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Intake of Own Mother's Milk during the First Days of Life Is Associated with Decreased Morbidity and Mortality in Very Low Birth Weight Infants during the First 60 Days of Life

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Key Words

Very low birth weight infant • Sepsis • Necrotizing enterocolitis • Enteral nutrition • Donor milk • Breast milk • Formula

Abstract

Background: The incidence of necrotizing enterocolitis (NEC) and possibly also of sepsis is lower in preterm infants fed their own mother's milk (hereafter 'mother's milk') compared with formula-fed infants. It is unclear whether this is caused by the protective properties of breast milk or by the absence of cow's milk. Especially in early life, mother's milk is often unavailable to preterm infants, while minimal enteral nutrition is initiated immediately. **Objectives:** To determine whether there is an association between intake of mother's milk during the first days of life and the combined outcome of sepsis, NEC and death over a prolonged period. **Methods:** Retrospective study in infants with a birth weight <1,500 g. Intake of mother's milk and formula during the first 10 days of life was recorded. The occurrence of sepsis, NEC and death was registered during the first 60 days. Data were analysed using Cox regression analysis, taking confounders

into account. **Results:** In total, 349 infants were included. Intake of mother's milk during the first 5 days of life was associated with a lower incidence of NEC, sepsis and/or death during the first 60 days of life (hazard ratio (HR) in the category 0.01–50% intake of mother's milk: 0.49, 95% confidence interval (CI) 0.28, 0.87; HR in the category 50.01–100% intake of mother's milk: 0.50, 95% CI 0.31, 0.83, both compared to no mother's milk). During days 6–10, the protective effect was only present if >50% of the total intake was mother's milk (HR = 0.37, 95% CI 0.22, 0.65). **Conclusion:** The type of enteral nutrition during the first 10 days of life is associated with the risk of NEC, sepsis and/or death during the first 60 days of life.

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Introduction

Preterm infants are susceptible to the development of necrotizing enterocolitis (NEC). No single causative agent has been identified for this devastating disease, which affects approximately 7% of very low birth weight (VLBW) infants (<1,500 g birth weight) [1]. Mortality

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from NEC is between 20 and 30%, the highest rate of mortality being recorded in infants requiring surgery [1]. Survivors are at risk for life-long complications, such as developmental delays and short-bowel syndrome. In addition, preterm infants are at risk of developing blood stream infections, the smallest and most premature infants having the greatest risk. The incidence of sepsis ranges from 20 to 54% in VLBW infants, with a mortality rate as high as 18% [2, 3]. Sepsis increases the risk of long-term neurodevelopmental impairment [4]. Episodes of sepsis are often considered to be related to the use of intravenous catheters, but they can originate in the gut via the enhanced translocation of luminal bacteria, especially in the VLBW population. The incidence of NEC is 2- to 6-fold lower in infants who are fed their own mothers' milk (hereafter 'mother's milk') compared to their formula-fed peers [5], and some studies suggest that it is protective against sepsis [6]. Therefore, mother's milk is considered to be the optimal nutrition because it contains various important bioactive substances that have bactericidal and immunomodulating activities, in addition to macronutrients and antioxidants. The first days of life are the most critical period for preterm infants due to a peak incidence of sepsis at day 7 [7], and other complications, such as intraventricular haemorrhage. We therefore hypothesized that feeding VLBW infants with mother's milk is especially important during this period and that improved gastro-intestinal health during early life will convey benefits to the infant over a prolonged period of time. This study investigates whether a greater intake of mother's milk during the first 10 days of life results in a decreased incidence of serious morbidity (i.e. sepsis and NEC) and mortality over the first 60 days of life.

Methods

Design and Setting

This retrospective audit was performed in the 30-bed level IIID neonatal intensive care unit (NICU) of the Erasmus MC – Sophia Children's Hospital in Rotterdam in the Netherlands, from April 1, 2009, to December 31, 2010. At the time of the study, infants were resuscitated from a gestational age of 24 weeks or more, except if there were contraindications. All VLBW infants admitted to the NICU within 24 h of birth were eligible to participate in this study. We excluded infants who were discharged or died within 72 h of birth. Infants that developed early-onset sepsis (verified by culture) or intestinal perforation within 72 h of birth were also excluded from the final analysis. The Institutional Review Board of the Erasmus MC waived approval for the study and informed consent was not necessary for this retrospective analysis.

