Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants (Review)

Morgan J, Young L, McGuire W

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 3

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants

Jessie Morgan[1], Lauren Young[1], William McGuire[1]

[1]Hull York Medical School & Centre for Reviews and Dissemination, University of York, York, UK

Contact address: William McGuire, Hull York Medical School & Centre for Reviews and Dissemination, University of York, York, Y010 5DD, UK. William.McGuire@hyms.ac.uk.

Editorial group: Cochrane Neonatal Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 3, 2013.
Review content assessed as up-to-date: 28 December 2012.

Citation: Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database of Systematic Reviews* 2013, Issue 3. Art. No.: CD001241. DOI: 10.1002/14651858.CD001241.pub4.

ABSTRACT

Background

Early enteral feeding practices are potentially modifiable risk factors for necrotising enterocolitis in very preterm or very low birth weight (VLBW) infants. Observational studies suggest that conservative feeding regimens that include slowly advancing enteral feed volumes reduce the risk of necrotising enterocolitis. However, slow feed advancement may delay establishment of full enteral feeding and be associated with metabolic and infectious morbidities secondary to prolonged exposure to parenteral nutrition.

Objectives

To determine the effect of slow rates of enteral feed advancement on the incidence of necrotising enterocolitis, mortality and other morbidities in very preterm or VLBW infants.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 12), MEDLINE, EMBASE and CINAHL (to December 2012), conference proceedings, and previous reviews.

Selection criteria

Randomised or quasi-randomised controlled trials that assessed the effect of slow (up to 24 ml/kg/day) versus faster rates of advancement of enteral feed volumes upon the incidence of necrotising enterocolitis in very preterm or VLBW infants.

Data collection and analysis

Data collection and analysis was performed using the standard methods of the Cochrane Neonatal Review Group.

Main results

We identified five randomised controlled trials in which a total of 588 infants participated. Few participants were extremely preterm, extremely low birth weight or growth restricted. The trials defined slow advancement as daily increments of 15 to 20 ml/kg and faster advancement as 30 to 35 ml/kg. Meta-analyses did not detect statistically significant effects on the risk of necrotising enterocolitis (typical risk ratio (RR) 0.97, 95% confidence interval (CI) 0.54 to 1.74) or all-cause mortality (RR 1.41, 95% CI 0.81 to 2.74). Infants who had slow advancement took significantly longer to regain birth weight (reported median differences two to six days) and to establish full enteral feeding (two to five days).

Authors' conclusions

The available trial data suggest that advancing enteral feed volumes at slow rather than faster rates does not reduce the risk of necrotising enterocolitis in very preterm or VLBW infants. Advancing the volume of enteral feeds at slow rates results in several days delay in regaining birth weight and establishing full enteral feeds but the long term clinical importance of these effects is unclear. The applicability of these findings to extremely preterm, extremely low birth weight or growth restricted infants is limited. Further randomised controlled trials in these populations may be warranted to resolve this uncertainty.

PLAIN LANGUAGE SUMMARY

Slowly advancing milk feeds does not reduce the risk of necrotising enterocolitis in very low birth weight infants

Very preterm (< 32 weeks) or very low birth weight infants (< 1500 grams) are at risk of developing a severe bowel disorder called 'necrotising enterocolitis'. It is thought that one possible way to prevent this condition is to limit the amount of milk feeds that infants receive each day for the first few weeks after birth. Five randomised controlled trials have assessed the effect of slowly (rather than more quickly) increasing the volume of milk feeds given to very preterm or very low birth weight infants. Analysis of these trials did not reveal any effect on the risk of necrotising enterocolitis. Infants fed more slowly regained birth weight and attained full enteral feeding several days later than infants fed more quickly.

BACKGROUND

Description of the condition

Necrotising enterocolitis (NEC), a syndrome of acute intestinal necrosis of unknown aetiology, affects about 5% of very preterm (< 32 weeks) or very low birth weight (VLBW) (< 1500 grams) infants (Holman 1997). The associated mortality rate is > 20%. Infants who develop NEC experience more nosocomial infections, have lower levels of nutrient intake, grow more slowly, and have longer durations of intensive care and hospital stay than gestation-comparable infants who do not develop NEC (Bisquera 2002; Guthrie 2003). NEC 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 (Stoll 2004; Soraisham 2006; Rees 2007; Pike 2012).

Description of the intervention

Short gestational age at birth is the major clinical risk factor for developing NEC (Beeby 1992; Luig 2005). The other putative major risk factor is intrauterine growth restriction, especially if associated with absent or reversed end-diastolic flow velocities in Doppler studies of the fetal aorta or umbilical artery (Bernstein 2000; Garite 2004; Dorling 2005). 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 2007). Other differences in enteral feeding regimens, such as the timing of introduction of feeds and the size of the daily volume increments, may also contribute to inter-unit variation in the incidence of NEC. Multicentre benchmarking studies have found that those neonatal centres where enteral feeding is introduced earlier and feeding volumes advanced more quickly tend to have higher incidences of NEC (Uauy 1991). Observational studies have suggested that delaying the introduction of enteral feeds beyond the first few days after birth, or increasing the volume of feeds by less than about 24 ml/kg body weight each day, may be associated with a lower risk of developing NEC in very preterm or VLBW infants (Brown 1978; McKeown 1992; Patole 2005; Henderson 2009).

Why it is important to do this review

There are potential disadvantages associated with slowing the advancement of enteral feed volumes, such as delaying the establishment of full enteral nutrition (Flidel-Rimon 2004). Prolonged use of parenteral nutrition is associated with infectious and metabolic risks that may have adverse consequences for survival, growth, and development (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; Chauhan 2008; Hartel 2009).

Other Cochrane reviews address the questions of whether delaying the introduction of any enteral milk feeding or restricting feed volumes to trophic levels (minimal enteral nutrition) affect the risk of NEC in very preterm or VLBW infants (Bombell 2009; Morgan 2011). This review focused on the question of whether advancing feed volumes at slow rates compared to faster rates affects the risk of NEC, mortality and other morbidities.

OBJECTIVES

To determine the effect of slow rates of enteral feed advancement 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

Controlled trials utilising either random or quasi-random patient allocation.

