# Effect of Donor Milk on Severe Infections and Mortality in Very Low-Birth-Weight Infants

The Early Nutrition Study Randomized Clinical Trial

**Willemijn E. Corpeleijn, MD; Marita de Waard, MD; Viola Christmann, MD; Johannes B. van Goudoever, PhD; Marijke C. Jansen-van der Weide, PhD; Elisabeth M. W. Kooi, PhD; Jan F. Koper, MD; Stefanie M. P. Kouwenhoven, BSc; Hendrik N. Lafeber, PhD; Elise Mank, BSc; Letty van Toledo, PhD; Marijn J. Vermeulen, PhD; Ineke van Vliet, BSc; Diny van Zoeren-Grobben, PhD**

**IMPORTANT** Infections and necrotizing enterocolitis, major causes of mortality and morbidity in preterm infants, are reduced in infants fed their own mother’s milk when compared with formula. When own mother’s milk is not available, human donor milk is considered a good alternative, albeit an expensive one. However, most infants at modern neonatal intensive care units are predominantly fed with own mother’s milk. The benefits of add-on donor milk over formula are not clear.

**OBJECTIVE** To determine whether providing donor milk instead of formula as supplemental feeding whenever own mother’s milk is insufficiently available during the first 10 days of life reduces the incidence of serious infection, necrotizing enterocolitis, and mortality.

**DESIGN, SETTINGS, AND PARTICIPANTS** The Early Nutrition Study was a multicenter, double-blind randomized clinical trial in very low-birth-weight infants (birth weight <1500 g) admitted to 1 of 6 neonatal intensive care units in the Netherlands from March 30, 2012, through August 17, 2014. Intent-to-treat analysis was performed.

**INTERVENTIONS** Infants received pasteurized donor milk or preterm formula during the first 10 days of life if own mother’s milk was not (sufficiently) available.

**MAIN OUTCOMES AND MEASURES** The primary end point was cumulative occurrence of serious infection (sepsis or meningitis), necrotizing enterocolitis, or mortality during the first 60 days of life.

**RESULTS** A total of 930 infants were screened for inclusion; 557 were excluded, resulting in 373 infants (183 receiving donor milk and 190 receiving formula) who were evaluated by intent-to-treat analysis (median birth weight, 1066 g; mean gestational age, 28.4 weeks). Own mother’s milk comprised 89.1% and 84.5% of total mean intake during the intervention period for the donor milk and formula groups, respectively. The incidence of the combined outcome was not different (85 [44.7%] [formula] vs 77 [42.1%] [donor milk]; mean difference, 2.6%; 95% CI, −12.7% to 7.4%). The adjusted hazard ratio was 0.87 (95% CI, 0.63-1.19; P = .37).

**CONCLUSIONS AND RELEVANCE** In the current study, pasteurized donor milk and preterm formula as supplemental feeding during the first 10 days of life yielded similar short-term outcomes in very low-birth-weight infants regarding safety and efficacy when own mother’s milk availability was insufficient. Future studies investigating longer duration of use of human donor milk on short-term and long-term outcomes are necessary.

**TRIAL REGISTRATION** trialregister.nl Identifier: NTR3225

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Johannes B. van Goudoever, PhD, Department of Pediatrics, VU University Medical Center, Room 2H 9D-11, PO Box 7057, 1007 MB, Amsterdam, the Netherlands (h.vangoudoever@vumc.nl).


Published online May 2, 2016.
Approximately 10% of infants worldwide are born premature. Of those, approximately 15% weigh less than 1500 g and are classified as having a very low birth weight (VLBW). Sepsis and necrotizing enterocolitis (NEC) cause morbidity and mortality in VLBW infants. The incidence of sepsis varies from 20% to 40%, whereas the incidence of NEC is approximately 7%. One-third of infants with severe NEC do not survive the neonatal period. Long-term sequelae in survivors include neurodevelopmental delay and short-bowel syndrome. Very low-birth-weight infants fed with their own mother’s milk have 6 to 10 times lower NEC incidence and a decreased sepsis incidence compared with formula feeding. The exact underlying mechanism is unknown, but 2 hypotheses prevail: human milk contains bioactive substances that reduce sepsis and NEC risk, or alternatively, cow’s milk-based formula contains factors that increase risks.

