Preventing necrotising enterocolitis in very preterm infants: current evidence

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Abstract

Necrotising enterocolitis (NEC) is the most common serious gastrointestinal disorder affecting very preterm or very low birth weight infants. The risk is inversely proportional to gestational age and weight at birth. Fetal growth restriction and compromise may be additional specific risk factors. Postnatally, a variety of practices have been implicated in the pathogenesis of NEC including formula feeding, early and rapid advancement of enteral feed volumes, and exposure to H_2-receptor antagonists. NEC, particularly severe NEC requiring surgical intervention, is associated with acute morbidity and mortality, prolonged hospital stay, and adverse long term neuro-developmental outcomes. With the exception of feeding with human milk, only limited evidence is currently available to support interventions to prevent NEC. Promising strategies that merit further evaluation in randomized controlled trials include the use of standardized feeding protocols and immuno-prophylaxis with prebiotics and probiotics.

Keywords breast milk; lactoferrin; necrotising enterocolitis; probiotics; very low birth weight

Epidemiology and outcomes

Necrotising enterocolitis (NEC) is a syndrome of acute intestinal necrosis of unknown aetiology affecting about 5% of all very preterm (less than 32 weeks) or very low birth weight (VLBW: less than 1500 g) and about 10% of all extremely preterm (less than 28 weeks) or extremely low birth weight (ELBW: less than 1000 g) infants (Table 1, Figure 1). Although treatment with antenatal corticosteroids reduces the risk of developing NEC by 50%, the overall incidence of NEC has not changed markedly in the past 20 years because of increases in early neonatal survival rates for extremely preterm and ELBW infants.

The rate of NEC-associated acute mortality is generally reported to be greater than 10% overall and more than 25% for infants with NEC severe enough to require a surgical intervention (which occurs in up to one-third of infants with NEC).

Very preterm or VLBW infants who develop NEC experience more on-going morbidity than gestation-comparable infants who do not develop NEC. Infants with NEC have a higher incidence of nosocomial infections, lower levels of nutrient intake, grow more slowly, and have longer durations of intensive care and hospital stay. NEC, particularly severe NEC requiring surgical intervention, is also associated with a higher incidence of long-term neurological disability which may be a consequence of infection and under-nutrition during a critical period of brain development.

Pathogenesis and risk factors

NEC is a postnatal condition. There are no reports of fetal NEC. The risk of developing NEC and the severity of the disease is inversely related to gestational age and weight at birth. The other putative major risk factor is intrauterine growth restriction secondary to suboptimal placental support. Although our understanding of the disease process remains incomplete, the currently accepted unifying model for the pathogenesis of NEC includes contribution and interaction of three key components:

- a susceptible immature gastro-intestinal tract.
- a precarious intestinal vascular supply (secondary to compensatory diversion to other vital organs).
- additional luminal factors secondary to milk feeding; increased intestinal metabolic demand, alteration of mucosal integrity, disturbance of optimal microbiological ecological balance, locally invasive gastrointestinal infection.

Genetic contribution

Studies comparing the concordance of disease in monozygotic versus dizygotic twins suggest that familial factors may contribute to the risk of NEC. To date, association studies (usually small scale studies focussing on inflammatory mediators) have not detected any specific and substantial genetic risk factors. Much larger family-based whole genome screening studies would be required to define important genetic contributions to NEC susceptibility. However, because NEC is a sporadic disease which occurs infrequently in individual centres, this sort of investigation would require a co-ordinated multinational effort to achieve recruitment of sufficient participants to provide a meaningful analysis.

Enteral feeding

Since most VLBW infants who develop NEC have received some milk feeds, it has long been postulated that differences between enteral feeding practices contribute to inter-unit variation in the incidence of NEC (Figure 2).

Breast milk versus formula milk

Large observational studies have demonstrated that infants who received their mother's expressed breast milk as their primary source of enteral nutrition are much less likely to develop NEC than infants fed with cow milk formula. However, because these studies did not randomly allocate infants to breast milk versus formula, the possibility that the effect on NEC was due to other known or unknown confounding factors could not be excluded. Infants who did not receive maternal expressed milk may have

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Clinical findings of NEC (modified Bell classification)

I: 'Suspected' NEC:
- Temperature instability, apnoea, bradycardia, lethargy
- Gastric retention, abdominal distention, emesis, blood in stool
- Normal, or intestinal dilation and mild ileus on abdominal radiograph

II. 'Definite' NEC
- As above plus:
- Absent bowel sounds ± abdominal tenderness ± abdominal cellulitis or right lower quadrant mass
- Radiological evidence of intestinal dilation, ileus, or pneumatosis intestinalis ± ascites

III. 'Advanced' NEC
- As above plus
- hypotension, bradycardia, severe apnoea, respiratory and metabolic acidosis, coagulopathy, or neutropenia
- signs of peritonitis, marked tenderness, and abdominal distention ± radiological evidence of intestinal perforation (pneumo-peritoneum)

Table 1

had other risk factors for NEC such as intrauterine growth restriction secondary to maternal ill health.