Types of participants

Enterally-fed very preterm (< 32 weeks) or VLBW (< 1500 grams) newborn infants.

Types of interventions

Advancement of enteral feeds at no more than 24 ml/kg (birth weight or current body weight) per day versus faster rates of feeds advancement. Infants should have received the same type of milk and in both groups the advancement of feed volume should have commenced within five days of introduction of enteral feeds.

Types of outcome measures

Primary outcomes

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

or 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.

(i) 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).

(ii) Long-term growth: weight, height, or head circumference (or proportion of infants who remained below the 10th percentile for the index population's distribution) assessed at intervals from six months of age.

4. Neurodevelopment.

(i) Death or severe neurodevelopmental disability defined as any one or a combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment. Each component was to be analysed individually as well as part of the composite outcome.

(ii) Neurodevelopmental scores in survivors aged greater than, or equal to, 12 months of age measured using validated assessment tools.

(iii) Cognitive and educational outcomes in survivors aged more than five years.

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 (http://neonatal.cochrane.org/).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 12), MEDLINE (1966 to December 2012), EMBASE (1980 to December 2012), and CINAHL (1982 to December 2012) 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]. The search outputs were limited with the relevant search filters for clinical trials. We did not apply a language restriction.

We searched ClinicalTrials.gov and Current Controlled Trials for completed or ongoing trials.

Searching other resources

We examined the reference lists in all studies identified as potentially relevant.

We searched the abstracts from the annual meetings of the Pediatric Academic Societies (1993 to 2012), the European Society for Pediatric Research (1995 to 2012), the UK Royal College of Paediatrics and Child Health (2000 to 2012), and the Perinatal Society of Australia and New Zealand (2000 to 2012). 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 (http://neonatal.cochrane.org/).

Selection of studies

Two review authors screened the titles and abstracts of all studies identified by the above search strategy. We assessed the full texts of any potentially eligible reports and those studies that did not meet all of the inclusion criteria were excluded. We discussed any disagreements until consensus was achieved.

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. Any disagreements were discussed until consensus was achieved. 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. Additional information from the trial authors was requested to clarify methodology and results as necessary. We evaluated and reported the following issues in the 'Risk of bias' tables.

1. Sequence generation. We categorised the method used to generate the allocation sequence as:
   i) low risk, any random process e.g. random number table; computer random number generator;
   ii) high risk, any non-random process e.g. odd or even date of birth; patient case-record number;
   iii) unclear.
2. Allocation concealment. We categorised the method used to conceal the allocation sequence as:
   i) low risk, e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes;
   ii) high risk, open random allocation; unsealed or non-opaque envelopes; alternation; date of birth;
   iii) unclear.
3. Blinding. We assessed blinding of participants, clinicians and caregivers, and outcome assessors separately for different outcomes and categorised the methods as:
   i) low risk;
   ii) high risk;
   iii) unclear.
4. 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:
   i) low risk, < 20% missing data;
   ii) high risk, $\geq$ 20% missing data;
   iii) unclear.

Measures of treatment effect

We calculated risk ratio (RR) and risk difference (RD) for dichotomous data and weighted mean difference (WMD) for continuous data, with respective 95% confidence intervals (CI). The number needed to treat for benefit (NNTB) or harm (NNTH) was determined for a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials and the neonatal unit (or subunit) for cluster randomised trials.

Assessment of heterogeneity

If more than one trial was included in a meta-analysis, we examined the treatment effects of individual trials and the 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

substantial (I^2 > 50%) heterogeneity was detected, we explored the possible causes (for example differences in study design, participants, interventions, or completeness of outcome assessments) in sensitivity analyses.

Data synthesis

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

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 extremely low birth weight (ELBW) (< 1000 grams) or extremely preterm gestational age (< 28 weeks);
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

See: Characteristics of included studies; Characteristics of excluded studies.

Five randomised controlled trials fulfilled the review eligibility criteria: Rayyis 1999; Caple 2004; Salhotra 2004; Krishnamurthy 2010 (see Characteristics of included studies).

Included studies

Population

A total of 588 infants participated in the five included trials. The trials were undertaken in neonatal care centres in North America (Rayyis 1999; Caple 2004), India (Salhotra 2004; Krishnamurthy 2010) and Turkey (Karagol 2012) within the past 10 to 15 years. All of the trials specified participant birth weight eligibility criteria:

- Rayyis 1999 < 1500 grams;
- Caple 2004 1000 to 2000 grams;
- Salhotra 2004 < 1250 grams;
- Krishnamurthy 2010 1000 to 1500 grams;
- Karagol 2012 750 to 1250 grams.

Since most participants in Caple 2004 were of birth weight < 1500 grams or gestational age < 32 weeks, a consensus decision to include the trial was made. Infants born 'small for gestational age' (birth weight < 10th percentile of the index population's distribution) were not eligible to participate in Caple 2004 but were included in the other trials. More than 95% of the participants in Salhotra 2004 were 'small for gestational age'. One third of participants in Karagol 2012 were ELBW infants.

Interventions and comparisons

All trials commenced interval bolus intragastric feeding within one to five days after birth. Infants were randomly allocated to one of two rates of daily increments in enteral feed volume:

- Rayyis 1999 15 versus 35 ml/kg/day;
- Caple 2004 20 versus 35 ml/kg/day;
- Salhotra 2004 15 versus 30 ml/kg/day;
- Krishnamurthy 2010 20 versus 30 ml/kg/day;
- Karagol 2012 20 versus 30 ml/kg/day.

In one trial, only formula-fed infants were eligible to participate (Rayyis 1999). In Caple 2004, Krishnamurthy 2010 and Karagol 2012 infants received either expressed breast milk or formula, or a combination of both. In Salhotra 2004, all participating infants were exclusively fed with expressed breast milk. All of the trial protocols specified indications for interrupting or ceasing enteral feeding such as residual gastric contents of more than about one-third of the previous feed volume, frequent vomiting, abdominal distention, or detection of blood in the stools (including occult blood).

