Cochrane Library

Cochrane Database of Systematic Reviews

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

Oddie SJ, Young L, McGuire W

Oddie SJ, 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 2017, Issue 8. Art. No.: CD001241.
DOI: 10.1002/14651858.CD001241.pub7.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

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

Sam J Oddie[1], Lauren Young[2], William McGuire[3]

[1]Bradford Royal Infirmary, Bradford, UK. [2]Paediatric Intensive Care Unit, Birmingham Children's Hospital, Birmingham, UK. [3]Centre for Reviews and Dissemination, The University of York, York, UK

Contact address: William McGuire, Centre for Reviews and Dissemination, The 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 (no change to conclusions), published in Issue 8, 2017.

Citation: Oddie SJ, 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* 2017, Issue 8. Art. No.: CD001241. DOI: 10.1002/14651858.CD001241.pub7.

ABSTRACT

Background

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

Objectives

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

Search methods

We used the standard Cochrane Neonatal search strategy to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 5), MEDLINE via PubMed (1966 to June 2017), Embase (1980 to June 2017), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to June 2017). We searched clinical trials databases, conference proceedings, previous reviews, and reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-randomised trials.

Selection criteria

Randomised or quasi-randomised controlled trials that assessed effects of slow (up to 24 mL/kg/d) versus faster rates of advancement of enteral feed volumes upon the incidence of NEC in very preterm or VLBW infants.

Data collection and analysis

Two review authors assessed trial eligibility and risk of bias and independently extracted data. We analysed treatment effects in individual trials and reported risk ratio (RR) and risk difference (RD) for dichotomous data, and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We used a fixed-effect model for meta-analyses and explored potential causes of heterogeneity via sensitivity analyses. We assessed the quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

We identified 10 RCTs in which a total of 3753 infants participated (2804 infants participated in one large trial). Most participants were stable very preterm infants of birth weight appropriate for gestation. About one-third of all participants were extremely preterm or extremely low

birth weight (ELBW), and about one-fifth were small for gestational age (SGA), growth-restricted, or compromised in utero, as indicated by absent or reversed end-diastolic flow velocity (AREDFV) in the fetal umbilical artery. Trials typically defined slow advancement as daily increments of 15 to 20 mL/kg, and faster advancement as daily increments of 30 to 40 mL/kg. Trials generally were of good methodological quality, although none was blinded.

Meta-analyses did not show effects on risk of NEC (typical RR 1.07, 95% CI 0.83 to 1.39; RD 0.0, 95% CI -0.01 to 0.02) or all-cause mortality (typical RR 1.15, 95% CI 0.93 to 1.42; typical RD 0.01, 95% CI -0.01 to 0.03). Subgroup analyses of extremely preterm or ELBW infants, or of SGA or growth-restricted or growth-compromised infants, showed no evidence of an effect on risk of NEC or death. Slow feed advancement delayed establishment of full enteral nutrition by between about one and five days. Meta-analysis showed borderline increased risk of invasive infection (typical RR 1.15, 95% CI 1.00 to 1.32; typical RD 0.03, 95% CI 0.00 to 0.05). The GRADE quality of evidence for primary outcomes was "moderate", downgraded from "high" because of lack of blinding in the included trials.

Authors' conclusions

Available trial data do not provide evidence that advancing enteral feed volumes at daily increments of 15 to 20 mL/kg (compared with 30 to 40 mL/kg) reduces the risk of NEC or death in very preterm or VLBW infants, extremely preterm or ELBW infants, SGA or growth-restricted infants, or infants with antenatal AREDFV. Advancing the volume of enteral feeds at a slow rate results in several days of delay in establishing full enteral feeds and may increase the risk of invasive infection.

PLAIN LANGUAGE SUMMARY

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

Review question

Does limiting the rate of increase in milk feeds that very low birth weight infants receive each day during the first few weeks after birth reduce the risk of severe bowel problems?

Background

Very low birth weight infants (infants weighing < 1500 grams at birth) are at risk of developing a severe bowel disorder called necrotising enterocolitis (where the bowel becomes inflamed and dies). It is thought that one way to prevent this condition may be to limit the milk feeds that infants receive each day for the first few weeks after birth.

Study characteristics

We searched for clinical trials comparing slow versus faster rates of increase in the amount of milk fed to newborn infants who were very low birth weight. When performing searches updated in June 2017, we found 10 trials involving 3753 infants in total.

Key results

Combined analysis of these trials did not show an effect of slow feeding on the risk of necrotising enterocolitis or death (moderate-quality evidence) but did suggest that infants fed more slowly might have higher risk of acquiring a severe infection than infants fed more quickly (low-quality evidence).

Conclusions

Slow feeding does not appear to provide benefits and may cause some harms.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Slow compared with faster rates of enteral feed advancement for preventing necrotising enterocolitis in very preterm or very low birth weight infants

Slow compared with faster rates of enteral feed advancement for preventing necrotising enterocolitis in very preterm or very low birth weight infants

Patient or population: very preterm or very low birth weight infants
Setting: neonatal care facility
Intervention: slow rates of enteral feed advancement
Comparison: faster rates of enteral feed advancement

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with faster rates of enteral feed advancement	Risk with slow rates of enteral feed enhancement				
Incidence of necrotising enterocolitis - All infants	Study population		RR 1.07 (0.83 to 1.39)	3738 (10 studies)	⊕⊕⊕⊖ MODERATE	Downgraded for "risk of bias" - all trials unblinded
	54 per 1000	59 per 1000 (46 to 77)				
Mortality - All infants	Study population		RR 1.15 (0.93 to 1.42)	3553 (9 studies)	⊕⊕⊕⊖ MODERATE	Downgraded for "risk of bias" - all trials unblinded
	72 per 1000	82 per 1000 (67 to 102)				
Feed intolerance (causing interruption of enteral feeding)	Study population		RR 1.20 (0.95 to 1.50)	606 (7 studies)	⊕⊕⊕⊖ MODERATE	Downgraded for "risk of bias" - all trials unblinded
	292 per 1000	351 per 1000 (278 to 439)				
Incidence of invasive infection	Study population		RR 1.15 (1.00 to 1.32)	3391 (8 studies)	⊕⊕⊖⊖ LOW	Downgraded for "risk of bias" - all trials unblinded, and for imprecision (lower bound of 95% CI consistent with "no effect")
	172 per 1000	200 per 1000 (172 to 229)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI)

CI: confidence interval; RR: risk ratio

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 (Gagliardi 2008; Holman 1997; Moro 2009). Infants who develop NEC experience more 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). The associated mortality rate is greater than 20%. Compared with their peers, infants who develop NEC have a higher incidence of long-term neurological disability, which may be a consequence of infection and undernutrition during a critical period of brain development (Berrington 2012; Pike 2012; Rees 2007; Shah 2012; Soraisham 2006; Stoll 2004).

Description of the intervention

Low gestational age at birth is the major clinical risk factor for developing NEC (Beeby 1992). The other major risk factor is intrauterine growth restriction, especially if it is associated with absent or reversed end-diastolic flow velocities in Doppler studies of the foetal aorta or umbilical artery (Bernstein 2000; Dorling 2005; Garite 2004; Luig 2005; Samuels 2017). Most very preterm or VLBW infants who develop NEC have received enteral milk feeds. Evidence shows that feeding with artificial formula rather than human milk increases the risk of developing NEC (Quigley 2014). Other differences in enteral feeding regimens, such as the timing of introduction of feeds and the size of daily volume increments, may also contribute to inter-unit variation in the incidence of NEC (Chauhan 2008). Multi-centre benchmarking studies have found that neonatal centres where enteral feeding is introduced earlier and feeding volumes are advanced more quickly tend to report 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 20 to 24 mL/kg body weight each day, is associated with lower risk of developing NEC in very preterm or VLBW infants (Brown 1978; Henderson 2009; McKeown 1992; Patole 2005).