On the basis of the clear benefits of own mother’s milk, many efforts are conducted to provide infants with own mother’s milk as soon as possible after preterm birth. However, lactation onset is often delayed after premature delivery, resulting in insufficient amounts of milk during the first critical days. Several guidelines propose pasteurized human donor milk supplementation over preterm formula. Pasteurization limits pathogen transmission but also reduces milk quality. To determine whether completely human milk-based diets during the first 10 days of life reduce the incidence of serious infection, NEC, and mortality, we compared pasteurized donor milk and preterm formula supplementation when own mother’s milk was insufficiently available.

Methods

Study Design
The Early Nutrition Study was a double-blind, parallel randomized clinical trial (RCT) at 6 neonatal intensive care units (NICUs) in the Netherlands. Enrollment occurred from March 30, 2012, through August 17, 2014. This investigator-initiated study was approved by the ethical committee of VU University Medical Center (Amsterdam, the Netherlands). A contract research organization (Clinical Research Unit, Amsterdam Medical Center, Amsterdam, the Netherlands) covered regulatory aspects and source document verification. An independent data safety monitoring board, including a patient organization representative, monitored safety and quality. The trial protocol can be found in Supplement 1.

Study End Points
The primary end point was the composite incidence of NEC, serious infection (sepsis or meningitis), or all-cause mortality between 72 hours and 60 days of life. Sepsis was defined as 1 positive blood culture result with non-coagulase-negative staphylococci or 1 positive blood culture with a coagulase-negative staphylococci pathogen and C-reactive protein level greater than 10 mg/L (to convert to nanomoles per liter, multiply by 9.524) within 2 days of blood culture or 2 positive blood cultures results with coagulase-negative staphylococci drawn within 2 days. Meningitis was defined by positive cerebrospinal fluid culture result. Necrotizing enterocolitis was defined as a Bell stage of II or higher. Bronchopulmonary dysplasia (defined as supplemental oxygen after day 28 of life and abnormalities on pulmonary radiography), intraventricular hemorrhage (defined according to Volpe), retinopathy of prematurity (defined according to the International Classification of Retinopathy of Prematurity), and persistent ductus arteriosus (confirmed by echocardiography) were measured as routine comorbidity parameters during follow-up. Secondary end points were time to an enteral intake of at least 120 mL/kg/day and days receiving parenteral nutrition (defined as any parenteral lipid emulsion or amino acid administration).

Participants
Infants with a birth weight less than 1500 g were eligible if parents gave written informed consent, and data were deidentified. Because the study started shortly after birth, informed consent was given before delivery if possible. Exclusion criteria were maternal drug or alcohol abuse during pregnancy, major congenital anomalies or birth defects, congenital infection (culture-proven early-onset sepsis or suspected TORCH [toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes infection]), perinatal asphyxia with umbilical or first neonatal pH less than 7.0, and any cow’s milk-based product intake before randomization. Infants were included at level 3 NICUs of VU University Medical Center, Academic Medical Center (Amsterdam, the Netherlands), Radboud University Medical Center (Nijmegen, the Netherlands), University Medical Center Groningen (Groningen, the Netherlands), Erasmus MC-Sophia Children’s Hospital (Rotterdam, the Netherlands), and Isala Clinic (Zwolle, the Netherlands). These centers provide approximately 70% of Dutch neonatal intensive care.

Randomization and Masking
Participants were randomly assigned to receive pasteurized donor milk or preterm formula (Nenatal Start [Nutricia Advanced Medical Nutrition]) or Hero Prematuur 1 [Hero]) if own mother’s milk was insufficiently available. The Dutch Human Milk Bank (located at VU University Medical Center)
provided the donor milk. Donors were screened according to international guidelines, and their milk underwent Holder pasteurization (30 minutes at 62.5°C). The attending physician or investigators (W.E.C., M.d.W., V.C., E.M.W.K., J.F.K., S.M.P.K., L.V.T., M.J.V., D.v.Z.-G.) used online randomization software with various block sizes and a 1:1 allocation ratio.

Infants were stratified according to birth weight (<1000 or ≥1000 g), small or appropriate size for gestational age (small for gestational age was defined as a birth weight <-2 SDs according to the growth curves from Niklasson and Albertsson-Wikland or Visser et al., depending on which was routinely used at the participating wards), and by center. Parents, nurses, physicians, and researchers were unaware of allocation. The data safety monitoring board members (unaware of allocation) had insight into group differences and could deblind in case of safety concerns or overwhelming benefit. Study nutrition was prepared by milk kitchen staff made aware of group allocation but providing no clinical care. Study nutrition was delivered to wards in amber syringes (VYGON Nederland BV Valkenswaard and Becton Dickinson BV Breda) with the amount of liquid but not its characteristics visible. Own mother’s milk was always given primarily to infants and, only when insufficient, supplemented with study nutrition.