Outcomes

All of the trials reported the incidence of NEC (Bell stage II/III) confirmed radiologically, or at surgery or autopsy. The other reported outcomes included time to regain birth weight, time to establish full enteral feeding, duration of hospital stay and rates of invasive infection.

Excluded studies

Two trials were excluded (Book 1976; Berseth 2003) (see Characteristics of excluded studies). In Book 1976, enteral feeding volumes were advanced at 10 ml/kg/day versus 20 ml/kg/day, that is both groups received 'slow' advancement of feed volumes. In Berseth 2003, infants were randomly allocated to either a stable (not progressively increased) trophic feeding volume or to feed volume advancement at 20 ml/kg/day.

Risk of bias in included studies

The methodological quality of the included trials was generally good. In all five trials, methods to ensure adequate allocation concealment were employed and complete or near-complete assessments of the primary outcomes were reported. None of the trials were able to conceal the feeding strategies from parents, caregivers or clinical investigators. The assessment of abdominal radiographs (for diagnosis of NEC) was clearly masked in three studies. In Salhotra 2004 and Karagol 2012 it was unclear whether precautions had been taken to ensure that radiological assessors were blinded to the allocation group.

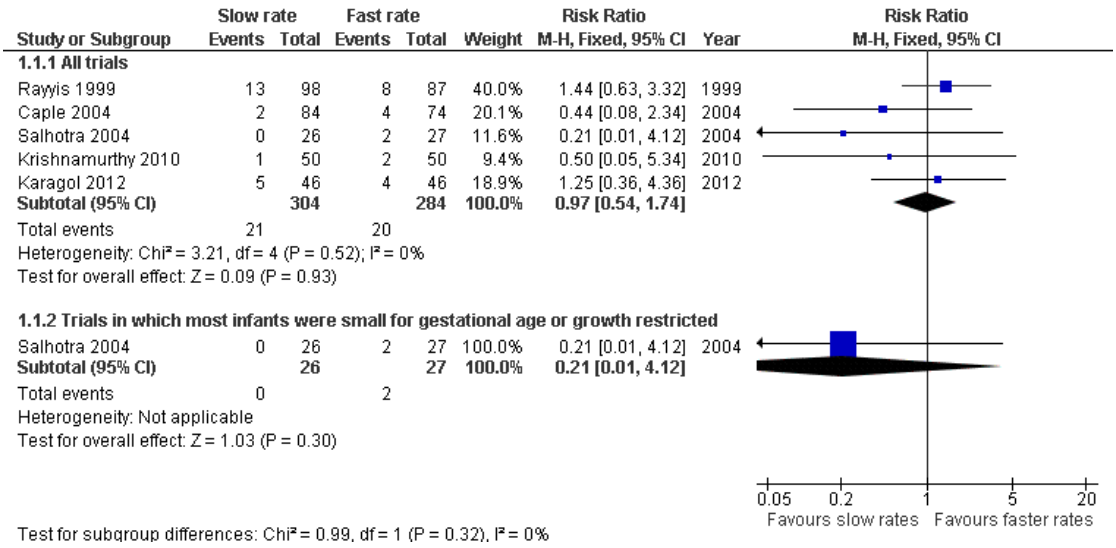
Effects of interventions

Primary outcomes

Incidence of necrotising enterocolitis (Outcome 1.1)

Meta-analysis did not detect a statistically significant effect: typical RR 0.97 (95% CI 0.54 to 1.74); typical RD -0.00 (95% CI -0.04 to 0.04) (Figure 1). There was not any statistical evidence of heterogeneity (I^2 = 0%).

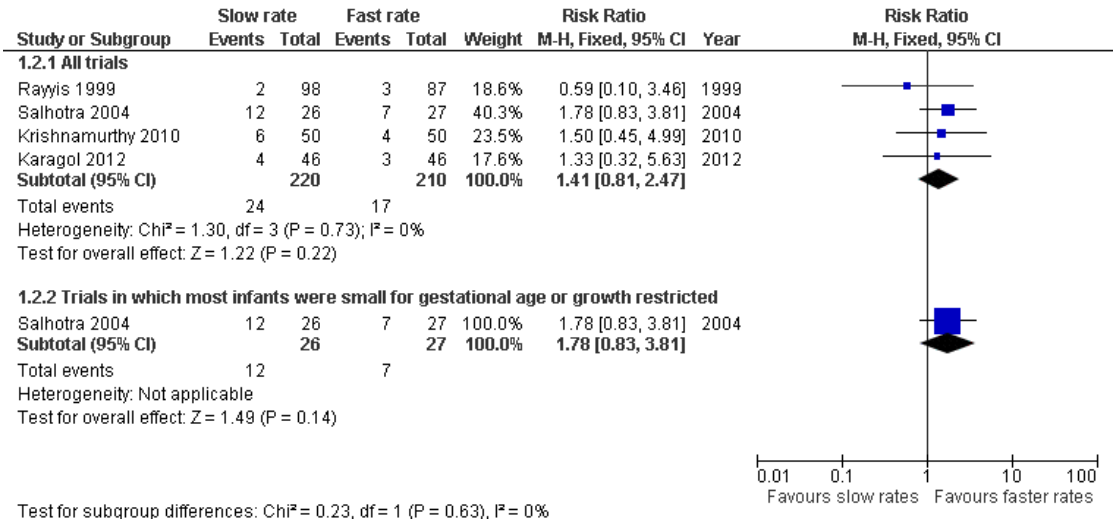
Figure 1. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.1 Incidence of necrotising enterocolitis.



Mortality (Outcome 1.2)

Meta-analysis did not find a statistically significant difference: typical RR 1.41 (95% CI 0.81 to 2.47); typical RD 0.03 (95% CI -0.02 to 0.08) (Figure 2). There was not any statistical evidence of heterogeneity (I^2 = 0%).

Figure 2. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.2 Mortality.



Secondary outcomes

Growth

All five trials reported that it took a statistically significantly longer time to regain birth weight in infants in the slow rate of advancement group:

- Rayyis 1999, median difference 3 (95% CI not given) days;
- Caple 2004, median difference 2 (95% CI 1, 3) days;
- Salhotra 2004, median difference 5 (95% CI not given) days;
- Krishnamurthy 2010, median difference 6 (95% CI not given) days;
- Karagol 2012, mean difference 3.8 (95% CI not given) days.

