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*Original Article*

# Risk Factors for Nosocomial Infection in the Neonatal Intensive Care Unit by the Japanese Nosocomial Infection Surveillance (JANIS)

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**We evaluated the infection risks in the neonatal intensive care unit (NICU) using data of NICU infection surveillance data. The subjects were 871 NICU babies, consisting of 465 boys and 406 girls, who were cared for between June 2002 and January 2003 in 7 medical institutions that employed NICU infection surveillance. Infections were defined according to the National Nosocomial Infection Surveillance (NNIS) System. Of the 58 babies with nosocomial infections, 15 had methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Multiple logistic regression analysis demonstrated that the odds ratio for nosocomial infections was significantly related to gender, birth weight and the insertion of a central venous catheter (CVC). When the birth weight group of more than 1,500 g was regarded as the reference, the odds ratio was 2.35 in the birth weight group of 1,000–1,499 g and 8.82 in the birth weight group of less than 1,000 g. The odds ratio of the CVC (+) for nosocomial infection was 2.27. However, other devices including artificial ventilation, umbilical artery catheter, umbilical venous catheter, and urinary catheter were not significant risk factors. The incidence of MRSA infection rapidly increased from 0.3% in the birth weight group of more than 1,500 g to 2.1% in the birth weight group of 1,000–1,499 g, and to 11.1% in the birth weight group of less than 1,000 g. When the birth weight group of more than 1,500 g was regarded as the reference, multiple logistic regression analysis demonstrated that the odds ratio was 7.25 in the birth weight group of 1,000–1,499 g and 42.88 in the birth weight group of less than 1,000 g. These odds ratios were significantly higher than that in the reference group. However, the application of devices did not cause any significant differences in the odds ratio for MRSA infection.**

**Key words:** risk factors, nosocomial infection, neonatal intensive care unit, JANIS

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Advanced medical technology such as the closed system of a central line and tracheal tube in the neonatal intensive care unit (NICU) has improved the quality and length of life of neonates born with prematurity and congenital defects. However, nosocomial infection risks are high in NICU babies due to their immature immune systems and the need for invasive diagnosis and treatment, causing high mortality and increases in medical costs [1–6]. NICU babies with higher immaturity must undergo more treatments, and are often subject to maintenance of central venous catheter (CVC) and A-line routes, tracheal intubation, and catheter indwelling in the bladder are often performed [1, 2]. These treatments can increase the incidence of infections especially because the skin and mucosa are immature [1, 2]. Among nosocomial infections, methicillin-resistant *Staphylococcus aureus* (MRSA) infections have caused serious problems at NICUs in Japan since the 1980s [7].

The incidence of nosocomial infection ranges from 6% to 25%, with a large amount of variation by birth weight and treatment condition [8–12]. Nosocomial infections could be prevented by instituting careful bacteriologic surveillance, improving hand hygiene, and limiting antibiotics and invasive procedures [13–19]. Therefore, it is very important to determine the incidence of nosocomial infection, the organisms involved, and the locations of the infections. In addition, we evaluate the increases in nosocomial or MRSA infection risks associated with artificial ventilation, CVC, catheterization in the umbilical artery or vein, or catheter indwelling in the bladder.

## Subjects and Methods

Nosocomial infections in NICUs have been investigated as part of the Japanese nosocomial infection surveillance (JANIS) system [20]. The subjects were 871 NICU babies, consisting of 465 boys and 406 girls, who were treated between June 2002 and January 2003 in 7 of the 9 institutions that participated in the NICU infection surveillance. Since the number of NICU babies in the remaining 2 institutions was limited, data from these institutions were excluded. Nosocomial infections were defined according to the national nosocomial infection surveillance (NNIS) system [21]. Only one infection was identified for each baby. The birth weights of the babies were classified into 3 groups: more than 1,500 g, 1,000–1,499 g, and less than 1,000 g. The incidence of infections was determined in the birth weight groups. The causal bacteria of infections were also investigated. The risks of nosocomial infections were examined by multiple logistic regression analysis using gender, birth weight, artificial ventilation, CVC, catheterization in the umbilical cord artery or vein, and catheter indwelling in the bladder. The incidence of infection was also examined in the birth weight groups and the groups with or without CVC, respectively. The incidence of MRSA infection was determined in the birth weight groups. Finally, the risks of MRSA infections were examined by multiple logistic regression analysis using gender, birth weight, artificial ventilation, CVC, catheterization in the umbilical cord artery or vein, and catheter indwelling in the bladder.