There have not been any randomized controlled trials of maternal breast milk versus formula milk feeding in VLBW infants. Such trials are now unlikely to be conducted because of lack of clinical and ethical equipoise. Several trials of feeding very preterm infants with *donated* expressed breast milk versus formula milk, either as the sole enteral diet or as a supplement when maternal breast milk is not available, have been conducted. Meta-analysis of these trials demonstrates a significantly higher risk of NEC in formula-fed infants (Figure 3).

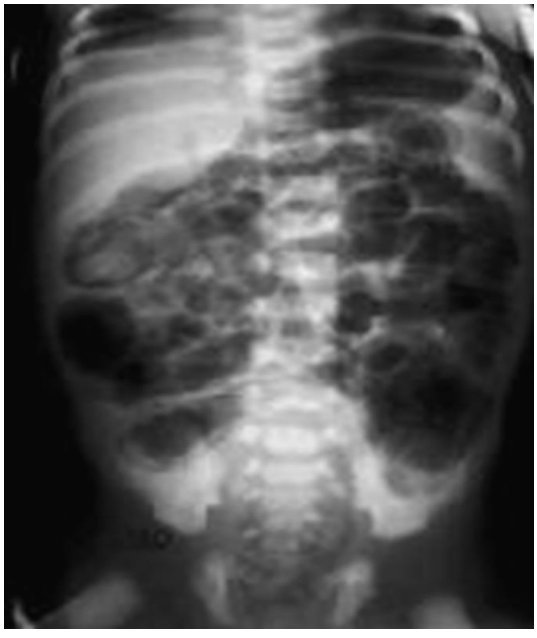

Figure 1 Pneumatosis intestinalis in acute NEC.

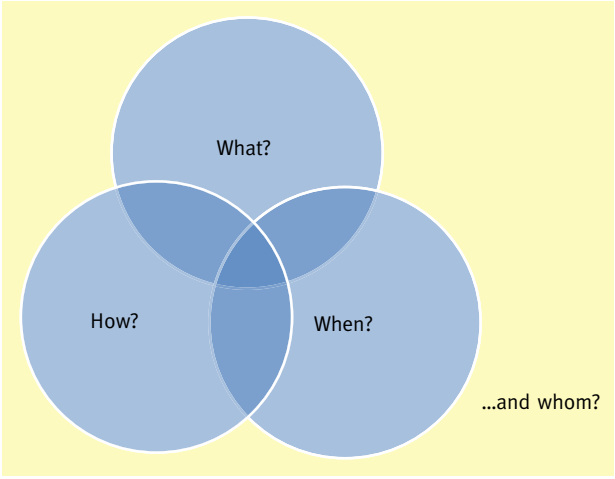

Figure 2 Enteral feeding strategies affect the risk of NEC.

As expressed breast milk generally contains fewer calories, protein and other nutrients than maternal milk, additional nutrient supplementation (typically with a commercially-available cow milk multi-nutrient fortifier) is usually used to promote growth and development. A North American multi-centre randomized controlled trial has demonstrated that use of a human milk multi-nutrient fortifier extracted from donated breast milk (rather than a cow milk fortifier) as an adjunct to feeding with maternal or donated expressed breast milk has an additional, synergistic effect in reducing risk of NEC in very preterm infants.

The key question raised by these studies is whether the substantial capital and opportunity costs of supplying donated breast milk would be better invested in promoting evidence-based practices to ensure mothers are optimally supported to express their own breast milk. Several evidence-based interventions are available to support mothers wising to express breast milk for their babies (Table 2, Figure 4). The challenge is to ensure that these are implemented consistently and broadly, and especially to vulnerable and socially-disadvantaged women who are less likely to provide expressed breast milk. Supporting mothers to express breast milk for their very preterm infants may be one of the most effective (and cost-effective) interventions currently available for reducing the incidence of NEC. Infant feeding practices in neonatal units, including the use of expressed breast milk, should be included in audit and benchmarking processes.

Timing of introduction and rate of advancement of enteral feeds

After accounting for availability of breast milk, the incidence of NEC tends to be higher in neonatal units where enteral feeding is introduced earlier and feeding volumes are advanced quickly. However, the data currently available from randomized controlled trials do not suggest that any specific feeding strategy affects the risk of very preterm or VLBW infants developing NEC (Figure 5) and a lack of blinding may have led to an overestimation of the size of any effect.

Competing outcomes

Given the paucity of high-level evidence, the recommended and implemented strategies for early enteral feeding of very preterm