Longer-term growth parameters were not reported by any of the trials.

Neurodevelopment

None of the trials assessed any neurodevelopmental outcomes.

Time to establish full enteral feeding

All five of the trials reported that it took statistically significantly longer to establish full enteral feeds in infants in the slow rate of advancement group:

- Rayyis 1999, median difference 4 (95% CI not given) days;
- Caple 2004, median difference 3 (95% CI 2 to 3) days;
- Salhotra 2004, mean difference 4.8 (95% CI not given) days;
- Krishnamurthy 2010, median difference 2 (95% CI not given) days;
- Karagol 2012, mean difference 3.2 (95% CI not given) days.

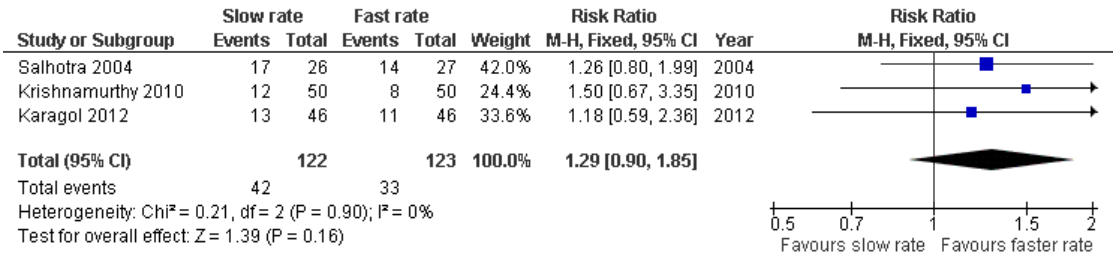
Time to establish full oral feeding

Not reported by any of the included trials.

Feeds intolerance (causing interruption of enteral feeding) (Outcome 1.3)

Meta-analysis of data from Salhotra 2004, Krishnamurthy 2010 and Karagol 2012 did not find a statistically significant difference: typical RR 1.29 (95% CI 0.90 to 1.85); typical RD 0.08 (95% CI -0.03 to 0.19) (Figure 3).

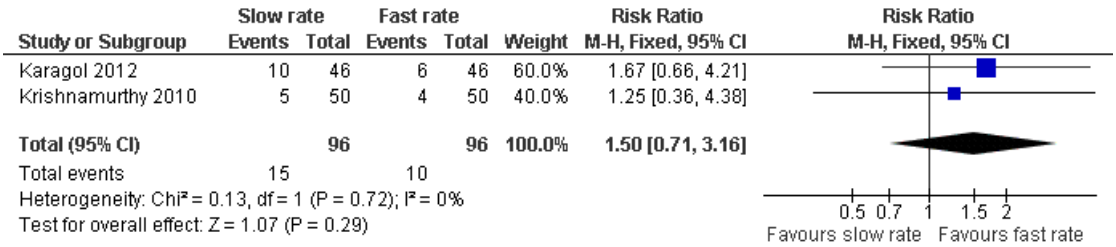
Figure 3. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.3 Feeds intolerance (causing interruption of enteral feeding).



Incidence of invasive infection (Outcome 1.4)

Meta-analysis of data from Krishnamurthy 2010 and Karagol 2012 did not detect a statistically significant effect: typical RR 1.50 (95% CI 0.71 to 3.16); typical RD 0.05 (95% CI -0.04 to 0.15) (Figure 4).

Figure 4. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.4 Incidence of invasive infection.



Duration of hospital stay

Two trials did not detect a statistically significant difference:

- Rayyis 1999, median difference 4 (95% CI not given) days;
- Caple 2004, mMedian difference 5 (95% CI -1 to 8) days.

Two trials reported that the duration of hospital stay was statistically significantly longer in infants in the slow rate of advancement group:

- Krishnamurthy 2010, median difference 1.5 (95% CI not given) days;
- Karagol 2012, mean difference 6 (95% CI not given) days.

Subgroup analyses

1. Exclusively formula-fed infants (Rayyis 1999). No statistically significant differences were detected:
   - NEC RR 1.44 (95% CI 0.63 to 3.32); RD 0.04 (95% CI -0.05 to 0.13);
   - mortality RR 0.59 (95% CI 0.10 to 3.46); RD -0.01 (95% CI -0.06 to 0.03).

2. Infants at least partially fed with human milk. Subgroup data were not available.

3. ELBW or extremely preterm infants. None of the trials recruited predominantly ELBW or extremely preterm infants.

4. Infants with intrauterine growth restriction (Salhotra 2004). No statistically significant differences:
   - NEC RR 0.21 (95% CI 0.01 to 4.12); RD -0.07 (95% CI -0.19 to 0.04) (Figure 1);

- mortality RR 1.78 (95% CI 0.83 to 3.81); RD 0.20 (95% CI -0.05 to 0.46) (Figure 2).

DISCUSSION

Summary of main results

The currently available trial data do not provide evidence that slowly advancing enteral feed volumes reduces the risk of NEC in very preterm or VLBW infants. The boundaries of the 95% CI for the estimate of risk difference are consistent with either one extra or one fewer case of NEC in every 25 infants who have slow rates of feed advancement. Infants who had slow advancement of feed volumes regained their birth weight two to six days later than infants who had faster rates of advancement. The clinical importance of this effect is unclear as long-term growth or developmental outcomes have not been assessed. Similarly, infants who had feed volumes advanced at a slow rate established full enteral feeding two to five days later than infants who had faster rates of advancement. Whether this is associated with important clinical adverse consequences such as a higher rate of nosocomial infection secondary to prolonged use of parenteral nutrition is not yet known as few studies have reported this outcome. Despite the effect on the establishment of enteral feeding, the included trials did not find consistent evidence of an important effect on the duration of hospital admission.