The trial started with first enteral nutrition, usually within 6 hours after birth and only after written informed consent. The attending physician determined the parenteral nutrition amount and type and the enteral nutrition amount, according to local protocols. The intervention lasted for 10 days or less on hospital transfer or death. Ten centers provide neonatal intensive care in the Netherlands. General policy is to transfer VLBW infants to local hospitals with post-intensive care high-care facilities on patient stability without invasive respiratory support given at a postconceptional age of 30 weeks and a body weight of 1000 g or more. No study nutrition was given after transfer, and supplementation was switched to preterm formula if own mother’s milk was insufficient. Follow-up on the appearance of primary and comorbidity outcomes continued until 60 days of age in all cases. In addition, in all infants retinopathy of prematurity was followed up until full retinal vascularization was reached.

Because neither own mother’s milk nor donor milk meet VLBW infants’ high protein and energy demands, human milk fortifier should be added. Fortifiers derived from human milk are unavailable in the Netherlands; therefore, cow’s milk–based fortifiers are added. No fortifier was given until day 10 to compare a completely human milk based diet with a diet (partially) based on cow’s milk protein. After intervention, all infants received own mother’s milk (with or without fortifier at the attending physician’s discretion) or preterm formula.

### Statistical Analysis

On the basis of our retrospective report, the estimated cumulative composite outcome incidence was 40% after 60 days. We considered an absolute incidence reduction of 40% to 25% as clinically relevant. To detect such a change with 80% power (α = .05, 2-tailed), 165 infants per group were needed. We estimated that approximately 10% of eligible infants would be fed exclusively own mother’s milk during the intervention period. To allow for this and the inclusion of twins (only the first born was randomized and analyzed, but the sibling received the same intervention for ethical reasons), we aimed to include 198 infants per group. Both intent-to-treat and per-protocol analyses were conducted. To account for censored infants (eg, through hospital transfer), Cox proportional hazards regression analysis was used to assess effects of donor milk on time until occurrence of a primary end point. The model was adjusted for stratification variables (weight relative to gestational age, birth weight <1000 or ≥1000 g, and study center). Factors investigated as potential confounders or effect modifiers were birth weight, Apgar score 5 minutes after birth, gestational age, sex, and Score for Neonatal Acute Physiology II. Logistic regression analysis tested the effect of donor milk on comorbidity outcomes: bronchopulmonary dysplasia, intraventricular hemorrhage, retinopathy of prematurity, and persistent ductus arteriosus. P < .05 was considered statistically significant.

### Results

#### Enrollment

The participating centers admitted 930 VLBW infants during the study period. In total, 377 infants were randomized. Four infants’ informed consent procedure did not comply with requirements, so data of 373 infants were analyzed in the intent-to-treat analysis (Figure 1). Exclusion criteria (congenital infection or anomaly) became clear in 18 infants, only after starting the intervention. In those cases, the intervention was stopped immediately. Modified intent-to-treat analysis was performed without them. Figure 1 lists the reasons for excluding 76 infants from the per-protocol analysis. Baseline characteristics were well balanced between the 2 groups (Table 1).

#### Study Nutrition

The amount of study nutrition that infants received was comparable between groups, but the donor milk group tended to receive more of their own mother’s milk during the intervention period (eTable in Supplement 2). Twelve infants (3.4%) received their own mother’s milk exclusively during the intervention period (7 in the donor milk and 5 in the formula group), whereas 30 infants (8.5%) received donor milk or formula exclusively (12 and 18 infants, respectively). Medians of 89.1% and 84.5% of the total enteral intake were own mother’s milk in the donor milk and formula groups, respectively. After the intervention period, 56.5% and 64.1% of infants were exclusively fed with own mother’s milk in the formula and donor milk groups respectively, whereas 13.6% (formula group) vs. 11.8% (donor milk group) of infants were exclusively fed with formula. The remaining infants were fed with a mixture.

