Septicemia in the First Week of Life in a Norwegian National Cohort of Extremely Premature Infants

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ABSTRACT. *Objectives.* **To investigate the incidence, causes, predictors, and outcomes of septicemia in the first week of life in a national cohort of extremely premature infants.**

Methods. **A prospective study of survival of all infants with gestational age of <28 weeks or birth weight of <1000 g who were born in Norway in 1999–2000 was performed. Data on the maternal prenatal history, delivery, and neonatal course, including detailed information on episodes of microbiologically verified septicemia, were collected on predefined forms. Septicemia was reported in 2 groups, ie, episodes diagnosed on the day of delivery (ie, very early-onset septicemia [VEOS]) and episodes diagnosed from day 2 to day 7 of life (ie, early-onset septicemia [EOS]). Logistic regression models were used for the selection of variables for predictor analysis in each group.**

Results. **Of 462 included infants, VEOS occurred for 15 (32.5 per 1000 population) and EOS for 15 (35.5 per 1000 population). The most prevalent bacteria were *Escherichia coli* in VEOS ($n = 9$) and staphylococci (coagulase-negative staphylococci and *Staphylococcus aureus*) ($n = 15$) in EOS. Case fatality rates were 40% and 13%, respectively. Independent predictive factors for VEOS were clinical chorioamnionitis (odds ratio [OR]: 10.5; 95% confidence interval [CI]: 3.3-33.4) and high maternal age (OR: 1.2; 95% CI: 1.0-1.3), whereas not receiving systemic antibiotic therapy within 2 days of age (OR: 13.6; 95% CI: 3.7-50.2) and receiving nasal continuous positive airway pressure (n-CPAP) support at 24 hours of age (OR: 9.8; 95% CI: 2.5-38.4) independently predicted septicemia after the first day of life.**

Conclusions. **Whereas vertically transmitted septicemia was dominated by Gram-negative bacteria, with predictors being exclusively of maternal origin, EOS was dominated by typically nosocomial flora, with n-CPAP treatment at 24 hours of age being a powerful predictor. Early n-CPAP treatment, as opposed to mechanical ventilation, as a powerful predictor of septicemia in the early neonatal period, even with adjustment for early systemic antibiotic treatment, is a new observation among extremely premature infants that warrants additional study.** *Pediatrics* **2005;115:e262–e268. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1834;** ***early-onset septicemia, neonatal septicemia, population-based study, prospective study, very low birth weight, extreme prematurity, predictor analysis, logistic regression.***

ABBREVIATIONS. GA, gestational age; BW, birth weight; n-CPAP, nasal continuous positive airway pressure; VEOS, very early-onset septicemia; EOS, early-onset septicemia; CRIB, Clinical Risk Index for Babies; FSC, forward stepwise conditional; OR, odds ratio; CI, confidence interval; VLBW, very low birth weight; CONS, coagulase-negative staphylococci; IQR, interquartile range.

Early-onset systemic infections among very low birth weight (VLBW) infants (ie, birth weight [BW] of <1500 g) are infrequent, with incidence rates within the first 3 days of life ranging between 1.5%[1] and 2.7%.[2] However, case fatality rates are high, ranging from 26% to 36%.[1–3] Reported risk factors for vertically transmitted infections are numerous among these infants and include early gestational age (GA), prolonged rupture of membranes, lack of prenatal care, preeclampsia, amnionitis, vaginal delivery, no prenatal steroid treatment, and male gender.[1,3] Traditionally, Gram-positive bacterial flora (group B streptococci) has dominated in early-onset septicemia (EOS)[3] among VLBW infants. A shift toward predominately Gram-negative bacterial flora was noted recently among these infants.[1,2] However, knowledge regarding the incidence, risk factors, and outcomes of septicemia during the first week of life in well-defined national populations of extremely premature infants is limited. The aims of this study were to examine prospectively the incidence, causes, predisposing factors, and outcomes of early-onset, blood culture-verified, systemic infections in a national cohort of extremely premature infants.