Overall completeness and applicability of evidence

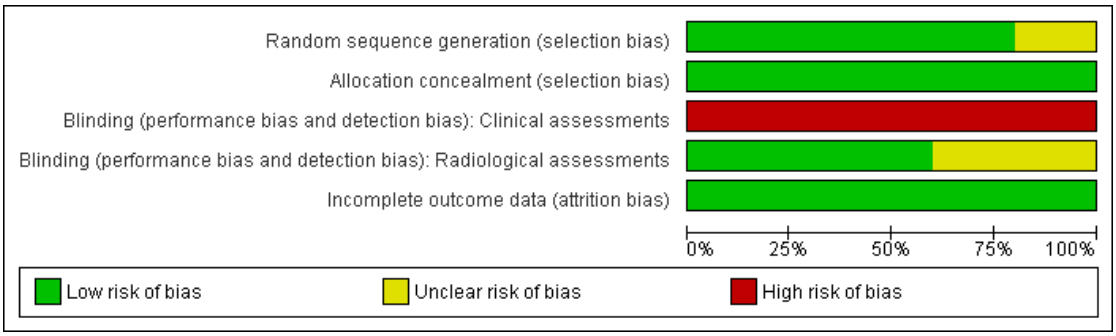
These findings should be applied with caution for several reasons. None of the studies included predominantly ELBW or extremely preterm infants, known to be at the highest risk of NEC (Luig 2005). One third of the participants in Karagol 2012 were of ELBW but only a minority of infants in the two larger trials weighed < 1000 grams or were < 28 weeks gestation at birth, or had evidence of intrauterine growth restriction (Rayyis 1999; Caple 2004). Infants who had severe respiratory distress requiring oxygen supplementation or ventilatory support were not eligible to participate in three of the trials (Salhotra 2004; Krishnamurthy 2010; Karagol 2012). The findings may not be applicable to these populations, at highest risk of developing feed intolerance or NEC. Less than one-half of the total number of participating infants were fed with breast milk. Evidence exists that artificial formula feeding increases the risk of feed intolerance and NEC (Quigley 2007). The risk-benefit balance of enteral feeding strategies may differ between human milk-fed and formula-fed very preterm or VLBW infants. It is also unclear whether the findings can be applied to infants who receive continuous infusion of intragastric feeds as all of the infants in the included trials received enteral feeds as interval boluses. Randomised controlled trials have reported conflicting findings about the effect of continuous enteral infusion on feed tolerance in very preterm or VLBW infants (Premji 2011).

Although the finding that slow enteral feed volume advancement delays the establishment of full enteral feeds seems intuitive, it is also plausible that advancing feed volumes faster could have resulted in more feed intolerance and therefore a delay in the establishment of full enteral feeding. The included trials all prespecified definitions of feed intolerance that mandated interrupting or ceasing feed volume advancement, principally the detection of 'gastric residuals' (the gastric content aspirated prior to a planned gastric tube feed) and abdominal distension. However, the trial reports presented only limited data on the frequency of these outcomes. Furthermore, only limited evidence exists that the volume or colour of gastric residuals is predictive of the risk of NEC for infants whose feed volumes are advanced conservatively (Mihatsch 2002; Cobb 2004; Bertino 2009). Similarly, the clinical importance of abdominal distension or bowel loops visible through the abdominal wall (without other features of intra-abdominal pathology) is unclear, especially in the modern era when early and prolonged use of continuous positive airway pressure results in intestinal gaseous distension.

Quality of the evidence

The included trials were generally of good methodological quality but, in common with other trials of feeding interventions in this population, it was not possible to mask caregivers and clinical assessors to the nature of the intervention (Figure 5). Although the lack of blinding may have resulted in surveillance and ascertainment biases, this is more likely to have caused an overestimation of the incidence of feed intolerance and NEC in infants whose feed volumes were advanced faster. The assessment of abdominal radiographs for signs of NEC was masked in most trials to ensure that the diagnosis of severe 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 over-ascertainment of NEC in the infants who had faster rates of feed volume advancement (Tyson 2007).

Figure 5. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Agreements and disagreements with other studies or reviews

This review specifically focused on the comparison of slow versus faster rates of feed volume advancement and did not compare progressive advancement with enteral fasting or trophic feeding (minimal enteral nutrition). Only one randomised controlled trial has compared trophic feeding with progressive enteral feed volume advancement (at daily increments of 20 ml/kg) (Berseth 2003). Although the trial found the risk of NEC to be statistically significantly higher in the infants whose feed volumes were progressively advanced, this finding should be interpreted cautiously. The trial was stopped early following an interim analysis and therefore the finding of an effect on the incidence of NEC may be spurious (Montori 2005). Caregivers and assessors were not blind to the intervention. As discussed above, this may have resulted in several sources of bias that are likely to cause an over-estimation of the incidence of NEC in infants whose feed volumes are being advanced.

AUTHORS' CONCLUSIONS

Implications for practice

These data suggest that slowly advancing enteral feed volumes does not reduce the risk of NEC in very preterm or VLBW infants. Increasing the volume of enteral feeds at slow rates (< 24 ml/kg/day) results in several days delay in the time taken to regain birth weight and establish full enteral feeds. The long-term clinical importance of these effects is unclear. Only limited data are available on the effect of this intervention on outcomes for extremely preterm or ELBW infants or infants who are growth restricted. Although current practice tends to favour a conservative approach to enteral feeding in these populations, it also needs to be considered that there are other possible consequences of slowly advancing feed volumes such as prolonging the use of parenteral nutrition that may be associated with important adverse clinical outcomes.

Implications for research

Further randomised controlled trials could provide more precise estimates of the effects of different rates of daily increases in enteral feed volumes on important outcomes for very preterm or VLBW infants. Trials should aim to ensure the participation of ELBW and extremely preterm infants as well as infants with evidence of compromised intrauterine growth so that subgroup analyses can be planned for these populations at high risk of NEC. Masking caregivers 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 neurodisability rates, it is essential that trials are powered and structured to assess these outcomes.

ACKNOWLEDGEMENTS

We gratefully acknowledge the contributions of Drs Kennedy, Tyson, Chamnanvanakij and Bombell to previous iterations. We are grateful to Dr Namasivayam Ambalavanan for providing further details and data from his trial (Rayyis 1999).