## Results

Table 1 shows the incidence of infections in the birth weight groups. In the boys, the incidence (95% CI) of infections was 32.7% (29.4–36.5%) in the birth weight group of less than 1,000 g, 11.1% (8.0–15.4%) in the birth weight group of 1,000–1,499 g, and 4.2% (3.7–4.8%) in the birth weight group of more than 1,500 g. In the girls, it was 15.9% (12.0–21.0%) in the birth weight group of less than 1,000 g, 4.9% (1.8–13.0%) in the birth weight group of 1,000–1,499 g, and 3.1% (2.6–3.8%) in the birth weight group of more than 1,500 g. In both genders combined, it was 25.2% (23.3–27.3%) in the birth weight group of less than 1,000 g, 8.4% (6.6–10.8%) in the birth weight group of 1,000–1,499 g, and 3.7% (3.4–4.0%) in the birth weight group of more than 1,500 g. Table 2 shows the causal bacteria of nosocomial infections. Of the 58 babies with nosocomial infections, 26 (44.8%) were infected with *Staphylococcus* species, 5 (8.6%) with *Escherichia coli*, 2 (3.4%) with *Streptococcus agalactiae*, 2 (3.4%) with *Enterococcus faecalis*, 2 (3.4%) with *Klebsiella* species, and 2 (3.4%) with *Pseudomonas* species. There were 20 babies (34.5%) with infected with resistant bacteria, of whom 75% had MRSA infection.

Table 3 shows the location of nosocomial infections. There were 60 infections because there were 2 double infections. One male baby had sepsis with

**Table 1** Incidence of nosocomial infection by gender and birth weight

| | Birth weight (g) | Subjects (N) | Infections (N) | Incidence (95% CI) |
|---|---|---|---|---|
| Male | Less than 1,000 | 55 | 18 | 32.7% (29.4%～36.5%) |
| | 1,000～1,499 | 54 | 6 | 11.1% ( 8.0%～15.4%) |
| | 1,500 or more | 356 | 15 | 4.2% ( 3.7%～ 4.8%) |
| | Subtotal | 465 | 39 | 8.4% ( 8.0%～ 8.8%) |
| Female | Less than 1,000 | 44 | 7 | 15.9% (12.0%～21.0%) |
| | 1,000～1,499 | 41 | 2 | 4.9% ( 1.8%～13.0%) |
| | 1,500 or more | 321 | 10 | 3.1% ( 2.6%～ 3.8%) |
| | Subtotal | 406 | 19 | 4.7% ( 4.2%～ 5.2%) |
| Both | Less than 1,000 | 99 | 25 | 25.2% (23.3%～27.3%) |
| | 1,000～1,499 | 95 | 8 | 8.4% ( 6.6%～10.8%) |
| | 1,500 or more | 677 | 25 | 3.7% ( 3.4%～ 4.0%) |
| Total | | 871 | 58 | 6.7% ( 6.4%～ 6.9%) |