Why it is important to do this review

Potential disadvantages associated with slowing the advancement of enteral feed volumes include delaying establishment of full enteral nutrition and extending the duration of receipt of parenteral 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 from these other potential clinical outcomes when feeding policies and practices for very preterm or VLBW infants are determined (Flidel-Rimon 2006; Härtel 2009).

Other Cochrane reviews have addressed the questions of whether delaying the introduction of any enteral milk feeding or restricting feed volumes to trophic levels (minimal enteral nutrition) affects the risk of NEC in very preterm or VLBW infants (Morgan 2013; Morgan 2014a). This review focused on the question of whether advancing feed volumes at slow rates compared with faster rates affected risks of NEC, mortality, and other morbidities.

OBJECTIVES

To determine effects 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 random or quasi-random participant 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 feed advancement. All infants should have received the same type of milk, and in both groups advancement of feed volume should have commenced within five days of introduction of enteral feeds.

Types of outcome measures

Primary outcomes

- NEC confirmed at surgery or at autopsy or by at least two of the following features (Walsh 1986)
  - 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)
- All-cause mortality during the neonatal period and before hospital discharge

Secondary outcomes

- Growth
  - 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)
  - 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
- Neurodevelopment
  - Death or severe neurodevelopmental disability defined as any one or a combination of the following: non-ambulatory cerebral palsy, developmental delay (developmental quotient < 70), auditory and visual impairment. Each component was to be analysed individually and as part of the composite outcome
  - Neurodevelopmental scores for survivors aged 12 months or greater measured by validated assessment tools
  - Cognitive and educational outcomes among survivors older than five years of age

- Time to establish full enteral feeding (independently of parenteral nutrition)
- Time to establish oral feeding (independently of parenteral nutrition or enteral tube feeding, or both)
- Feed intolerance (defined as a requirement to cease enteral feeds)
- Incidence of invasive infection as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, or urine, or from a normally sterile body space
- Duration of hospital stay (days)

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 5), MEDLINE via PubMed (2015 to June 2017), Embase (2015 to June 2017), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 2015 to June 2017) using search terms adapted for individual databases: ("Infant-Nutrition"/all subheadings OR Infant Formula OR milk OR formula OR trophic feeding OR minimal enteral nutrition OR gut priming), plus database-specific limiters for randomised controlled trials (RCTs) and neonates (see Appendix 1). We did not apply language restrictions.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization International Trials Registry and Platform www.whoint/ictrp/search/en/; the ISRCTN Registry).

Searching other resources

We searched the reference lists of any articles selected for inclusion in this review to identify additional relevant articles.

We searched abstracts from annual meetings of the Pediatric Academic Societies (1993 to 2017), the European Society for Paediatric Research (1995 to 2016), the UK Royal College of Paediatrics and Child Health (2000 to 2017), and the Perinatal Society of Australia and New Zealand (2000 to 2016). Trials reported only as abstracts were eligible if sufficient information was available from the report or through contact with study authors to fulfil the inclusion criteria.

Data collection and analysis

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

Selection of studies

WM screened titles and abstracts of all records identified by the search and coded records as "order" or "exclude". A second review author assessed all records coded as "order" and made the final decision about which records should be ordered as full-text articles. Two review authors read the full texts and used a checklist to assess each article's eligibility for inclusion on the basis of prespecified inclusion and exclusion criteria.

Data extraction and management

WM and SO extracted data independently using a data collection form to aid extraction of information on design, methods, participants, interventions, outcomes, and treatment effects from each included study. We discussed disagreements until we reached consensus. If data from trial reports were insufficient, we contacted trialists to ask for further information.

Assessment of risk of bias in included studies

Two review authors (WM and SO) independently assessed risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

We resolved disagreements by discussion or by consultation with a third assessor. See Appendix 2 for a detailed description of risk of bias for each domain.

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 (CIs). When we deemed it appropriate to combine two or more study arms, we obtained treatment effects from combined data using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We determined the number needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH) for a statistically significant difference in RD.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials. For cluster-randomised trials (had we identified any for inclusion), we planned to undertake analyses at the level of the individual while accounting for clustering in the data by using methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We requested additional data from trial investigators when data on important outcomes were missing or were reported unclearly. When data remained missing, we examined the impact on effect size estimates by performing sensitivity analyses.

Assessment of heterogeneity

We examined treatment effects in individual trials and heterogeneity between trial results by inspecting forest plots if more than one trial was included in a meta-analysis. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate or high (I^2 > 50%) levels of heterogeneity, we explored possible causes (e.g. differences

in study design, participants, or interventions; completeness of outcome assessments) by performing sensitivity analyses.

Data synthesis

We used a fixed-effect model for meta-analyses.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: incidence of NEC, mortality, feed intolerance, and invasive infection.

Two review authors independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in assessment of the quality of a body of evidence according to one of four grades.

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.

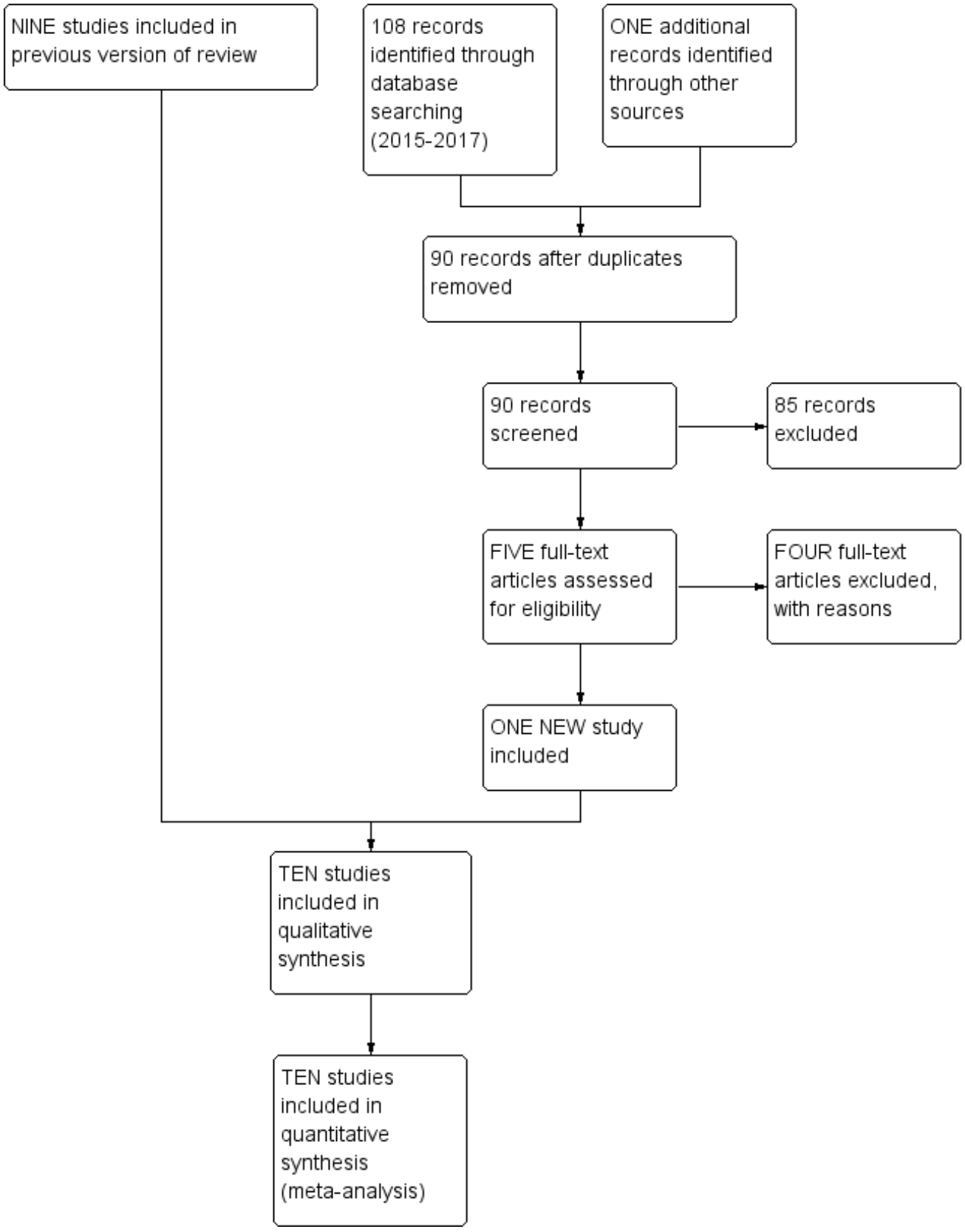
- Trials in which most infants were exclusively formula-fed.
- Trials in which most infants were at least partially fed with human milk (maternal or donor).
- Trials in which most participants were of extremely low birth weight (ELBW) (< 1000 g) or extremely preterm gestational age (< 28 weeks).
- Trials in which participants were infants with intrauterine growth restriction.
- Infants with absent or reversed end-diastolic flow velocities detected on antenatal Doppler studies of the foetal aorta or umbilical artery.

