

## The Efficacy of Clinical Strategies to Reduce Nosocomial Sepsis in Extremely Low Birth Weight Infants

The aim of this study was to evaluate the efficacy of clinical strategies to reduce nosocomial sepsis (NS) in extremely low birth weight infants (ELBWI) less than 1,000 g. Data from the period before (P1, 1995-2000) and after (P2, 2001-2002) implementation of the strategies were collected and analyzed. The intervention strategies included restriction of antibiotic therapy, less use of invasive procedures such as umbilical vessel catheterization and endotracheal intubation, establishment of guidelines for hand-washing, infant handling, and central intravascular line management. NS was defined as positive blood cultures in symptomatic patients after the third day of life with the use of antibiotics for more than 5 days. Although the gestational age (GA) and birth weight (BW) were significantly lower in P2 (GA 26.7  $\pm$  2.1 wk; BW 796  $\pm$  130 g) compared to P1 (GA 27.2  $\pm$  1.6 wk; BW 857  $\pm$  121 g), the incidence of NS decreased significantly from 70% (69/99) in P1 to 17% (24/71) in P2 with the implementation of the intervention strategies. The coagulase negative *Staphylococcus* infection was also significantly reduced from 34% in P1 to 11% in P2. The implementation of the clinical strategies was quite effective in reducing the incidence of NS in ELBWI.

**Key Words :** Nosocomial Infection; Cross Infection; Infants, Very Low Birth Weight; Invasive Procedures; Intubation; Catheterization; *Staphylococcus*

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## INTRODUCTION

Nosocomial sepsis (NS), the most common form of nosocomial infection (1-4), is a common and serious problem in neonates admitted to the neonatal intensive care unit (NICU), and is accompanied by significantly high mortality and morbidity (5-7). Extremely low birth weight infants (ELBWI) less than 1,000 g are particularly susceptible to NS (8-10), probably due to immature immune function, increased use of devices including endotracheal intubation and catheterization and prolonged hospital stay (8-10). Furthermore, as the risk of NS is inversely proportional to gestational age and birth weight, the rate of NS may increase with the current improving survival of ELBWI (11-15).

The variable incidence of NS among NICUs (6, 7, 16, 18) suggests that environmental factors in NICU might contribute to the risk of NS, and the rate of NS could be related to the clinical practice style and management decisions (6, 7, 13, 16). Some investigations have also suggested that selected interventions could lower the risk of NS (17-20). Thus the development of new effective therapeutic strategies could reduce the rate of NS and improve the clinical outcome of ELBWI (17-20).

Based on the surveillance and our previous NS risk factor identification studies in the NICU (21, 22), an intervention

strategy was designed and executed with the goal of reducing NS in ELBWI. This paper presents the results of this approach.

## MATERIALS AND METHODS

### Patients and methods

A total of 170 ELBWI admitted to the NICU at SMC for more than 3 days, from 1 January 1995 through 31 December 2002 were included in this study. Ninety nine ELBWI were during period 1 (P1; 1 January 1995 to 31 December 2000; before the intervention strategy), and 71 infants were during period 2 (P2; 1 January 2001 to 31 December 2002; after the introduction of the strategy). NS was defined as positive blood cultures in symptomatic patients after the third day of life with the use of antibiotics for more than 5 days. Data for patients admitted to the NICU during P1 were obtained retrospectively, and during P2 were collected prospectively and analyzed.

### Intervention strategy

The intervention strategy consisted of alterations in the clinical practice to reduce the rate of NS in ELBWI based on

the risk factors such as antibiotics, umbilical vessel catheterization, and prolonged endotracheal intubation identified in our previous studies (21, 22), and the establishment of guidelines for hand-washing, infant handling, and care of central intravascular lines. The use of antibiotics was strictly restricted to symptomatic patients with clinical and laboratory findings highly suggestive of sepsis, stopped if the blood culture remained negative after 48 hr, and prophylactic usage was prohibited. Umbilical vessel catheters were inserted only in patients with hemodynamic instability or severe respiratory distress, and removed as soon as possible. To shorten the duration of endotracheal intubation and mechanical ventilation, the patients were extubated aggressively and the less invasive nasal continuous positive airway pressure (NCPAP) was applied as early as possible. Hand-wash with alcohol and chlorhexidine-containing solution was recommended before and after all patient contact for all personnel caring for neonates in the NICU. Glove use for all patient contact was recommended with special emphasis on the handling of diapers. Aseptic care maneuvers of central intravascular lines, including the placement of three-way stopcocks on the sterile drape, and the access only with sterile gloves, were developed.