**Table 2** Organism causing nosocomial infection

| Organism | Male (%) | Female (%) | Total (%) |
|---|---|---|---|
| *Staphylococcus* species | 18 (46.2) | 8 (42.1) | 26 (44.8) |
| MRSA | 9 (23.1) | 6 (31.6) | 15 (25.9) |
| MSSA | 1 ( 2.6) | 1 ( 5.3) | 2 ( 3.4) |
| CNS | 8 (20.0) | 1 ( 5.3) | 9 (15.5) |
| *Escherichia coli* | 4 (10.3) | 1 ( 5.3) | 5 ( 8.6) |
| *Streptococcus agalactiae* | 1 ( 2.6) | 1 ( 5.3) | 2 ( 3.4) |
| *Enterococcus faecalis* | 1 ( 2.6) | 1 ( 5.3) | 2 ( 3.4) |
| *Klebsiella* species | 1 ( 2.6) | 1 ( 5.3) | 2 ( 3.4) |
| *Klebsiella pneumoniae* | 0 ( 0.0) | 1 ( 5.3) | 1 ( 1.7) |
| *Pseudomonas* species | 0 ( 0.0) | 2 (10.1) | 2 ( 3.4) |
| *Pseudomonas aeruginosa* | 0 ( 0.0) | 1 ( 5.3) | 1 ( 1.7) |
| *Haemophilus influenza* | 1 ( 2.6) | 0 ( 0.0) | 1 ( 1.7) |
| *Acinetobacter calcoaceticus* | 1 ( 2.6) | 0 ( 0.0) | 1 ( 1.7) |
| *Bacillus* species | 1 ( 2.6) | 0 ( 0.0) | 1 ( 1.7) |
| *Candida albicans* | 1 ( 2.6) | 0 ( 0.0) | 1 ( 1.7) |
| *Chlamydia trachomatis* | 1 ( 2.6) | 0 ( 0.0) | 1 ( 1.7) |
| Others | 6 (15.4) | 3 (15.8) | 9 (15.5) |
| Unknown | 3 ( 7.7) | 2 (10.5) | 5 ( 8.6) |
| Total | 39 (100) | 19 (100) | 58 (100) |

**Table 3** Location of nosocomial infection

| Location | Male (%) | Female (%) | Total (%) |
|---|---|---|---|
| Sepsis (defined and suspected) | 11 (26.8) | 3 (15.8) | 14 (23.3) |
| Pneumonia | 4 ( 9.8) | 3 (15.8) | 7 (11.7) |
| Neuroinfection | 4 ( 9.8) | 1 ( 5.3) | 5 ( 8.3) |
| Staphylococcal scaled skin syndrome (SSSS) | 5 (12.2) | 0 ( 0.0) | 5 ( 8.3) |
| Bacteremia | 2 ( 4.9) | 1 ( 5.3) | 3 ( 5.0) |
| Others | 15 (36.6) | 11 (57.9) | 26 (43.3) |
| Total | 41 (100) | 19 (100) | 60 (100) |

Note: There were 2 double infections.

neuroinfection and the other male had both a urinary tract infection and staphylococcal scaled skin syndrome. Of the 60 infection cases, 14 (23.3%) had sepsis, 7 (11.7%) had pneumonia, 5 (8.3%) had neuroinfection, 3 (5.0%) had bacteremia. For organisms causing sepsis, 8 *Staphylococcus species* (2 MRSA, 5 CNS, and 1 MSSA), 2 *Escherichcia coli*, 2 *Pseudomonas* species, 1 *Streptococcus agalactiae*, and 1 *Enterococcus faecalis* were identified.

Table 4 shows the results of multiple logistic regression analysis of nosocomial infections. The risk of infection was significantly higher in the boys than in the girls, and the odds ratio was 1.86. The birth weight was the most important predictor of nosocomial infections. When the birth weight group of more than 1,500 g was regarded as the reference, the odds ratio was 2.35 in the birth weight group of 1,000–1,499 g and 8.82 in the birth weight group of less than 1,000 g, indicating that the risk of nosocomial infection increased as the birth weight decreased. CVC (odds ratio, 2.27) was a significant risk factor for nosocomial infection, and artificial ventilation (odds ratio, 1.49), catheterization in the umbilical cord vein (odds ratio, 1.46), and catheter indwelling in the bladder (odds ratio, 1.34) increased the risk of nosocomial infection, but the increases were not significant.