#### Primary Outcome

The cumulative incidence of the composite outcome was 44.7% (95% CI, 37.6%–51.9%) and 42.1% (95% CI, 34.9%–49.3%) in the preterm formula and donor milk groups, respectively (Figure 2), with a mean difference of 2.6% (95% CI, −12.7% to 7.4%). The adjusted hazard ratio was 0.87 (95% CI, 0.63–1.19; P = .37).
At a total of 94 events (57.7%) occurred during the first 10 days of life during the intervention period (58.8% in the formula vs. 56.8% in the donor milk group). Neither modified intent-to-treat nor per-protocol analyses revealed significant differences in the incidence of the primary end point (43.1% and 47.1% in the formula group and 42.0% and 40.3% in the donor milk groups, respectively). The adjusted hazard ratio for the per-protocol analysis was 0.73 (95% CI, 0.51-1.04; \( P = .08 \)).

Large amounts of own mother’s milk (>50% of total enteral intake) tended to be associated with a reduced risk of the cumulative incidence of serious infections, NEC, or mortality (eFigure in Supplement 2).

Secondary Outcome

The median time to reach an enteral intake of 120 mL/kg/day was 11.0 days in the formula group and 10.0 days in the donor milk group (adjusted hazard ratio, 1.20; 95% CI, 0.94-1.51; \( P = .14 \)). The total number of days receiving parenteral nutrition did not differ between the 2 groups (median, 12.0 and 11.0 days for the formula and donor milk groups, respectively).

Table 1. Characteristics of the Patients at Baseline*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donor Milk (n = 183)</th>
<th>Formula (n = 190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, mean (SD), wk</td>
<td>28.3 (2.3)</td>
<td>28.6 (2.2)</td>
</tr>
<tr>
<td>Birth weight, median (IQR), g</td>
<td>1065 (830-1265)</td>
<td>1077 (854-1275)</td>
</tr>
<tr>
<td>Birth weight &lt;1000 g</td>
<td>77 (42.1)</td>
<td>82 (43.2)</td>
</tr>
<tr>
<td>SGA</td>
<td>24 (13.1)</td>
<td>25 (13.2)</td>
</tr>
<tr>
<td>Male sex</td>
<td>92 (50.3)</td>
<td>104 (54.7)</td>
</tr>
<tr>
<td>Apgar score at 5 min, median (IQR)</td>
<td>8 (6.0-9.0)</td>
<td>8 (7.0-9.0)*</td>
</tr>
<tr>
<td>Born via cesarean section</td>
<td>97 (53.0)</td>
<td>108 (56.9)</td>
</tr>
<tr>
<td>Completed course of prenatal corticosteroids</td>
<td>124 (67.8)*</td>
<td>134 (70.5)</td>
</tr>
<tr>
<td>SNAP II, median (IQR)</td>
<td>9 (5.0-19.5)</td>
<td>9 (5.0-19.0)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; SGA, small for gestational age; SNAP, Score for Neonatal Acute Physiology.

*Data are presented as number (percentage) of infants unless otherwise indicated. No significant differences were found between the 2 groups in the listed categories.

* Data missing for 1 infant.

a Use of data not allowed.

b Parents withdrew consent but allowed use of all data, also during the follow-up period.
Comorbidity

Table 3 gives the incidences of comorbidity. No significant differences were found in any of the studied parameters.

Adverse Events

Five infants in the donor milk group and 8 infants in the formula group experienced an adverse event other than those described above. These adverse events included spontaneous intestinal perforation without signs of NEC (n = 2), posthemorrhagic ventricular dilatation (n = 1), osteomyelitis (n = 1), and pneumothorax (n = 1) in the donor milk group and gastric perforation (n = 1), cardiac tamponade (n = 2), posthemorrhagic ventricular dilatation (n = 1), pneumothorax (n = 2), lung bleeding (n = 1), and pneumatoceles (n = 1) in the formula group.

Discussion

In this multicenter, blinded RCT in VLBW infants the effect of pasteurized donor milk compared with formula supplementing own mother’s milk directly after birth was investigated. Neither negative nor beneficial effects of the use of pasteurized donor milk were found.

