Trends in Epidemiology of Neonatal Sepsis in a Tertiary Center in Korea: A 26-Year Longitudinal Analysis, 1980-2005

There were many reports of longitudinal changes in the causative organisms of neonatal sepsis in Western countries but few in Asia. We aimed to study longitudinal trends in the epidemiology of neonatal sepsis at Seoul National University Children's Hospital (SNUCH), a tertiary center in Korea, and compared the results to previous studies of Western countries. The medical records of all of the neonates who were hospitalized at SNUCH from 1996 to 2005 with positive blood cultures were reviewed. We also compared the findings to previous 16-yr (1980-1995). One hundred and forty-nine organisms were identified in 147 episodes from 134 infants. In comparison with the previous 16-yr studies, there was a decrease in the number of Escherichia coli infections (16.2% vs 8.7%; odds ratio [OR] 0.495; 95% confidence interval [CI], 0.255-0.962; \( P = 0.035 \)), but an increase in Staphylococcus aureus (16.6% vs 25.5%; OR 1.720; 95% CI, 1.043-2.839; \( P = 0.033 \)) and fungal infections (3.3% vs 18.7%; OR 6.740; 95% CI, 2.981-15.239; \( P < 0.001 \)), predominantly caused by Candida species. In conclusion, the incidence of sepsis caused by E. coli decreases, but S. aureus and fungal sepsis increases significantly. Compared with Western studies, the incidence of sepsis caused by S. aureus and fungus has remarkably increased.

**Key Words:** Sepsis; Organism; Epidemiology
card (bioMerieux, Hazelwood, MO, USA). The antibiotic susceptibilities of the microorganisms were determined using the National Committee for Clinical Laboratory Standards (NCCLS) disk-diffusion method.

**Definition**

Fever (hyperthermia) and hypothermia were defined as having a core temperature of >38.0°C and <36.5°C, respectively. Apnea and bradycardia were included as clinical sign of sepsis only when the episodes were newly developed or the frequency and duration of the episodes increased. Hypoglycemia and hyperglycemia were defined as having a blood glucose of <40 mg/dL and >140 mg/dL, respectively (1).

The criteria for the diagnosis of neonatal sepsis required isolation of the microorganism from a blood culture and at least one clinical sign or symptom. For instance, in cases that had microorganisms common in skin contamination (e.g., diphtheroids, Bacillus species, Propionibacterium species or micrococci), a definition of sepsis was defined by documentation of a sign or symptom such as a fever, hypothermia, apnea, bradycardia, hypoglycemia and hyperglycemia along with either pathogen isolation from two blood cultures drawn on separate occasions or at least one peripheral blood culture from a patient with a central venous catheter (8). Sepsis of CONS was reviewed using criteria for the diagnosis of CONS defined by Bizzarro et al. (1). Sepsis was classified as early onset (EOS, ≤ 4 days of life), late onset (LOS, 5-30 days) and late onset (LOS, > 30 days) (1).

A sepsis-related death was defined when death occurred within 7 days of a positive blood culture or when the clinical signs and symptoms of sepsis manifested (1). Sepsis-related mortality was calculated with the numerator representing the number of episodes of sepsis.

**Statistics**

The results were analyzed using SPSS version 12.0 (SPSS, Inc., Chicago, IL, USA). A Student’s t-test was used for comparison of the continuous variables. Pearson’s chi-square test or Fisher’s exact test (both two-sided) were used for comparison of the categorical variables when necessary. A value of $P < 0.05$ was considered to be statistically significant.

**RESULTS**

During 10 yr (Period III; 1996-2005) of this study, there was a total of 13,742 live births and a total of 1,479 outborn neonates in SNUCH. The numbers of live births declined from a total of 1,888 in 1996 to a total of 1,001 in 2005. The inborn admission rate of extremely low birth weight (ELBW) infants (birth weight <1,000 g) was 11.1 per 1,000 live births and the admission rate of infants weighing 1,000 g to 1,500 g was 19.4 per 1,000 live births.

