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[Intervention Review]

Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants

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ABSTRACT

Background

The introduction of enteral feeds for very preterm (less than 32 weeks' gestation) or very low birth weight (VLBW; less than 1500 g) infants is often delayed for several days or longer after birth due to concern that early introduction may not be tolerated and may increase the risk of necrotising enterocolitis (NEC). However, delaying enteral feeding could diminish the functional adaptation of the gastrointestinal tract and prolong the need for parenteral nutrition with its attendant infectious and metabolic risks.

Objectives

To determine the effect of delayed introduction of progressive enteral feeds on the incidence of NEC, mortality and other morbidities in very preterm or VLBW infants.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2014, Issue 8), MEDLINE (1966 to September 2014), EMBASE (1980 to September 2014), CINAHL (1982 to September 2014), conference proceedings and previous reviews.

Selection criteria

We included randomised or quasi-randomised controlled trials that assessed the effect of delayed (more than four days after birth) versus earlier introduction of progressive enteral feeds on the incidence of NEC, mortality and other morbidities in very preterm or VLBW infants.

Data collection and analysis

Two review authors independently assessed trial eligibility and risk of bias and undertook data extraction. We analysed the treatment effects in the individual trials and reported the risk ratio (RR) and risk difference for dichotomous data and mean difference for continuous data, with respective 95% confidence intervals (CI). We used a fixed-effect model in meta-analyses and explored the potential causes of heterogeneity in sensitivity analyses.

Main results

We identified nine randomised controlled trials in which 1106 infants participated. Few participants were extremely preterm (less than 28 weeks' gestation) or extremely low birth weight (less than 1000 g). The trials defined delayed introduction of progressive enteral feeds as later than four to seven days after birth and early introduction as four days or less after birth. Meta-analyses did not detect statistically significant effects on the risk of NEC (typical RR 0.93, 95% CI 0.64 to 1.34; 8 trials; 1092 infants) or all-cause mortality (typical RR 1.18, 95% CI 0.75

to 1.88; 7 trials; 967 infants). Four of the trials restricted participation to growth-restricted infants with Doppler ultrasound evidence of abnormal fetal circulatory distribution or flow. Planned subgroup analyses of these trials found no statistically significant effects on the risk of NEC or all-cause mortality. Infants who had delayed introduction of enteral feeds took longer to establish full enteral feeding (reported median differences two to four days).

Authors' conclusions

The evidence available from randomised controlled trials suggested that delaying the introduction of progressive enteral feeds beyond four days after birth did not reduce the risk of developing NEC in very preterm or VLBW infants, including growth-restricted infants. Delaying the introduction of progressive enteral feeds resulted in a few days' delay in establishing full enteral feeds but the clinical importance of this effect was unclear. The applicability of these findings to extremely preterm or extremely low birth weight was uncertain. Further randomised controlled trials in this population may be warranted.

PLAIN LANGUAGE SUMMARY

No evidence that delayed introduction of progressive enteral feeds prevents necrotising enterocolitis in very low birth weight infants

Background

Very preterm (less than 32 weeks' gestation) or very low birth weight (less than 1500 g) infants are at risk of developing a severe bowel disorder called necrotising enterocolitis, where parts of the bowel become inflamed and start to die. One possible way to prevent this condition is to delay the introduction of milk feeds until several days (or longer) after birth.

Study characteristics

We search scientific databases for clinical trials assessing the effect of delayed (more than four days after birth) versus earlier introduction of progressive enteral feeds (where breast or formula milk is fed directly by a tube into the stomach) on the incidence of necrotising enterocolitis, death and general health in very low birth weight infants. The evidence is current to September 2014.

Key results

We found nine trials with 1106 infants that assessed the effect of delayed rather than early introduction of milk feeds for very preterm or very low birth weight infants. Data from these trials did not provide any evidence that delaying enteral feeding reduces the risk of necrotising enterocolitis.

Quality of the evidence

The included trials were generally of reasonable methodological quality but, in common with other trials of feeding interventions in infants, it was not possible to mask carers and clinical assessors to the given treatment.

BACKGROUND

Description of the condition

Necrotising enterocolitis (NEC) is an important cause of morbidity, mortality and neuro-disability in very preterm (less than 32 weeks' gestation) or very low birth weight (VLBW: less than 1500 g) infants. Extremely low birth weight (ELBW: less than 1000 g) and extremely preterm (less than 28 weeks' gestation) infants are at greatest risk (Bisquera 2002; Holman 2006; Rees 2007; Berrington 2012). Intrauterine growth restriction may be an additional specific risk factor, especially if associated with circulatory redistribution demonstrated by absent or reversed end-diastolic flow velocities in antenatal Doppler studies of the fetal aorta or umbilical artery (Bernstein 2000; Garite 2004; Dorling 2005; Kamoji 2008).

Description of the intervention

Most very preterm or VLBW infants who develop NEC have received enteral milk feeds. Evidence exists that feeding with artificial formula rather than human milk increases the risk of developing NEC (Quigley 2014). The timing of the introduction and the rate of progression of enteral feed volumes may also be modifiable risk factors for the development of NEC (Brown 1978; Uauy 1991; Henderson 2009). Data from observational studies suggest that using feeding regimens that include delaying the introduction of progressive enteral feeds until beyond about four to seven days after birth reduces the risk of NEC (Patole 2005; Hay 2008).