METHODS

In a population-based, prospective study of perinatal mortality, survival, and morbidity rates for infants with BW of <1000 g or GA of 22^0 to 27^6 weeks in Norway,[4] extensive data on episodes of microbiologically verified septicemia were recorded. All 21 Norwegian neonatal units participated in the study, which was approved by the national ethics committee on medical research. Infants were eligible after parental consent was obtained at the time of admission to a neonatal intensive care unit. Detailed

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information describing the pregnancy, delivery, resuscitation, condition, and treatment during the first week of life was collected on predefined forms by the local participating neonatologist. Collected data were optically scanned into a central database at the Medical Birth Registry of Norway, which coordinated the study and linked data to the compulsory reported data of the Medical Birth Registry of Norway obtained for all births in Norway after 16 weeks of pregnancy; this ensured inclusion of all eligible infants.[5]

Septicemia was defined as the growth of bacteria or fungi in blood cultures in conjunction with clinical signs of systemic infection. Standard practices for obtaining blood for culturing included drawing blood from a peripheral vein, after skin cleansing with 70% alcohol or a chlorhexidine solution, or from a central catheter at the time of insertion. In episodes with a monomicrobial coagulase-negative staphylococci (CONS) isolate and those with polymicrobial isolates, an increase in C-reactive protein levels was required for inclusion. Very early-onset septicemia (VEOS) was defined as septicemia diagnosed within 24 hours after delivery and EOS as septicemia diagnosed between 2 and 7 days of age.

The occurrence of septicemia was treated as a binary variable. Results are presented as medians with interquartile ranges (IQRs), proportions with percentages, or odds ratios (ORs) with 95% confidence intervals (CIs). Continuous data were compared with the Mann-Whitney *U* test and proportions with the χ^2 test or Fisher's exact test, as appropriate.

Logistic regression analysis was applied in the selection of variables for predictor analysis, with baseline defined as status at delivery (VEOS) or on the second day of life (EOS). Because of significant colinearity between BW and GA, adjustments were made only for GA in the regression models. Entering both factors into the models led to results essentially equal to those presented. Because the outcome of interest (septicemia) was relatively infrequent, a model aimed at reducing the number of variables for the final multivariate logistic regression analysis, including forward stepwise conditional (FSC) regression analysis, was developed. Finally, independently predictive variables in the FSC analysis were entered into the multivariate logistic regression model with adjustment for GA. Corrections for multiple comparisons were not performed because the main outcome measures showed very low *P* values (≤.001).

P values of <.05 were considered significant. Statistical analyses were performed with SPSS version 11.0 software (SPSS, Chicago, IL).

RESULTS

Study Sample

During the study period, 119 611 infants were born alive in Norway, of whom 462 of 464 eligible infants (99.6%) were enrolled after transfer to an intensive care unit. Two sets of parents refused enrollment. None of the patients contracted both VEOS and EOS. One or more blood cultures were obtained during the first week of life for 65% of the infants. Table 1 presents a description of the study population.

TABLE 1. Selected Characteristics of Extremely Premature Infants With Septicemia in the First Week of Life in Norway, 1999–2000