RESULTS

Description of studies

Ten RCTs fulfilled review eligibility criteria (Caple 2004; Jain 2016; Karagol 2013; Krishnamurthy 2010; Modi 2015; Raban 2014a; Raban 2014b; Rayyis 1999; Salhotra 2004; SIFT 2016) (see Characteristics of included studies table and study flow diagram - Figure 1).

Figure 1. Study flow diagram: review update.



Included studies

Population

A total of 3753 infants participated in the included trials. Almost 75% of the total number of infants were participants in a recent large multi-centre trial (SIFT 2016). Trials were undertaken at neonatal care centres in North America (Caple 2004; Rayyis 1999), India (Jain 2016; Krishnamurthy 2010; Modi 2015; Salhotra 2004), Turkey (Karagol 2013), South Africa (Raban 2014a; Raban 2014b), and the UK and Ireland (SIFT 2016).

All 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 2013: 750 to 1250 grams.
- Jain 2016: 1000 to 1249 grams.
- Raban 2014a: < 1001 grams.
- Raban 2014b: < 1001 grams.
- Modi 2015: 750 to 1250 grams.
- SIFT 2016: < 1500 grams.

Most participants in Caple 2004 and Jain 2016 were of birth weight less than 1500 grams or gestational age less than 32 weeks; therefore, we made a consensus decision to include these trials. Infants born 'small for gestational age' (birth weight < 10th percentile of the index population distribution) were not eligible to participate in Caple 2004 but were included in the other trials. More than 95% of participants in Salhotra 2004 were small for gestational age. One-third of participants in Karagol 2013 were ELBW infants. All participants in Jain 2016 had antenatal evidence of absent or reversed end-diastolic flow.

Interventions and comparisons

All trials commenced interval bolus intragastric feeding typically within the first seven 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.
- Caple 2004: 20 versus 35 mL/kg.
- Salhotra 2004: 15 versus 30 mL/kg.
- Krishnamurthy 2010: 20 versus 30 mL/kg.
- Karagol 2013: 20 versus 30 mL/kg.
- Jain 2016: 20 versus 30 mL/kg.
- Raban 2014a: 24 versus 36 mL/kg.
- Raban 2014b: 24 versus 36 mL/kg.
- Modi 2015: 15 to 20 versus 30 to 40 mL/kg.
- SIFT 2016: 18 versus 30 mL/kg.

In one trial, only formula-fed infants were eligible to participate (Rayyis 1999). In Caple 2004, Jain 2016, Karagol 2013, Krishnamurthy 2010, Modi 2015, and SIFT 2016, infants received expressed breast milk or formula, or a combination. In Raban 2014a, Raban 2014b, and Salhotra 2004, participating infants were fed exclusively with expressed breast milk. Most 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 distension, or detection of blood in the stools (including occult blood). SIFT 2016 did not prespecify these criteria but allowed clinicians and caregivers to apply unit-specific policies and practices.

Outcomes

All trials reported the incidence of NEC confirmed radiologically or at surgery or at autopsy. Other reported outcomes included time to regain birth weight, time to establish full enteral feeding, duration of hospital stay, and rates of invasive infection.

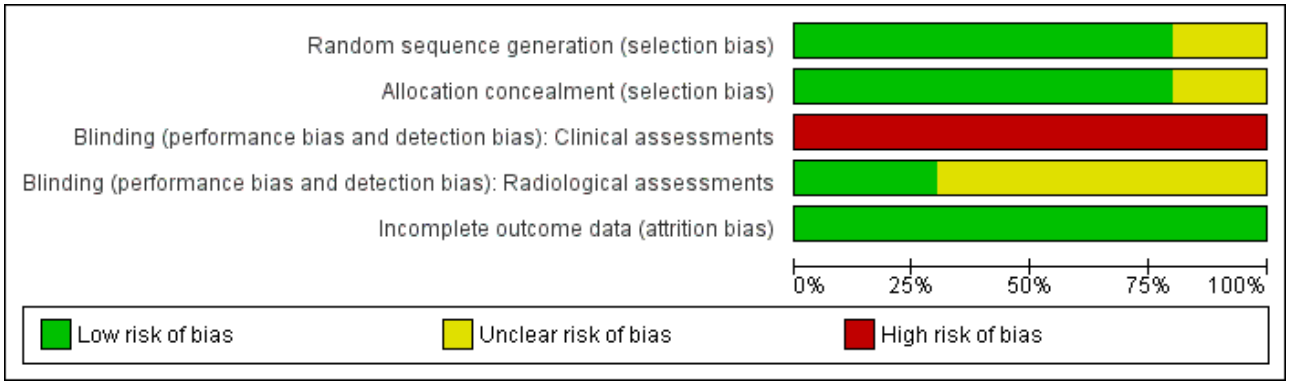
Excluded studies

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

Risk of bias in included studies

The methodological quality of the included trials was generally good (Figure 2). All trials employed methods to ensure adequate allocation concealment and reported complete or near-complete assessments of primary outcomes. None of the included trials were able to conceal feeding strategies from parents, caregivers, or clinical investigators. Three studies clearly masked assessment of abdominal radiographs (for diagnosis of NEC). In Karagol 2013, Modi 2015, Raban 2014a, Raban 2014b, Salhotra 2004, and SIFT 2016, it remains unclear whether precautions had been taken to ensure that radiological assessors were blinded to the allocation group.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

See: **Summary of findings for the main comparison** Slow compared with faster rates of enteral feed advancement for preventing necrotising enterocolitis in very preterm or very low birth weight infants

Primary outcomes

Incidence of necrotising enterocolitis

Meta-analysis did not show an effect on the risk of NEC (typical RR 1.07, 95% CI 0.83 to 1.39; RD 0.00, 95% CI -0.01 to 0.02; 10 studies, 3742 infants; I^2 = 21%) (Analysis 1.1; Figure 3). The funnel plot did not indicate small study or publication bias (Figure 4).