Why it is important to do this review

In current clinical practice, the introduction of progressive enteral feeds for very preterm or VLBW infants is often preceded by a period of enteral fasting or 'minimal enteral nutrition' (Boyle 2004; Patole 2004; Hay 2008; Klingenberg 2012). However, there may also be potential disadvantages associated with delaying the introduction of progressive enteral feeds. Because gastrointestinal hormone secretion and motility are stimulated by enteral milk, delayed enteral feeding could diminish the functional adaptation of the gastrointestinal tract (Berseeth 1990; Burrin 2002). Prolonging the duration of use of parenteral nutrition may be associated with infectious and metabolic complications that increase mortality and morbidity, prolong hospital stay, and adversely affect growth and development (Flidel-Rimon 2004; Stoll 2004). It has been argued that the risk of NEC should not be considered in isolation of these other potential clinical outcomes when determining feeding policies and practice for very preterm or VLBW infants (Flidel-Rimon 2006; Hay 2008; Hartel 2009).

This review focused on the comparison of delayed versus earlier introduction of progressive enteral feeding; that is, advancing the volume of milk feeds beyond minimal enteral nutrition levels. We addressed the effect of minimal enteral nutrition, the early introduction of small volume enteral feeds (up to 24 mL/kg/day) without advancing the feed volumes for at least five days versus enteral fasting in another Cochrane review (Morgan 2013a).

OBJECTIVES

To determine the effect of delayed introduction of progressive enteral feeds on the incidence of NEC, mortality and other morbidities in very preterm or VLBW infants.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials or cluster-randomised trials.

Types of participants

VLBW (less than 1500 g) or very preterm (less than 32 weeks' gestation) newborn infants.

Types of interventions

Delayed introduction (four or more days after birth) of progressive enteral feeds versus earlier introduction of enteral feeds. We defined progressive enteral feeding as the intention to advance feed volumes in excess of minimal enteral nutrition levels (24 mL/kg/day) within five days of commencement or by one week after birth.

Infants in each group should have received the same type of milk (breast milk or formula), the same route and mode of feeding (intra-gastric or transpyloric, bolus gavage or continuous) and the same rate of feed volume advancement in both groups.

Types of outcome measures

Primary outcomes

1. NEC confirmed by at least two of the following features:
 - a. abdominal radiograph showing pneumatosis intestinalis or gas in the portal venous system or free air in the abdomen;
 - b. abdominal distension with abdominal radiograph with gaseous distension or frothy appearance of bowel lumen (or both);
 - c. blood in stool;
 - d. lethargy, hypotonia or apnoea (or combination of these).

Or by a diagnosis confirmed at surgery or autopsy (Walsh 1986).

2. All-cause mortality during the neonatal period and prior to hospital discharge.

Secondary outcomes

3. Growth:
 - a. time to regain birth weight and subsequent rates of weight gain, linear growth, head growth or skinfold thickness growth up to six months (corrected for preterm birth);
 - b. long-term growth: weight, height or head circumference (with or without proportion of infants who remain below the 10th percentile for the index population's distribution) assessed at intervals from six months of age.
4. Neurodevelopment:
 - a. death or severe neurodevelopmental disability defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70),

auditory and visual impairment. Each component was analysed individually as well as part of the composite outcome;

b. neurodevelopmental scores in survivors aged 12 months or greater measured using validated assessment tools;

c. cognitive and educational outcomes in survivors aged more than five years old.

5. Time to establish full enteral feeding (independently of parenteral nutrition).

6. Time to establish oral feeding (independently of parenteral nutrition or enteral tube feeding, or both).

7. Feed intolerance (defined as a requirement to cease enteral feeds).

8. Incidence of invasive infection as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, urine or from a normally sterile body space.

9. Duration of hospital stay (days).

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group (neonatal.cochrane.org/).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2014, Issue 8), MEDLINE (1966 to September 2014), EMBASE (1980 to September 2014) and CINAHL (1982 to September 2014) using a combination of the following text words and MeSH terms: [Infant, Newborn OR Infant, Premature OR Infant, Low Birth Weight OR Infant, Very Low Birth Weight/ OR infan* OR neonat* OR preterm OR prem*] AND "Infant-Nutrition"/ all subheadings OR Infant Formula OR milk OR formula OR trophic feeding OR minimal enteral nutrition OR gut priming]. We limited the search outputs with the relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We applied no language restrictions.

We searched ClinicalTrials.gov (clinicaltrials.gov) and Current Controlled Trials (www.controlled-trials.com/) for completed or ongoing trials.

Searching other resources

We examined the references in all studies identified as potentially relevant.

We searched the abstracts from the annual meetings of the Pediatric Academic Societies (1993 to 2014), the European Society for Pediatric Research (1995 to 2014), the UK Royal College of Paediatrics and Child Health (2000 to 2014) and the Perinatal Society of Australia and New Zealand (2000 to 2013). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group (neonatal.cochrane.org/).

Selection of studies

Two review authors screened the title and abstract of all studies identified by the above search strategy. We assessed the full text of any potentially eligible reports and excluded those studies that did not meet all of the inclusion criteria. We discussed any disagreements until we achieved consensus.

Data extraction and management

We used a data collection form to aid extraction of relevant information from each included study. Two review authors extracted the data separately. We discussed any disagreements until we reached consensus. We contacted the investigators for further information if data from the trial reports were insufficient.

