ARTICLE

Improving Survival of Vulnerable Infants Increases Neonatal Intensive Care Unit Nosocomial Infection Rate

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Objective: To determine the factors associated with an increasing rate of nosocomial infections in infants with very low birth weights.

Methods: Retrospective review of clinical and nosocomial infection databases for all infants with birth weights of 1500 g or less admitted to an academic neonatal intensive care unit between January 1, 1991, and December 31, 1997 (N=1184). Two study periods were compared: 1991-1995 and 1996-1997.

Results: Among the 1085 infants who survived beyond 48 hours, the proportion who developed nosocomial infections increased from 22% to 31% ($P=.001$) and the infection rate increased from 0.5 to 0.8 per 100 patient-days ($P<.001$) during the period from 1996 to 1997. In that same period, the median duration of indwelling vascular access increased from 10 to 16 days ($P<.001$), and the median duration of mechanical ventilation increased from 7 to 12 days ($P<.001$). Although the device-specific rate of bloodstream or respiratory infections did not change, the increase in infections was directly attributable to the increasing proportion of infants who required these devices. In both study periods, the peak incidence of initial infection occurred between 10 and 20 days of age. For the entire sample, proportional hazard models identified birth weight, duration of vascular access, and postnatal corticosteroid exposure as significant contributors to the risk of infection.

Conclusions: The increasing number of technology-dependent infants was the primary determinant in the increase of nosocomial infections. Because these infections occur in a small proportion of infants, understanding the host factors that contribute to this vulnerability is necessary to decrease nosocomial infections in neonatal intensive care units.

Arch Pediatr Adolesc Med. 2001;155:1098-1104

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IMPROVEMENTS in obstetrical and neonatal intensive care have reduced the morbidity and mortality rates of infants with very low birth weights. Antibiotic administration at the onset of preterm labor or rupture of maternal amniotic membranes decreases the risk of intrapartum acquisition of pathogens and may prolong pregnancy. Antenatal corticosteroid administration and postnatal surfactant administration decrease the incidence, severity, and mortality of neonatal respiratory distress syndrome and may decrease the likelihood of bacteremia in these infants.[1-8] Although these interventions effectively improve pulmonary outcomes, nosocomially acquired infections still affect up to 25% of infants in neonatal intensive care units (NICUs), with a disproportionate share occurring in infants with a birth weight of less than 1500 g.[9-14] Infection control practices and surveillance are invaluable for preventing acquisition and spread of these infections and for identifying environmental factors that may contribute to clusters of infections. However, extensive investigations often fail to yield specific sources, and the clusters may spontaneously disappear. This suggests that environmental or host factors that have yet to be identified also contribute to the acquisition of nosocomial infections.

During ongoing routine surveillance, we noted an increase in the nosocomial infection rate in the St Louis Children's Hospital NICU (St Louis, Mo) and were concerned that changes in the environment or care practices might be contributing to this higher infection rate. We were further concerned, based on the identification of clusters of colonization with gram-negative organisms, that the microbiological spectrum of the nosocomial infections occurring in our NICU was changing. Therefore, to determine if the rate and microbiological spectrum of nosocomial

SUBJECTS AND METHODS

We retrospectively reviewed the clinical and nosocomial infection databases for all infants admitted between January 1, 1991, and December 31, 1997 (N=4827). Because the overall infection rate increased in 1996, we divided the data into 2 study periods: 1991-1995 and 1996-1997 (**Figure 1**). Although infants with very low birth weights (≤1500 g) made up 25% of NICU admissions during the 7 years studied, they accounted for 92% of nosocomial infections in the NICU. Therefore, we limited the study to this group (N=1184).