REFERENCES

References to studies included in this review

Caple 2004 *{published data only}*
Caple J, Armentrout D, Huseby V, Halbardier B, Garcia J, Sparks JW, et al.Randomized, controlled trial of slow versus rapid feeding volume advancement in preterm infants. *Pediatrics* 2004;**114**(6):1597–600.

Karagol 2012 *{published data only}*
Karagol BS, Zenciroglu A, Okumus N, Polin RA. Randomised controlled trial of slow versus rapid enteral feeding advancements on the clinical outcomes of preterm infants with 750-1250g. *JPEN. Journal of Parenteral and Enteral Nutrition* 2013;**37**(2):223–8.

Krishnamurthy 2010 *{published data only}*
Krishnamurthy S, Gupta P, Debnath S, Gomber S. Slow versus rapid enteral feeding advancement in preterm newborn infants 1000-1499 g: a randomized controlled trial. *Acta Paediatrica* 2010;**99**(1):42–6.

Rayyis 1999 *{published data only}*
Rayyis SF, Ambalavanan N, Wright L, Carlo WA. Randomized trial of "slow" versus "fast" feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants. *Journal of Pediatrics* 1999;**134**(3): 293–7.

Salhotra 2004 *{published data only}*
Salhotra A, Ramji S. Slow versus fast enteral feed advancement in very low birth weight infants: a randomized control trial. *Indian Pediatrics* 2004;**41**(5):435–41.

References to studies excluded from this review

Berseth 2003 *{published data only}*
Berseth CL, Bisquera JA, Paje VU. Prolonging small feeding volumes early in life decreases the incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2003;**111**(3):529–34.

Book 1976 *{published data only}*
Book LS, Herbst JJ, Jung AL. Comparison of fast- and slow-feeding rate schedules to the development of necrotizing enterocolitis. *Journal of Pediatrics* 1976;**89**(3):462–6.

Additional references

Beeby 1992
Beeby PJ, Jeffery H. Risk factors for necrotising enterocolitis: the influence of gestational age. *Archives of Disease in Childhood* 1992;**67**(4 Spec No):423–5.

Bernstein 2000
Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. *American Journal of Obstetrics and Gynecology* 2000;**182**(1 Pt 1):198–206.

Bertino 2009
Bertino E, Giuliani F, Prandi G, Coscia A, Martano C, Fabris C. Necrotizing enterocolitis: risk factor analysis and role of gastric residuals in very low birth weight infants. *Journal of Pediatric Gastroenterology and Nutrition* 2009;**48** (4):437–42. [PUBMED: 19330932]

Bisquera 2002
Bisquera JA, Cooper TR, Berseth CL. Impact of necrotizing enterocolitis on length of stay and hospital charges in very low birth weight infants. *Pediatrics* 2002;**109**(3):423–8.

Bombell 2009
Bombell S, McGuire W. Early trophic feeding for very low birth weight infants. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/ 14651858.CD000504.pub3]

Brown 1978
Brown EG, Sweet AY. Preventing necrotizing enterocolitis in neonates. *JAMA* 1978;**240**(22):2452–4.

Chauhan 2008
Chauhan M, Henderson G, McGuire W. Enteral feeding for very low birth weight infants: reducing the risk of necrotising enterocolitis. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2008;**93**(2):F162–6. [PUBMED: 18006565]

Cobb 2004
Cobb BA, Carlo WA, Ambalavanan N. Gastric residuals and their relationship to necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2004;**113**(1 Pt 1):50–3.

Dorling 2005
Dorling J, Kempley S, Leaf A. Feeding growth restricted preterm infants with abnormal antenatal Doppler results. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2005;**90**(5):F359–63.

Flidel-Rimon 2004
Flidel-Rimon O, Friedman S, Lev E, Juster-Reicher A, Amitay M, Shinwell ES. Early enteral feeding and nosocomial sepsis in very low birthweight infants. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2004;**89** (4):F289–92.

Flidel-Rimon 2006
Flidel-Rimon O, Branski D, Shinwell ES. The fear of necrotizing enterocolitis versus achieving optimal growth in preterm infants--an opinion. *Acta Paediatrica* 2006;**95**(11): 1341–4.

Garite 2004
Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases morbidity and mortality among premature neonates. *American Journal of Obstetrics and Gynecology* 2004;**191**(2):481–7.

Guthrie 2003
Guthrie SO, Gordon PV, Thomas V, Thorp JA, Peabody J, Clark RH. Necrotizing enterocolitis among neonates in the United States. *Journal of Perinatology* 2003;**23**(4):278–85.

Hartel 2009
Härtel C, Haase B, Browning-Carmo K, Gebauer C, Kattner E, Kribs A, et al.Does the enteral feeding advancement

affect short-term outcomes in very low birth weight infants? . *Journal of Pediatric Gastroenterology and Nutrition* 2009;**48** (4):464–70.

Henderson 2009
Henderson G, Craig S, Brocklehurst P, McGuire W. Enteral feeding regimens and necrotising enterocolitis in preterm infants: a multicentre case-control study. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2009;**94**(2): F120–3. [PUBMED: 17768154]

Holman 1997
Holman RC, Stoll BJ, Clarke MJ, Glass RI. The epidemiology of necrotizing enterocolitis infant mortality in the United States. *American Journal of Public Health* 1997; **87**(12):2026–31.

Luig 2005
Luig M, Lui K, NSW & ACT NICUS Group. Epidemiology of necrotizing enterocolitis--Part II: Risks and susceptibility of premature infants during the surfactant era: a regional study. *Journal of Paediatrics and Child Health* 2005;**41**(4):174–9. [PUBMED: 15813870]

McKeown 1992
McKeown RE, Marsh TD, Amarnath U, Garrison CZ, Addy CL, Thompson SJ, et al.Role of delayed feeding and of feeding increments in necrotizing enterocolitis. *Journal of Pediatrics* 1992;**121**(5 Pt 1):764–70.

Mihatsch 2002
Mihatsch WA, von Schoenaich P, Fahnenstich H, Dehne N, Ebbecke H, Plath C, et al. The significance of gastric residuals in the early enteral feeding advancement of extremely low birth weight infants. *Pediatrics* 2002;**109**(3): 457–9.

