Late-Onset Septicemia in a Norwegian National Cohort of Extremely Premature Infants Receiving Very Early Full Human Milk Feeding

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ABSTRACT. *Objectives.* **To investigate the occurrence of and risk factors for late-onset septicemia (LOS) in a national cohort of extremely premature infants who received very early full human milk feeding.**

Methods. **A prospective study of all infants born in Norway in 1999 and 2000 with gestational age of <28 weeks or birth weight of <1000 g was performed. Extensive clinical information, including data on feeding practices and episodes of septicemia, was collected on predefined forms. LOS was defined as growth of bacteria or fungi in blood cultures in conjunction with clinical symptoms consistent with systemic infection occurring after day 6 of life. Cox regression models, including models allowing for time-dependent covariates, were applied in the analysis of LOS.**

Results. **Of 464 eligible infants, 462 (99.6%) were enrolled and 405 (87.7%) survived until day 7. LOS was diagnosed for 80 (19.7%). The predominant pathogens were coagulase-negative staphylococci, followed by *Candida* spp. Case fatality rates associated with septicemia were 10% in general and 43% for *Candida* spp septicemia. Necrotizing enterocolitis or bowel perforation was diagnosed for 19 infants (4%). Enteral feeding with human milk was initiated within the third day for 98% of patients, and 92% were receiving full enteral feeding (FEF) with human milk within the third week. Both high Clinical Risk Index for Babies scores and an umbilical venous catheter in situ at 7 days of age significantly predicted LOS. However, the overall most influential risk factor for LOS was the number of days without establishment of FEF with human milk, with an adjusted relative risk of 3.7 (2.0–6.9) for LOS if FEF was not established within the second week of life.**

Conclusions. **The incidence and case fatality rate of septicemia for this cohort of extremely preterm infants were lower than values in comparable studies. The main difference, compared with other studies, was the feeding practice, and the data suggest that very early FEF with human milk significantly reduces the risk of LOS among extremely premature infants.** *Pediatrics* **2005;115:e269–e276. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1833;** ***late-onset septicemia, very low birth weight, human milk feeding, necrotizing enterocolitis, mortality, prospective study, population-based study, Cox regression.***

ABBREVIATIONS. GA, gestational age; CONS, coagulase-negative staphylococci; BW, birth weight; LOS, late-onset septicemia; VLBW, very low birth weight; FEF, full enteral feeding; UVC, umbilical venous catheter; CRIB, Clinical Risk Index for Babies; NEC, necrotizing enterocolitis; NICHD, National Institute of Child Health and Human Development; CRP, C-reactive protein; FSC, forward stepwise conditional; CI, confidence interval; RR, relative risk; IQR, interquartile range.

Late-onset septicemia (LOS) remains an important cause of death, morbidity, and long-term sequelae among premature infants.[1–9] The reported incidence of LOS among infants with birth weight (BW) of <1500 g ranges between 16 and 30%,[1–4,8,9] approaching 50% among infants with BW of <1000 g,[8] and case fatality rates are high (17–21%).[1–3,8] Gram-positive bacterial flora, mainly coagulase-negative staphylococci (CONS), has dominated bloodstream recovery for some years.[1,5,10,11] However, among the smallest infants, systemic fungal infections have become a major problem, with high case fatality rates and high rates of severe sequelae among survivors.[7] For these patients, the risk of invasive infection is high, dependent on a number of clinical factors, and inversely related to BW and gestational age (GA).[1–4,8,9]

Enteral feeding with human milk is generally regarded as beneficial[12,13] and may reduce the incidence of necrotizing enterocolitis (NEC) and LOS among premature and very low birth weight (VLBW) infants (ie, BW of <1500 g).[14–17] However, there is a lack of consensus regarding what, how, and when to feed,[1,2,18–21] and knowledge is limited regarding the effect of very early, full enteral feeding (FEF) with human milk on the incidence and severity of septicemia among extremely premature infants. In Norway, very early tube feeding with human milk has long traditions, and the purpose of this study was to assess the effect of this feeding practice on the risk and occurrence of nosocomial septicemia among extremely premature infants.

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METHODS

Study Design and Protocol

In a nationwide prospective study of perinatal mortality, survival, and morbidity rates among infants with BW of <1000 g or GA of 22^0 to 27^6 weeks in Norway,[22] extensive data on episodes of microbiologically verified septicemia were collected. All 21 Norwegian neonatal departments, of which 5 are academic departments, participated in the study. The study was approved by the ethics committee on medical research and took place between January 1, 1999, and December 31, 2000.