### Statistical analysis

Data were given as mean  $\pm$  standard deviation. Student *t*-test was used to compare normally distributed continuous

**Table 1.** Demographic profile and risk factors associated with nosocomial sepsis in extremely low birth weight infants

	Period 1 (n=99)	Period 2 (n=71)
Gestational age (wks)	27.3 $\pm$ 1.6	26.7 $\pm$ 2.1*
Body weight (g)	857 $\pm$ 121	796 $\pm$ 130*
Male (%)	53 (54)	30 (42)
Inborn (%)	83 (84)	66 (93)
Cesarean section (%)	63 (64)	47 (66)
Survival (%)	67 (68)	52 (73)
Hospitalization days (days)	84 $\pm$ 54	82 $\pm$ 51
1st day antibiotics (%)	72 (73)	25 (35)*
Antibiotics duration (days)	32 $\pm$ 25	21 $\pm$ 20*
UVC (%)	64 (65)	22 (31)*
UVC duration (days)	3 $\pm$ 3	2 $\pm$ 4*
UAC (%)	73 (74)	49 (69)
UAC duration (days)	7 $\pm$ 6	5 $\pm$ 4*
PCVC (%)	87 (88)	64 (90)
PCVC-start day (days)	7 $\pm$ 5	6 $\pm$ 6
PCVC duration (days)	24 $\pm$ 22	27 $\pm$ 22
Ventilator duration (days)	40 $\pm$ 41	26 $\pm$ 25*
NCPAP (%)	52 (53)	53 (75)*
NCPAP-start days (days)	25 $\pm$ 26	19 $\pm$ 24
NCPAP duration (days)	5 $\pm$ 8	13 $\pm$ 16*

\**p* < 0.05 vs. Period 1.

Period 1: 1994.10-2000.12, Period 2: 2001.1-2002.12.

1st day antibiotics, antibiotics use at 1st day of life; UAC, Umbilical artery catheter; UVC, Umbilical vein catheter; PCVC, Percutaneous central venous catheter; NCPAP, Nasal continuous positive airway pressure.

variables and comparisons of categorical data were performed with chi-square test. A *p* value of <0.05 was considered to indicate statistical significance. Odd ratios and 95% confidence intervals were calculated and multiple logistic regression analysis was performed with risk factors. The Statistical Package for the Social Sciences (SPSS) (version 11.5) was used for statistical analysis.

## RESULTS

### Demographic findings

Gestation age (GA) and birth weight (BW) were significantly lower in P2 compared to P1 (Table 1). There were no significant differences in sex, mode of delivery, inborn, survival, and hospitalization days between the two study periods. With the implementation of clinical strategies, the use of antibiotics at the first day of life and duration of antibiotic therapy, the use and duration of umbilical catheters, and the duration of endotracheal intubation and mechanical ventilation were significantly reduced and the use and duration of NCPAP were significantly increased in P2 compared to P1. The use and duration of percutaneous central venous catheter (PCVC) were not significantly different between the two periods. In the multivariate logistic regression analyses, only antibiotics duration was independent risk factor for nosocomial sepsis (Table 2).

### Incidence of nosocomial sepsis

The overall and weight-stratified incidence, and episodes of NS were significantly reduced, and death attributable to NS tended to improve in P2 compared to P1 (Table 3).

### Spectrum of organism

With the reduction of the incidence of NS, Coagulase negative *Staphylococcus* (CONS) infection was significantly decreased

**Table 2.** Logistic regression model for risk factors associated with nosocomial sepsis in extremely low birth weight infants

	Odds ratio	95% CI	<i>p</i> -value
Gestational age (wks)	0.73	0.43-1.23	0.24
Body weight (g)	0.99	0.99-1.00	0.04
1st day antibiotics (%)	0.24	0.05-1.16	0.08
Antibiotics duration (days)	0.95	0.91-0.99	0.01
UVC (%)	8.16	1.00-66.71	0.05
UVC duration (days)	1.37	0.82-2.28	0.23
UAC (%)	0.27	0.02-1.27	0.35
UAC duration (days)	0.63	0.39-1.02	0.06
Ventilator duration (days)	0.97	0.93-1.02	0.21
NCPAP (%)	1.21	0.19-8.15	0.82
NCPAP duration (days)	1.02	0.97-1.08	0.45

**Table 3.** The incidence of nosocomial sepsis in extremely low birth weight infants

	Period 1 (n=99)	Period 2 (n=71)
Nosocomial sepsis (%)	69 (70)	17 (24)*
Weight (g)		
<750	15 (75)	8 (31)*
750-1,000	54 (68)	9 (20)*
Death attributed to NS (%)	17 (17)	6 (9)
Episodes of nosocomial sepsis	125	19*

\* $p < 0.05$  vs. Period 1. NS, Nosocomial sepsis.

in P2 compared to P1 (Table 4). The distribution of other pathogenic organisms was not significantly different between the two study periods.