Figure 3. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.1 Incidence of necrotising enterocolitis.

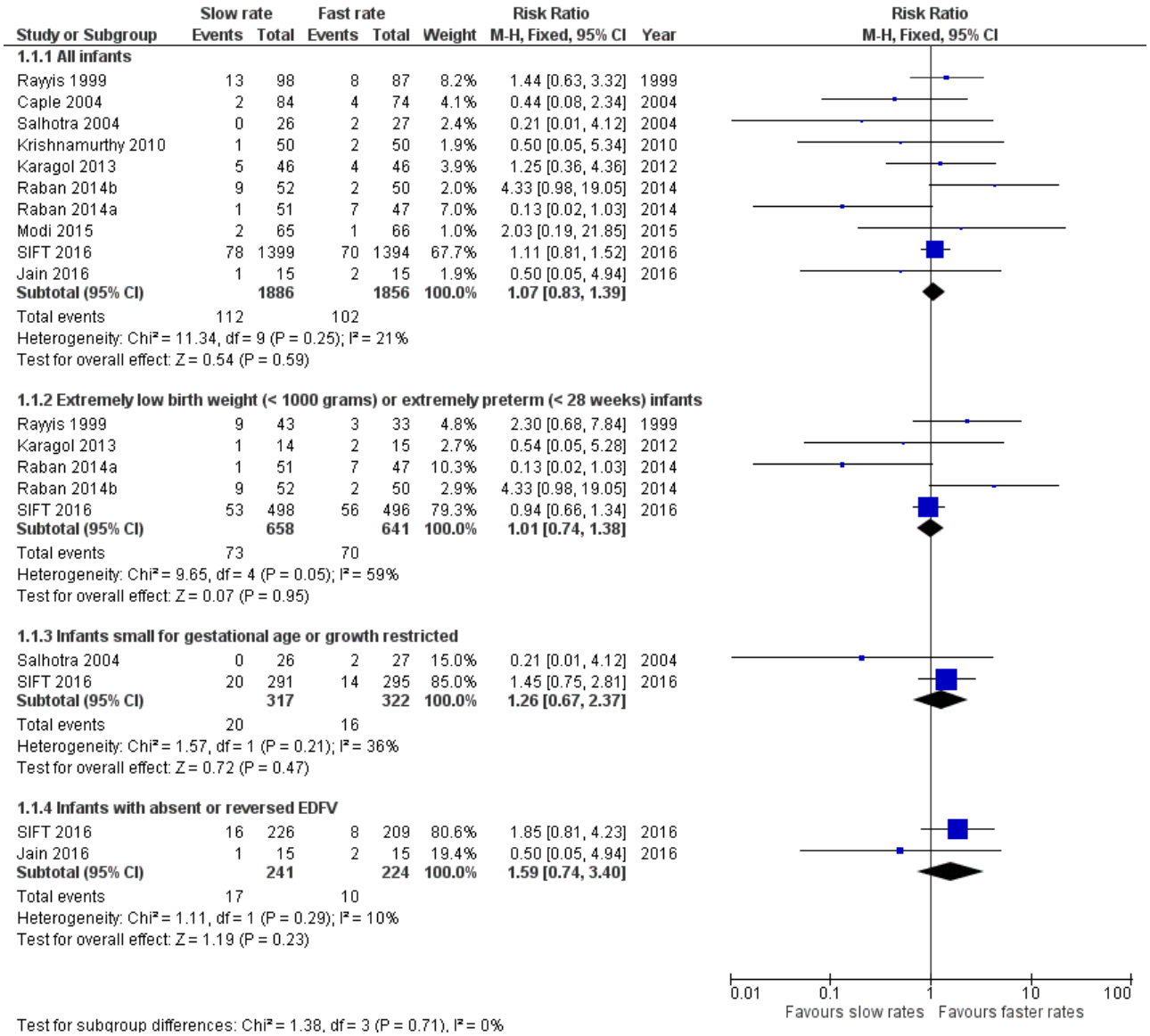
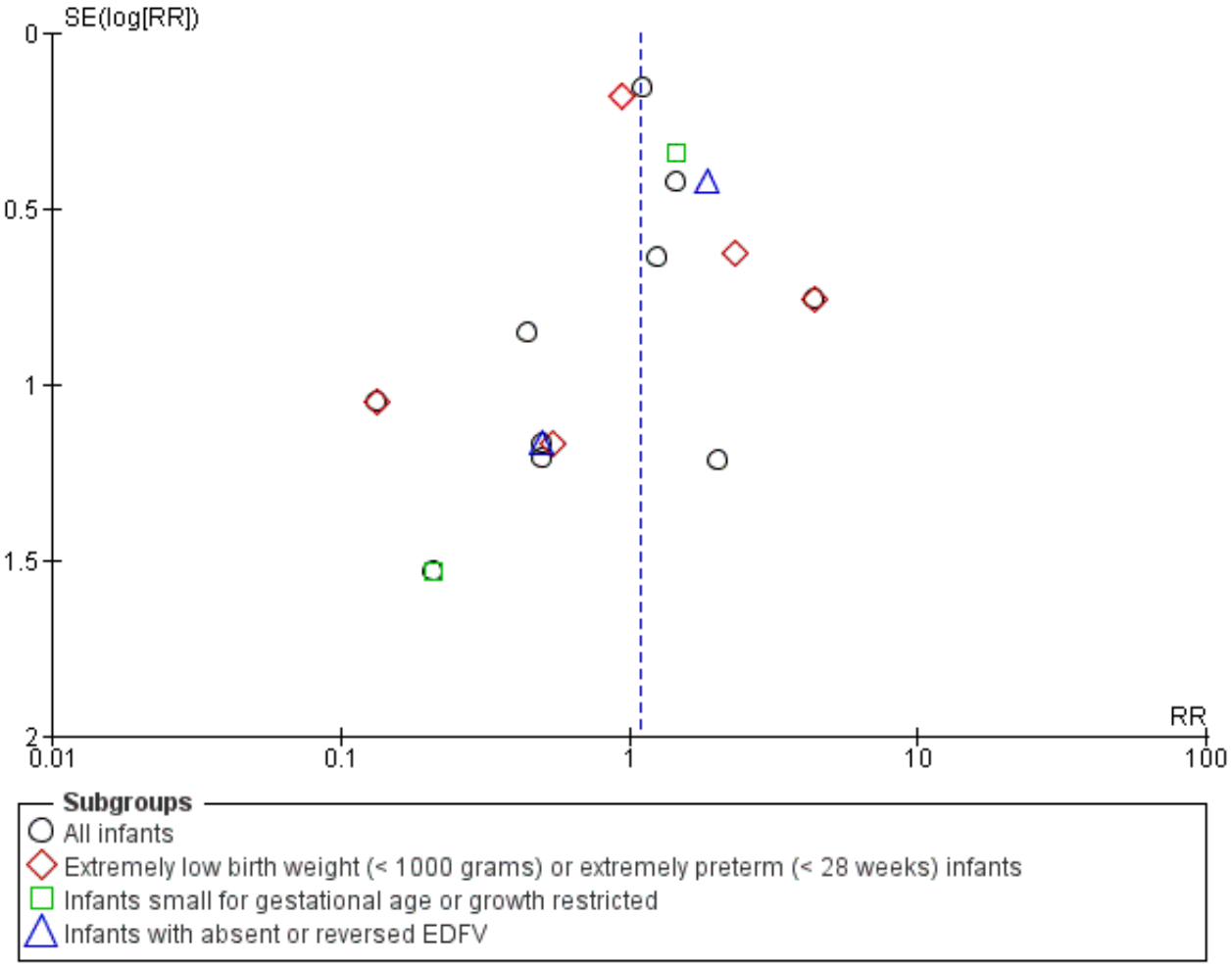


Figure 4. Funnel plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.1 Incidence of necrotising enterocolitis.