This article focuses on LOS defined, in agreement with others[23] and our own previous reports[5] as microbiologically verified septicemia occurring after day 6 of life. Infants were enrolled after written parental consent was obtained, at the time of admission to a neonatal intensive care unit. Data were collected on standardized forms by the participating neonatologist. Data included detailed information on pregnancy, delivery, and the neonatal course until death or discharge home. Standard practices for obtaining blood cultures included obtaining blood from a peripheral vein, after skin cleansing with alcohol or a chlorhexidine solution, or from a central catheter at the time of insertion. For each episode of systemic antibiotic treatment, data on clinical symptoms at the initiation of treatment, the clinical course, microbiologic results, and results of blood tests, including C-reactive protein (CRP) levels, were recorded. Septicemia was defined as microbial growth in blood cultures with clinical symptoms consistent with systemic infection. In episodes with a monomicrobial CONS isolate and those with polymicrobial isolates, an increase in CRP levels during treatment was required for inclusion. The data were optically scanned into a central database at the Medical Birth Registry of Norway, which coordinated the study and ensured ascertainment. Collected data were linked with the Medical Birth Registry of Norway database, which includes data based on compulsory reported information for all pregnant women and deliveries after 16 weeks of gestation in Norway.[24]

Participating centers had a common policy of achieving FEF with the mother's milk or banked donor milk as early as possible, although there was no consensus in terms of a detailed protocol for feeding strategies. All centers had their own human milk bank facilities, which were recently described elsewhere,[25] and mothers were strongly encouraged to begin expressing breast milk from the time of delivery. Orogastric or nasogastric tube feeding with human milk, with the tube left in place between meals and changed daily, was usually started within a few hours after delivery, with 1 to 2 mL of milk every 2 or 3 hours, increasing by 0.5 to 1.0 mL every 6 to 8 hours as tolerated. FEF was accomplished subsequently with intermittent meals or continuous pump feeding. Enteral nutrition was supplemented with parenteral glucose administration from day 1 and usually with administration of amino acids and lipids from day 2 and day 3, respectively. Parenteral nutrition was provided through a peripheral vein, an umbilical venous catheter (UVC), or a central venous catheter until a defined total daily volume of enteral and parenteral nutrition was reached. Protein, calorie, and mineral fortification (Pre Semp; Semper AB, Stockholm, Sweden) was initiated (aim: 130 kcal/kg per day with at least 3.1 g protein/kg per day) when 50 to 100% of FEF (170–180 mL/kg per day within 7–8 days of age) was achieved. Vitamins and folic acid were provided separately as enteral mixtures from day 4 or 5, whereas iron was administered as an enteral mixture from 6 weeks of age.

Statistical Analyses

Unless otherwise stated, results are presented as medians with interquartile ranges (IQRs), proportions with percentages, or relative risks (RRs) with 95% confidence intervals (CIs). Proportions were compared in 2×2 tables, and significance was tested with the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared with the Mann-Whitney *U* test.

The proportional-hazards method (Cox regression) was used in the selection and analysis of predictors and risk factors for LOS. Baseline was defined as status at 7 days of age and outcome as the time to the first occurring episode of LOS. Identification of the most suitable baseline variables for analysis involved several steps. First, univariate Cox regression analyses were applied to a substantial number of variables describing maternal health and previous pregnancies, the current pregnancy, delivery, and the neonatal period until death or discharge home. Next, 2 steps of forward stepwise conditional (FSC) Cox regression analysis were performed. In the first step, significant variables from univariate analyses, associated according to time of occurrence, treatment modality, or morbidity pattern, were assembled in subgroups and FSC analysis was performed within the subgroups. The variable within each subgroup presenting the greatest RR of LOS was thereafter assigned to 1 of 2 main groups, ie, prenatal/early perinatal factors or late perinatal/postperinatal factors. In a second FSC analysis, independently predictive variables within each of the main groups were identified. Finally, with adjustment for GA, multivariate Cox regression analysis was performed, including all independently predictive variables from FSC analyses of the main groups in the model. Because of colinearity between BW and GA ($P < .01$), adjustments were made only for GA in the regression models. Entering both factors into the models led to results essentially equal to those presented.

An extended Cox regression model, allowing for time-dependent covariates, was applied to investigate the RR of LOS after the first week of life. Continuous variables were truncated at the time of occurrence of the first episode of LOS, and a positive contribution from a binary variable was included only if it preceded the time of the first LOS episode. With independently predictive baseline variables in the regression model, time-dependent covariates were entered in a FSC procedure, keeping in the model variables that were independently predictive of outcome when a new variable was entered. Finally, with adjustment for GA, multivariate Cox regression analysis was performed with significant predictors from baseline analyses and independently predictive time-dependent variables in the model.