Feeding Protocol

Minimal enteral feeding (MEF) was started on the first day of life, typically within 6 h of birth. The only reasons to withhold MEF were large gastric retentions, suspected intestinal atresia or NEC. Depending on birth weight, the amount of MEF given was 0.5–2.0 ml, 6 times daily by bolus feeding. If MEF was tolerated well, hourly feedings were started on the second day of life. The Erasmus MC – Sophia Children's Hospital did not have access to donor milk at the time of the study. If the amount of mother's milk was insufficient, infants were always supplemented with preterm formula (Nenatal Start, Nutricia Zoetermeer). The protein fraction of this formula contains intact cow's milk protein.

Data Collection and Definitions

Information on the type of enteral nutrition (mother's milk or formula) that infants received during the first 10 days of life were extracted from the Patient Data Monitoring System. The proportion of mother's milk intake of total enteral intake (mother's milk intake in millilitres/total enteral intake in millilitres) was calculated as well as the cumulative intake of mother's milk (total intake of mother's milk in millilitres/kilogram body weight). The Patient Data Monitoring System computer system was designed to record extensive data on patients, such as medication use, physiological parameters and ventilator data. Every time, formula or mother's milk was administered (8–24 times per day), the type and amount were entered in the system. As each NICU bed is equipped with a computer, physicians and nurses could directly enter information when they administered nutrition and medication, ensuring reliable documentation. Potential confounding variables were recorded for the first 10 days of life. These included the use of intravenous antibiotics and antimycotics, indwelling catheters (venous and arterial umbilical catheters and percutaneously inserted central catheters were included), parenteral nutrition (intravenous administration of lipids and amino acids) and mechanical ventilation (endotracheal ventilation). Sepsis was prospectively monitored as part of the infection surveillance programme. Sepsis was defined as a positive blood culture and a C-reactive protein level >10 mg/l [2]. All abdominal X-rays were examined for the occurrence of NEC, defined as Bell's stage II or III [8]. If patients had undergone surgery, the operation reports were consulted to confirm the diagnosis.

Statistical Methods

A multivariable, Cox proportional hazards regression analysis was performed to estimate the effect of the proportion of mother's milk intake (or the cumulative intake in millilitres/kilogram birth weight) on the likelihood of sepsis, NEC or death. Two separate analyses were performed. In the first analysis, we investigated the effect of the proportion of mother's milk intake during the first 5 days of life on an event (sepsis/NEC/death) occurring between day 6 and 60. In the second analysis, we investigated the effect of the proportion of mother's milk intake during day 6–10 on an event between day 11 and 60. In the second analysis, only patients that did not have an event during day 1–5 were included. If an event occurred before day 5 (analysis 1) or between day 6–11 (analysis 2), the proportion of mother's milk was calculated for the days preceding the event. Time to event was calculated from birth to either discharge, age 60 days (no event) or event. For infants who developed sepsis or NEC and died as a result, the time to

Table 1. Characteristics of study infants and enteral intake grouped by outcome

Characteristics	NEC, sepsis or death (n = 96)	Survivors, without sepsis/NEC (n = 253)	p value
Gestational age, weeks	27.4 (23.9–37.0)	29.1 (24.0–32.1)	<0.001
Birth weight, g	920 (470–1,490)	1,090 (360–1,495)	<0.001
Birth weight <–2 SD, n	2 (2%)	17 (7%)	
Cumulative mother's milk intake (day 1–5), ml/kg	24 (0–167)	36 (0–281)	0.13
Cumulative mother's milk intake (day 6–10), ml/kg	109 (0–643)	218 (0–740)	<0.001
Mother's milk intake (day 1–5), % of total enteral intake	39 (0–100)	50 (0–100)	0.24
Mother's milk intake (day 6–10), % of total enteral intake	100 (0–100)	100 (0–100)	0.15

The results are expressed as medians and range (shown in parentheses unless otherwise indicated).

event was calculated from birth to the onset of sepsis/NEC. Potential covariates and confounders were evaluated by adding them to the model, one at a time. These variables were: antibiotics (yes/no), antimycotics (yes/no), indwelling catheters (yes/no), mechanical ventilation (yes/no), parenteral nutrition (yes/no), gestational age (days), birth weight (grams), small for gestational age (yes/no) and gender. Only variables that had a statistically significant effect were retained in the final model. The proportional hazard assumption of all models was tested using the Schoenfeld residuals for all models. All analyses were completed using the software package R, Version 2.13.1 (The R Foundation for Statistical Computing).