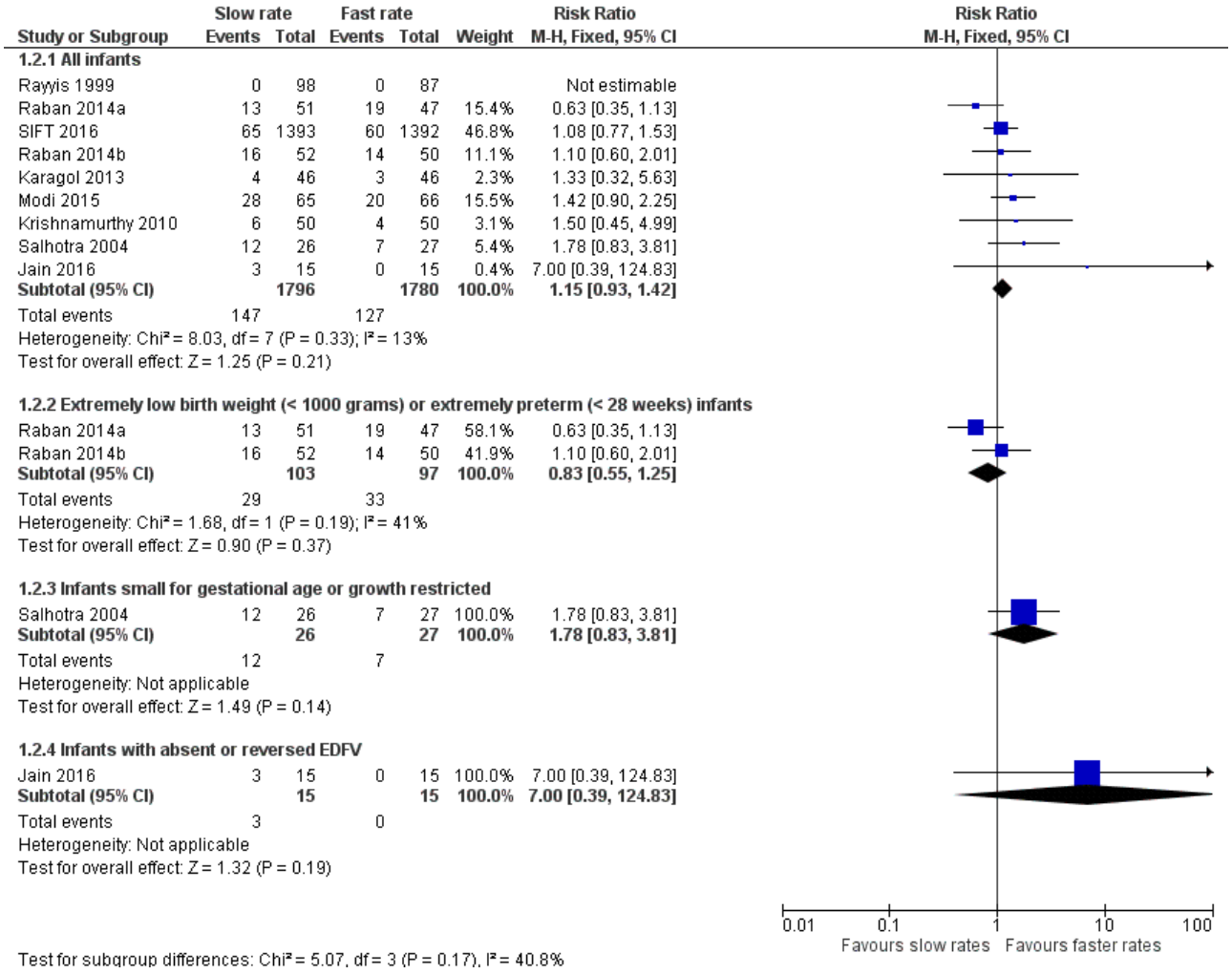
Subgroup analyses did not show an effect in:

- trials where most infants were exclusively formula-fed: RR 1.44 (95% CI 0.63 to 3.32); RD 0.04 (95% CI -0.05 to 0.13); one study (Rayyis 1999), 185 infants;
- trials where most infants were at least partially fed with human milk: RR 1.04 (95% CI 0.79 to 1.37); RD 0.00 (95% CI -0.01 to 0.02); nine studies (all except Rayyis 1999), 3557 infants; I^2 = 26%;
- extremely preterm or ELBW infants: RR 1.01 (95% CI 0.74 to 1.38); RD 0.00 (95% CI -0.03 to 0.03); five studies, 1299 infants; I^2 = 59% (Figure 3);
- infants with intrauterine growth restriction: RR 1.26 (95% CI 0.67 to 2.37); RD 0.01 (95% CI -0.02 to 0.05); two studies, 639 infants; I^2 = 36% (Figure 3); or
- infants with evidence of absent or reversed end-diastolic flow velocity (AREDFV): RR 1.59 (95% CI 0.74 to 3.40); RD 0.03 (95% CI -0.02 to 0.07); two studies, 465 infants; I^2 = 10% (Figure 3).

Mortality

Meta-analysis did not show an effect on risk of mortality (typical RR 1.15, 95% CI 0.93 to 1.42; RD 0.01, 95% CI -0.01 to 0.03; nine studies, 3576 infants; I^2 = 13%) (Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.2 Mortality.



Subgroup analyses did not show an effect in:

- trials where most infants were exclusively formula-fed: RR not estimable (no deaths in either group); RD 0.00 (95% CI -0.02 to 0.02); one study (Rayyis 1999), 185 infants;
- trials where most infants were at least partially fed with human milk: RR 1.15 (95% CI 0.93 to 1.42); RD 0.01 (95% CI -0.01 to 0.03); eight studies (all except Rayyis 1999), 3391 infants; I^2 = 13%;
- extremely preterm or ELBW infants: RR 0.83 (95% CI 0.55 to 1.25); RD -0.06 (95% CI -0.19 to 0.07); two studies, 200 infants; I^2 = 41% (Figure 5)*;
- infants with intrauterine growth restriction: RR 1.78 (95% CI 0.83 to 3.81); RD 0.20 (95% CI -0.05 to 0.46); one study (Salhotra 2004), 53 infants (Figure 5)*; or
- infants with evidence of AREDFV: RR 7.00 (95% CI 0.39 to 124.83); RD 0.20 (95% CI -0.02 to 0.42); one study (Jain 2016), 30 infants (Figure 5)*.

[*Subgroup data not yet available for SIFT 2016.]