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

RESULTS

LOS Episodes

Of 119 611 births, 464 (3.87 per 1000 population) were eligible for the study after transfer for intensive care. Enrollment was accepted for 462 infants (99.6%). Four hundred five infants (87.6%) survived until day 7. Thirty percent of the infants had ≥1 transfer between units before death or discharge home. Demographic and treatment characteristics of these infants are listed in Table 1.[26]

Among 80 infants (197 per 1000 patients at risk), 97 episodes of LOS occurred (81 monomicrobial and 16 polymicrobial) (Table 2). One to 4 blood cultures were obtained for 47% of the infants after day 6. The frequencies of LOS among infants with BWs of <1000 and 750 g were 220 per 1000 patients and 311 per 1000 patients, respectively. The median age at the onset of the first episode was 16 days (11–29 days), with 65% of the episodes occurring within 21 days of age. Infants who contracted LOS were of lower BW and GA, presented higher Clinical Risk Index for Babies (CRIB) scores,[27] and were significantly more often endotracheally intubated and given surfactant in the delivery room. Greater proportions of patients received systemic steroid therapy against chronic lung disease and qualified for a diagnosis of chronic lung disease, defined as the need for supplemental oxygen at 36 weeks of postconceptional age. Furthermore, these infants spent more than twice as many days undergoing mechanical ventilation, spent nearly twice as many days undergoing nasal continuous positive airway pressure, had a UVC or central venous catheter in situ more than 3 times longer, and spent more days in the hospital, compared with infants without LOS (Table 1).

TABLE 1. Selected Variables for Extremely Premature Infants With and Without LOS in Norway, 1999–2000

Variable	LOS		*P* Value
	With (n = 80)	Without (n = 325)	
BW, g, median (IQR)	763 (636–897)	865 (742–977)	<.001
GA, wk, median (IQR)	26 (24–27)	27 (26–27)	<.001
Maternal age, y, median (IQR)	31 (26–34)	29 (26–34)	NS
Maternal prenatal steroids, no.	72	279	NS
Intrapartum antibiotics given, no.	30	80	.020
Single gestation, no.	64	253	NS
Girls, no.	33	147	NS
Caesarean section, no.	40	218	.004
Small for GA, no.	19	94	NS
CRIB score, median (IQR)	6 (3–9)	4 (2–7)	<.001
Apgar score at 1 min, median (IQR)	6 (3–8)	6 (4–8)	NS
Apgar score at 5 min, median (IQR)	8 (6–9)	8 (7–9)	NS
Intraventricular hemorrhage, grade 3–4,* no.	11	25	NS
Receiving oxygen at 36 wk GA, no.	34	93	.01
Systemic steroids against chronic lung disease, no.	40	98	.001
Treatment against suspected NEC, no.	9	10	.005
Days to reach FEF (survivors), median (IQR)	16 (10–20)	10 (7–14)	<.001
BW regained, d (survivors), median (IQR)	15 (11–19)	14 (11–17)	NS
Endotracheal intubation at delivery, no.	64	223	.045
Receiving early surfactant (ie, in delivery room), no.	52	161	.013
Days on mechanical ventilation (survivors), median (IQR)	8 (3–31)	3 (1–9)	<.001
Days on nasal continuous positive airway pressure (survivors), median (IQR)	42 (28–58)	29 (11–43)	<.001
Days with umbilical arterial catheter, median (IQR)	4 (0–8)	0 (0–4)	<.001
Days with UVC, median (IQR)	7 (0–10)	1 (0–6)	<.001
Days with central venous catheter (any),† median (IQR)	8 (3–11)	3 (0–9)	.004
Days to discharge (survivors), median (IQR)	97 (79–119)	84 (68–98)	<.001

For medians with IQRs, the Mann-Whitney *U* test was used; for numbers, the χ^2 test was used. NS indicates not significant.
* According to Papile et al.[26]
† Sum of days with an UVC, a percutaneous long line, and a surgically inserted central venous catheter.

