Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review

W McGuire, M Y Anthony

Objective: To determine if enteral feeding with donor human milk compared with formula milk reduces the incidence of necrotising enterocolitis (NEC) in preterm or low birthweight infants.

Methods: Systematic review and meta-analysis of randomised controlled trials.

Results: Four small trials, all initiated more than 20 years ago, fulfilled the prespecified inclusion criteria. None of the trials individually found any statistically significant difference in the incidence of NEC. However, meta-analysis found that feeding with donor human milk was associated with a significantly reduced relative risk (RR) of NEC. Infants who received donor human milk were three times less likely to develop NEC (RR 0.34, 95% confidence interval [CI] 0.12 to 0.99), and four times less likely to have confirmed NEC (RR 0.25; 95% CI 0.06 to 0.98) than infants who received formula milk.

Conclusions: It may be appropriate to consider further larger trials to compare growth, development, and the incidence of adverse outcomes, including NEC, in preterm infants who receive donor human milk versus formula milk.

Human breast milk is the recommended source of enteral nutrition for preterm infants. A putative benefit is that the delivery of immunoprotective factors to the immature gut mucosa may decrease the risk of necrotising enterocolitis (NEC). Case-control data indicate that NEC is less common in infants nourished with human milk than in those fed with formula milk. Large prospective studies have found a lower incidence of NEC in preterm infants fed with their own mother’s expressed breast milk compared with those fed with formula milk.2 However, the outcomes in these non-randomised trials may have been affected by known and unknown confounding variables related to maternal preference for feeding with human milk. A recent Cochrane systematic review did not find any randomised controlled trials that compared feeding of preterm infants with their own mother’s expressed breast milk versus formula milk. This may be due to a perceived difficulty of allocating an alternative enteral feed to infants whose mothers wish to feed with expressed breast milk.

When the expressed breast milk of the preterm infant’s mother is not available, an alternative is banked milk from donor mothers. However, donor human milk, typically the breast milk of mothers who have delivered at term, has a lower content of protein and host defence protein than the breast milk of a mother who has delivered a preterm infant.2,3 Feeding with unfortified donor human milk, especially when compared with nutrient supplemented formula milk, is associated with lower rates of growth in preterm infants, at least in the short term. However, it is unclear whether the non-nutrient components of donor human milk may confer immunoprotective benefits. The aim of this systematic review is to examine the evidence that enteral feeding with donor human milk versus formula milk reduces the risk of development of NEC in preterm infants.

Methods
Prespecified inclusion criteria
Randomised and quasi-randomised controlled trials comparing enteral feeding with donor human milk versus formula milk in preterm (< 37 weeks gestation) or low birthweight (< 2.5 kg) infants were included. The allocated milk feed should have formed the entire enteral intake, not a supplement to the expressed breast milk of the mother. Trials in which parenteral nutritional support is available during the period of advancement of enteral feeds were acceptable, provided that the groups received similar treatment other than the type of milk feed. The following outcomes were considered:

- NEC, as defined and reported by individual trials;
- confirmed NEC, radiological confirmation showing gas in the portal venous system or free air in the abdomen, or when NEC is confirmed at surgery or autopsy.

Search strategy for identification of studies
The standard search strategy of the Cochrane Neonatal Review Group was used. This included electronic searches of the Cochrane Controlled Trials Register (CCTR, 2001, Issue 2), Medline (1966 to October 2001), and Embase (1980 to October 2001). No language restriction was applied. References in studies identified as relevant, and in previous reviews and standard textbooks of neonatal medicine and nutrition were examined.

The search strategy involved the following keywords, using the search fields of abstract, MeSH subject heading, exploded subject heading, publication type, registry number word, subject heading word, text word, and title: (1) “Infant-Newborn”/ all subheadings; (2) infan*; (3) neonat*; (4) newborn; (5) prematur*; (6) preemie; (7) low birth weight; (8) (small or light) near3 (date* or gestational age); (9) LDW; (10) VLBW; (11) SGA; (12) growth restrict*; (13) growth retard*; (14) IUGR; (15) explode “Infant-Nutrition”/ all subheadings; (16) explode “Feeding-Methods”/ all subheadings; (17) milk; (18) breast near3 feed*; (19) breast near3 fed; (20) formula, (21) PT = “CLINICAL-TRIAL”).

Abbreviations: NEC, necrotising enterocolitis; RR, relative risk; CI, confidence interval; RD, risk difference
The title and abstract of studies identified by the above search strategy were screened by the first reviewer. The full text of the report of each study identified as of potential relevance was rescreened by both reviewers. The decision to include or exclude a specific study was made by consensus of the two reviewers.

The criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the included trials. Quality of the trials was evaluated in terms of allocation concealment, blinding of parents or carers and assessors to intervention, and completeness of assessment in all randomised subjects. Additional information was requested from the authors of each trial to clarify methodology and results as necessary.

A data collection form was used to aid extraction of relevant information and data from each included study. Each reviewer extracted the data separately, compared data, and resolved differences by consensus. Effects were expressed as relative risk (RR) and 95% confidence interval (CI) and risk difference (RD) and 95% CI for a categorical data, fixed effect model for meta-analysis.

RESULTS
Description of studies

Eleven trials that appeared to be relevant were identified in the first round of screening. Four of these trials fulfilled the inclusion criteria and contributed to the meta-analysis. Table 1 gives details of the methods and quality assessment, and table 2 gives details of participant characteristics, interventions, and outcomes. Seven of the trials were excluded in the second round of screening, with complete agreement between the reviewers. Five of these trials (six reports) randomised preterm infants to feeding with donor human milk versus formula, but did not report NEC as an outcome. Two trials were non-randomised, although this was not clear from the title and abstract.

Necrotising enterocolitis

None of the four included trials showed any statistically significant difference in the incidence of NEC. When the data from the trials were combined in a meta-analysis, we found a borderline statistically significant difference in the incidence of NEC: RR 0.34 (95% CI 0.12 to 0.99); RD −0.05 (95% CI −0.1 to 0.00) (fig 1).

In a post hoc analysis, we included the data from a trial in which infants received donor human milk or formula as a supplement to the expressed breast milk of the infant's mother. The investigators did not find any significant difference in the incidence of NEC. When the data were combined with those of the previously included trials, the

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<th>Table 1</th>
<th>Characteristics of included studies: methods</th>
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<tr>
<td>Trial (year published)</td>
<td>Method of randomisation</td>
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<tr>
<td>Gross (1983)12</td>
<td>Random number table</td>
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<tr>
<td>Lucas (1990)6</td>
<td>Sealed envelopes</td>
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<tr>
<td>Svenningsen (1982)10</td>
<td>Not stated</td>
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<tr>
<td>Tyson (1983)11</td>
<td>Sealed envelopes</td>
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<tr>
<th>Table 2</th>
<th>Characteristics of included studies: participants, intervention, and outcome</th>
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<tr>
<td>Trial (year published)</td>
<td>Participants</td>
</tr>
<tr>
<td>Gross (1983)12</td>
<td>67 preterm infants (27–33 weeks gestation)</td>
</tr>
<tr>
<td>Tyson (1983)11</td>
<td>81 very low birth weight infants, excluding infants with “any significant illness” or those who required ventilatory support at day 10 of life</td>
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Given the uncertainty about the clinical applicability of these findings, further studies should be undertaken. NEC remains a major cause of death and debility in preterm infants, and improved strategies for prevention are required. However, there are concerns about the nutritional adequacy of donor breast milk. Future studies would be able to compare growth, development, and adverse events in infants fed with nutrient fortified donor human milk versus formula milk. Implementing this intervention would require the re-establishment of donor milk banks that were closed in the 1980s, despite the lack of data to suggest a significant risk of transmission of HIV and other infectious agents via donor milk. The costs and feasibility of using donor human milk should be compared with those of other interventions that might reduce the incidence of NEC, such as the supplementation of formula milk with immunoglobulin. These trials should be undertaken in infants who are at very high risk of developing NEC, such as very low birthweight infants. Carers and assessors should be blind to the intervention because the threshold for investigation or diagnosis may be affected by knowledge of the type of milk received. About 900 infants would be required to participate in a large (about 30 centres with an established donor milk bank) pragmatic trial in order to detect the estimated size of effect found in this review (with 95% confidence and at 80% power).

### DISCUSSION

The data available from the included trials suggest that feeding with donor human milk rather than formula milk may reduce the incidence of NEC in preterm or low birthweight infants. NEC is three times less likely, and confirmed NEC is less likely if 20 infants receive donor human milk rather than formula milk. The data available from the included trials suggest that feeding with donor human milk on the risk of NEC. It may be at increased risk of developing NEC. Carers and assessors should be blind to the intervention because the threshold for investigation or diagnosis may be affected by knowledge of the type of milk received. About 900 infants would be required to participate in a large (about 30 centres with an established donor milk bank) pragmatic trial in order to detect the estimated size of effect found in this review (with 95% confidence and at 80% power).

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### REFERENCES


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