	VEOS			EOS		
	With	Without	*P* Value*	With	Without	*P* Value
No. of patients	15	447		15	433	
BW, g, median (IQR)	780 (675–855)	841 (700–966)		720 (630–841)	850 (712–965)	
GA, wk, median (IQR)	25 (25–27)	26 (25–27)		27 (26–28)	26 (25–27)	
GA of <26 wk, no.	8	144		3	138	
Single gestation, no.	12	343		13	332	
Girls, no.	9	195		3	194	
Caesarean section, no.	9	272		13	264	.044
Small for GA, no.	4	121		10	112	<.001
CRIB score, median (IQR)	8 (2–14)	5 (2–8)	.029	5 (4–7)	5 (2–8)	
Apgar score at 1 min, median (IQR)	3 (2–6)	6 (4–8)	.033	7 (5–8)	6 (4–8)	
Apgar score at 5 min, median (IQR)	7 (6–8)	8 (6–9)		8 (7–9)	8 (6–9)	
Maternal age, y, median (IQR)	35 (30–37)	29 (26–33)	.002	28 (24–35)	27 (26–34)	
No. of previous pregnancies, median (IQR)	1.5 (0–3)	0 (0–1)	.034	0 (0–1)	0 (0–1)	
Maternal prenatal steroids given, no.	12	319		11	312	
Maternal intrapartum antibiotics given, no.	9	116	.004	3	120	
Preeclampsia, no.	0	90		8	82	.001
Rupture of membranes >24 h, no.	10	101	<.001	2	102	
Clinical chorioamnionitis, no.	9	55	<.001	1	61	
Endotracheal intubation at delivery, no.	14	326		8	318	
Surfactant received in the delivery room, no.	12	233	.033	8	230	
Surfactant received in the intensive care unit, no.	10	276		5	272	
Receiving surfactant (any time), no.	14	369		10	361	
No. of surfactant doses received, median (IQR)	2 (1–3)	1 (1–3)		1 (0–1)	1 (1–2)	.013
Mechanical ventilation at 24 h of age, no.	9	280		3	286	<.001
n-CPAP at 24 h of age, no.	4	109		11	102	<.001
Systemic antibiotics within the second day, no.	15	395		6	396	<.001
Leukopoenia at delivery	4	49		4	48	
Total white blood cell count at delivery, 10^9 cells per L, median (IQR)	7.3 (4.0–16.6)	10.0 (6.5–16.8)		6.9 (4.7–11.2)	9.9 (6.5–17.1)	
Early documented hypotension, no.	9	214		7	208	
Early treatment against hypoperfusion, no.	10	234		9	228	
Early red blood cell transfusion, no.	9	141	.021	7	141	
Early plasma or albumin volume expansion, no.	8	148		6	147	
Early saline or Ringer volume expansion, no.	5	112		3	110	
Early vasopressor treatment, no.	8	183		2	182	.026
Early systemic steroids against hypotension, no.	2	38		2	38	
Initial treatment at a university hospital, no.	11	288		14	285	.018
Age when enteral feeding initiated, d, median (IQR)	0.5 (0–1)	0 (0–1)		0 (0–1)	0 (0–1)	.032
Umbilical arterial catheter in situ, no.	8	225		8	221	
Umbilical venous catheter in situ, no.	11	269		12	262	

* Unless otherwise stated, *P* is >.05.

VEOS

Patients

Fifteen of the 462 infants (32 per 1000 population) were diagnosed with VEOS. The predominant pathogen was *Escherichia coli*, which was identified in 9 of 15 positive blood cultures (60%) (Table 2). The overall case fatality rate was 40%, including 2 of 9 infants (22%) with *E coli* septicemia and 2 of 3 infants (66%) with group B streptococcal septicemia.

Maternal Prenatal Factors

No association between VEOS and the administration of prenatal steroids, preeclampsia, cervical conization, cervical incompetence, cervical banding, or delivery mode was seen in univariate analyses. Intrapartum antibiotics were given to 27% of the mothers, were administered more often to mothers of infants with VEOS (Table 1), and were predictive of VEOS in a univariate analysis (Table 3). Antibiotics were given at any time during pregnancy to 42% of mothers and within 72 hours to 28%, and neither factor was associated with VEOS in the final analysis. Of 112 patients with a known antibiotic administered within 72 hours of delivery, 77% received only penicillin (benzylpenicillin or ampicillin). For 3 of 6 infants with VEOS at GA of ≥25 weeks to ≤27 weeks who were delivered to mothers who did not receive antepartum or intrapartum antibiotics, risk factors for vertically transmitted infection, such as clinical chorioamnionitis and/or premature rupture of membranes for >24 hours, were present.

Patient Factors

BW, GA, gender, multiple gestations, Apgar score at 5 minutes, intrauterine growth restriction (small for GA),[6] first total white blood cell count, and leukopenia at delivery (white blood cell count of $<1.5 \times 10^9$ cells per L) were not associated with VEOS in univariate analyses. Significantly higher Clinical Risk Index for Babies (CRIB) scores (OR: 1.2; 95% CI: 1.0–1.3; $P = .007$) were seen among infants with VEOS. However, CRIB scores were not included in additional predictor analyses of VEOS because the score can be calculated no earlier than 12 hours of age.