Secondary outcomes

Growth

Seven trials reported that infants in the slow-rate-of-advancement group took a longer time to regain birth weight.

- Rayyis 1999: median difference 2 days.
- Caple 2004: MD 2 days (95% CI 1 to 3).
- Salhotra 2004: median difference 5 days.
- Krishnamurthy 2010: median difference 6 days.
- Karagol 2013: MD 3.8 days (CI not given).
- Raban 2014a: data not available.
- Raban 2014b: data not available.

Jain 2016 and Modi 2015 did not report growth.

SIFT 2016 did not show any statistically significant differences in weight (MD 0.00, 95% CI -0.08 to 0.08) nor in head circumference (MD 0.00, 95% CI -0.13 to 0.13) z-scores at hospital discharge (Analysis 1.3; Analysis 1.4).

None of the included trials have yet reported post-hospital discharge growth parameters.

Neurodevelopment

None of the trials have yet reported neurodevelopmental outcomes.

Time to establish full enteral feeding

Seven trials reported that it took longer to establish full enteral feeds in infants in the slow-rate-of-advancement group.

- Rayyis 1999: median difference 4 days.
- Caple 2004: MD 3 days (95% CI 2 to 3).
- Salhotra 2004: MD 4.8 days (CI not given).
- Krishnamurthy 2010: median difference 2 days.
- Karagol 2013: MD 3.2 days (CI not given).
- Jain 2016: MD 0.6 days (CI not given).
- Modi 2015: MD 4 days (CI not given).
- SIFT 2016: median difference 3 days.

Raban 2014a and Raban 2014b did not report this outcome.

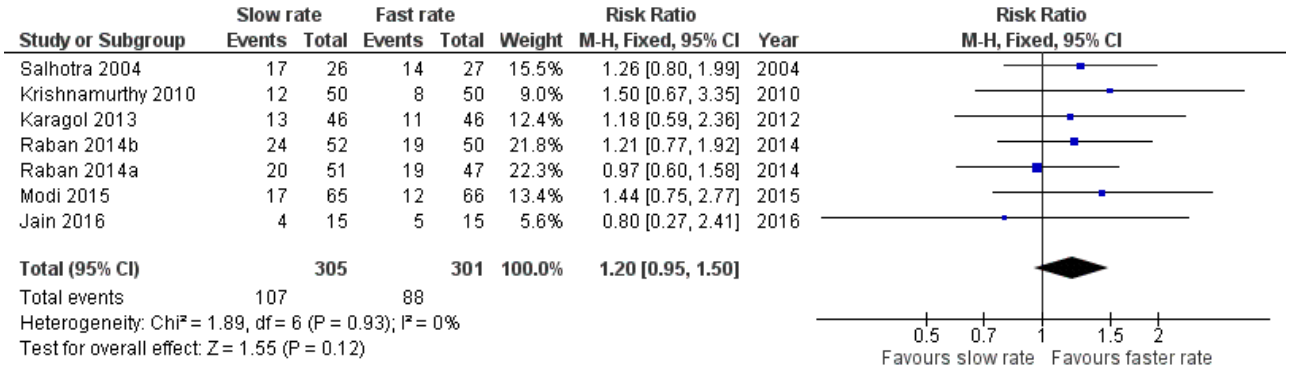
Time to establish full oral feeding

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

Feed intolerance (causing interruption of enteral feeding) (Outcome 1.5)

Meta-analysis of data from seven trials (659 infants) did not show a difference (typical RR 1.20, 95% CI 0.95 to 1.50; typical RD 0.05, 95% CI -0.02 to 0.12; $I^2 = 0\%$) (Analysis 1.5; Figure 6).

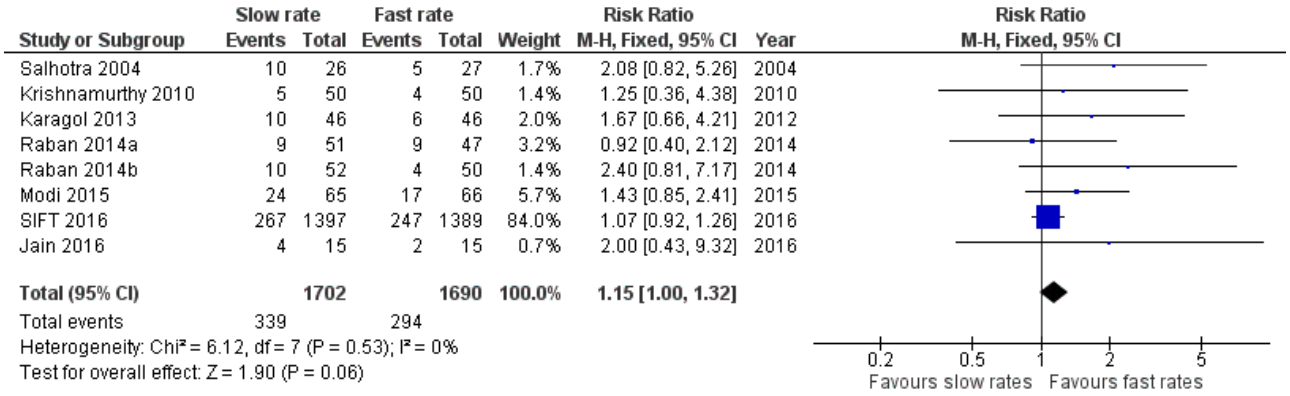
Figure 6. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.5 Feed intolerance (causing interruption of enteral feeding).



Incidence of invasive infection (Outcome 1.6)

Meta-analysis of data from seven trials (3392 infants) showed borderline higher risk among infants who received slow advancement of enteral feed volumes (typical RR 1.15, 95% CI 1.00 to 1.32; typical RD 0.03, 95% CI -0.00 to 0.05; $I^2 = 0\%$) (Analysis 1.6; Figure 7).

Figure 7. Forest plot of comparison: 1 Slow versus faster rates of feed advancement, outcome: 1.6 Incidence of invasive infection.



Duration of hospital stay

Four trials did not show a statistically significant difference in duration of hospital stay.

- Rayyis 1999: median difference 4 days.
- Caple 2004: MD 5 days (95% CI -1 to 8).
- Raban 2014a: data not available.
- Raban 2014b: data not available.
- SIFT 2016: median difference 0 days (54 vs 54 days).

Two trials reported that duration of hospital stay was longer among infants in the slow-rate-of-advancement group.

- Krishnamurthy 2010: median difference 1.5 days.
- Karagol 2013: MD 6 days (CI not given).

The other trials did not report duration of hospital stay (Jain 2016; Modi 2015; Salhotra 2004).

DISCUSSION

Summary of main results

Available trial data do not provide evidence that advancing enteral feed volumes at slow rates (15 to 20 mL/kg/d) compared with faster rates (30 to 40 mL/kg/d) reduces the risk of necrotising enterocolitis (NEC) in very low birth weight (VLBW) infants. The boundaries of the 95% confidence interval (CI) for the estimate of effect are consistent with either two extra or one fewer cases of NEC in every 100 infants who have slow rates of feed advancement. Meta-analysis of data from these trials did not show an effect on all-cause mortality, and prespecified subgroup analyses revealed no statistically significant effects on risk of NEC or death among extremely low birth weight (ELBW) or extremely preterm infants, nor among infants with growth restriction or evidence of absent or reversed end-diastolic flow velocity (AREDFV). Meta-analysis of data from eight trials showed borderline higher risk of late-onset infection among infants who had slow advancement of enteral feeds. The point estimate suggested that an extra episode of late-onset infection occurs for every 33 infants who have slow feed advancement.