Because we were interested only in nosocomially acquired infections, we excluded infections identified within 48 hours of admission and transplacentally acquired infections. Definitions for nosocomial infections were in accordance with those of the National Nosocomial Infections Surveillance (NNIS) System of the Centers for Disease Control and Prevention.[15] Infections, regardless of source, were included only if a positive bacterial or fungal culture occurred in association with a clinical syndrome and initiation of antibiotic therapy. We also excluded 16 positive eye drainage cultures and 11 positive wound cultures. The surveillance period for each infant ended at death, discharge, transfer to another facility, or the end of the study period. Information collected included birth weight, gestational age, length of stay in the NICU, survival, number and source of infections, age at the time of infection, the organism(s) responsible, exposure to corticosteroids while in the NICU, and presence and duration of mechanical ventilation or long-term vascular access. The duration of long-term vascular access was calculated as the total number of days during which an umbilical venous or arterial catheter, Broviac catheter, peripherally inserted central venous catheter, or peripheral arterial catheter was present.

To determine if maternal antibiotic or corticosteroid administration contributed to the risk of acquiring a nosocomial infection, we obtained computerized pharmacy records (available from July 1993 forward) for every mother who gave birth at our primary obstetrical service to an infant with a very low birth weight who was transferred to the NICU (n=338).

The data were analyzed using Statistical Analysis System software (SAS Institute, Cary, NC). *t* Tests were used to compare normally distributed continuous variables; Wilcoxon rank sum comparisons were used for nonparametric data. Comparisons of categorical data and estimates of relative risk (RR) between groups were performed with Cochran-Mantel-Haenszel χ^2 analyses, and 2-tailed *P* values were calculated. We also developed proportional hazard models to identify independent factors that contributed to the risk of infection or death in a multivariate model.[16,17] The Washington University Human Studies Committee approved the study.

infections were changing and to further determine if peripartum antibiotic usage might be contributing to a change in epidemiology, we reviewed all nosocomial infections in infants with birth weights of 1500 g or less in the NICU from 1991 to 1997.

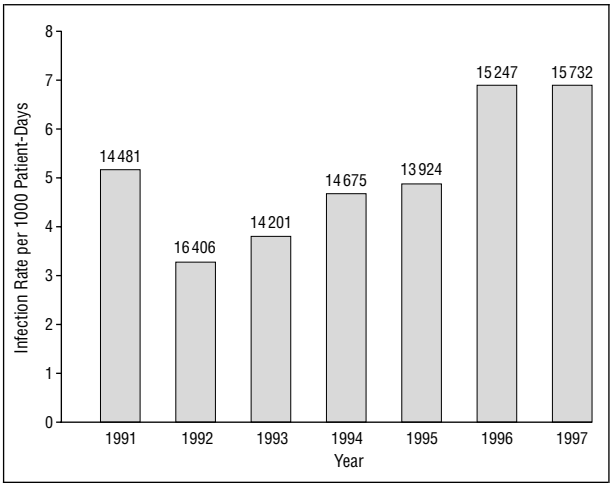

Figure 1. Annual nosocomial infection rate per 1000 patient-days for all infants in the St Louis Children's Hospital neonatal intensive care unit (St Louis, Mo) for the 1991-1997 period. The numbers above the bars indicate the total number of patient-days in the year. After a decrease between 1991 and 1992, the rate increased steadily but not significantly until 1996.

RESULTS

DEMOGRAPHICS

Of the 1184 infants with very low birth weights admitted to the NICU during the study period, 99 had lengths of stay less than 48 hours and thus were excluded. Of these 99 infants, 84 died within 48 hours of birth; the remaining 15 were briefly admitted after their neonatal period for specialized procedures. Of the 84 infants who died, 66 were born in the 1991-1995 period, and 18 were born in the 1996-1997 period (8% and 5% of the study population, respectively; *P*=.06). These infants had median birth weights of 727 g and 631 g between 1991 and 1995, and 1996 and 1997, respectively (*P*=.06), and median gestational ages of 25 and 24 weeks, respectively (*P*=.08).