Assessment of risk of bias in included studies

We used the criteria and standard methods of the Cochrane Neonatal Review Group to assess the methodological quality of any included trials (neonatal.cochrane.org/). We requested additional information from the trial authors to clarify methodology and results as necessary. We evaluated and reported the following issues in the 'Risk of bias' tables:

- Sequence generation: we categorised the method used to generate the allocation sequence as:
 - low risk: any random process (e.g. random number table, computer random number generator);
 - high risk: any non-random process (e.g. odd or even date of birth, participant case-record number);
 - unclear risk.
- Allocation concealment: we categorised the method used to conceal the allocation sequence as:
 - low risk (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes);
 - high risk (e.g. open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
 - unclear risk.
- Blinding: we assessed blinding of participants, clinicians and carers, and outcome assessors separately for different outcomes and categorised the methods as:
 - low risk;
 - high risk;
 - unclear risk.
- Incomplete outcome data: we described the completeness of data including attrition and exclusions from the analysis for each outcome and any reasons for attrition or exclusion where reported. We assessed whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised completeness as:
 - low risk: less than 20% missing data;
 - high risk: 20% or greater missing data;
 - unclear risk.

Measures of treatment effect

We calculated risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CI). We planned to

determine the number needed to treat for an additional beneficial outcome (NNTB) or additional harmful outcome (NNTH) for any statistically significant differences in the RD.

Unit of analysis issues

The unit on analysis was the participating infant in individually randomised trials and the neonatal unit (or sub-unit) for cluster-randomised trials.

Assessment of heterogeneity

If we included more than one trial in a meta-analysis, we examined the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than sampling error. If we detected substantial (I^2 greater than 50%) heterogeneity, we explored the possible causes (e.g. differences in study design, participants, interventions or completeness of outcome assessments) in sensitivity analyses.

Data synthesis

We used the fixed-effect model in Review Manager 5 for meta-analysis (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses:

1. trials in which most infants were exclusively formula-fed;
2. trials in which most infants were at least partially fed with human milk (maternal or donor);
3. trials in which most participants were of ELBW (less than 1000 g) or extremely preterm (less than 28 weeks' gestation);
4. trials in which participants were infants with intrauterine growth restriction, or infants with absent or reversed end-diastolic flow velocities detected on antenatal Doppler studies of the fetal aorta or umbilical artery.

RESULTS

Description of studies

We identified 13 reports for screening.

Included studies

Nine trials fulfilled the review eligibility criteria: Ostertag 1986; Khayata 1987; Davey 1994; Karagianni 2010; Pérez 2011; Abdelmaaboud 2012; Leaf 2012; Armanian 2013; Arnon 2013 (see Characteristics of included studies table).

Population

A total of 1106 infants participated in the included trials.

The three smallest trials were undertaken in neonatal care centres in North America during the 1980s and early 1990s.

1. Ostertag 1986: 38 VLBW infants assessed to be at high risk of developing NEC.
2. Khayata 1987: 12 VLBW infants.

3. Davey 1994: 62 clinically stable preterm infants of birth weight less than 2000 g who had a low umbilical artery catheter *in situ*. Since most participants were of birth weight less than 1500 g or gestational age less than 32 weeks, we made a consensus decision to include the trial.

The six more recent trials were performed in the 2000s to 2010s.

1. Karagianni 2010: single-centre study in Greece, 84 infants less than 35 weeks' gestation with a birth weight less than 10th percentile and evidence of abnormal fetal blood flow patterns on Doppler ultrasound of the umbilical artery.
2. Pérez 2011: single-centre study in Columbia, 239 very preterm or VLBW infants.
3. Leaf 2012: 54-centre trial in the UK and Ireland, 404 infants (a) less than 35 weeks' gestation, (b) birth weight less than 10th percentile and (c) evidence of abnormal fetal blood flow patterns on Doppler ultrasound studies. Since most participants were of birth weight less than 1500 g, we made a consensus decision to include the trial.
4. Abdelmaaboud 2012: single-centre study in Qatar, 125 preterm infants with intrauterine growth restriction and abnormal Doppler flow patterns on ultrasound of the umbilical artery. Since most participants were of birth weight less than 1500 g, we made a consensus decision to include the trial.
5. Armanian 2013: single-centre study in Iran, 82 VLBW infants.
6. Arnon 2013: single-centre study in Israel, 60 small for gestation age preterm infants. Since most participants were of birth weight less than 1500 g, we made a consensus decision to include the trial.

Interventions/comparisons

1. Eight trials defined 'delayed' introduction of enteral feeds as later than day four to seven after birth (Ostertag 1986; Davey 1994; Karagianni 2010; Pérez 2011; Abdelmaaboud 2012; Leaf 2012; Armanian 2013; Arnon 2013) and one trial defined it as day 10 after birth (Khayata 1987).
2. 'Early' feeding varied from day one to four after birth.

In seven trials, infants received breast milk, artificial formula or a combination of the two (Davey 1994; Karagianni 2010; Pérez 2011; Abdelmaaboud 2012; Leaf 2012; Armanian 2013; Arnon 2013). In two trials, infants received only formula-feed (Ostertag 1986; Khayata 1987). Infants received enteral feeds by gavage at one- or two-hourly intervals in all of the trials except Ostertag 1986, where infants received feeds by continuous intragastric infusion. In Ostertag 1986, infants were initially fed with a sterile water infusion slowly progressing to a 2.5% dextrose solution followed by half-strength formula. They reached full-strength formula milk seven days after initiating enteral feeds.

All of the trial protocols, except that of the smallest trial (Khayata 1987), specified criteria and indications for advancing (daily increments of 15 to 30 mL/kg) or interrupting enteral feed (e.g. residual gastric contents not greater than 3 to 5 mL or one-third to one-half of the previous feed volume, frequent vomiting, abdominal distention or detection of blood in the stools).