Table 5 shows the incidence of nosocomial infections in the birth weight groups and the CVC (+) and CVC (−) groups. The incidence of nosocomial infection was higher in the lower birth weight groups or the

**Table 4** Results of logistic regression analysis concerning nosocomial infection

| Risk factors | N (%) | Odds ratio | (95% CI) |
|---|---|---|---|
| Gender | | | |
| Male | 465 (53.4%) | 1.86 | (1.04–3.35) |
| Female | 406 (46.6%) | 1.00 | (reference) |
| Birth weight (g) | | | |
| Less than 1,000 | 99 (11.4%) | 8.82 | (4.80–16.21) |
| 1,000～1,499 | 95 (10.9%) | 2.35 | (1.02–5.38) |
| 1,500 or more | 677 (77.7%) | 1.00 | (reference) |
| Artificial ventilation | 240 (27.6%) | 1.49 | (0.82–2.72) |
| CVC | 279 (32.0%) | 2.27 | (1.28–4.02) |
| Umbilical artery catheter | 61 ( 7.0%) | 0.87 | (0.34–2.56) |
| Umbilical venous catheter | 52 ( 6.0%) | 1.46 | (0.60–3.54) |
| Urinary catheter | 135 (15.5%) | 1.34 | (0.69–2.60) |

**Table 5** Incidence of nosocomial infection by birth weight and CVC

| | Birth weight (g) | CVC | Subjects (N) | Infections (N) | Incidence (95% CI) |
|---|---|---|---|---|---|
| Male | 1,500 and more | − | 260 | 8 | 3.1% ( 2.4%～ 3.9%) |
| | 1,500 and more | + | 96 | 7 | 7.3% ( 5.5%～ 9.6%) |
| | 1,000～1,499 | − | 27 | 4 | 14.8% ( 9.1%～24.2%) |
| | 1,000～1,499 | + | 27 | 2 | 7.4% ( 2.8%～19.7%) |
| | Less than 1,000 | − | 27 | 5 | 18.5% (12.5%～27.4%) |
| | Less than 1,000 | + | 28 | 13 | 46.4% (27.9%～64.9%) |
| | Subtotal | | 465 | 39 | 8.4% ( 8.0%～ 8.8%) |
| Female | 1,500 and more | − | 238 | 4 | 1.7% ( 1.0%～ 2.7%) |
| | 1,500 and more | + | 83 | 6 | 7.2% ( 5.2%～10.0%) |
| | 1,000～1,499 | − | 23 | 1 | 4.3% ( 0.6%～30.9%) |
| | 1,000～1,499 | + | 18 | 1 | 5.5% ( 0.8%～39.4%) |
| | Less than 1,000 | − | 20 | 3 | 15.0% ( 7.8%～28.8%) |
| | Less than 1,000 | + | 24 | 4 | 16.7% (10.2%～27.2%) |
| | Subtotal | | 406 | 19 | 4.7% ( 4.2%～ 5.2%) |
| Total | | | 871 | 58 | 6.7% ( 6.4%～ 6.9%) |

CVC (+) group, except for the birth weight group of 1,000–1,499 g with CVC (+). In the boys, the incidence (95% CI) of nosocomial infection was 3.1% (2.4–3.9%) in the birth weight group of more than 1,500 g with CVC (−) but 46.4% (27.9–64.9%) in the birth weight group of less than 1,000 g with CVC (+). In the girls, it was 1.7% (0.1–2.7%) in the former but 16.7% (10.2–27.2%) in the latter.

Table 6 shows the incidence of MRSA infection in the birth weight groups. The incidence (95% CI) of MRSA infection was 0.3% (0.1–0.8%) in the birth weight group of more than 1,500 g, 2.1% (0.8–5.6%) in the birth weight group of 1,000–1,499 g, and 11.1% (9.3–13.3%) in the birth weight group of less than 1,000 g, indicating a rapid increase in the incidence of MRSA infection with decreases in birth weight.