After this exclusion, the final study population contained 1085 infants, with 747 and 338 infants in the 1991-1995 and 1996-1997 groups, respectively. There were no differences between the 1991-1995 and 1996-1997 periods with respect to birth weight distribution, race, sex, survival after 48 hours, or length of stay (**Table 1**). Gestational age was statistically but not clinically different between the 2 study periods: 28.2 vs 27.8 weeks, 1991-1995 and 1996-1997, respectively. Postnatal corticosteroid use increased significantly in the later study period. Also in this period, survival through the first 48 hours of life increased from 92% to 95% (*P*=.06) (Table 1).

INFECTION RATE

The proportion of infants who experienced at least 1 infection increased from 22% to 31% in the later surveillance period (*P*=.001) (**Table 2**). The number of infections normalized for patient-days was also significantly higher in the 1996-1997 period. Overall, 266 infants ac-

Table 1. Demographic Data of Infants With Very Low Birth Weights Admitted to the Neonatal Intensive Care Unit*

	1991-1995 (n = 747)	1996-1997 (n = 338)	P†
Birth weight, g, median (range)	1060 (455-1499)	1031 (430-1499)	.19
Birth weight, g, No. (%)‡			
<750	110 (15)	61 (18)	.16
750-999	204 (27)	92 (27)	>.99
1000-1249	224 (30)	97 (29)	.67
1250-1499	209 (28)	88 (26)	.51
Gestational age, wk			
Median (range)	28 (22-36)	28 (23-36)	.01
Mean (SD)	28.2 (2.4)	27.8 (2.4)	
Race			
African American	46	44	.33
Sex			
F	50	48	.56
Steroid use	35	46	.001
Survival to 48 h	92	95	.06
Survival from day 3 to discharge	89	87	.33
Length of stay, d, median (range)	52 (3-250)	53 (3-309)	.76

*Data are presented as percentage unless otherwise indicated.
†All continuous variables were compared using Wilcoxon rank sum analyses.
‡Indicates proportion of infants with very low birth weights during the study period.

Table 2. Birth Weight–Specific Rates of Infection*

	1991-1995	1996-1997	P
Infants with 1 or more infections	22	31	.001
Infections by birth weight category, g			
<750	44	57	.09
750-999	28	38	.10
1000-1249	20	24	.41
1250-1500	6	12	.05
No. of infections per 100 patient-days	0.5	0.8	<.001
No. of infections per 100 patient-days by birth weight, g			
<750	1.0	1.3	.12
750-999	0.6	0.9	.01
1000-1249	0.4	0.6	.34
1250-1500	0.2	0.4	.01

*Data are presented as percentage unless otherwise indicated.

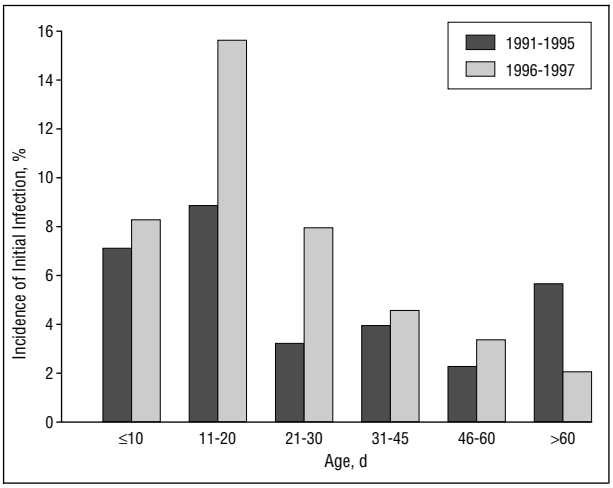

Figure 2. The incidence of initial infection in infants with very low birth weights according to age in specified intervals. The incidence was calculated by dividing the number of infants who developed their first infection within the interval by the difference between the number of infants hospitalized at the beginning of the interval and those with previous infections who were still hospitalized. The peak incidence occurred in the 10- to 20-day interval for both the 1991-1995 and 1996-1997 study periods.

quired 391 infections; 30% of the study group accounted for 52% of the infections, with a similar proportion in each study period. The peak incidence of initial infection in both study periods occurred between 10 and 20 days of age, with 73% of all initial infections arising in this interval (**Figure 2**). Forty-three infants (6%) in the 1991-1995 period and 31 infants (9%) in the 1996-1997 period experienced more than 1 infection ($P=.04$). In both periods, approximately 55% of the subsequent infections occurred by 60 days of age.