Results

During the study period, 381 VLBW infants were admitted to the NICU within 24 h after birth, of whom 32 were excluded from this study. Eighteen infants were discharged within 72 h to a post-IC High Care centre and 12 infants died before 72 h of age. Of these 12 cases, most were below 25 weeks of gestation (n = 7). Acute respiratory failure (58%) and group B streptococcal infection (25%) were the most common causes of death within 72 h. Two infants were diagnosed with intestinal perforation within 72 h after birth, which was likely the result of placental insufficiency in utero due to severe pre-eclampsia. The first infant had received a total of 5 ml of his mother's milk before developing intestinal perforation on the second day of life and the second infant had received 1.5 ml of formula before developing intestinal perforation on the second day of life. As a result, a total of 349 patients were included in the final analysis. Patient characteristics per outcome group are summarized in table 1. In total, 2% of the infants received a diet that consisted exclusively of their mother's milk during the first 10 days of life.

Table 2. Results of Cox regression for time to event (sepsis/NEC/death)

Variable	HR	95% CI	p value
<i>Model 1¹</i>			
0.01–50% mother's milk	0.41	0.23–0.74	0.003
>50% mother's milk	0.43	0.26–0.71	<0.001
Male gender	0.73	0.48–1.11	0.14
Indwelling catheters	0.31	0.18–0.53	<0.001
Antibiotics	0.22	0.09–0.58	0.002
Gestational age	0.97	0.96–0.99	0.002
<i>Model 2²</i>			
0.01–50% mother's milk	0.53	0.20–1.36	0.180
>50% mother's milk	0.31	0.18–0.54	<0.001
Gender	0.62	0.39–0.99	0.044
Gestational age	0.97	0.95–0.98	<0.001

Note: only covariates that were statistically significant were included in the final model.

¹ Model based on percent mother's milk from birth to day 5.

² Model based on percent mother's milk from day 6 to 10, stratified by parenteral nutrition (0–2/3–4/5 days).

The majority (86%) of the infants received a mix of pre-term formula and their mothers' milk, and the remaining 12% of infants only received formula. Infants were able to tolerate full enteral feeding (defined as ≥ 120 ml/kg/day) after an average of 11 days [median, interquartile range (IQR) 8–15]. Intake of mother's milk did not influence time to full enteral feeding. The average duration of stay at the NICU was 17 days (median, IQR 9–36). On average, infants that received higher amounts of formula had a shorter stay; however, the group of infants that received high amounts (>50% of enteral intake) of their mothers'

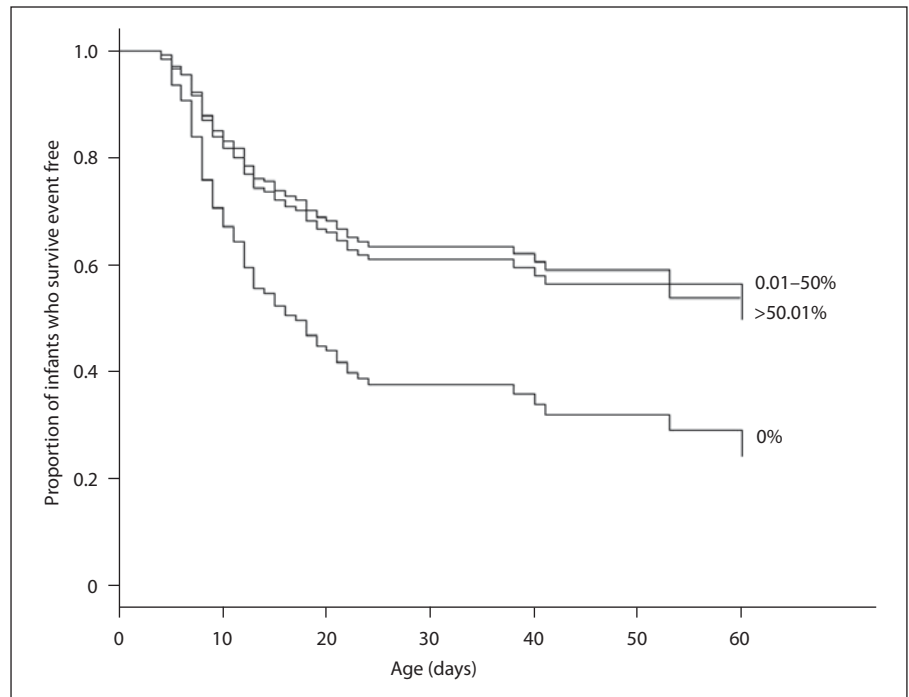


Fig. 1. Adjusted survival curves for sepsis, NEC or death by proportion of mother's milk to total intake over the first 5 days of life. The lines represent the proportion of mother's milk to total in-take.