## DISCUSSION

In the present study, the implementation of the intervention strategy was quite effective in reducing the incidence of NS in ELBWI, the highest risk group of NS (17-20). As NS is the important cause of increased mortality rates, morbidities, prolonged hospitalization days and high medical costs (6, 23), the significant reduction in the rate of NS would also improve the clinical outcome in ELBWI. Our data on the tendency of improved survival despite significantly lower GA and BW in P2 compared to P1 also support this assumption.

In this study, the intervention strategies were designed and implemented based on the surveillance and risk factors of NS in ELBWI identified in our previous studies (21, 22), and the incidence of NS was significantly reduced with the implementation of this strategy. Although it is difficult to say which of the practices in this intervention strategy actually played an important role, these strategies as a whole were quite effective in reducing the incidence of NS in ELBWI.

Empirical use of antibiotics increases the risk of opportunistic infections and the development of antibiotic resistant organisms over time (24-27). The over-use of antibiotics was associated with the increased incidence of NS in NICU (6, 16, 19, 24). In the present study, the incidence of NS in ELBWI was significantly reduced with less use and duration of antibiotic therapy. Multiple logistic regression analysis showed that significant independent predictors of NS in ELBWI included decreasing antibiotics duration. Thus, the rational use of antibiotics including the optimal choice of drug and optimal duration of therapy should be appropriately established to reduce the risk of NS in ELBWI.

Endotracheal intubation and assisted ventilation are recognized risk factors for NS in the NICU due to the colonization of humidified air with hydrophilic micro-organisms (4, 28), to physical trauma of passing an endotracheal tube (12, 29), and to transient bacteremia during routine suction (4, 28, 29). Goldman et al. (23) reported that endotracheal intubation increased the risk of nosocomial infection by seven

**Table 4.** Distribution of pathogens associated with nosocomial sepsis in extremely low birth weight infants

Organism (%)	Period 1 (n=125)	Period 2 (n=19)
Gram-positive organism	79 (63)	10 (53)
CONS	43 (34)	2 (11)*
MRSA	23 (18)	7 (37)
<i>Enterococcus/</i>	13 (10)	0 (0)
Group D <i>Streptococcus</i>		
Others	0 (0)	1 (5)
Gram-negative organism	24 (19)	3 (16)
<i>Klebsiella</i>	8 (6)	0 (0)
<i>Enterobacter</i>	9 (7)	1 (5)
<i>Escherichia coli</i>	4 (3)	1 (5)
<i>Pseudomonas</i>	2 (2)	0 (0)
Others	1 (1)	1 (5)
Candida	22 (18)	6 (32)
<i>Candida albicans</i>	7 (6)	5 (26)*
<i>Candida parasilosis</i>	7 (6)	1 (5)
Others	8 (6)	0 (0)

CONS, Coagulase negative *Staphylococcus*; MRSA, Methicillin resistant *Staphylococcus aureus*.

times. Infants, on mechanical ventilation for longer periods, showed an increased incidence of NS (6, 16). In the present study, the aggressive early weaning from invasive mechanical ventilation to less invasive NCPAP was associated with the reduced incidence of NS in ELBWI.

It is widely recognized that central intravascular catheters are a potent source of infection, since they can become easily colonized with bacteria from the skin surrounding the exit site (4, 12), from transient bacteremia (30, 31), or via the gastrointestinal tract (30). Longer duration of catheterization is related to an increased risk of catheter colonization and catheter-related infections (5, 31-33). Umbilical catheters are at particularly high risk of infection, given the luxuriant flora of the umbilical stump. When the umbilical vein and artery catheters were maintained for more than 5 days, the risk of NS was increased by 21 and 16 times, respectively (33). In the present study, the insertion of umbilical catheters was strictly restricted, and the catheters, once inserted, were removed as soon as possible. This strategy, we believe, have contributed to the significant reduction of NS in this study. As the use and duration of PCVC were not significantly different between the two study periods in this study, meticulous aseptic care of the central line may have accounted for the reduction of NS. Thus, the PCVC may not be a potent source of infection as umbilical vessel catheters.

CONS are a common skin commensal and the most frequent organism associated with NS in ELBWI (5, 16, 19, 22, 28). The presence of indwelling central vascular catheters is identified as an important risk factor for CONS infection in the NICU (28, 31, 32, 34, 35). Recent studies suggested that CONS infection was decreased with the protocol for central intravascular line care and reduction of the use and duration of central line (18, 19). The significant reduction in the rate

of CONS infection observed in this study might be attributable to less use and duration of umbilical vessel catheters, and to the establishment of the guidelines of central intravascular line management.

Prolonged antibiotic therapy, intravascular catheter use, and lower GA are well known risk factors for *Candida* sepsis (26, 27). In the present study, despite the less use and duration of antibiotic therapy and umbilical vessel catheters, the incidence of *Candida* sepsis was not significantly reduced in P2 compared to P1. It is difficult to explain this result, further studies might be needed.

In summary, the implementation of the intervention strategies was quite effective in reducing the incidence of NS and improving the clinical outcome in ELBWI.

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