Infants who had slow advancement of feed volumes established full enteral feeding and regained birth weight several days later than infants who had faster rates of advancement of feed volumes. The clinical importance of these effects is unclear, as longer-term growth or developmental outcomes were not assessed. The included trials did not show consistent evidence of an important effect on duration of hospital admission.

Overall completeness and applicability of evidence

Most participants in the included trials were stable very preterm or VLBW infants of birth weight appropriate for gestational age. About one-third of all participants were extremely preterm or ELBW, and about one-fifth were small for gestational age, growth-restricted, or compromised in utero, as indicated by AREDFV in the foetal umbilical artery. Infants who had severe respiratory distress requiring oxygen supplementation or ventilatory support were eligible to participate in all but three of the trials (Karagol 2013; Krishnamurthy 2010; Salhotra 2004). Therefore, review findings should be applicable across these populations at highest risk of developing feed intolerance or NEC (Luig 2005).

Most participating infants were fed, at least partially, with breast milk. Evidence indicates that artificial formula feeding increases risks of feed intolerance and 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, but available data were insufficient to show effects of different rates of feed advancement on important outcomes for infants fed exclusively with artificial formula. It is also unclear whether review findings can be applied to infants who receive continuous infusion of intragastric feeds, as a vast majority of the infants in 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 establishment of full enteral feeds may seem intuitive, it is plausible that advancing feed volumes faster could have resulted in more feed intolerance and therefore a delay in establishment of full enteral feeding. Included trials prespecified definitions of feed intolerance that mandated interrupting or ceasing feed volume advancement, principally detection of prefeed 'gastric residuals' (gastric content aspirated before a planned gastric tube feed) and abdominal distension. However, trial reports presented only limited data on the frequency of these outcomes. Furthermore, limited evidence suggests that the volume or colour of gastric residuals is predictive of risk of NEC for infants whose feed volumes are advanced conservatively (Cobb 2004; Bertino 2009; Mihatsch 2002). 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 GRADE quality of evidence for primary outcomes was "moderate", downgraded from "high" because of lack of blinding in the included trials (Summary of findings for the main comparison). Although these trials were generally of good methodological quality, 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 2). Lack of blinding may have resulted in surveillance and ascertainment biases. It is more likely, however, to have caused an overestimation of the incidence of feed intolerance and NEC among infants whose feed volumes were advanced faster. Assessment of abdominal radiographs for signs of NEC was masked in most trials to ensure that the diagnosis of severe NEC (confirmed by radiological detection of gas in the bowel wall or portal tract) was not prone to bias. However, as 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 among infants who had faster rates of feed volume advancement (Tyson 2007).

Potential biases in the review process

The main concern with the review process is the possibility that findings are subject to publication and other reporting biases. We attempted to minimise this threat by screening the reference lists of included trials and related reviews and searching the proceedings of major international perinatal conferences to identify trial reports that are not (yet) published in full form in academic journals. Only one of the meta-analyses that we performed included sufficient trials to explore symmetry of funnel plots as a means of identifying possible publication or small study bias, and this did not show sufficient asymmetry to raise concerns (Figure 3).

Agreements and disagreements with other studies or reviews

This review focused specifically 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 this trial found the risk of NEC to be statistically significantly higher among infants whose feed volumes were progressively advanced, this finding should be interpreted cautiously. The trial was stopped early following an interim analysis; therefore, the finding of an effect on the incidence of NEC may be spurious (Montori 2005). Caregivers and assessors were not blinded to the intervention. As discussed above, this may have resulted in several sources of bias that are likely to cause an overestimation of the incidence of NEC among infants whose feed volumes are being advanced.

AUTHORS' CONCLUSIONS

Implications for practice

Advancing enteral feed volumes at slow rates (slower than 24 mL/kg/d) does not reduce the risk of feed intolerance, NEC, or death in very preterm or VLBW infants, including extremely preterm or ELBW infants, or in infants who are growth-restricted or growth-compromised in utero. Advancing the volume of enteral feeds at faster rates (daily increments of 30 to 40 mL/kg) shortens by several days the time taken to regain birth weight and establish full enteral feeds, and may reduce the risk of late-onset invasive infection.

Implications for research

Additional randomised controlled trials are unlikely to alter these effect estimates for feed intolerance, NEC, or death. Data on longer-term outcomes, principally growth and development beyond infancy, may be available from the largest of the existing completed trials when follow-up assessment has been completed.

ACKNOWLEDGEMENTS

We are grateful to Drs. Namasivayam Ambalavanan, Siddarth Ramji, Manoj Modi, and Kanya Mukhopadhyay for providing details and data (Rayyis 1999; Salhotra 2004; Modi 2015; Jain 2016).

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. [DOI: 10.1542/peds.2004-1232; PUBMED: 15574620]

Jain 2016 *{published data only}*

* Jain S, Mukhopadhyay K, Jain V, Kumar P. Slow versus rapid enteral feed in preterm neonates with antenatal absent end diastolic flow. *Journal of Maternal-Fetal & Neonatal Medicine* 2016;**29**(17):2828-33. [DOI: 10.3109/14767058.2015.1105954; PUBMED: 26452650]

Mukhopadhyay K, Jain S. Feed intolerance and necrotising enterocolitis in rapid vs slow feeding in preterm neonates with absent end diastolic flow: a randomised controlled trial. Proceedings of the Pediatric Academic Societies and Asian Society for Pediatric Research; 2014 May 3-6; Vancouver. 2014.

Karagol 2013 *{published data only}*

Karagol BS, Zenciroglu A, Okumus N, Polin RA. Randomized controlled trial of slow versus rapid enteral feeding advancements on the clinical outcomes of preterm infants with 750-1250g. *Journal of Parenteral and Enteral Nutrition* 2013;**37**(2):223-8. [DOI: 10.1177/0148607112449482; PUBMED: 22664861]

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. [DOI: 10.1111/j.1651-2227.2009.01519.x; PUBMED: 20002013]

Modi 2015 *{published data only}*

* Modi M, Ranji S, Jain A, Sharma P, Gupta N. A randomised trial of aggressive feeding regimen in infants with birth weight ≤ 1250 grams. Proceedings of the Pediatric Academic Societies Annual Conference; 2015 Apr 25-28; San Diego, CA. 2015.

Raban 2014a *{published data only}*

Raban MS, Santhakumaran S, Keraan Q, Joolay Y, Uthaya S, Horn AR, et al. A randomised controlled trial of high or low volume initiation and rapid or slow advancement of milk feeds for infants ≤ 1000 g. Proceedings of the South African Paediatric Association Congress; 2014 Sept 10-14; Cape Town. 2014. [DOI: 10.1186/ISRCTN96923718]

Raban 2014b *{published data only}*

Raban MS, Santhakumaran S, Keraan Q, Joolay Y, Uthaya S, Horn AR, et al. A randomised controlled trial of high or low volume initiation and rapid or slow advancement of milk feeds for infants ≤ 1000 g. Proceedings of the South African Paediatric Association Congress; 2014 Sept 10-14; Cape Town. 2014. [DOI: 10.1186/ISRCTN96923718]

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. [PUBMED: 10064664]

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. [PUBMED: 15181294]

SIFT 2016 *{published data only}*

SIFT Investigators Group. Early enteral feeding strategies for very preterm infants: current evidence from Cochrane reviews. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2013;**98**(6):F470-2. [DOI: 10.1136/archdischild-2012-303260; PUBMED: 23766343]

SIFT Investigators Group. SIFT: Outcomes at discharge. BAPM Annual General & Scientific Meeting; September 15-16, 2016; Watershed, Bristol. 2016.