TABLE 2. Microbial Isolates in LOS Among Extremely Premature Infants in Norway 1999–2000

	Monomicrobial		Polymicrobial		Isolates in Polymicrobial Cultures
	No.	%	No.	Sum*	
CONS	39	47	3	17	CONS + CONS†/CONS + CONS†/CONS + CONS†
Staphylococcus aureus	10	12			
Group B streptococci	7	9	2	3	Group B streptococci + CONS/group B streptococci + group B streptococci†
Enterococcus spp	1	1			
Other Gram-positive cocci‡	1	1	1	1	Other Gram-positive cocci + CONS
Escherichia coli	1	1	1	1	*E coli* + *Candida* spp + CONS
Klebsiella spp	6	8	2	2	*Klebsiella* spp + CONS/*Klebsiella* spp + other Gram-negative rods
Other Gram-negative rods§	8	10	2	4	Other Gram-negative rods + CONS/other Gram-negative rods + other Gram-negative rods
Candida spp	8	10	5	6	*Candida* spp + CONS/*Candida* spp + CONS/*Candida* spp + CONS/*Candida* spp + CONS/*Candida* spp + CONS + CONS†
No. of blood cultures	81		16		

* Sum of microbial isolates in polymicrobial cultures.
† Different strains according to antibiograms.
‡ *Streptococcus mitis* or *Clostridium difficile*.
§ *Citrobacter* spp, *Serratia marcessens*, *Enterobacter* spp, *Pseudomonas* spp, *Acinetobacter baumani*, or *Diphteroides* spp.

In monomicrobial cultures, the most frequent pathogen was CONS, which was identified in 47% of cases (CRP levels: 5–273 mg/L), followed by *Staphylococcus aureus* in 12%, *Candida* spp and other Gram-negative rods in 10% each, and *Klebsiella* spp and group B streptococci in 8% each (Table 2). In 6 polymicrobial episodes of septicemia with CONS (7 isolates) and *Candida* spp (6 isolates), infants had peak CRP values between 10 and 310 mg/L (median: 83 mg/L) during treatment. In 2 episodes, 1 with 2 isolates of group B streptococci and the other with group B streptococci and CONS, CRP levels exceeded 276 mg/L; in 3 polymicrobial cultures growing 6 strains of CONS, CRP values ranged from 26 to 61 mg/L. In the remaining 5 polymicrobial episodes, the patients' CRP peaked levels between 21 and 42 mg/L. Nineteen blood cultures containing 21 bacterial isolates were dismissed as contaminated, and CONS were the most frequent contaminants, ie, 17 of 21 isolates (81%), including 5 monomicrobial CONS isolates.

Eight infants (10%) died during treatment of septicemia. *Candida* spp were identified in 6 cases and *Klebsiella* spp and CONS in 1 each. Infants with *Can-*

dida spp septicemia ($n = 14$) had a significantly increased risk of death (GA-adjusted RR: 7.2; 95% CI: 2.8-18.3; $P < .001$), compared with the rest of the population. Clinical signs indicating NEC were noted for 19 infants (4%), including 9 patients (2.2%) with pneumatosis, air in the bile tree, or other evidence of NEC, of whom 5 died during treatment of septicemia (associated with *Candida* spp in all cases).

Enteral feeding with human milk was commenced within 1, 2, or 3 days for 61%, 92%, and 96% of the infants, respectively. Among infants who reached FEF ($n = 382$), this was established within the third week of life for 89% (Fig 1). The proportions of infants who reached FEF before 2 weeks of age were not significantly different if feeding was initiated on day 1 (71%), day 2 (71%), or day 3 (65%). At FEF, 92% received their own mother's milk, 6% banked donor milk, and 2% preterm formula. Standard fortification (data not shown) and FEF were established significantly later for infants diagnosed with LOS (Table 1).

Baseline Predictors of LOS

In the univariate Cox regression analyses, a large number of prenatal and postnatal factors were scrutinized for association with LOS. Significant baseline variables are presented in Table 3, which also outlines the grouping of variables for FSC Cox regression analyses, within the subgroups and the main groups. BW and GA were inversely associated with increased RRs of LOS (Table 3).

Two steps of FSC analysis, as described above, identified vaginal delivery and CRIB scores within the prenatal/early perinatal group and being on mechanical ventilation at 7 days of age, having had an umbilical arterial catheter inserted, having a UVC in situ at 7 days of age, and receiving initial intensive care treatment at a university hospital as being independently predictive of later LOS (unadjusted RRs not shown). Multivariate Cox regression analysis, with adjustment for GA and inclusion of all independently predictive variables from FSC analyses of the main groups in the model, resulted in CRIB score and having a UVC in situ at 7 days of age as being the only baseline variables independently predictive of LOS (Table 3).