milk were significantly younger than infants that received solely formula. When we corrected for birth weight, the effect on length of stay disappeared. The overall incidence of sepsis in the studied population was 22.9% and the incidence of NEC was 6.3%. Thirty-three infants (9.4%) died before day 60 of life. The median day of onset for the combined outcome sepsis, NEC or death was day 9 (IQR 7–14) of life.

The results of the multivariable Cox analyses are summarized in table 2. The group of infants who received milk from their own mothers during the first 5 days of life had a significantly lower risk of sepsis, NEC or mortality (fig. 1). Additionally, the intake of their mothers' milk during day 6–10 of life was associated with a decreased risk of sepsis, NEC or mortality (fig. 2). However, this was only significant in the infants who received more than 50% of their enteral nutrition as their mothers' milk. The results did not change when we assessed the influence of the absolute cumulative intake (expressed as millilitres/kilogram body weight) on the incidence of the combined primary outcome (data not shown). The assumption of proportional hazards was not violated in either model.

Discussion

In this retrospective study, we show that the intake of mother's milk during the first 10 days of life is associated with a decreased combined morbidity and mortality during the first 60 days of life. The results of this study are consistent with the findings of Meinen-Derr et al. [9] and Sisk et al. [10], who showed that there is a dose-related association between mother's milk intake and a reduced risk of NEC or death after the first 2 weeks of life. A new finding from this study is that mother's milk intake during the first 10 days of life is also associated with the prevention of sepsis over a prolonged period. These studies provide support for the hypothesis that mother's milk intake is especially important during the first few days of life, as is also seen in animal studies [11]. The biological mechanism is unknown, but it could be attributed to the protective effects of the various bioactive substances present in human milk. Human milk contains factors that may have bactericidal actions (e.g. lactoferrin), immunomodulating actions (e.g. TGF- β) bifidogenic properties (oligosaccharides) and maturation-inducing properties (e.g. IGF-1). Alternatively, or concomitantly, the higher incidence of serious morbidity and mortality in infants with a lower intake of mothers' milk could be caused by the greater intake of immunogenic cow's milk

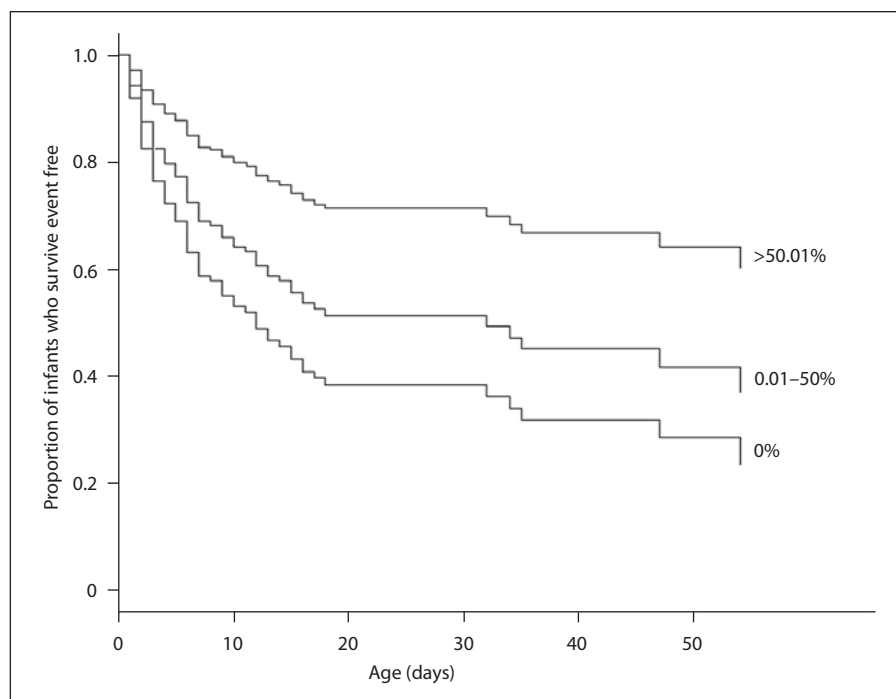


Fig. 2. Adjusted survival curves for sepsis, NEC or death by proportion of mother's milk to total intake over day 6–10 of life. The lines represent the proportion of mother's milk to total intake.