Table 7 shows the results of the multiple logistic regression analysis of MRSA infection. As in the results of the multiple logistic regression analysis of nosocomial infection including MRSA infection, the risk of MRSA infection increased with decreases in birth weight. When the birth weight group of more than 1,500 g was regarded as the reference, the odds ratio was 7.25 in the birth weight group of 1,000–1,499 g and 42.88 in the birth weight group of less than 1,000 g. The odds ratio was higher (1.33) for catheterization in the umbilical cord artery, showing

**Table 6** Incidence of MRSA infection by birth weight

| Birth weight (g) | Subjects (N) | Infections (N) | Incidence (95% CI) |
|---|---|---|---|
| 1,500 or more | 677 | 2 | 0.3% (0.1%～ 0.8%) |
| 1,000～1,499 | 95 | 2 | 2.1% (0.8%～ 5.6%) |
| Less than 1,000 | 99 | 11 | 11.1% (9.3%～13.3%) |
| Total | 871 | 15 | 1.7% (1.5%～ 2.0%) |

**Table 7** Results of logistic regression analysis concerning MRSA infection

| Risk factors | N (%) | Odds ratio | (95% CI) |
|---|---|---|---|
| Gender | | | |
| Male | 465 (53.4) | 1.28 | (0.43– 3.75) |
| Female | 406 (46.6) | 1.00 | (reference) |
| Birth weight (g) | | | |
| Less than 1,000 | 99 (11.4) | 42.88 | (9.35–196.76) |
| 1,000～1,499 | 95 (10.9) | 7.25 | (1.00– 3.87) |
| 1,500 or more | 677 (77.7) | 1.00 | (reference) |
| Artificial ventilation | 240 (27.6) | 0.78 | (0.26– 2.35) |
| CVC | 279 (32.0) | 0.97 | (0.33– 2.85) |
| Umbilical artery catheter | 61 ( 7.0) | 1.33 | (0.34– 5.23) |
| Umbilical venous catheter | 52 ( 6.0) | 0.84 | (0.17– 4.10) |
| Urinary catheter | 135 (15.5) | 1.01 | (0.33– 3.26) |

**Table 8** Outcomes of infected patients

| Outcome | Nosocomial infection | MSRA infection | Non-infection |
|---|---|---|---|
| Death | 6 | 3 | 17 |
| Subjects | 58 | 15 | 813 |
| Death rate | 10.3% (7.5%–14.3%) | 20.0% (10.4%–38.4%) | 2.1% (1.9%–2.3%) |
| Odds ratio (95% CI) | 5.4 (2.0–14.3) | 11.7 (3.0–45.3) | Reference |

that it had a higher risk, but artificial ventilation (odds ratio, 0.78), CVC (odds ratio, 0.97), catheterization in the umbilical cord vein (odds ratio, 0.84), and catheter indwelling in the bladder (odds ratio, 1.01) did not show increases in the risk of MRSA infection.

Table 8 shows the outcomes of the infections. The mortality (95% CI) was 10.3% (7.5–14.3%) in nosocomial infections, 20.0% (3.0–38.4%) in MRSA infection, and 2.1% (1.9–2.3%) in non-infection. The relative risk (95% CI) of nosocomial infection to non-infection was 5.4 (2.0–14.3), and that of MRSA infection to non-infection was 11.7 (3.0–45.3).

## Discussion

Numerous studies have indicated that the risk of nosocomial infection increases with decreases in birth weight, and that birth weight was the most important risk factor [8–12, 22]. However, the incidence of nosocomial infection is very different among studies [8–12, 22]. For example, the present study showed that the incidence of nosocomial infections was 25.2% for babies with low birth weight of less than 1,000 g, 8.4% for those with birth weight of 1,000 g to 1,499 g, 3.7% for those with birth weight of 1,500 g or more. In contrast, it was previously reported that the incidence of nosocomial infections was 48% in babies with birth weight of less than 1,500 g [22]. Although only one infection was documented in our study, the incidence in the study was not considered to be high compared to other studies.