Outcomes

Eight of the trials reported the incidence of NEC (confirmed radiologically, or at surgery or autopsy) (Ostertag 1986; Davey

1994; Karagianni 2010; Pérez 2011; Abdelmaaboud 2012; Leaf 2012; Armanian 2013; Arnon 2013). The other reported outcomes included mortality, time to establish full enteral feeding, growth and duration of hospital stay. Only two trials reported the incidence of invasive infection (Leaf 2012; Arnon 2013).

Excluded studies

We excluded eight studies after full-text screening (Higgs 1974; Glass 1984; LaGamma 1985; Wilson 1997; Weiler 2006; Said 2008;

Sanghvi 2013; Chetry 2014) (see Characteristics of excluded studies table).

Risk of bias in included studies

Quality assessments are described in the Characteristics of included studies table and summarised in Figure 1.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

The smallest trial (12 infants) was reported in abstract form only and methodological details were not described (Khayata 1987).

The other trials had various methodological weaknesses. In five trials, methods to ensure adequate allocation concealment were not described. None of the trials concealed the feeding strategies from parents, carers or clinical investigators. Complete or near-complete assessments of the primary outcomes were reported and data were available to undertake intention-to-treat analyses as required.

Effects of interventions

Primary outcomes

Necrotising enterocolitis (Outcome 1.1)

Meta-analysis did not detect a statistically significant effect (typical RR 0.93, 95% CI 0.64 to 1.34; typical RD -0.01, 95% CI -0.04 to 0.03; 8 trials; 1092 infants). There was no statistical evidence of heterogeneity (Figure 2).

Figure 2. Forest plot of comparison: 1 Delayed versus early introduction of progressive enteral feeding, outcome: 1.1 Necrotising enterocolitis.

Mortality prior to discharge (Outcome 1.2)

Meta-analysis did not detect a statistically significant effect (typical RR 1.18, 95% CI 0.75 to 1.88; typical RD 0.01, 95% CI -0.02 to

0.04; 7 trials, 967 infants). There was no statistical evidence of heterogeneity (Figure 3).

Figure 3. Forest plot of comparison: 1 Delayed versus early introduction of progressive enteral feeding, outcome: 1.2 Mortality prior to discharge.

Secondary outcomes

Growth

Two trials did not detect a statistically significant difference in the median time to regain birth weight:

1. Davey 1994: 13 days for both groups (range not reported; 62 infants);
2. Abdelmaaboud 2012: 13 days in the delayed group compared with 14 days in the early introduction group (range not reported; 125 infants).

Two trials did not detect statistically significant differences in the rate of weight gain but the reports did not provide data to allow quantitative synthesis (Khayata 1987; Pérez 2011).

None of the other trials reported hospital growth parameters.

None of the trials assessed any long-term (post-hospital discharge) growth parameters.

Neurodevelopment

None of the trials assessed neurodevelopmental outcomes.

Time to establish full enteral feeding

The median time to establish full enteral feeding was longer in the delayed introduction group but the reports did not provide data to allow quantitative synthesis:

1. Ostertag 1986: not reported;
2. Khayata 1987: not reported;
3. Davey 1994: three days;
4. Karagianni 2010: three days;
5. Pérez 2011: four days;
6. Abdelmaaboud 2012: two days;
7. Leaf 2012: three days;
8. Armanian 2013: five days;
9. Arnon 2013: three days.

Time to establish full oral feeding

None of the trials assessed time to establish full oral feeding.

Feed intolerance (Outcome 1.3)

Meta-analysis of data from three trials did not detect a statistically significant difference in feed intolerance (typical RR 0.84, 95% CI 0.62 to 1.15; typical RD -0.06, 95% CI -0.17 to 0.05; 288 infants; Figure 4) (Karagianni 2010; Abdelmaaboud 2012; Armanian 2013).

Figure 4. Forest plot of comparison: 1 Delayed versus early introduction of progressive enteral feeding, outcome: 1.3 Feed intolerance.

One trial did not detect a statistically significant difference but the report did not provide data to allow quantitative synthesis (Davey 1994).

None of the other trials reported the incidence of feed intolerance.

Incidence of invasive infection (Outcome 1.4)

Meta-analysis of data from two trials did not detect a statistically significant difference (typical RR 1.27, 95% CI 0.95 to 1.70; typical RD 0.07, 95% CI -0.01 to 0.15; 457 infants) (Leaf 2012; Arnon 2013).

Duration of hospital stay (Outcome 1.5)

Meta-analysis from three trials showed a statistically significant longer duration in the delayed feeding group (MD 2.11 days, 95% CI 0.31 to 3.90; 346 infants; Figure 5). The meta-analysis contained substantial heterogeneity (Chi² = 7.66; degrees of freedom (df) = 2; P value = 0.02; I² = 74%).

Figure 5. Forest plot of comparison: 1 Delayed versus early introduction of progressive enteral feeding, outcome: 1.5 Duration of hospital admission (days).

Another two trials did not detect a statistically significant effect but the reports did not provide data to allow quantitative synthesis (Abdelmaaboud 2012; Leaf 2012).

Subgroup analyses

- Two trials only recruited exclusively formula-fed infants (Ostertag 1986; Khayata 1987). Only Ostertag 1986 reported the effect on NEC (RR 1.08, 95% CI 0.40 to 2.94; RD 0.02, 95% CI -0.27 to 0.31; 38 infants) or mortality (RR 1.44, 95% CI 0.57 to 3.61; RD 0.12, 95% CI -0.18 to 0.42; 38 infants).
- Trials in which most infants were at least partially fed with human milk (maternal or donor): subgroup data not available.
- ELBW or extremely preterm infants: none of the trials recruited predominantly ELBW or extremely preterm infants.
- Four trials recruited only infants with intrauterine growth restriction and abnormal flow velocities detected on antenatal Doppler studies (Karagianni 2010; Abdelmaaboud 2012; Leaf 2012; Arnon 2013). Meta-analysis did not detect any statistically significant differences in the incidence of NEC (typical RR 0.87, 95% CI 0.54 to 1.41; typical RD -0.01, 95% CI -0.06 to 0.03; 673 infants; Figure 2) or mortality (typical RR 1.06, 95% CI 0.55 to 2.05; typical RD 0.00, 95% CI -0.04 to 0.05; 548 infants; Figure 3).