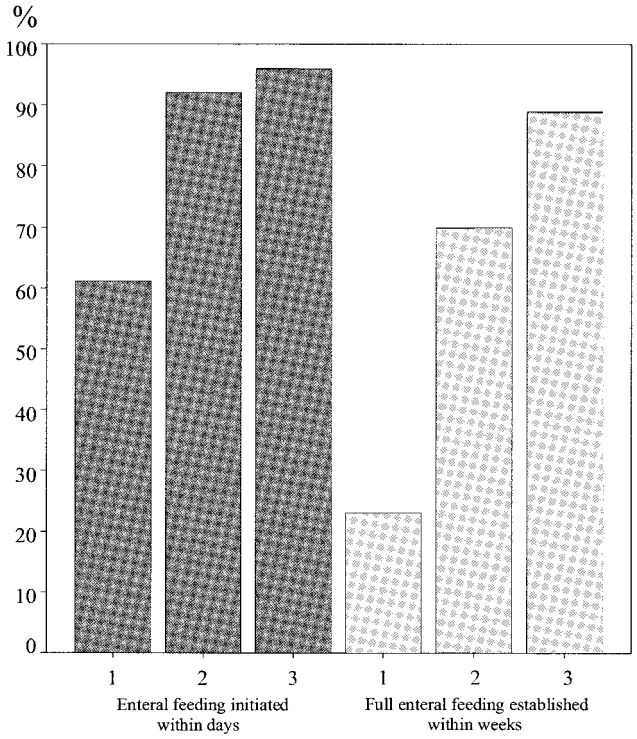

Fig 1. Cumulative proportions of infants initiated on enteral feeding (black bars) and established on FEF with human milk (gray bars), according to age, among extremely premature infants in Norway, 1999–2000.

Effects of Time-Dependent Covariates on the Risk of LOS

In the extended Cox regression model, allowing for time-dependent covariates, the risk of LOS after the first week of life was investigated. With substitution of having a UVC in situ on day 7 with days with a UVC before LOS, results from the multivariate Cox regression analysis of baseline variables were confirmed; both CRIB score and days with a UVC before LOS were independently predictive of LOS (data not shown). In SFC regression analyses, the time-dependent covariates investigated were days with a central venous catheter (days with a UVC plus days with a percutaneous central line plus days with a surgical central line), days with an umbilical arterial catheter, days with a peripheral arterial catheter, days on a ventilator, days receiving oxygen, diagnosis or treatment of a symptomatic duct, diagnosis of suspected or verified NEC, chronic lung disease (defined as receiving oxygen at 36 weeks of postconceptional age), and postnatal age at establishment of FEF with human milk. The only time-dependent variable shown to be independently predictive of LOS was days without establishment of FEF with human milk (unadjusted RR not shown). Entering significant baseline predictive variables (CRIB score and days with a UVC before LOS) and days before LOS without establishment of FEF with human milk into the GA-adjusted multivariate Cox regression model showed that GA and days before LOS without establishment of FEF with human milk were the only factors independently predictive of LOS after the first week of life (Table 4).

As illustrated in Fig 2, the cumulative survival time free from LOS was significantly associated with the postnatal age when FEF with human milk was established. If establishment occurred during week 1, 2, 3, or ≥4, it was associated with 9%, 11%, 37%, and 40% LOS rates, respectively. With adjustment for GA, CRIB score, and days with a UVC before first LOS, not being established on FEF with human milk within 2 weeks of age was associated with a RR of future LOS of 3.7 (95% CI: 2.0–6.9; $P < .001$).

To investigate in greater detail the role of delayed FEF with human milk as a risk factor for subsequent LOS, the time-dependent Cox model was repeated. All factors from the previous model were kept, and days before LOS without establishment of FEF was substituted with a separate analysis of each specific day between day 8 and day 14 before LOS without FEF as a binary variable. As illustrated in Fig 3, the

TABLE 3. Predictors of LOS at 7 Days of Age Among Extremely Premature Infants in Norway, 1999–2000