Very Early Treatment Factors

The need for endotracheal intubation at delivery, very early surfactant treatment (ie, in the delivery room) (although more frequent for patients with VEOS) (Table 1), insertion of an umbilical venous catheter or umbilical arterial catheter, and whether initial treatment took place in a university hospital were not predictive of VEOS. The FSC regression procedure, with variables predictive of VEOS in univariate analyses in the model, identified clinical chorioamnionitis and maternal age as being independently predictive of outcomes. Adjusting for GA in the multivariate logistic regression model confirmed this result (Table 3).

EOS

Patients

EOS occurred for 15 of 433 infants (35 per 1000 population) who survived to the second day. The median age at onset was 6 days (IQR: 4-6 days), and the microbial pattern was dominated by CONS (7 of 13 monomicrobial isolates). The maximal C-reactive protein levels were 67 mg/L (IQR: 38-99 mg/L) for infants with monomicrobial CONS infections, 49 mg/L (IQR: 32-98 mg/L) for those with *Staphylococcus aureus* infections, 180 mg/L for those with *Candida* spp infections, and 98 mg/L for those with *Klebsiella* spp infections. The case fatality rate was 13%, without fatalities associated with CONS septicemia (Table 2).

In selection of predictors of EOS, variables reflecting clinical status and intensive care treatment during the first 2 days of life were examined in addition to the variables investigated in VEOS analysis. Results are presented in Table 4.

Maternal Prenatal Factors

Of the factors listed in Table 1, preeclampsia, which complicated 53% of the pregnancies with EOS, was the only factor predictive of EOS (Table 4).

Patient Factors

BW, GA, multiple gestations, gender, Apgar scores at 1 and 5 minutes, CRIB score, documented early hypotension (mean arterial blood pressure in milli-

TABLE 2. Positive Blood Cultures in the First Week of Life Among Extremely Premature Infants in Norway, 1999–2000

	No. Monomicrobial	No. Polymicrobial (No. of Microbial Isolates)	No. of Associated Deaths
VEOS (day 1)			
Group B streptococci	3		2
Escherichia coli	9		2
Listeria spp	1		1
Bacillus spp		1 (2) *Bacillus* spp + *Bacillus* spp*	
Candida spp	1		1
Total blood cultures	14	1	6
EOS (day 2–7)			
Staphylococcus aureus	5	1 (1) *Staphylococcus aureus* + CONS	
CONS	7	(3)	
Klebsiella spp	1		1
Candida spp		1 (1) *Candida* spp + CONS + CONS†	1
Total blood cultures	13	2	2

* Two different strains of *Bacillus* spp.
† Two different strains of CONS.

TABLE 3. ORs of VEOS Associated With Selected Variables Among Extremely Premature Infants in Norway, 1999–2000

Variable	Patients With Variable and VEOS (%)	Univariate Analysis			Multivariate Analysis*		
		OR	95% CI	*P* Value	OR	95% CI	*P* Value
GA							
≥26 wk	2.3	1.0			1.0		
≤25 wk	5.3	2.4	0.9–6.8	.096	1.1	0.4–3.6	.828
BW							
≥750 g	2.6	1.0					
≤749 g	4.7	1.8	0.7–5.2	.239			
Apgar score at 1 min							
≥8	2.4	1.0					
4–7	1.8	3.3	0.9–12.9				
0–3	7.7	0.7	0.2–3.3	.032			
Maternal age	NA	1.2	1.1–1.3	.004	1.2	1.0–1.3	.006
No. of previous pregnancies	NA	1.3	1.1–1.7	.016			
Intrapartum antibiotics given							
No	1.8	1.0					
Yes	7.2	4.2	1.5–12.3	.007			
Maternal antibiotics ≥72 h of delivery							
No	1.8	1.0					
Yes	6.9	4.0	1.4–11.5	.009			
Rupture of membranes ≥24 h							
No	1.4	1.0					
Yes	9.0	6.9	2.3–20.5	.001			
Clinical chorioamnionitis							
No	1.5	1.0			1.0		
Yes	14.1	10.7	3.7–31.2	<.001	10.5	3.3–33.4	<.001

NA indicates not applicable.
* ORs adjusted for GA.