DISCUSSION

Summary of main results

Analyses of data from nine randomised controlled trials with 1106 infants did not provide evidence that delayed introduction of progressive enteral feeds reduced the risk of NEC. The boundaries of the 95% CI for the estimate of effect are consistent with either four fewer or three extra cases of NEC in every 100 infants who had delayed introduction of progressive enteral feeds. Meta-analysis of data from these trials did not indicate an effect on all-cause mortality with the 95% CI boundaries being consistent with either two fewer or four more deaths in every 100 infants who had delayed introduction of progressive enteral feeds. Similarly, pre-specified subgroup meta-analyses showed no effect of delayed introduction of enteral feeds on NEC or mortality in infants with growth restriction or antenatal evidence of absent end-diastolic flow velocities.

Infants who had delayed introduction of feeds achieved full enteral feeding several days later than infants who had earlier introduction. Whether this was associated with important clinical adverse consequences, such as a higher rate of nosocomial infection secondary to prolonged use of parenteral nutrition or a longer duration of hospital admission, remains unclear.

Overall completeness and applicability of evidence

These data are relevant to current practice since most of the included trials were conducted in the 2000s with infants receiving 'modern' antenatal care including exposure to antenatal corticosteroids and exogenous surfactant, interventions that reduce the risk of NEC or death in this population (Roberts 2006; Seger 2009; Soll 2009; Soll 2010). Four of these trials specifically recruited infants thought to be at higher risk of developing NEC due to intrauterine growth restriction and abnormal fetal circulatory distribution or flow. This widens the applicability of the findings since this is the population for which most clinical uncertainty and variation in practice with regard to early feeding strategies exists (Boyle 2004). Previously, this population of infants has been specifically excluded from participating in many trials of early enteral feeding practices (Tyson 2007).

Evidence exists that artificial formula feeding increases the risk NEC (Quigley 2014). The risk-benefit balance of enteral feeding strategies may differ between human milk-fed and formula-fed very preterm or VLBW infants. Currently there are insufficient data to comment on whether there is a differential effect of the timing of the introduction of enteral feeds depending on whether infants received human breast milk versus formula.

It is also unclear whether the findings can be applied to infants who receive continuous infusion of intragastric feeds, as most of the infants in the included trials received enteral feeds as interval gastric boluses. Randomised controlled trials have reported conflicting findings about the effect on continuous enteral infusion on feed tolerance in VLBW (and especially ELBW) infants (Premji 2011).

Most of the included trials were undertaken in neonatal care centres in middle- or high-income countries. It is less clear how applicable this evidence is to neonatal care practices in low-income countries. Conservative strategies, such as delayed introduction of enteral feeds, may confer substantial nutritional disadvantage in settings with less technologically developed healthcare provision where adjunctive parenteral nutrition is not readily and safely available. In some low- or middle-income countries where severe infection (diarrhoea, pneumonia, septicaemia) is a much more important cause of mortality and morbidity, the nutritional and immunological advantages of early feeding, particularly with breast milk, may outweigh any risks associated with enteral feeding for very preterm or VLBW infants (Narayanan 1981; de Silva 2004). We identified two feasibility trials undertaken in India in the late 2000s/early 2010s that compared exclusive enteral feeding (no parenteral fluid) from birth with gradual introduction of enteral feeds over several days in VLBW infants with birth weight greater than 1000 g

(Sanghvi 2013; Chetry 2014). While these trials were not eligible for inclusion in this review, neither found evidence of an effect on NEC or other adverse outcomes.

Quality of the evidence

The included trials were generally of reasonable methodological quality but, in common with other trials of feeding interventions in this population, it was not possible to mask carers and clinical assessors to the nature of the intervention. Although the lack of blinding may have resulted in surveillance and ascertainment biases, this is more likely to have caused an underestimation of the incidence of NEC in infants whose enteral feeding was delayed. The assessment of abdominal radiographs was masked in three studies to ensure that the diagnosis of stage II/III NEC (confirmed by the radiological detection of gas in the bowel wall or portal tract) was not prone to bias. However, since the microbial generation of gas in the bowel wall is substrate dependent, infants who received more enteral milk (substrate) may have been more likely to demonstrate this radiological sign than infants with equally severe bowel disease who had less intraluminal substrate. This 'substrate effect' is also more likely to cause under-ascertainment of NEC in the infants whose enteral feeding was delayed (Tyson 2007).

Potential biases in the review process

The definition of delayed introduction of progressive feeds may vary between different subpopulations of very preterm or VLBW infants who have different empiric risks for developing feed intolerance and NEC. The effects of enteral feeding are likely to be very different for a mechanical ventilator-dependent or inotrope-dependent infant of birth weight less than 700 g compared with a clinically stable infant of birth weight greater than 1400 g. For this Cochrane review, we defined delayed introduction as later than four days after birth since some observational studies have found the risk of NEC to be lower when feeds are introduced five to seven days after birth (Patole 2005). For ELBW or extremely preterm infants, it may be more appropriate to define delayed introduction as more than seven days after birth (or even later). Small-intestinal motility is poorly organised before about 28 weeks' gestation resulting in a higher risk of feed intolerance. In addition, enteral feeds are often delayed in this population because of respiratory or metabolic instability or because of other putative risk factors for NEC, such as the existence of a patent ductus arteriosus, the use of non-steroidal anti-inflammatory drugs or the presence of an umbilical arterial catheter (Boyle 2004).