Of the 58 babies with nosocomial infections, 26 (44.8%) had *Staphylococcus* species and 5 (8.6%) had *Escherichia coli*. The number of MRSA infections was 15 (25.9%). Usukura *et al.* reported that MRSA infection was observed in 38.8%, and MRSA was the most important causal bacterium among nosocomial infections in babies with very low birth weight [7]. Although the proportion of MRSA carriers has decreased in Japan [7], the result shows that it is still a major pathogen. Coagulase-negative *Staphylococcus* (CNS), which is a major pathogen for NICU infections in North America [12, 24], was observed in 5 (8.6%) cases. In the US, gram-negative bacilli have been identified as the most common pathogens causing nosocomial infection in NICUs [25]. We did not observe this trend in the present study.

The incidence of sepsis was 7.1% for babies with birth weight of less than 1,000 g, 1.1% for those with birth weight of 1,000 g to 1,499 g and 0.9% for those with birth weight of 1,500 g and more in the present study. Sato reported that sepsis incidence was 17.9% for babies with birth weight of less than 1,000 g, 7.9% for those with birth weight of 1,000 g to 1,499 g and 1.2% for those with birth weight of 1,500 g and more at a hospital in Japan between 1981 and 2001 [26]. Our study suggests that the incidence of sepsis has decreased remarkably among babies whose birth weights were less than 1,500 g. Of the cases of sepsis, 8 (57.1%) were caused by *Staphylococcus* species and two were caused by MRSA in the present study. This finding is consistent with the report that *Staphylococcus* species are major pathogens of sepsis among NICU babies in Japan [26, 27].

In the present study, the risk of nosocomial infection was significantly high among babies with CVC. It is remarkable that 13 of 14 sepsis cases had CVC. CVC infection could be caused at the time of catheterization by inappropriate disinfection of the insertion site or insertion manipulation and by contamination of the insertion site or the catheter itself by insufficient performance of the maximal barrier precaution [28–30]. During catheter indwelling, infection could occur by an invasion of resident bacteria, which grow on the skin of the patient, along the catheter from the insertion site [24]. Bacteria could also invade via a contaminated drug solution or via the catheter by inappropriate handling of its connection sites or T-shaped stopcock [24].

Other devices including artificial ventilation, umbilical artery catheter, umbilical venous catheter, and urinary catheter were not significant risk factors in the present study. Auriti *et al.* reported that the relative risk of nosocomial infections was 5.87 for CVC, 3.59 for mechanical ventilation, and 1.56 for catheterization in the bladder [22]. This discrepancy might be related to the incidence of nosocomial infection, which was 19.6% in their study, higher than in our study.

We estimated the incidence of nosocomial infection in the birth weight groups and the groups with or without CVC by gender because birth weight, CVC, and gender were significant risk factors. Since the number of subjects was limited, the incidence of nosocomial infection varied, but it is believed that an

incidence that can be used as the standard can be determined by accumulating data from a larger number of patients.

Low birth weight was a potent risk factor of MRSA infection in the study. In the birth weight group of less than 1,000 g, the odds ratio was very high (42.88), indicating a close correlation between the host factor and MRSA infection. On the other hand, no increases in the risk of infection due to the application of devices such as artificial ventilation therapy, CVC, umbilical artery catheter, umbilical venous catheter, or urinary catheter were observed.

Although the number of subjects was limited, our study shows that gender, birth weight, and CVC are risk factors for nosocomial infection. It is very important for NICU workers to carefully manage catheter indwelling, appropriate techniques, early catheter replacement, and the introduction of the closed system are important in order to prevent nosocomial infection related to CVC [28–30]. Moreover, workers should wash their hands after the treatment of each baby and should wear gloves in the NICU [15, 16].

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