TABLE 4. ORs of EOS Associated With Selected Variables Among Extremely Premature Infants in Norway, 1999–2000

Variable	Patients With Variable and EOS (%)	Univariate Analysis			Multivariate Analysis*		
		OR	95% CI	*P* Value	OR	95% CI	*P* Value
GA							
≥26 wk	3.9	1.0			1.0		
≤25 wk	2.1	0.5	0.1–1.8	.289	3.0	0.6–14.9	.175
BW							
≥750 g	2.2	1.0					
≤749 g	5.3	2.5	0.9–6.9	.089			
Preeclampsia							
No	2.0	1.0			1.0		
Yes	8.9	4.9	1.7–13.9	.003	2.7	0.7–9.6	.132
Intrauterine growth							
Adequate for GA	1.5	1.0					
Small for GA	8.2	5.7	1.9–17.1	.002			
Surfactant in intensive care unit							
No	5.8	1.0					
Yes	1.8	0.3	0.1–0.9	.029			
No. of surfactant doses	NA	0.5	0.3–0.9	.019			
Early vasopressor treatment							
No	4.9	1.0					
Yes	1.1	0.2	0.1–0.9	.043			
Mechanical ventilation at 24 h of age							
No	7.5	1.0					
Yes	1.0	0.1	0.1–0.5	.002			
n-CPAP at 24 h of age							
No	1.2	1.0			1.0		
Yes	9.7	8.9	2.8–28.6	<.001	9.8	2.5–38.4	.001
Initial treatment at a university hospital							
No	0.6	1.0			1.0		
Yes	4.9	8.1	1.1–61.9	.044	5.5	0.6–47.2	.122
Receiving systemic antibiotics the 2nd day							
No	19.6	16.1	5.4–47.6	<.001	13.6	3.7–50.2	<.001
Yes	1.5	1.0			1.0		

NA indicates not applicable.
* Adjusted ORs, with all listed variables in the column in the model.

meters of mercury less than GA in completed weeks), first white blood cell count, and leukopenia at delivery were not predictive of EOS. Although delivery through the caesarean route was more frequent among infants with EOS (Table 1), delivery route was not predictive of EOS in a univariate anal-

ysis. Small-for-GA status, seen for 66% of those with EOS (Tables 1 and 4), was the only patient factor predictive of EOS in univariate analyses.

Treatment Factors

There was no difference in the proportions of infants with or without EOS being endotracheally intubated at delivery, receiving very early surfactant treatment, receiving surfactant in the intensive care unit, or receiving surfactant at all. However, the number of surfactant doses given to infants with EOS was significantly lower (Table 1), which also predicted EOS in a univariate analysis (Table 4). Early volume expansion (any), treatment with plasma, albumin, or red blood cells, and the use of systemic steroid therapy to treat circulatory problems within the first 2 days of life did not predict EOS. Insertion of an umbilical venous catheter or an umbilical arterial catheter also did not predict EOS. Receiving early vasopressor treatment, receiving initial intensive care treatment at a university hospital, and not being treated with antibiotics within the first 2 days of life were, however, predictive of EOS (Table 4).

Whereas mechanical ventilation at 24 hours of age was associated with a low OR of EOS, receiving nasal continuous positive airway pressure (n-CPAP) support at the same age, which was the case for 73% of those with EOS (Table 1), was highly predictive of EOS (unadjusted OR: 8.9) (Table 4). Although not part of baseline analyses, other treatment factors in the first week, such as days with an umbilical arterial catheter or an umbilical venous catheter, days with mechanical ventilation (data not shown), and time of initiation of enteral feeding (although significantly earlier for infants with EOS) (Table 1), were not predictive of EOS in univariate analyses.