AUTHORS' CONCLUSIONS

Implications for practice

The available data from randomised controlled trials do not provide evidence that delaying the introduction of progressive enteral feeds beyond four days after birth reduces the risk of necrotising enterocolitis (NEC), mortality, and other morbidities in very preterm or very low birth weight (VLBW) infants. Delaying the introduction of progressive enteral feeds may result in several days' delay in establishing full enteral feeds but the long-term clinical importance of these effects is unclear. Subgroup analyses of trials in which participating infants had evidence of intrauterine growth restriction or abnormal circulatory distribution or flow did not find any statistically significant effects. However, only limited data are available on the effect of this intervention on outcomes for extremely preterm or extremely low birth weight (ELBW) infants.

Implications for research

Further randomised controlled trials of delayed versus early introduction of progressive enteral feeds could provide more precise estimates of the effects on important outcomes for extremely preterm or ELBW infants. With regard to stable VLBW infants with birth weight greater than 1000 g (or very preterm infants with gestational age 28 to 31 weeks), the key research question is now whether exclusive enteral feeding from birth is better than gradual introduction.

Masking carers and investigators to the nature of this intervention is unlikely to be possible. Since the unblinded evaluation of feed intolerance and NEC is subject to surveillance and ascertainment biases, trials could aim to assess more objective outcomes, principally mortality and long-term growth and development. Furthermore, since conservative feeding strategies may result in other 'competing outcomes', such as invasive infection that may affect long-term survival and neuro-disability rates, it is essential that trials are powered and structured to assess these outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abdelmaaboud 2012

Methods	Randomised controlled trial
Participants	<p>Preterm infants, 28-36 weeks' gestation with birth weight < 10th centile, antenatal ultrasound showing intrauterine growth restriction, absent or reversed end diastolic flow on Doppler waveforms of the umbilical artery with evidence of cerebral redistribution, arterial cord pH $\geq$ 7.0 and base deficit $\geq$ -12 and 5-minute Apgar score of > 5.</p> <p>Infants were excluded if there was any major congenital abnormality, twin-twin transfusion, intrauterine transfusion, exchange transfusion, rhesus iso-immunisation, significant multi-organ failure, inotropic drug support or minimal enteral feeding had already started</p> <p>Setting: single centre: Women's Hospital, Hamad Medical Corporation, Qatar</p>
Interventions	Early introduction of progressive enteral feeds on day 3 (62 infants) versus late introduction of enteral feeds on day 6 (63 infants)
Outcomes	Incidence of NEC (stage II/III), time to reach full enteral feeds (sustained for 72 hours), rates of feed intolerance, mortality and duration of hospital stay
Notes	> 90% of participants were VLBW

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated tables
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Clinical assessments	High risk	Carers not blinded to intervention group
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	No information on blinding of radiological assessors to intervention groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment

Armanian 2013

Methods	Randomised controlled trial
Participants	VLBW infants Infants were excluded if there was a congenital abnormality Setting: Isfahan Faculty of Medicine, Iran
Interventions	Delayed introduction of progressive enteral feeds (only minimal volumes until day 7 (47 infants) versus early introduction on day 3 (35 infants) Infants received either unfortified breast milk or formula (no subgroup data available). Volumes and rates of advancement or progressive feeds were the same in both groups (20 mL/kg/day)
Outcomes	Incidence of NEC, mortality, days to full enteral feeds, duration of hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Clinical assessments	High risk	Carers not blinded to intervention group
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	No information on blinding of radiological assessors to intervention groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment

Arnon 2013

Methods	Randomised controlled trial
Participants	Preterm infants, birth weight < 10th centile*, and antenatal evidence of absent or reversed end diastolic flow on Doppler waveforms of the umbilical artery Infants were excluded if there was a major congenital abnormality, receipt of mechanical ventilation or enteral feeding had already started Setting: single centre: Meir Medical Centre, Kfar Saba, Tel Aviv, Israel
Interventions	Delayed progressive enteral feeding (day 4-5 after birth, 30 infants) versus earlier enteral feeding (day 2 after birth, 30 infants)

Arnon 2013 (Continued)

Infants received expressed breast or formula or both

Outcomes	Incidence of NEC, mortality, nosocomial infection, days to reach full enteral feeds, duration of hospital stay
Notes	*Most participants were VLBW (range 963-1683 g) Original study published in Portuguese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Clinical assessments	High risk	Carers not blinded to intervention group
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	No information on blinding of radiological assessors to intervention groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment

Davey 1994

Methods	Randomised controlled trial
Participants	62 preterm infants with birth weight < 2000 g who were clinically stable and who had an umbilical artery catheter in place Infants were excluded if they had a lethal condition or had received a double-volume exchange transfusion Setting: Division of Neonatology, Department of Pediatrics, University of Rochester Medical Center, US
Interventions	Delayed introduction of enteral feeds (median 5 days; 31 infants) versus earlier introduction (median 2 days; 31 infants) Infants received either breast milk or diluted formula (no subgroup data available). Volumes and rates of advancement were the same in both groups
Outcomes	Days to regain birth weight, days to full enteral feeding, duration of hospital stay, incidence of NEC and mortality
Notes	The trial inclusion criterion for birth weight was < 2000 g. Since > 80% of infants were VLBW or very preterm, we decided to include the trial

