Since 1980, CONS have been the major pathogens for LOS in neonates and are responsible for up to 75% of

hospital-acquired, late-onset, neonatal sepsis (31). There are several risk factors for CONS infection, including prematurity, longer hospital stays, more central vascular catheter insertions, more time with mechanical ventilation, and more parenteral nutrition (32-34).

In the present study, gestational age and birth weight were not independent risk factors for increased neonatal sepsis, unlike the results of previous studies (35, 36). Central vascular catheters and prolonged hospitalization rather than prematurity itself were significantly associated with an increased sepsis rate, particularly CONS in ELBW infants. The survival rate of ELBW infants was significantly increased during period II, and this could lead to longer hospital stays and a greater number of invasive procedures. Therefore, as NICUs improve in both the quality and quantity of care, more efforts are needed to minimize central catheter use and the length of hospital stay, for example, by promoting enteral feeding.

Despite the increase in neonatal sepsis cases, the total SRM was similar for both periods. Among the ELBW infants, there was a marked increase in neonatal sepsis between periods I and II, but the SRM decreased to a borderline-significant degree. Regarding the pathogens responsible for sepsis-related deaths, period II saw an increase in the incidence of MRSA and MRSE. These pathogens are associated with increased morbidity and mortality among premature infants (3). Therefore, bacterial resistance should be considered whenever staphylococcal disease is suspected or

confirmed in patients, and empirical vancomycin therapy should be considered until the susceptibility pattern of the organism is known.[37]In our unit, vancomycin has been used as the initial empirical antibiotic when the patient was colonized with MRSA or had central vascular catheters for more than 7 days.

In conclusion, the inborn admission rate, particularly for ELBW infants, increased significantly with NICU expansion and was accompanied by improved survival and longer hospital stays. The total incidence of neonatal sepsis increased significantly between the two study periods, particularly in ELBW infants. The incidence of LOS and LLOS caused by CONS also increased remarkably. Our data suggest that central vascular catheters and prolonged hospitalization could be independent risk factors for the increased sepsis rate, particularly sepsis due to CONS.

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국문 초록

목표: 빠르게 확장하고 발전한 신생아 집중치료실에서 입원 양상 및 신생아 패혈증의 역학 변화를 조사하였다.

방법: 1996년부터 2013년(기간 I: 1996−2005, 기간 II: 2006−2013) 사이에 신생아 집중치료실에 입원한 신생아 중 혈액 배양 검사로 패혈증이 확진된 환자의 자료를 후향적으로 수집하였다.

결과: 초극소저체중 출생아의 입원수가 기간 I과 II 사이에 유의하게 증가하였다(출생 1,000명 당 11.1 vs. 28.7명, $P< 0.001$). 두 기간 사이에 초극소저체중 출생아의 생존율이 증가하였으며(57.5 vs. 80.1%, $P< 0.001$), 입원 기간 또한 증가하였다(중앙값: 64 vs. 80일, $P = 0.001$). 신생아 패혈증의 빈도는 전체 입원 환자와 초극소저체중 출생아 모두에서 유의하게 증가하였다(전체 환자, 출생 1,000명 당 5.9 vs. 12.7건; 초극소저체중 출생아, 출생 1,000명 당 189.5 vs. 290.1건). 초극소저체중 출생아에서 coagulase−negative *Staphylococcus* (CONS)에 의한 패혈증의 빈도가 기간 II에서 유의하게 증가하였다(8.8 vs. 25.4%, $P = 0.039$). 다변량 분석을 시행하였을 때, 중심 정맥 카테터와 입원 기간의 연장이 초극소저체중 출생아에서 패혈증, 특히 CONS에 의한 감염의 증가와 독립적으로 연관되었다.

결론: 신생아 집중치료실의 확장에 따라 초극소저체중 출생아의 입원율이 증가하였고, 그와 동반하여 생존율이 향상되었으며 입원 기간이 연장되었다. 초극소저체중 출생아에서의 신생아 패혈증이 증가하였으며, CONS가 주요 병원체로 부각되었다. 본 연구를 통해 중심 정맥 카테터와 입원 기간의 연장이 패혈증, 특히 CONS에 의한 감염 증가의 위험

인자가 될 수 있음을 제시하는 바이다.

주요어: Coagulase-negative *Staphylococci*, 역학, 초극소저체중 출생아, 신생아 집중치료실, 패혈증

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