Predictors	Patients with Variable and LOS, Frequency (%)	Univariate Cox Regression			Multivariate Cox Regression*		
		RR	95% CI	*P* Value	RR	95% CI	*P* Value
Prenatal/early perinatal group							
Patient factors							
GA, wk	NA	0.8	0.6–0.9	<.001	0.9	0.8–1.2	.624
BW, g	NA	0.9	0.9–0.9	<.001			
Maternal prenatal factors							
Intrapartum antibiotics given	27	1.7	1.1–2.6	.025			
Vaginal delivery	27	1.9	1.2–2.9	.005	1.5	0.9–2.6	.129
Early vitality and morbidity scores							
Apgar score at 5 min	NA	0.9	0.8–0.9	.026			
CRIB score	NA	1.1	1.1–1.2	<.001	1.1	1.0–1.2	.039
Early respiratory morbidity							
Endotracheal intubation at delivery	22	1.7	1.0–3.0	.048			
Surfactant in delivery room	24	1.8	1.1–2.8	.014			
Receiving surfactant	22	2.4	1.1–5.3	.025			
No. of surfactant doses given	NA	1.2	1.1–1.5	.014			
Mechanical ventilation at 24 h of age	23	1.8	1.1–2.9	.027			
Early circulatory problems							
Documented early hypotension	24	1.6	1.0–2.5	.034			
Treatment of early compromised perfusion	24	1.7	1.1–2.7	.019			
Early plasma/albumin volume expansion	25	1.7	1.1–2.7	.017			
Early vasopressor treatment	26	1.7	1.1–2.7	.015			
Systemic steroid therapy for early hypotension	35	2.2	1.1–4.0	.033			
Late perinatal/postperinatal group							
Early neurologic morbidity†							
Subependymal/intraventricular hemorrhage, grade 1–2	29	1.8	1.2–2.9	.008			
Subependymal/intraventricular hemorrhage, grade 3–4	31	2.2	1.1–4.1	.017			
Hematologic factors							
>2 red blood cell transfusions during first week	27	1.7	1.0–2.8	.043			
Ventilation factors							
Mechanical ventilation at 7 d of age	29	2.0	1.3–3.1	.002	1.2	0.7–2.0	.605
Arterial catheters							
Umbilical arterial catheter inserted	26	2.3	1.4–3.6	.001	1.6	0.9–2.7	.067
Umbilical arterial catheter in situ at 7 d of age	32	2.2	1.4–3.5	.001			
Venous catheters							
UVC inserted	25	2.5	1.5–4.1	.001			
UVC at 7 d of age	32	2.9	1.9–4.5	<.001	2.0	1.2–3.3	.005
Place of intensive care treatment							
University hospital	23	1.8	1.1–3.1	.018	1.6	0.9–2.7	.072

NA indicates not applicable.
* All variables listed in the column were included in the regression model.
† According to Papile et al.[26]

TABLE 4. Baseline Predictors and Time-Dependent Risk Factors for LOS Among Extremely Premature Infants in Norway, 1999–2000

Variable	Multiple Cox Regression*		
	RR	95% CI	*P* Value
GA	0.8	0.7–0.9	.033
CRIB score	1.1	0.9–3.9	.113
Days with UVC before first LOS	1.9	0.9–3.9	.064
Days before first LOS without FEF	2.2	1.2–4.1	.012

* All variables were included in the model.

influence of delayed FEF on the risk of LOS was significant from day 10 to day 14.

DISCUSSION

In this study, very early FEF with human milk was associated with a markedly reduced incidence of LOS, a low incidence of confirmed NEC, and low case fatality rates in general and for LOS in particular. The strengths of this study are 99.6% enrollment of a large national cohort and predetermined criteria for reporting septicemia. For the study, no attempts were made to establish uniform standards of care, feeding practices, diagnostic procedures, or treatment practices among the participating centers. Consequently, we report the outcomes of current practices in Norway. The observational design, as opposed to a randomized, interventional study, may be criticized. However, given the large size, the nearly complete participation, and the large number of participating neonatal units, confounding factors could be largely adjusted for in the analyses.

The advantage of very early feeding with human milk is supported by the low rates of LOS and of possible complications related to early feeding, such

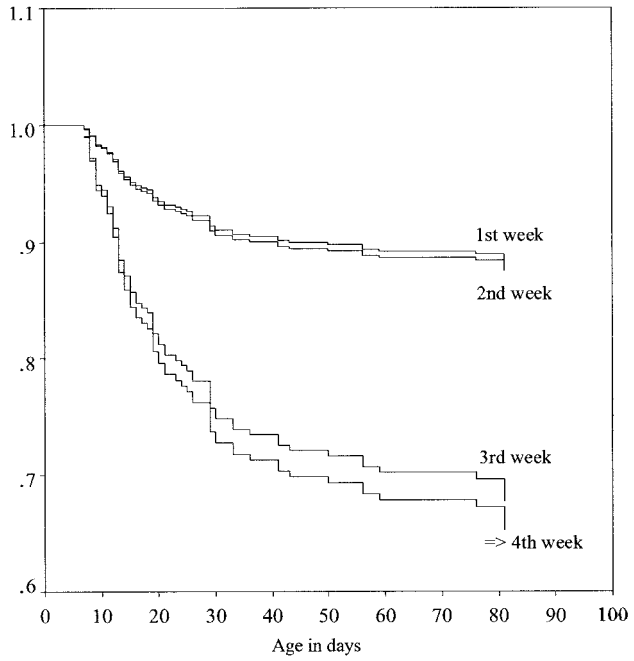

Fig 2. Survival free from LOS according to week of establishment of FEF with human milk among extremely premature infants in Norway, 1999–2000.