FSC regression analysis with variables predictive in univariate analyses in the model identified n-CPAP treatment at 24 hours of age, maternal preeclampsia, receiving initial intensive care treatment at a university hospital, and not being treated with antibiotics within the second day as being independently predictive of EOS. However, with adjustment for GA in a multivariate logistic regression model, receiving n-CPAP treatment at 24 hours of age and not receiving antibiotics on the second day were the only factors independently predictive of EOS in the population (Table 4).

DISCUSSION

In this large, prospective, nearly complete, national cohort of extremely premature infants, septicemia occurring during the first 24 hours of life, ie, presumably acquired from the mother, was caused mainly by *E coli*, and greater maternal age and chorioamnionitis were the only predictive factors in a logistic regression model. Septicemia occurring between day 2 and day 7 of life was caused mainly by staphylococci, presumably acquired postnatally. Compared with those who did not develop early postnatal sepsis, the only predictive factors for sepsis were not receiving systemically administered antibiotics on the second day of life and receiving early n-CPAP treatment, as opposed to mechanical ventilation, which suggests that the healthiest infants were at greatest risk.

In agreement with others[7] and our own previous reports,[8] we report early septicemia as septicemia diagnosed within the first week of life, allowing for differentiation between congenital septicemia diagnosed on the day of delivery and septicemia occurring after the first day of life. Extremely premature infants are frequently exposed to multiple invasive procedures from the time of delivery. We think that, if the inclusion period for vertically transmitted septicemia is extended to 3 days, then the risk of including early-onset, nosocomially acquired septicemia in cases of vertical transmission is substantial. However, the possibility of intrapartum acquisition of *S aureus*, diagnosed after the first day, cannot be ruled out completely. Extreme prematurity has been found to be the main risk factor for vertically transmitted infections among VLBW infants.[1,2] Our findings indicate, however, that within a population of extremely premature infants, factors other than the degree of prematurity play more crucial roles as determinants of congenital septicemia and EOS.

Factors predictive of VEOS were all of maternal origin. Not surprisingly, and as extensively reviewed by others,[9,10] most of these factors are related to maternal predelivery inflammatory and infectious conditions, with a diagnosis of clinical chorioamnionitis being the most significant predictor.

Our VEOS rate significantly exceeds recently reported rates of septicemia within 72 hours of age among VLBW infants in the National Institute of Child Health and Human Development study,[1] and the difference becomes even more pronounced when rates for infants with BW of <1000 g are compared (19.8 cases per 1000 population vs 38.5 cases per 1000 population). There may be several causes for these differences. Study population characteristics may be different and diagnostic procedures and methods may differ, as may the institutional policies of investigating septicemia and using prophylactic antibiotics. One possible explanation is the lower rate of antibiotic treatment during pregnancy in the present study (42% vs 65%), particularly during the last 72 hours (28% vs 63%). Our lower rate of maternal antibiotic administration should be taken into consideration when our results are compared with those in other settings. Although death rates among infants with verified septicemia diagnosed within the first 3 days did not differ between the present study and the National Institute of Child Health and Human Development study (40% and 38%, respectively), a tendency (although not statistically significant) toward a higher death rate for septicemia was observed for the present population (13% vs 6%). A potential for improvement in perinatal care might be present, and more liberal use of intrapartum antibiotic therapy might have reduced the rates of vertically transmitted septicemia. Indeed, mothers of 3 infants with VEOS did not receive intrapartum antibiotic therapy despite recognized risk factors for infection. Contrary to what is commonly reported for vertically transmitted septicemia among term infants, namely, predominance of low maternal age,[11]

we found that high rather than low maternal age represented a significant risk factor for congenital septicemia.

The microbial VEOS pattern in the present study confirms recent suggestions that Gram-negative bacteria have evolved to be the most prevalent cause of vertically transmitted septicemia among very premature infants.[1,2] The reason for this remains controversial, and concerns have been raised that more frequent use of maternal antibiotic treatment during pregnancy might have reduced the incidence of Gram-positive septicemia while facilitating growth of Gram-negative bacterial flora.[12,13] The large proportion of Gram-negative septicemia despite the rather moderate use of maternal systemic antibiotic therapy in the present study does not convincingly support this theory.