proteins. The protein fraction of cow's milk differs remarkably from the protein fraction of human milk, both in quantity and quality. In particular, the casein fraction of cow's milk shows relatively little homology to human casein. Casein derived from cow's milk is chemotactic for neutrophils and promotes the secretion of biological products such as cytokines. These cytokines may in turn induce or exacerbate an inflammatory response by modulating vascular tone and permeability. Hyperactivation of the immune system could be a critical factor in the development of NEC. The observation that formula-fed infants have a higher intestinal permeability compared to their breast-fed peers could also be explained by the chemotactic actions of casein. Furthermore, increased intestinal permeability may facilitate translocation of intestinal bacteria, thereby increasing the infants' susceptibility to sepsis. Abdelhamid et al. [12] recently showed that the blood mononuclear cells of infants with sepsis or NEC have an enhanced pro-inflammatory cytokine response upon stimulation with bovine casein when compared to healthy controls.

According to the feeding protocols currently in use, MEF is started immediately after preterm birth, usually within a few hours. Mother's milk is often unavailable because the onset of lactation is often delayed after preterm births. An increasing number of hospitals operate

milk banks to supply these infants with donor milk. Meta-analyses show that feeding infants with donor milk reduces the incidence of NEC but also results in a slower growth rate [13]. Reduced postnatal growth has been associated with unfavourable neurodevelopmental outcomes [14]. However, in a randomized study comparing infants fed donor milk and preterm formula, the two study groups had comparable neurodevelopmental outcomes at 18 months of age [15]. The slower growth rate is caused by the lower protein and energy content of donor milk. Most donors have delivered at term, and the caloric content of the milk is diminished by repetitive freeze-thawing. Additionally, the Holder pasteurization process used for donor milk inactivates bile salt-stimulated lipase, likely decreasing the absorption of fat from the milk. In addition, the pasteurization of donor milk can partially or completely inactivate many of the bioactive substances that are thought to be responsible for the protective benefits of human milk [16]. However, using donor milk in the first 10 days of life avoids the introduction of cow's milk proteins, which could provide additional benefits. The lower nutritional content of donor milk is less concerning during this period because infants are receiving the majority of their nutrition via the parenteral route.

A notable finding of this study was that the presence of an indwelling catheter seemed to be associated with a decreased risk of the combined outcome sepsis, NEC or mortality. However, when stratified for the administration of parenteral nutrition, this effect was no longer significant. Because all infants received parenteral nutrition during the first 5 days of life (89% received parenteral nutrition for the entire 5 days), we could not stratify for parenteral nutrition during the first period. This finding could be further explained by the presence of peripheral intravenous catheters in infants without an indwelling catheter. Prospective infection surveillance data from 2,126 patients (99,964 patient-days) show that indwelling catheters and peripheral intravenous catheters have similar adjusted HRs for the development of sepsis [17], both increasing the risk of sepsis by a factor of approximately 6. Peripheral intravenous catheters are replaced every 36 h; the median number of attempts to properly place the peripheral intravenous catheters is 2 (IQR 2–4) [unpubl. data]. It can be hypothesized that the aseptic procedure

of inserting an indwelling catheter has a protective effect compared to the commonly less sterile conditions during the insertion of a peripheral intravenous catheters [17].

An important weakness of this study is its retrospective design. A higher intake of mother's milk during days 1–10 of life might be predictive of the volume of mother's milk intake after day 10. Nevertheless, the majority of incidents took place during the early postnatal period, with a peak incidence at day 9. As such, these early incidents were not confounded by nutrition in the late postnatal phase. Whether benefits may be derived from avoiding the introduction of cow's milk protein during early postnatal life, by supplementing mother's milk with donor milk or elemental formula if necessary, should be investigated in a randomized controlled trial. The results of this study highlight the importance of mother's milk during the first, most vulnerable days of life and emphasize that all efforts should be made to initiate lactation rapidly after a preterm birth.

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