A total of 502 blood cultures were positive from 310 patients. After a review of all 310 patients, 147 episodes were defined as neonatal sepsis from 134 patients. One hundred and twenty-six episodes (85.7%) occurred in patients who were in admitted to the NICU and 21 episodes occurred in patients who were admitted to the pediatric intensive care unit or pediatric wards. The percentage of male from all of the populations was 57.1%, the mean gestational age was 32 ± 5 weeks and the mean birth weight was 1,835 ± 1,113 g. The total sepsis rate of inborn neonates was 5.9 per 1,000 live births and infants with a lower birth-weight had higher sepsis rates (Table 1). There were 12 sepsis-related mortality cases and the overall mortality rate was 9.0% (12/134).

Apnea (19.7%) and fever (19.7%) were the most common symptoms of sepsis. There were significant differences in the symptoms of sepsis, based on the gestational age. Apnea and bradycardia were common in the total population, whereas fever was common only in the ≥ 32 weeks postmenstrual age (PMA) group, and hyperglycemia was more frequent in the < 32 weeks PMA group (Fig. 1).

**Table 1.** Sepsis rates for inborn infants by birth weight (1996-2005)

| Birth weight (g) | Number of live births | Number of inborn cases of sepsis (Episodes) | Cases per 1,000 live births |
|-----------------|-----------------------|---------------------------------------------|-----------------------------|
| < 750           | 68                    | 16 (18)                                     | 235.3                       |
| 750-999         | 85                    | 13 (14)                                     | 152.9                       |
| 1,000-1,499     | 267                   | 30 (33)                                     | 112.4                       |
| 1,500-1,999     | 368                   | 8 (9)                                       | 21.7                        |
| ≥ 2,000         | 12,954                | 14 (16)                                     | 1.1                         |
| Total           | 13,742                | 81 (90)                                     | 5.9                         |

**Ethics statement**

The study protocol was approved by the institutional review boards of the Seoul National University Hospital (IRB No. H-0902-033-272). Informed consent was waived by the IRB.
Of the 147 episodes of neonatal sepsis, 90 (61.1%) episodes were in the inborn neonates and 57 (38.9%) episodes were in the outborn cases (Table 2). Of the 90 episodes in the inborn neonates, 7 (7.8%) were EOS, 63 (70.0%) were LOS and 20 (22.2%) were LLOS (Table 2). During the study period, 149 microorganisms were isolated from the 147 episodes of sepsis. Gram-positive bacteria accounted for 65 (43.6%), Gram-negative bacteria for 56 (37.6%), and fungus for 28 (18.8%) episodes. The common microorganisms found were *S. aureus* (n = 38, 25.5%), *Candida* species (n = 25, 16.8%), *Klebsiella pneumoniae* (n = 19, 13.4%), *E.

Table 2. Causative organisms of neonatal sepsis at SNUCH (1996-2005)