DEVICE USE AND INFECTION

The proportion of infants with long-term vascular catheters was significantly greater in the later study period (88% vs 94% of infants, 1991-1995 and 1996-1997, respectively; $P=.002$). In addition, the median duration of catheter use increased in the later study period from 10 days per infant to 16 days per infant (range, 0-193 days; $P<.001$), and from 30 to 42 catheter-days per 100 patient-days ($P<.001$). Despite the increase in use of vascular catheters, the rate of bacteremia normalized for duration of vascular access did not change (**Figure 3**A and B). Similarly, the proportion of infants who required mechanical ventilation increased in the later study period (90% vs 97%; $P=.001$). The median duration of ventilation increased from 7 days per infant (range, 0-200 days) to 12 days per infant (range, 0-206 days; $P<.001$) and from 29 to 38 ventilator-days per 100 patient-days ($P<.001$). However, the rate of respiratory infections normalized for ventilator days did not change (**Figure 4**A and B). These device use and associated infection rates were comparable with those published by the NNIS for the period from 1990 to 1998 (data not shown).[15]

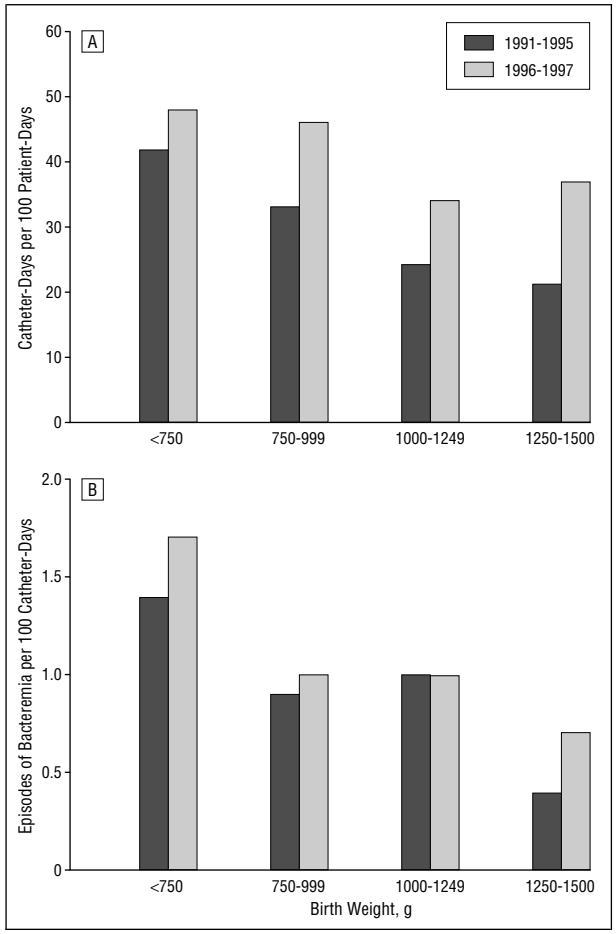

Figure 3. Vascular catheter use and bacteremia by birth weight group. A, The number of catheter-days was significantly greater in the 1996-1997 period for all birth weight subgroups ($P<.001$ for all). B, The number of episodes of bacteremia normalized for vascular catheter-days was not different for any of the birth weight subgroups between the 2 periods ($P>.20$ for all).