Davey 1994 (Continued)

Infants in the delayed introduction group commenced enteral feeds when the umbilical artery catheter had been removed for 24 hours and the infant was clinically stable. Infants in the earlier introduction group commenced feeds with the umbilical artery catheter in situ

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation method not reported
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) Clinical assessments	High risk	Not stated but unlikely that carers were blinded to intervention groups
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial excluded 2 infants in the early introduction group post-randomisation due to protocol violation. All other participants were accounted for

Karagianni 2010

Methods	Randomised controlled trial
Participants	<p>84 singleton newborn infants of gestational age 27- 34 weeks' and birth weight < 10th percentile who also had antenatal Doppler ultrasound evidence within 7 days before birth of 'pathological fetal perfusion', defined as uterine or umbilical arterial pulsatility index > 90th percentile and middle cerebral arterial pulsatility index < 10th percentile for gestational age</p> <p>Infants were excluded with a major congenital anomaly or infection or had received exchange transfusion or inotrope support</p> <p>Setting: Neonatology Department, Aristotle University, Thessaloniki, Greece</p>
Interventions	<p>Delayed (> 5 days after birth; 42 infants) versus early ($\leq$ 5 days; 42 infants) introduction of enteral feeds (expressed breast milk or preterm formula milk)</p> <p>Minimal enteral feeding was continued until day 7 after birth and then feed volumes were advanced at daily targeted increments of 15 mL/kg</p>
Outcomes	Incidence of NEC, mortality*, days to full enteral feeds*, duration of hospital stay*
Notes	<p>*Unpublished data courtesy of Dr Karagianni</p> <p>Of the 84 infants enrolled, 81 completed the study. 3 infants died before 5 days after birth. We have included these infants in the intention-to-treat analysis of mortality > 90% of infants were VLBW</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Karagianni 2010 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding (performance bias and detection bias) Clinical assessments	High risk	Carers and clinical assessors not blinded to allocation groups
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	No information available about blinding of radiological assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were included in the analyses

Khayata 1987

Methods	Randomised controlled trial
Participants	12 VLBW infants
Interventions	Delayed introduction of enteral feeds (day 10 after birth; 7 infants) versus earlier introduction (< 4 days; 5 infants) All infants received standard calorie formula. Volumes and rates of advancement were the same in both groups
Outcomes	Growth during the first 6 weeks after birth
Notes	This trial was reported as an abstract only. Further (unpublished) methodological or outcome data were not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) Clinical assessments	High risk	Not described but unlikely to be blinded
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	Not described

Khayata 1987 (Continued)

All outcomes

Leaf 2012

Methods	Randomised controlled trial
Participants	<p>404 preterm infants < 35 weeks' gestation and birth weight < 10th percentile and antenatal Doppler ultrasound evidence of:</p> <ol style="list-style-type: none"> 1. absent or reversed end diastolic flow velocities on at least 50% of the Doppler waveforms from the umbilical artery on at least 1 occasion during pregnancy <p>or</p> <ol style="list-style-type: none"> 2. 'cerebral redistribution', defined as occurring when both the umbilical artery pulsatility index > 95th percentile and the middle cerebral artery pulsatility index < 5th percentile for gestational age (Her-shkovitz 2000) <p>Infants were excluded with a major congenital anomaly, receipt of in-utero transfusion, multi-organ failure or need for inotrope support</p> <p>Setting: 54 neonatal care centres in UK and Ireland</p>
Interventions	<p>Delayed (day 5 after birth; 202 infants) versus early (day 2 after birth; 202 infants) introduction of milk feeds</p> <p>Protocol for advancing feed volumes was the same in both groups</p>
Outcomes	Days to full feeds (150 mL/kg/day) sustained for 3 days, incidence of NEC (all stages, and stage II/III), mortality, invasive infection, time to regain birth weight, duration of hospital stay
Notes	> 90% of infants were VLBW

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Central telephone randomisation
Blinding (performance bias and detection bias) Clinical assessments	High risk	Carers were not blinded to the allocation groups
Blinding (performance bias and detection bias) Radiological assessments	Low risk	All cases of NEC were reviewed independently by a committee that were blinded to the study groups
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 infants (1 from each group) were excluded from the trial after randomisation occurred (error in recruitment and consent withdrawal)

Ostertag 1986

Methods	Randomised controlled trial
Participants	38 VLBW infants assessed to be at 'high risk' of developing NEC based on a risk assessment score Setting: Perinatology Center, New York Hospital-Cornell Medical Center, New York, USA
Interventions	Delayed introduction of enteral feeds (day 7 after birth; 20 infants) versus earlier introduction (day 1; 18 infants) Infants received feeds by continuous intragastric infusion starting initially with sterile water, then progressing to 2.5% dextrose, diluted formula, then full-strength standard calorie formula milk. Volumes and rates of advancement were the same in both groups: constant infusion at 1 mL/hour for 7 days then daily increments of 10 mL/kg/day
Outcomes	Incidence of NEC and mortality
Notes	Further details about exclusions after randomisation kindly provided by Dr La Gamma (March 2009)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) Clinical assessments	High risk	Carers not blinded to allocation groups
Blinding (performance bias and detection bias) Radiological assessments	Low risk	Radiologists reviewing abdominal films were blinded to the group assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 infants died before 7 days after birth. The investigators excluded 1 infant before day 14 because of a feeding protocol violation. We have included all of these infants in the relevant intention-to-treat analyses