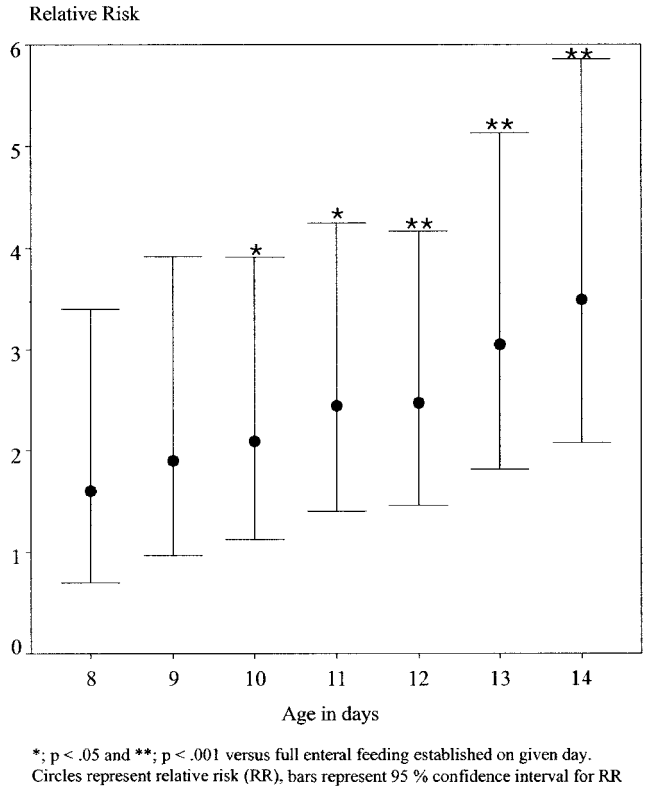

Fig 3. RR of future LOS if FEF with human milk is not established within a given age (in days) among extremely premature infants in Norway, 1999–2000.

as confirmed NEC (2.2%), compared with previous studies in which enteral feedings were initiated later and advanced much more slowly.[1,2] Our frequency of septicemia was similar to[2–4,9] or significantly lower than those in studies of larger infants, eg, VLBW infants ($P < .01$).[1,8] For infants with BW of <1000 g, our LOS rate of 22% was markedly lower than rates in 3 recently reported studies, which showed frequencies of 32%, 35%, and 48% [2,4,8] ($P < .01$). The difference in septicemia rates among infants with BW of <1000 g remained unchanged ($P < .01$) if 72 hours was used as a definition for LOS, as in the referenced studies; this yielded a LOS frequency of 23% in our study.

A microbial pattern with CONS as the most frequent isolate is in agreement with results reported by others.[1,2,4,8,9] *Candida* spp emerged as the second most frequent pathogen with 12% of the isolates, a proportion comparable to values previously reported for VLBW infants.[1,2,8,9] The low mortality rate for LOS in our study may partly be explained by the microbial pattern, ie, the high rate of CONS and the low rate of Gram-negative septicemia, particularly with *Pseudomonas* spp (1 case), compared with other studies.[8,9] CONS appears to be less virulent than most other pathogens, because only 1 of 39 patients with a monomicrobial CONS-positive blood culture died during treatment of LOS. In contrast, Gram-negative bacteria, and in particular *Pseudomonas* spp, are known to carry high case fatality rates (33–66%).[2,9] Septicemia caused by *Candida* spp remain a challenge for the smallest infants surviving the early neonatal period, because these fungi were identified for 75% of infants who did not survive treatment of LOS in the present study.

Possible reasons for the low incidence of confirmed NEC and LOS, including the low case fatality rate among patients with LOS in the present study, compared with other relevant studies,[1,2,4,8] may be explored by comparing specific aspects of treatment between the present study and a recent report from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network[2] (Table 5). The most striking differences were the proportions of infants with BW of <1000 g (ie, 43% in the NICHD study and 82% in the present study), the earlier initiation of and establishment of FEF with human milk in our study, and the markedly prolonged use of central venous catheters in the NICHD study.