Montori 2005
Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, et al.Randomized trials stopped early for benefit: a systematic review. *JAMA* 2005;**294**(17): 2203–9.

Morgan 2011
Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/ 14651858.CD001970.pub3]

Patole 2005
Patole SK, de Klerk N. Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies. *Archives of Disease in Childhood* 2005;**90**(2): F147–51.

Pike 2012
Pike K, Brocklehurst P, Jones D, Kenyon S, Salt A, Taylor D, et al.Outcomes at 7 years for babies who developed neonatal necrotising enterocolitis: the ORACLE Children Study. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2012;**97**(5):F318–22. [PUBMED: 22933088]

Premji 2011
Premji SS, Chessell L. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: 10.1002/ 14651858.CD001819.pub2]

Quigley 2007
Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/ 14651858.CD002971.pub2]

Rees 2007
Rees CM, Pierro A, Eaton S. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2007;**92**(3):F193–8.

RevMan 2011
Nordic Cochrane Centre. Review Manager (RevMan). 5.1. Copenhagen: Nordic Cochrane Centre, 2011.

Soraisham 2006
Soraisham AS, Amin HJ, Al-Hindi MY, Singhal N, Sauve RS. Does necrotising enterocolitis impact the neurodevelopmental and growth outcomes in preterm infants with birthweight < or =1250 g?. *Journal of Paediatrics and Child Health* 2006;**42**(9):499–504. [PUBMED: 16925534]

Stoll 2004
Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al.Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;**292**(19):2357–65.

Tyson 2007
Tyson JE, Kennedy KA, Lucke JF, Pedroza C. Dilemmas initiating enteral feedings in high risk infants: how can they be resolved?. *Seminars in Perinatology* 2007;**31**(2):61–73.

Uauy 1991
Uauy RD, Fanaroff AA, Korones SB, Phillips EA, Phillips JB, Wright LL. Necrotizing enterocolitis in very low birth weight infants: biodemographic and clinical correlates. National Institute of Child Health and Human Development Neonatal Research Network. *Journal of Pediatrics* 1991;**119**(4):630–8.

Walsh 1986
Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatric Clinics of North America* 1986;**33**(1):179–201.

References to other published versions of this review

Kennedy 2005
Kennedy KA, Tyson JE, Chamnanvanakij S. Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birth-weight infants. *Cochrane Database of*

Systematic Reviews 2005, Issue 2. [DOI: 10.1002/14651858.CD001241.pub2]

McGuire 2008

McGuire W, Bombell S. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD001241.pub2]

Morgan 2011a

Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD001241.pub3; PUBMED: 21412870]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Caple 2004

Methods	Randomised controlled trial
Participants	Preterm infants of birth weight 1000-2000 grams (appropriate birth weight for gestational age and of gestational age <35 weeks at birth), who were starting formula feeds Setting: Neonatal Unit, Department of Pediatrics, University of Texas Medical School, Houston, Texas, USA
Interventions	Feeds advancement at 20 ml/kg/day (N = 74) versus 30 ml/kg/day (N = 84)
Outcomes	NEC (Bell stage II/III) Time to regain birth weight, time to achieve full enteral feeds, and time to hospital discharge
Notes	Feeds were ceased if the residual gastric aspirate was more than one-third of the previous feed volume, or if there was frequent vomiting, abdominal distention, or bloody stools (including occult blood) We have not been able to obtain data on all-cause mortality from the principal investigators

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number sequence
Allocation concealment (selection bias)	Low risk	Blinded draw from envelope by caregivers not involved in study
Blinding (performance bias and detection bias) Clinical assessments	High risk	Care givers and clinical investigators were not blinded once allocation to intervention groups had occurred
Blinding (performance bias and detection bias) Radiological assessments	Low risk	Radiologists interpreting x-rays were blinded to the intervention group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three infants excluded after enrolment because of protocol violations have been included in this review and meta-analysis. Two infants (one in each group) were excluded because they were determined not to be eligible for enrolment (because of an in utero gastrointestinal perforation and fetal alcohol syndrome); these infants were not included in the meta-analysis

Karagol 2012

Methods	Randomised controlled trial
Participants	Preterm infants < 32 weeks gestation with birth weights of 750-1250 grams. 32% of participants weighed <1000 grams Exclusion criteria included major congenital malformations, severe respiratory distress, presence of umbilical vessel catheters, contraindications to enteral feeding, perinatal asphyxia or cardiovascular compromise Setting: Dr Sami Ulus Maternity Childrens' Education and Research Hospital, Division of Neonatology, Ankara, Turkey
Interventions	Slow advancement at 20 ml/kg/day (N=46) versus rapid advancement at 30 ml/kg/day (N=46)
Outcomes	NEC (stage II/III), all-cause mortality, time to regain birth weight, time to reach full enteral feeds, feed intolerance, duration of hospital stay, rates of invasive infection Subgroup analysis for ELBW infants
Notes	Feeds were ceased if any of the following occurred: gastric residuals > 5 ml/kg or >50% of feed volume, vomiting >3 times in 24 hours, increase in abdominal girth >2 cm between feeds, abdominal tenderness or erythema, reduced bowel sounds, blood in the stools or recurrent apnoea

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	Opaque sealed envelopes
Blinding (performance bias and detection bias) Clinical assessments	High risk	Caregivers and study investigators were not blinded
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	No reference to whether staff interpreting radiological images were blinded to the study groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow up

Krishnamurthy 2010

Methods	Randomised controlled trial
Participants	Preterm infants (birth weight 1000-1499 grams) and gestational age <34 weeks at birth. Exclusion criteria included respiratory distress, mechanical ventilation, inotrope support, and umbilical arterial or venous catheterisation

Krishnamurthy 2010 (*Continued*)

	Setting: Department of Paediatrics, University College of Medical Sciences, Dehli, India
Interventions	Feeds advancement at 20 ml/kg/day (N = 50) versus 30 ml/kg/day (N = 50)
Outcomes	NEC (stage II/III) Incidence of nosocomial infection, in-hospital mortality, time to regain birth weight, time to achieve full enteral feeds, and time to hospital discharge
Notes	All feeds were delivered by gavage via nasogastric tubes at 2 hourly intervals Feeds were ceased if the residual gastric contents were more than 50% of the previous feed volume (delayed if volume was 25-50%), or if there were more than 3 episodes of apnoea in the preceding hour, or abdominal distention or tenderness, or bloody stools (including occult blood) Parenteral nutrition was not available