Pérez 2011

Methods	Randomised controlled trial
Participants	239 very preterm or VLBW infants. Included infants had not received any previous enteral feeds Infants were excluded with congenital anomalies of the gastrointestinal tract, intrauterine growth restriction and respiratory or haemodynamic instability Setting: Ramón González Valencia de Bucaramanga University Hospital, Columbia
Interventions	Delayed enteral feeding (day 5 after birth, 104 infants) versus earlier enteral feeding (day 1-2 after birth, 135 infants) All infants received a combination of breast and formula milk. Feed volumes exceeded trophic volumes by the third day of enteral feeding

Pérez 2011 (Continued)

Outcomes	Incidence of NEC, mortality, duration of hospital stay, growth, days to reach full feeds (150 mL/kg/day)
Notes	Original study published in Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described (states "randomly assigned", and "controlled clinical trial")
Allocation concealment (selection bias)	Low risk	Not described
Blinding (performance bias and detection bias) Clinical assessments	High risk	Carers or investigators not blinded to allocation groups
Blinding (performance bias and detection bias) Radiological assessments	Low risk	Abdominal radiographs interpreted by radiologist who was independent from the study and blind to the allocation groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment for primary outcomes

NEC: necrotising enterocolitis; VLBW: very low birth weight.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chetry 2014	Both groups received early enteral feeds
Glass 1984	Infants were allocated alternately to either early (first day after birth) or delayed transpyloric enteral feeding. The delayed feeding group commenced enteral nutrition when assessed to be "clinically stable" but this included initiation within 4 days after birth
Higgs 1974	Infants in the delayed progressive enteral feeds group received total parenteral nutrition as a co-intervention
LaGamma 1985	This was not a randomised controlled trial
Said 2008	Infants in the delayed progressive enteral feeding group received minimal enteral nutrition prior to feed advancement as a co-intervention
Sanghvi 2013	Both groups received early enteral feeds
Weiler 2006	Infants in both groups received some enteral feeds before 4 days after birth
Wilson 1997	Infants in the delayed progressive enteral feeds group also received delayed advancement of parenteral nutrition as a co-intervention

DATA AND ANALYSES

Comparison 1. Delayed versus early introduction of progressive enteral feeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Necrotising enterocolitis	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All trials	8	1092	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.64, 1.34]
1.2 Trials of infants with intrauterine growth restriction or abnormal antenatal Doppler flow velocities	4	673	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.54, 1.41]
2 Mortality prior to discharge	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 All trials	7	967	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.75, 1.88]
2.2 Trials of infants with intrauterine growth restriction or abnormal antenatal Doppler flow velocities	3	548	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.55, 2.05]
3 Feed intolerance	3	288	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.62, 1.15]
4 Incidence of invasive infection	2	457	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.95, 1.70]
5 Duration of hospital admission (days)	3	346	Mean Difference (IV, Fixed, 95% CI)	2.11 [0.31, 3.90]

Analysis 1.1. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 1 Necrotising enterocolitis.

Analysis 1.2. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 2 Mortality prior to discharge.

Analysis 1.3. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 3 Feed intolerance.

Analysis 1.4. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 4 Incidence of invasive infection.

Analysis 1.5. Comparison 1 Delayed versus early introduction of progressive enteral feeding, Outcome 5 Duration of hospital admission (days).

WHAT'S NEW

Date	Event	Description
3 October 2014	New citation required but conclusions have not changed	Updated search in September 2014 identified two new trials for inclusion in this review update (Armanian 2013; Arnon 2013).
3 October 2014	New search has been performed	This updates the review "Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants" (Morgan 2013b).

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 1998

Date	Event	Description
13 January 2011	New search has been performed	<p>This updates the review "Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants" published in the Cochrane Database of Systematic Reviews, Issue 2, 2008 (Bombell 2008).</p> <p>Updated search includes three new trials (Ostertag 1986; Kara-gianni 2010; Leaf 2012).</p> <p>New authorship for this review update.</p>
13 January 2011	New citation required and conclusions have changed	The addition of new trial data has increased the total number of participating infants to 600 and modified the implications for practice and research.
2 February 2008	New search has been performed	<p>This updates the review "Early versus delayed initiation of progressive enteral feedings for parenterally fed low birth weight or preterm infants" published in the Cochrane Database of Systematic Reviews, Issue 1, 2000 (Kennedy 2000).</p> <p>The title has been changed to "Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants" and has a new authorship of Sarah Bombell and William McGuire. Changes made to the original protocol are outlined below:</p> <ol style="list-style-type: none"> 1. Introduction of progressive enteral feeds is defined as feed volumes more than 24 ml/kg/day (1 ml/kg/hour). 2. The population has been restricted to very low birth weight and very preterm infants 3. Subgroup analyses of extremely low birth weight and extremely preterm infants, and infants with evidence of intrauterine growth restriction or absent or reversed end-diastolic flow velocities in Doppler studies of the fetal aorta or umbilical artery were prespecified. <p>Search updated December 2007. No new trials were included, but one on-going trial was identified.</p> <p>The findings and implications for practice and research of the review have not changed overall.</p>
11 January 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Lauren Young and William McGuire updated the search, independently determined the eligibility of identified studies, assessed the methodological quality of the included trials, and extracted the relevant information and data.

All authors completed the final review.

DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Low Birth Weight; *Infant, Premature; Cause of Death; Enteral Nutrition [*methods]; Enterocolitis, Necrotizing [*prevention & control]; Infant, Extremely Low Birth Weight; Infant, Extremely Premature; Infant, Very Low Birth Weight; Parenteral Nutrition; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Humans; Infant, Newborn