|                     | Inborn |            |            |            | Outborn | Overall |
|---------------------|--------|------------|------------|------------|---------|---------|
|                     | EOS    | LOS        | LLOS       | Total      | EOS     | LOS     |
| Gram positive bacteria | 5 (62.5) | 24 (37.5)  | 7 (35.0)   | 36 (39.1)  | 29 (50.9) | 65 (43.6) |
| *Staphylococcus aureus* | 1 (12.5) | 15 (23.5)  | 6 (30.0)   | 22 (23.9)  | 16 (28.1) | 38 (25.5) |
| CONS                | 1* (12.5) | 4* (6.2)   | 1* (5.0)   | 6* (6.5)   | 6 (10.5)  | 12 (8.0)  |
| GBS                 |         |            |            |            | 3 (5.2)   | 3 (2.0)   |
| *Streptococcus mitis* | 1 (12.5) | 2 (3.1)    |            | 3 (3.2)    | 3 (2.0)   |
| *Streptococcus hemolyticus* |         |            |            |            | 1 (1.8)   | 1 (0.7)   |
| *Streptococcus pyogenes* |         |            |            |            | 1 (1.8)   | 1 (0.7)   |
| Enterococcus faecalis | 2 (3.1)  |            | 2 (2.2)    | 4 (2.7)    |
| Enterococcus faecium | 1* (12.5) | 1 (1.6)    | 2 (2.2)    | 2 (1.3)    |
| Enterococcus species | 1 (12.5) |            | 1 (1.1)    | 1 (0.7)    |
| Gram negative bacteria | 2 (25.0) | 23 (35.9)  | 8 (40.0)   | 33 (35.9)  | 23 (40.4) | 56 (37.6) |
| *Klebsiella pneumoniae* | 8 (12.5) | 5 (25.0)   | 13 (64.2)  | 1 (0.7)    | 3 (5.2)   | 3 (2.0)   |
| *Klebsiella oxytoca* |         |            | 1 (1.1)    | 1 (0.7)    |
| *Escherichia coli*   | 1 (12.5) | 4 (6.2)    | 1 (5.0)    | 6 (6.5)    | 7 (12.2)  | 13 (8.7)  |
| Enterobacter cloacae | 1 (12.5) | 2 (3.1)    | 3 (3.2)    | 3 (2.0)    |
| Enterobacter aerogenes |         |            | 1 (1.1)    | 1 (0.7)    |
| Acinetobacter baumannii |         | 5 (7.7)    | 5 (5.4)    | 1 (1.8)    | 6 (4.0)   |
| Acinetobacter calcoaceticus | 1 (1.6) | 1 (1.1)    |            | 1 (0.7)    |
| *Pseudomonas aeruginosa* | 1 (1.6) | 1 (1.1)    |            | 1 (0.7)    |
| *Pseudomonas fluorescens* |         |            | 1 (1.1)    | 1 (0.7)    |
| *Stenotrophomonas maltophilia* | 1 (1.6) | 1 (1.1)    | 1 (1.1)    | 2 (1.3)    |
| Serratia marcescens |         |            | 1 (1.1)    | 1 (0.7)    |
| Burkholderia cepacia | 1 (1.6)  | 1 (5.0)    | 2 (2.2)    | 2 (1.3)    |
| Fungus               |         |            |            |            | 9 (10.0)  | 28 (18.8) |
| *Candida albicans*   | 1 (12.5) | 17 (26.6)  | 5 (25.0)   | 23 (25.0)  | 5 (8.7)   | 28 (18.8) |
| *Candida parapsilosis* | 1* (14.1) | 2 (10.0)   | 12 (13.0)  | 2 (3.5)    | 14 (9.3)  |
| *Candida tropicalis* | 4 (6.2)  | 1 (5.0)    | 5 (5.4)    | 2 (3.5)    | 7 (4.7)   |
| *Candida glabrata*   | 1 (1.6)  | 1 (1.1)    |            | 1 (0.7)    |
| *Candida lusitania*  | 1 (1.6)  | 1 (1.1)    | 1 (1.1)    | 1 (0.7)    |
| Geotrichum candidum |         | 1 (5.0)    | 1 (1.1)    | 1 (0.7)    |
| Malassezia furfur |         |            |            |            | 1 (1.1)   | 1 (0.7)   |
| Malassezia species |         | 1 (5.0)    | 1 (1.1)    | 1 (0.7)    |
| Total               | 8 (100.0) | 64 (100.0) | 20 (100.0) | 92 (100.0) | 57 (100.0) | 149 (100.0) |

Data presented as number (%). *Mixed infection: CONS + Enterococcus faecium; †Mixed infection: CONS + Candida albicans. SNUCH, Seoul National University Children’s Hospital; EOS, early onset sepsis; LOS, late onset sepsis; LLOS, late, late onset sepsis; CONS, coagulase-negative Staphylococcus; GBS, Group B Streptococcus.

Fig. 2. Comparison of the percentage of the cause of neonatal sepsis; 1980-2005. Data presented as percent (%). CONS, coagulase-negative *Staphylococcus*; GBS, group-B *Streptococcus*; *P* < 0.05 vs Period I+II and Period III; †*P* < 0.05 vs Period I and Period II; ‡*P* < 0.05 vs Period I and Period III; §*P* < 0.05 vs Period II and Period III.