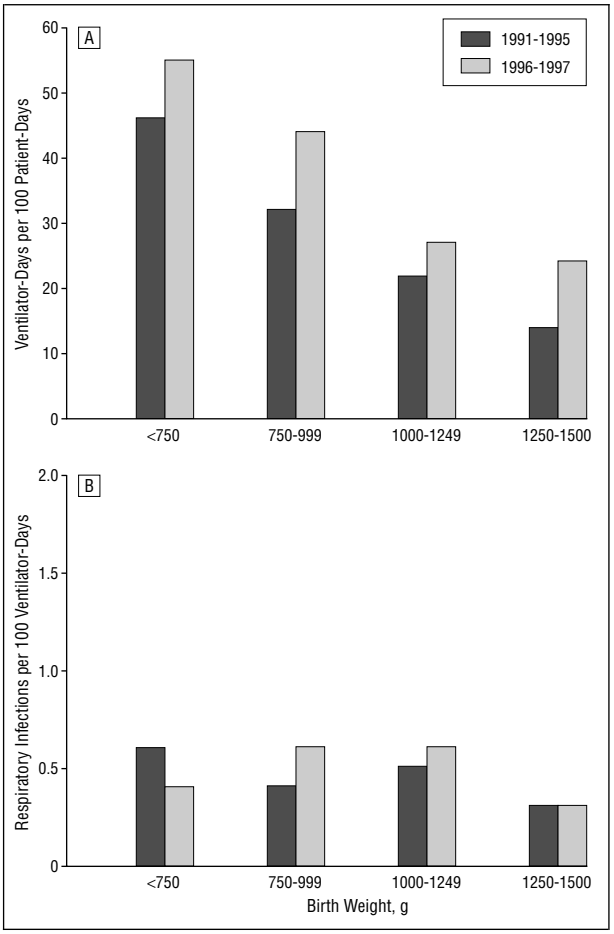

Figure 4. Ventilator use and respiratory infections by birth weight group. A, The number of ventilator-days was significantly greater in the 1996-1997 period for all birth weight subgroups ($P<.001$ for all). B, The number of respiratory infections normalized for ventilator-days was not different for any of the birth weight subgroups between the 2 periods ($P>.30$ for all).

The overall increase in infections was directly attributable to the increased number of infants who required these devices and their duration of use in the later period.

SOURCE AND SPECTRUM OF ORGANISMS

We found that 53% of the organisms were isolated from the bloodstream, 27% from the respiratory tract, 14% from the urinary tract, 4% from the gastrointestinal tract, and 1% from the cerebrospinal fluid. This distribution was similar in the 2 study periods. To determine if the increasing number of infections was accompanied by a shift in the spectrum of organisms, we analyzed the annual distribution of the specific pathogens (**Table 3**). Some annual variation in the types of organisms reflected small clusters of infection. The relative proportion of gram-negative to gram-positive organisms was not significantly greater in the 1996-1997 period (0.8 and 1.0, 1991-1995 and 1996-1997, respectively; $P=.17$); this was also true for fungal infections.

RISK OF INFECTION

To determine the degree to which different factors might have influenced the increased rate of infection, we developed a proportional hazard model for the entire sample to evaluate the risk of nosocomial infection (treated as a dichotomous variable) with respect to birth weight (treated as a continuous variable), study period, exposure to corticosteroids while in the NICU, and duration of mechanical ventilation and long-term vascular access (treated as continuous variables). After controlling for these factors, lower birth weight (RR, 1.002 per gram; 95% confidence interval [CI], 1.001-1.002), corticosteroid exposure (RR, 1.7; 95% CI, 1.2-2.3), and duration of central vascular access (RR, 1.01 per day; 95% CI, 1.005-1.015) significantly influenced the risk of infection. The duration of mechanical ventilation did not significantly influence the risk of infection (RR, 1.005 per day; 95% CI, 0.999-1.010).