Early n-CPAP treatment as an independent predictive factor for septicemia in the early neonatal period has not been reported previously for premature infants. It seems paradoxical that the presumably healthiest infants, ie, those with less need for surfactant and vasopressor support and no need for mechanical ventilation, were at highest risk of EOS. What could explain this observation? The vast majority of bacterial isolates identified for these patients were of a typically nosocomial origin, mainly staphylococci. Unless the amniotic fluid is contaminated, the upper airway of premature infants is normally sterile at delivery. By the third day of life, CONS and *S aureus* colonize the nasopharyngeal compartment of nearly all infants with BW of <1750 g.[14] However, the lower airway was found to be sterile for 60% of mechanically ventilated VLBW infants 1 week after intubation.[15] Unlike a bypassing endotracheal tube, a n-CPAP device acts directly on a heavily colonized compartment, driving a high flow of gas through the nostrils and nasopharyngeal compartment and into the lungs. Furthermore, n-CPAP treatment, particularly in the first days of treatment, requires relatively frequent suctioning of mucus from the upper airways to maintain a free flow of gas. We suggest that mechanical forces from the high gas flow through the n-CPAP device and frequent suctioning act on and potentially damage immature mucous membranes and epithelial linings of the upper airways, making way for a nosocomial bacterial invasion through broken defense barriers, which could partially explain the observed association.

It is also possible that surfactant therapy may offer protection against infection. In addition to reducing surface tension and improving oxygenation, pulmonary surfactant plays an important role in the innate host defense against infection.[16] The pulmonary collectins, of which surfactant proteins A and D are members, have been shown to opsonize bacteria and viruses, to promote phagocytosis by alveolar macrophages, and to regulate production of inflammatory substances.[17,18] Furthermore, both surfactant proteins A and D have been shown to possess direct bactericidal effects.[19] Although exogenous surfactant does not contain surfactant proteins A and D, studies of preterm infants given repeated doses of exogenous surfactant[20] and studies of animals[21] demonstrated stimulating effects of exogenous surfactant on endogenous surfactant production. Furthermore, in vivo studies with both surfactant protein A- and surfactant protein D-deficient mice demonstrated increased susceptibility to infections with a variety of Gram-negative and Gram-positive bacteria.[17] Theoretically, one could speculate regarding a combined effect of early nasopharyngeal nosocomial bacterial colonization, mechanical forces acting on immature epithelial linings, disruption of natural defense barriers against infection, insufficient endogenous surfactant deposits, and a diminished stimulus for endogenous surfactant synthesis promoting a significant association between early n-CPAP treatment and septicemia in the first week of life.

Our finding that early administration of systemic antibiotic therapy offered protection against septicemia in the early neonatal period was as expected. More surprising, however, was the finding that early n-CPAP treatment remained a very powerful predictor of septicemia during the same period even with adjustment for antibiotic treatment in the regression model.

This study showed that Gram-negative organisms were the predominant pathogens in vertically transmitted septicemia. Furthermore, prenatal factors such as high maternal age and prelabor infectious and inflammatory conditions outweighed the effects of GA and BW as predictors of vertically transmitted septicemia. Early administration of surfactant combined with n-CPAP treatment has been used widely in the Scandinavian countries for a number of years,[22,23] and it has been assumed that this regimen reduces the risk of pulmonary and other complications among infants with mild or moderate respiratory distress syndrome. Such benefits have not been proved, however, and this study suggests that early n-CPAP treatment may be a risk factor for septicemia. Although early n-CPAP treatment possibly offers pulmonary and other advantages, compared with mechanical ventilation, for the treatment of infants with mild or moderate respiratory distress, it is important to be aware of the potential side effects of early n-CPAP treatment. Our study was not specifically designed to address this issue, however, and it needs to be examined in randomized studies.

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