Studies on risks and benefits of feeding pasteurized donor milk instead of preterm formula to VLBW infants are scarce. A meta-analysis18 that included 1070 infants found that formula feeding increased the risk of NEC (both as exclusive diet; typical risk ratio, 2.77; 95% CI, 1.40-5.46). However, formula-fed infants had higher in-hospital growth rates, a finding associated with improved long-term development.19,20 Only 2 of the included trials were performed after the year 2000, with most trials dating back to the 70s and 80s. Since then, neonatal intensive care standards have changed and improved significantly, resulting in higher survival in VLBW infants.21

The 2 previous studies22,23 that fulfilled present state-of-the-art criteria of double-blind RCTs attempted to investigate effects of donor milk on short-term outcomes as well. Agreeing with our findings, Schanler et al22 found no effect of donor milk on late-onset sepsis or NEC incidence. However, they only included sepsis or NEC cases that occurred after a significant amount of enteral nutrition (50 mL/kg daily) was tolerated, in their setting after 16 to 18 days, when a substantial number of events should already have occurred.9,24 Furthermore, the underpowered study has been criticized on its design.25 Cristofalo et al23 found that premature infants fed donor milk enriched with a human milk-based fortifier needed less time on parenteral nutrition (primary outcome) compared with

Table 2. Primary End Point by Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Donor Milk (n = 183)</th>
<th>Formula (n = 190)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Day of Onset, Median (IQR)</td>
<td>No. (%)</td>
<td>Day of Onset, Median (IQR)</td>
</tr>
<tr>
<td>Primary composite outcome</td>
<td>77 (42.1)</td>
<td>10.0 (8.0-15.0)</td>
<td>85 (44.7)</td>
<td>9.0 (7.0-15.0)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>67 (36.6)</td>
<td>11.0 (8.0-16.0)</td>
<td>66 (34.7)</td>
<td>10.0 (7.0-15.0)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>11 (6.0)</td>
<td>10.0 (6.0-35.0)</td>
<td>11 (5.8)</td>
<td>9.0 (8.0-17.0)</td>
</tr>
<tr>
<td>NEC</td>
<td>17 (9.3)</td>
<td>11.0 (7.5-20.5)</td>
<td>17 (8.9)</td>
<td>15.0 (8.5-26.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>4 (23.5)</td>
<td>...</td>
<td>5 (29.4)</td>
<td>...</td>
</tr>
<tr>
<td>Cause of death</td>
<td>5 (29.4)</td>
<td>...</td>
<td>5 (29.4)</td>
<td>...</td>
</tr>
<tr>
<td>Death</td>
<td>25 (13.7)</td>
<td>11.0 (5.5-26.0)</td>
<td>23 (12.1)</td>
<td>9.0 (5.0-18.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ellipses, data not applicable; IQR, interquartile range; NEC, necrotizing enterocolitis.

* Adjusted for stratification factors small or appropriate size for gestational age, birth weight less than 1000 g or 1000 g or more, and study center.

* Adjusted for the confounders gestational age and sex.

* Could not be calculated because of small numbers.

* Adjusted for the confounders gestational age, sex, and birth weight score.

* Adjusted for the confounders gestational age, sex, birth weight, and Score for Neonatal Acute Physiology II.
infants fed preterm formula. Secondary outcomes included NEC, which was reduced in association with a complete human milk-based diet, although only 53 infants were included. Moreover, study nutrition was given exclusively, not in addition to own mother’s milk. The incidence of NEC was 21% in the preterm formula group, which is much higher than in most NICUs in developed countries, although population characteristics (100% formula fed) might induce relative high rates of NEC.

The Cochrane review18 found limited data from RCTs comparing feeding with formula milk vs (nutrient enriched) donor milk in modern medicine. Although our trial found that use of donor milk does not reduce the combined incidence of serious infections, NEC, or death, there was insufficient power to detect an effect of donor milk on NEC incidence itself. To detect significant effects on incidence of NEC alone, RCTs need approximately 500 infants per arm, assuming NEC incidence of approximately 10%.

In our current trial, the proportion of own mother’s milk during the first 10 days of life was high in both groups (eTable in Supplement 2) and seemed to be higher than reported in previous studies.25,26 This may have diluted the effect of our intervention. However, abundant availability of own mother’s milk reflects the current situation at most NICUs in developed countries; therefore, this study resembles common practice in most countries where donor milk banks are operating.

Europe and the United States have 206 and 18 active milk banks, respectively, and an additional 23 milk banks are planned to open in the near future.27,28 Annual operation costs of human donor milk banks are high, ranging from US$200 000 to US$300 000. In an era in which health care costs are increasing, new initiatives that are introduced within the health care system require thorough investigation. In hospitals with a longstanding tradition of using donor milk, it has been deemed unethical to randomize infants to receive formula, given the results from older RCTs comparing donor milk with term formula. However, recent trials, including our own, have found minimal short-term benefits of the use of donor milk. Bearing in mind the considerable costs of donor milk and the, albeit small, risk of transmission of pathogens, these trials are very much warranted.