To determine if maternal antibiotic or corticosteroid administration contributed to the risk of nosocomial infection, we evaluated the subset of infants born at our primary obstetrical service. This subset was comparable with the remainder of the population with respect to birth weight, gestational age, infection rate, and device use (data not shown). We then developed another proportional hazard model in which we added maternal antibiotic and corticosteroid administration (treated

Table 3. Annual Distribution of Specific Organisms*

Organism	1991	1992	1993	1994	1995	1996	1997
Coagulase-negative *Staphylococcus* species	32	26	31	25	37	29	22
Candida species	15	11	13	11	10	14	15
Enterococcus	8	9	7	11	5	12	9
Staphylococcus aureus	10	4	11	13	8	5	8
Pseudomonas species	5	15	4	3	7	12	9
Escherichia coli	5	6	11	10	7	5	11
Enterobacter species	7	6	7	13	3	10	3
Klebsiella species	5	6	4	5	10	6	8
Acinetobacter species	8	9	0	5	3	0	0
Serratia species	0	4	0	0	0	0	3
Citrobacter species	0	0	0	2	2	4	3
Other	5	4	12	2	8	3	9

*Data presented as proportion of isolates within the year.

as dichotomous variables) to birth weight and duration of device use (treated as continuous variables) to evaluate the risk of nosocomial infection. In this model, only lower birth weight (RR, 1.003 per gram; 95% CI, 1.002-1.004) and duration of central vascular access (RR, 1.008 per day; 95% CI, 1.001-1.015) significantly contributed to the risk of infection. In separate models using this subset of infants, none of these parameters significantly influenced the occurrence of nosocomial infections caused by yeast, gram-negative, or gram-positive organisms, most likely because of inadequate power in the analysis.

RISK OF DEATH

Deaths directly due to infection increased from 2% to 4% of the study population in the later period ($P=.02$). In addition, in each study period, the risk of death was significantly greater for infants who experienced an infection (RR, 1.8; 95% CI, 1.3-2.5 and RR, 1.8; 95% CI, 1.3-2.7 in the earlier and later period, respectively). Despite the greater number of infections in the later period, the attributable risk of mortality (9% and 13%, respectively) did not change ($P=.09$). In a proportional hazard model using the entire sample in which the risk of death was evaluated with respect to infection during hospitalization, study period, birth weight, corticosteroid exposure, and duration of device use, only lower birth weight (RR, 1.005 per gram; 95% CI, 1.004-1.006) and corticosteroid exposure (RR, 0.4; 95% CI, 0.2-0.7) significantly influenced the risk of death. Duration of central vascular access or mechanical ventilation was of borderline significance (RR, 0.99 per day; 95% CI, 0.98-1.0 for both variables). In separate proportional hazard models in which the risk of death was analyzed with respect to the source of infection (treated as categorical variables: bloodstream, respiratory tract, etc) or the type of organism (treated as categorical variables: gram-negative, gram-positive, or yeast), along with birth weight and device use, neither the source of infection nor the type of organism influenced the risk of death.

COMMENT

We observed a significant increase in the rate of nosocomially acquired infections for infants with very low birth weights in the St Louis Children's Hospital NICU between 1991 and 1997. We also found an increase in the frequency and duration of device use that paralleled the increase in infection rate, which suggests a larger population of technology-dependent infants who were vulnerable to acquiring infections. Although we did not have indexes to quantify the severity of illness, the observation that the duration of central catheter use or mechanical ventilation increased in the 1996-1997 period suggests a sicker population and does not simply reflect an increase in the perceived need for these interventions. Despite the greater use of these devices, infection rates associated with them did not change significantly over time, which suggests that practices relating to ventilator and indwelling vascular catheter management did not contribute to changes in the overall infection rate. This lack of change in device-associated infections occurred in the presence of 2 significant practice modifications: a decrease in the frequency with which ventilator tubing was changed (from every 3 days to every 2 weeks) and the development of a nursing team dedicated to placement of percutaneous central venous catheters. Despite these practice changes, our cumulative rates of device-associated infection were comparable with those reported by the NNIS between 1990 and 1998.[15] We also found that the 2 most prevalent sites of infection, the bloodstream and the respiratory tract, were similar in distribution to other reported studies.[18]