Of the 147 episodes of neonatal sepsis, 90 (61.1%) episodes were in the inborn neonates and 57 (38.9%) episodes were in the outborn cases (Table 2). Of the 90 episodes in the inborn neonates, 7 (7.8%) were EOS, 63 (70.0%) were LOS and 20 (22.2%) were LLOS (Table 2). During the study period, 149 microorganisms were isolated from the 147 episodes of sepsis. Gram-positive bacteria accounted for 65 (43.6%), Gram-negative bacteria for 56 (37.6%), and fungus for 28 (18.8%) episodes. The common microorganisms found were *S. aureus* (n = 38, 25.5%), *Candida* species (n = 25, 16.8%), *Klebsiella pneumoniae* (n = 19, 13.4%), *E.
coli (n = 13, 8.7%) and CONS (n = 12, 8.1%) (Table 2). There were two episodes of mixed infections. One mixed infection was the EOS of CONS with Enterococcus faecium and the other mixed infection was the LOS of CONS with Candida albicans.

EOS in inborn neonates included 8 cases and had no GBS cases and no predominant microorganisms. The most common microorganism of 63 LOS cases was Candida species (n = 17, 26.6%) followed by Staphylococcus aureus (n = 15, 23.4%) and Klebsiella pneumoniae (n = 8, 12.5%). There were 20 episodes of LLOS, and the predominant microorganisms were S. aureus (n = 6, 30.0%) and K. pneumoniae (n = 5, 25.0%). There were 57 episodes of neonatal sepsis in outborn neonates and the most common causative organism was S. aureus (n = 16, 28.1%). Most of the S. aureus isolates (36/38) were methicillin-resistant and all of the CONS isolates were methicillin-resistant. There were two episodes of mixed infections.

Fig. 2 shows the overall trend in sepsis cases over 26 yr in SNUCH. During the 26 yr, S. aureus was the most common causative organisms of neonatal sepsis. Compared to the decade just before the study period, the incidence of sepsis caused by S. aureus (Period I + II vs Period III; odds ratio [OR] 1.720; 95% confidence interval [CI], 1.043-2.839; P = 0.033) and fungus (Period I + II vs Period III: OR 6.740; 95% CI, 2.981-15.239; P < 0.001) were increased, but the incidence of sepsis caused by Escherichia coli (Period I + II vs Period III: OR 0.145; 95% CI, 0.066-0.325; P = 0.162) was decreased (Table 3).

DISCUSSION

The reported incidence of neonatal sepsis varies from 2.8 to 8.1 cases per 1,000 live births (9-11). The inborn neonatal sepsis rate for a recent 10-yr period at our center was 5.9 cases per 1,000 live births, and this result is similar to those at the Yale New Haven Hospi-

tal (7.1 cases per 1,000 live births) (1).

For the last 10 yr, most of the cases of inborn neonatal sepsis were LOS. There were only 7 (8.0%) cases of EOS out of 88 inborn neonatal sepsis cases at SNUCH. In Korea, the estimated incidence of GBS infection in newborns has been much lower than in other countries (12), due to the low prevalence rate of GBS colonization in pregnant women (13, 14). In fact, there were only 3 GBS sepsis cases in our study and all of these cases were outborn and LOS. This result might contribute to Korea’s lower incidence of EOS compared to other countries (1, 15).

Apnea, bradycardia, hyperglycemia and fever were common symptoms in neonates with sepsis. Apnea, bradycardia and hyperglycemia were more common in PMA < 32 weeks neonates. In contrast, a fever was more common symptom in PMA ≥ 32 weeks neonates. These results indicate that very preterm infants (< 32 weeks of PMA) with sepsis tend to show non-specific symptoms rather than a typical infection sign such as a fever. Therefore, careful evaluation of clinical status is important for the early detection of infectious disease in preterm infants.

The common causative organisms of neonatal sepsis were S. aureus, Candida species, K. pneumoniae, E. coli and CONS. Compared to other studies from Korea, the frequency of CONS and GBS was lower, but the frequency of Klebsiella species and Candida species was higher (15-17). These results may be due to the differences of characteristics of patients, policy of antibiotic uses and normal flora. Furthermore, our reports revealed that most S. aureus and CONS isolates were methicillin-resistant. This result reflects the observation that S. aureus and CONS colonization of infants hospitalized in the NICU was very prevalent. A higher rate of methicillin-resistant Gram-positive organism colonization in NICU infants has recently emerged worldwide, and is the major cause of neonatal blood-stream infections. A chemotherapeutic strategy for neonatal sepsis should