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	Opaque sealed envelopes
Blinding (performance bias and detection bias) Clinical assessments	High risk	Care givers and investigators were not blinded to the interventions
Blinding (performance bias and detection bias) Radiological assessments	Low risk	X-rays were interpreted by a radiologist blind to the intervention group
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up

Rayyis 1999

Methods	Randomised controlled trial
Participants	Very low birth weight infants of gestational age less than 34 weeks' at birth Setting: Neonatal Unit, Department of Pediatrics, University of Alabama, Birmingham, Alabama, USA
Interventions	Feeds advancement at 15 ml/kg/day (N = 98) versus 35 ml/kg/day (N = 87)
Outcomes	NEC (stage II/III). Time to regain birth weight, time to achieve full enteral feeds, and time to hospital discharge

Rayyis 1999 (*Continued*)

Notes	Infants for whom full or partial feeding with expressed breast milk was planned were not eligible to participate. Feeding was commenced using standard 'term' artificial formula, then switched to nutrient-enriched 'preterm' formula when full enteral feeding had been achieved Feeds were ceased if the residual gastric contents were more than 30% of the previous feed volume, or if there was abdominal distention or tenderness, or bloody stools (including occult blood)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding (performance bias and detection bias) Clinical assessments	High risk	Care givers and investigators not blinded to the intervention groups
Blinding (performance bias and detection bias) Radiological assessments	Low risk	Radiologist interpreting the x-rays was blinded to the study group
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 protocol violations occurred after enrolment but all infants were included the final data analysis

Salhotra 2004

Methods	Randomised controlled trial
Participants	Preterm infants of birth weight <1250 grams. More than 95% of the participants were 'small for gestational age'. Exclusion criteria included recurrent apnoea, respiratory distress requiring supplemental oxygen, and receipt of inotrope support Setting: Neonatal Unit , Maulana Azad Medical College (tertiary level teaching hospital) , New Delhi, India
Interventions	Feeds advancement at 15 ml/kg/day (N = 26) versus 30 ml/kg/day (N = 27)
Outcomes	NEC (stage II/III) Neonatal mortality, time to regain birth weight, time to achieve full enteral feeds, and time to hospital discharge
Notes	Feeds were ceased if the residual gastric content was more than 30% of the previous feed volume, or if there was abdominal distention Mortality data courtesy of Dr Namasivayam Ambalavanan

Salhotra 2004 (*Continued*)

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	Opaque sealed envelopes
Blinding (performance bias and detection bias) Clinical assessments	High risk	Investigators blinded at allocation stage but unclear if remained blinded thereafter. Caregivers not blinded to intervention group
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	No statement about blinding of radiological assessors to intervention group
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow up

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berseth 2003	Infants were allocated randomly to either a stable (not progressively increased) trophic feeding volume or to feed volume advancement at 20 ml/kg/day
Book 1976	Enteral feeding volumes were advanced at 10 ml/kg/day versus 20 ml/kg/day, that is, both groups received 'slow' advancement of feed volumes

DATA AND ANALYSES

Comparison 1. Slow versus faster rates of feed advancement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of necrotising enterocolitis	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All trials	5	588	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.54, 1.74]
1.2 Trials in which most infants were small for gestational age or growth restricted	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.12]
2 Mortality	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 All trials	4	430	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.81, 2.47]
2.2 Trials in which most infants were small for gestational age or growth restricted	1	53	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.83, 3.81]
3 Feeds intolerance (causing interruption of enteral feeding)	3	245	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.90, 1.85]
4 Incidence of invasive infection	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.71, 3.16]

WHAT'S NEW

Last assessed as up-to-date: 28 December 2012.

Date	Event	Description
28 December 2012	New citation required and conclusions have changed	Updated search in December 2012 identified one new trial for inclusion, increasing the total number of participating infants to 588 (from 496), narrowed confidence intervals for the estimates of effect
28 December 2012	New search has been performed	This updates the review 'Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants' (Morgan 2011a).

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 1998

Date	Event	Description
11 January 2011	New citation required and conclusions have changed	Addition of new data, and increasing the total number of participating infants to 496, narrowed the confidence intervals for the estimates of effect and modified the implications for practice and research
15 December 2010	New search has been performed	This updates the review "Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants" published in the Cochrane Database of Systematic Reviews, Issue 2, 2008 (McGuire 2008). Search updated in December 2010. One new trial included (Krishnamurthy 2010). New co-authors: Jessie Morgan and Lauren Young.
13 February 2008	New citation required but conclusions have not changed	New authorship: Bombell S, McGuire W
2 February 2008	New search has been performed	This updates the review "Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birth-weight infants" by Kennedy and Tyson, published in the Cochrane Database of Systematic Reviews, Issue 2, 2000 (Kennedy 2000) The title has been modified to read "Slow advancement of enteral feed volumes 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: 1. "Slow" rate of feed advancement has been defined as daily increments up to 24 ml/kg (body weight). 2. The population has been restricted to very low birth weight and very preterm infants. 3. Mortality, adverse neurodevelopment, growth parameters, and infection rates have been included as outcomes of interest. Search updated December 2007. One new trial has been included (Salhotra 2004). One trial previously included has now been excluded (Book 1976).

(*Continued*)

		The findings and implications for practice and research of the review have not changed overall
11 January 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Drs Morgan and Young 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

SOURCES OF SUPPORT

Internal sources

- Centre for Reviews and Dissemination, Hull York Medical School, UK.

External sources

- National Institute for Health Research (NIHR), UK.

Jessie Morgan and Lauren Young are NIHR Academic Clinical Fellows in Child Health.

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN267200603418C.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Very Low Birth Weight; Enteral Nutrition [*methods]; Enterocolitis, Necrotizing [*prevention & control]; Infant, Low Birth Weight; Infant, Newborn; Infant, Premature; Infant, Premature, Diseases [*prevention & control]; Parenteral Nutrition [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Humans