We were surprised to find a similar microbiological spectrum between the early and later periods of the study, specifically yeast and gram-negative infections, a spectrum that was also comparable with other published reports.[9,18-20] Although periodic clusters of organisms suggested a component of horizontal transmission and created the impression that an individual organism's prevalence was increasing, these clusters resolved without explanation or apparent trend. However, the observation that the proportion of infections caused by gram-negative organisms appeared to increase in the later study period suggests a trend that bears monitoring. Throughout the entire study period, ampicillin sodium and gentamicin sulfate were used almost exclusively for presumptive treatment of intrapartum-

What This Study Adds

Newborns with low birth weights who require intensive care are at increased risk for nosocomial infection, primarily because of the need for invasive technology. Despite rigorous infection control measures, we noticed an increased rate of nosocomial infection in the St Louis Children's Hospital NICU.

The increasing proportion of technology-dependent infants in our NICU was the predominant factor contributing to the increasing infection rate. The peak incidence for nosocomial infections occurred between 10 and 20 days of age, and the second-highest incidence occurred between 3 and 10 days of age. This observation suggests that biological factors in the infant and/or mother, rather than environmental factors, may contribute to the risk of infection. These factors need to be identified and examined in more detail.

acquired pathogens in the 48 hours after delivery; vancomycin hydrochloride and gentamicin were used after 7 days.

Antibiotic or corticosteroid administration, either in the peripartum or neonatal period, may alter the microbiological spectrum of organisms or increase the risk of infection, especially in the first days after birth.[21-23] However, these interventions may also influence the spectrum of later-onset infections thought to be nosocomially acquired, an issue that has not been previously evaluated. We did not have the opportunity to examine the antimicrobial sensitivity patterns of the organisms, nor did we examine the rate or microbiological spectrum of neonatal early-onset infections, either of which may be influenced by intrapartum antibiotic administration.[21,22] Although we did not have data on maternal antibiotic or corticosteroid administration for the entire population or duration of the study, these agents did not appear to significantly influence the risk or microbiologic distribution of nosocomial infections in the subset of infants for whom data were available.

Postnatal dexamethasone sodium phosphate administration to treat bronchopulmonary dysplasia has not been reported to increase the risk of infection. However, after controlling for study period and other clinical factors, we found that postnatal corticosteroid use contributed to a higher risk of infection yet a lower risk of death.[24-26] Because our data did not permit analysis of the temporal relationship between postnatal corticosteroid administration and infection, we could not assess the attributable risk of infection due to corticosteroid use. A larger prospective analysis would be more appropriate to address the effects of peripartum interventions and to test hypotheses about other practices that may influence long-term risk of infection.

Current epidemiologic techniques designed to identify risk factors for nosocomial infection in NICUs have consistently yielded similar results: the infants at greatest risk of nosocomial infection are the smallest and require the most interventions, and infection is a risk factor for adverse outcome.[12,13,20,27] Two other observations in our study warrant discussion. First, a small population of infants contributed disproportionately to the infection rate, and second, 73% of nosocomial infections occurred between 10 and 20 days of age, which is consistent with a median onset of 15 to 17 days in other reports of nosocomial bloodstream infections.[12,19,28,29] These observations suggest that a subset of infants with very low birth weights may have an underlying genetic or immunologic susceptibility to the pathogenic effect of ubiquitous organisms at critical periods in their postnatal development. For instance, in infants with evolving lung injury, disruption of innate immunologic factors such as surfactant proteins A or D or granulocyte-macrophage colony-stimulating factor could permit organisms to establish more widespread infection.[30-34] Along with attempts to decrease device-associated infection rates and to provide meticulous environmental surveillance and education about infection control procedures, efforts to understand and modify these biologic vulnerability factors will be necessary to significantly decrease the nosocomial infection rate in NICUs.

Accepted for publication March 27, 2001.

The authors would like to thank Gregory Storch, MD, for thoughtful suggestions for data analysis and careful review of the manuscript, and Laura Noce, RN, BSN, for providing nosocomial infection data.

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