**Table 3. Comparison of ratio of causative organisms between each period**

| Causative organisms | Period I + II 1980-1995 (n = 241) | Period III 1996-2005 (n = 149) | P value | Odds ratio (95% confidence interval) |
|---------------------|----------------------------------|--------------------------------|---------|-----------------------------------|
| Preterm             | 102/224 (45.5)                   | 89/134 (66.4)                 |         |                                   |
| Gram positive       |                                   |                                |         |                                   |
| Staphylococcus aureus | 40 (16.6)                       | 38 (25.5)                      | 0.033   | 1.720 (1.043-2.839)               |
| CONS                | 33 (13.7)                        | 12 (8.0)                       | 0.090   | 0.552 (0.276-1.106)               |
| GBS                 | 6 (2.5)                          | 3 (2.0)                        | 1.000   | 0.805 (0.198-3.268)               |
| Enterococcus species | 8 (3.3)                         | 7 (4.7)                        | 0.492   | 1.436 (0.510-4.044)               |
| Others              | 11 (4.6)                         | 5 (3.4)                        | 0.559   | 0.726 (0.247-2.132)               |
| Gram negative       |                                   |                                |         |                                   |
| Escherichia coli    | 39 (16.2)                        | 13 (8.7)                       | 0.035   | 0.495 (0.255-0.962)               |
| Klebsiella pneumoniae | 46 (19.1)                      | 19 (12.8)                      | 0.103   | 0.620 (0.347-1.105)               |
| Enterobacter species | 21 (8.7)                        | 4 (2.7)                        | 0.019   | 0.289 (0.097-0.859)               |
| Pseudomonas species | 12 (5.0)                         | 7 (4.0)                        | 0.900   | 0.941 (0.362-2.446)               |
| Serratia species    | 8 (3.3)                          | 1 (0.7)                        | 0.162   | 0.197 (0.024-1.593)               |
| Others              | 9 (3.7)                          | 12 (8.7)                       | 0.066   | 2.258 (0.928-5.497)               |
| Fungus              | 8 (3.3)                          | 28 (18.7)                      | 0.000   | 6.740 (2.981-15.239)              |
| Candida species     | 8 (3.3)                          | 26 (17.4)                      | 0.000   | 6.157 (2.706-14.006)              |
| Others              | 0 (0.0)                          | 2 (1.3)                        | 0.145   | -                                 |

Data presented as number (%). CONS, coagulase-negative Staphylococcus; GBS, group-B Streptococcus.
be re-evaluated and the appropriate use of antibiotics must be re-emphasized. Prophylactic use of antibiotics and broad-spectrum antibiotics use should be minimized (18).

In contrast to Western studies, our study showed a higher rate of sepsis caused by CONS and GBS (1, 4). In addition, the incidence of prolonged use of broad-spectrum antibiotics (22-25).

The incidence of prolonged use of broad-spectrum antibiotics is related to the fungal sepsis rate found in our institution dramatically decreased, but the number of cases and the increase in fungal cases was reduced, but the number of cases and the increase in fungal cases was increased (1, 4, 30).

In conclusion, the incidence of sepsis caused by S. aureus and fungal sepsis increased significantly. In contrast to Western studies, our study showed a higher rate of sepsis caused by S. aureus and Klebsiella species, and a lower rate of sepsis caused by CONS and GBS (1, 4). In addition, the incidence of sepsis caused by S. aureus and fungus has remarkably increased (1, 4, 30).

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AUTHOR SUMMARY

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We aimed to study longitudinal trends in the epidemiology of neonatal sepsis a tertiary center in Korea. The medical records of all of the neonates who were hospitalized at Seoul National University Children’s Hospital from 1996 to 2005 with positive blood cultures were reviewed. We also compared the findings to previous 16-yr (1980-1995). One hundred and forty-nine organisms were identified from 134 infants. In comparison with the previous 16-yr studies, there was a decrease in the number of Escherichia coli infections, but an increase in Staphylococcus aureus and fungal infections. In conclusion, the incidence of sepsis caused by E. coli decreases, but S. aureus and fungal sepsis increases significantly. Compared with Western studies, the incidence of sepsis caused by S. aureus and fungus has remarkably increased.