Our current trial reconfirms the benefits of feeding VLBW infants with raw own mother’s milk.5,9 Infants who received most of their nutrition as own mother’s milk had a tendency toward a decreased incidence of the primary end point compared with infants who received most of their nutrition as donor milk or formula (eFigure in the Supplement). Despite per-protocol analysis, it should be clear that these results are not free of bias. Mothers who provide enough of their own milk might differ from those who do not.

The trial does not provide information on why pasteurized donor milk lacks beneficial short-term effects. A common hypothesis is that Holder pasteurization destroys critical amounts of bioactive factors.12,29 Considerable research is being directed toward the development of more gentle pasteurization methods, but, to our knowledge, no RCTs investigated the effects on neonatal outcome. Besides pasteurization, other processing steps, such as freezing and thawing, may affect bioactive compounds and thus alter the quality of milk. An alternative hypothesis is that factors in milk unique to the specific mother-infant dyad are responsible for the protective effects, such as maternal lymphocytes that aid in induction of tolerance or secretory IgA directed toward pathogens shared by mother and child.12,29,30

The intervention period of our trial was short because a specific goal was to compare a completely human milk-based diet (own mother’s milk and donor milk) to a diet that also contains cow’s milk protein (formula). The introduction of cow’s milk-based fortifier was postponed until 11 days of life, as we found it not acceptable to withhold fortification from the participating infants for a longer period, since this would result in lower growth rates. Although most (57.7%) primary outcome events occurred within the first 10 days (Table 2), a considerable number of the infants experienced an event thereafter. It can thus be questioned whether the intervention period in our trial was too short.

The protective effect of human milk against sepsis and NEC is hypothesized to partially arise from avoiding immunogenic cow’s milk proteins, such as casein.26 The trial does not support this hypothesis since we could not find a detrimental effect of giving formula as compared to donor milk in

### Table 3. Prevalence of Comorbidity by Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th>Comorbidity Parameter</th>
<th>No./Total No. (%)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor Milk (n = 183)</td>
<td>Formula (n = 190)</td>
<td></td>
</tr>
<tr>
<td>ROP all stagesa</td>
<td>19/160 (11.9)</td>
<td>13/168 (7.7)</td>
<td>1.77 (0.76-4.13)</td>
</tr>
<tr>
<td>IVH grade ≥2</td>
<td>24/183 (13.1)</td>
<td>25/190 (13.2)</td>
<td>1.07 (0.54-2.11)</td>
</tr>
<tr>
<td>BPDc</td>
<td>47/167 (25.7)</td>
<td>46/174 (24.2)</td>
<td>1.10 (0.61-1.98)</td>
</tr>
<tr>
<td>PDA treatedd</td>
<td>41/183 (22.4)</td>
<td>43/190 (22.6)</td>
<td>0.967 (0.52-1.77)</td>
</tr>
</tbody>
</table>

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

a Adjusted for stratification factors small or appropriate size for gestational age, birth weight less than 1000 g or 1000 g or more, and study center.
b Patients who died before reaching full retinal vascularization were excluded.
c Corrected for the confounders gestational age and Score for Neonatal Acute Physiology II.
d Corrected for the confounders gestational age, Score for Neonatal Acute Physiology II, sex, and Apgar score at 5 minutes.

*Defined as supplemental oxygen after day 28 of life and abnormalities on pulmonary radiography. Patients who died before day 28 of life were excluded.

f Corrected for the confounders gestational age, SNAP II.
g Corrected for the confounders gestational age, SNAP II.
the first few days of life when own mothers milk was not available. This enables future trials (preferably powered to detect effects on sepsis, NEC, and mortality individually), to include a longer intervention period with addition of a cow’s milk based fortifier. Alternatively a human milk derived fortifier could be used.

Expectedly, a considerable proportion of the infants (14%) did not receive the intervention as planned until day 10 of life because of early transfer outside the NICU. However, information on occurrence of primary and secondary end points up to 60 days of life was collected for all these infants. Per-protocol analysis did not differ from the (modified) intent-to-treat analysis, making it unlikely that this influenced the results.

Conclusions

This double-blind RCT found no significant effect of pasteurized donor milk during the first 10 days of life for preventing serious infections, NEC, and all-cause mortality in premature neonates. The results of this trial stress the importance of providing premature neonates with raw milk from their own mother.

REFERENCES