Feeding with human milk, compared with formula, is probably advantageous for preterm infants, and it has been recommended that enteral feeding should be introduced as early as possible, to reduce the risk of systemic infection among very premature infants.[2,28] Obviously, prolonged vascular access creates a port of entry for microorganisms, with increased risk of septicemia. However, assessment of the potential significance of nutritional regimens in the occurrence of LOS is difficult, because such data are seldom reported or discussed in studies of neonatal septicemia.[3,4,8,9] Unlike others,[2] we were not able to demonstrate any association between LOS and time of commencing enteral feeding. Most likely this is explained by the very early introduction and rapid progress of enteral feeding in the present study, with nearly 80% of patients receiving full human milk feeding within 14 days after delivery. In other studies,[1,2] early feedings have generally been

TABLE 5. Comparison of Treatment Variables Between the NICHD Neonatal Research Network (1998–2000) and the Norwegian Extreme Prematurity Study (1999–2000)

Variable	Days With Variable									
	LOS*					No LOS				
	United States† (*N* = 1313)		Norway (*N* = 80)		*P* Value‡	United States (*N* = 4902)		Norway (*N* = 325)		*P* Value
	Mean	SE	Mean	SE		Mean	SE	Mean	SE	
Mechanical ventilation	23.7	0.50	17.3	2.69	<.001	11.6	0.26	8.72	0.92	<.001
Umbilical arterial catheter	4.9	0.13	4.9	0.68	1.0	3.7	0.07	2.6	0.25	<.001
UVC	4.0	0.14	6.7	0.90	.004	2.8	0.07	3.7	0.29	.001
Central venous catheter§	7.2	0.33	0.11	0.03	<.001	1.3	0.17	0.04	0.01	<.001
Percutaneous central line	16.4	0.41	4.0	0.5	<.001	8.5	0.21	3.7	1.1	<.001
Peripheral arterial line	2.6	0.13	4.3	1.0	.003	1.1	0.07	4.4	1.4	<.001
Hyperalimentation	33.1	0.47	NA			16.5	0.24	NA		
Enteral feedings begun	7.3	0.15	0.48	0.13	<.001	5.5	0.08	0.53	0.05	<.001
FEF	27.9	0.38	17.3	1.10	<.001	17.3	0.19	11.8	0.42	<.001
Regained BW	14.1	0.18	14.9	0.30	.341	13.7	0.10	14.9	0.30	.312
Duration of hospital stay	78.6	1.08	102	5.0	<.001	60.2	0.54	87.8	2.1	<.001

NA indicates not applicable.
* Defined as occurring after 3 days of age in the United States and after 6 days of age in Norway.
† NICHD data.[2]
‡ Calculated with unpaired *t* tests.
§ Surgically inserted central venous catheter.

defined as being started and accomplished much later than in the present study. It has been claimed that enteral feeding history and the need for prolonged intravenous access reflect the severity of illness among VLBW infants.[1] However, attitudes regarding what to feed and how to progress with feeding may also reflect traditions, local practices and experiences, the availability of human milk, and fear of transmitting infectious diseases through donor human milk. The feeding regimen applied in the present study population is based on experience, which has evolved with time in the Scandinavian countries and has proved to be safe and well tolerated.

Whether very early feeding per se or the human milk made the reported feeding regimen possible and protective against septicemia remains controversial, because virtually all infants received breast milk. Several observations may favor breast milk. The immunologic and antiinfective properties of human milk have been reviewed extensively elsewhere.[12,13] Clinical studies have shown a reduced risk of NEC, LOS, and meningitis among preterm infants fed human milk, compared with formula-fed infants.[14–16] In a recent systematic review, premature infants who were fed donor human milk experienced a 4 times reduced risk of NEC, compared with infants fed formula.[29]

Formula-fed infants may develop a more virulent Gram-negative and less diverse intestinal colonization pattern,[30,31] which may promote a greater proportion of serious Gram-negative infections among these infants. The Vermont Oxford Network recently declared that, for VLBW infants, institution of early feeding with breast milk should have the highest priority among efforts to reduce the occurrence of nosocomial bacteremia.[28] The present study strongly supports that concept. It demonstrates that very early feeding, at least with human milk, is possible at a much earlier age than commonly reported[1,2] and advocated.[15] Indeed, an adjusted RR of 3.7, indicating a nearly fourfold reduction in the risk of LOS if FEF is established within the second week, underscores the importance of establishing very early FEF with human milk among these infants. The possible benefits of human milk feeding on long-term neurodevelopmental outcomes[32] strengthen the indication for using human milk as the main nutritional source for extremely premature infants.

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