* SIFT Investigators Group. SIFT: Speed of increasing feeds trial. Hot Topics in Neonatology Annual Meeting; December 5-7, 2016; Washington, DC. 2016.

SIFT Investigators Group. The Speed of Increasing milk Feeds Trial (SIFT); Results at Hospital Discharge. Pediatric Academic Societies Annual Meeting; May 6-9, 2017; San Francisco, CA. 2017 (See: https://registration.pas-meeting.org/2017/reports/rptPAS17_Abstracts.asp).

SIFT Investigators Group. The Speed of Increasing milk Feeds: a randomised controlled trial. *BMC Pediatrics* 2017;**17**(1):39. [DOI: 10.1186/s12887-017-0794-z; PUBMED: 28129748]

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. [PUBMED: 12612232]

Book 1976 *{published data only}*

Book LS, Herbst JJ, Jung A. Comparison of fast- and slow-feeding rate schedules to the development of necrotizing enterocolitis. *Journal of Pediatrics* 1976;**89**(3):463-6. [PUBMED: 989057]

Gray 2017 *{published data only}*

Gray MM, Medoff-Cooper B, Enlow EM, Mukhopadhyay S, DeMauro SB. Every three-hour versus every six-hour oral feeding in preterm infants: a randomised clinical trial. *Acta Paediatrica* 2017;**106**(2):236-41. [PUBMED: 27862264]

Ibrahim 2017 *{published data only}*

Ibrahim NR, Kheng TH, Nasir A, Ramli N, Foo JLK, Syed Alwi SH, et al. Two-hourly versus 3-hourly feeding for very

low birthweight infants: a randomised controlled trial. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2017;**102**(3):F225-9. [PUBMED: 27671836]

Jayaraman 2017 *{published data only}*

Jayaraman D, Mukhopadhyay K, Bhalla AK, Dhaliwal LK. Randomized controlled trial on effect of intermittent early versus late kangaroo mother care on human milk feeding in low-birth-weight neonates. *Journal of Human Lactation* 2017:890334416685072. [PUBMED: 28152330]

Tewari 2017 *{published data only}*

Tewari VV, Dubey SK, Kumar R, Vardhan S, Sreedhar CM, Gupta G. Early versus late enteral feeding in preterm intrauterine growth restricted neonates with antenatal doppler abnormalities: an open-label randomized trial. *Journal of Tropical Pediatrics* 2017:[Epub ahead of print]. [PUBMED: 28369652]

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. [PUBMED: 1586186]

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. [PUBMED: 10649179]

Berrington 2012

Berrington JE, Hearn RI, Bythell M, Wright C, Embleton ND. Deaths in preterm infants: changing pathology over 2 decades. *Journal of Pedodontics* 2012;**160**(1):49-53.e1. [DOI: 10.1016/j.jpeds.2011.06.046; PUBMED: 21868028]

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. [PUBMED: 11875136]

Brown 1978

Brown EG, Sweet AY. Preventing necrotizing enterocolitis in neonates. *JAMA* 1978;**240**(22):2452-4. [PUBMED: 101680]

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. [DOI: 10.1136/adc.2007.115824; 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. [PUBMED: 14702446]

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. [DOI: 10.1136/adc.2004.060350; PUBMED: 16113150]

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. [DOI: 10.1136/adc.2002.021923; PUBMED: 15210657]

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. [DOI: 10.1080/08035250600719713; PUBMED: 17062457]

Gagliardi 2008

Gagliardi L, Bellu R, Cardilli V, De Curtis M. Necrotising enterocolitis in very low birth weight infants in Italy: incidence and non-nutritional risk factors. *Journal of Pediatric Gastroenterology and Nutrition* 2008;**47**(2):206-10. [DOI: 10.1097/MPG.0b013e318174e855; PUBMED: 18664876]

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. [DOI: 10.1016/j.ajog.2004.01.036; PUBMED: 15343225]

GRADEpro GDT [Computer program]

GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 12 May 2017. Hamilton (OPN): GRADE Working Group, McMaster University, 2014.

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. [DOI: 10.1038/sj.jp.7210892; PUBMED: 12774133]

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. [DOI: 10.1136/adc.2007.119560; PUBMED: 17768154]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

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. [PUBMED: 9431297]

Härtel 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. [DOI: 10.1097/MPG.0b013e31818c5fc3; PUBMED: 19322056]

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. [DOI: 10.1111/j.1440-1754.2005.00583.x; 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. [PUBMED: 1432431]

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. [PUBMED: 11875141]

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. [DOI: 10.1001/jama.294.17.2203; PUBMED: 16264162]

Morgan 2013

Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. *Cochrane Database of Systematic Reviews* 2013, Issue 3. [DOI: 10.1002/14651858.CD000504.pub3; PUBMED: 19588318]

Morgan 2014a

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* 2014, Issue 12. [DOI: 10.1002/14651858.CD001970.pub3; PUBMED: 21412877]

Moro 2009

Moro M, Pérez-Rodriguez J, Figueras-Aloy J, Fernández C, Doménech E, Jiménez R, et al. Predischarge morbidities in extremely and very low-birth-weight infants in Spanish neonatal units. *American Journal of Perinatology* 2009;**26**(5):335-43. [DOI: 10.1055/s-0028-1110083; PUBMED: 19090453]

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. Fetal and Neonatal Edition* 2005;**90**(2):F147-51. [DOI: 10.1136/adc.2004.059741; PUBMED: 15724039]

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. [DOI: 10.1136/fetalneonatal-2011-300244; 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; PUBMED: 22071802]

Quigley 2014

Quigley MA, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2014, Issue 4. [DOI: 10.1002/14651858.CD002971.pub2; PUBMED: 24752468]

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. [DOI: 10.1136/adc.2006.099929; PUBMED: 16984980]

Samuels 2017

Samuels N, van de Graaf RA, de Jonge RCJ, Reiss IKM, Vermeulen MJ. Risk factors for necrotizing enterocolitis in neonates: a systematic review of prognostic studies. *BMC Pediatrics* 2017;**17**(1):105. [DOI: 10.1186/s12887-017-0847-3; PUBMED: 28410573]

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE Working Group. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. https://gdt.gradepro.org/app/handbook/handbook.html. Updated October 2013.

Shah 2012

Shah TA, Meinzen-Derr J, Gratton T, Steichen J, Donovan EF, Yolton K, et al. Hospital and neurodevelopmental outcomes of extremely low-birth-weight infants with necrotizing enterocolitis and spontaneous intestinal perforation. *Journal*

of Perinatology 2012;**32**(7):552-8. [DOI: 10.1038/jp.2011.176; PUBMED: 22157625]

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. [DOI: 10.1111/j.1440-1754.2006.00910.x; 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. [DOI: 10.1001/jama.292.19.2357; PUBMED: 15547163]

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. [DOI: 10.1053/j.semperi.2007.02.008; PUBMED: 17462490]

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. [PUBMED: 1919897]

Walsh 1986

Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatric Clinics of North America* 1986;**33**(1):179-201. [PUBMED: 3081865]

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; PUBMED: 18425870]

Morgan 2011

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]

Morgan 2014b

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* 2014, Issue 12. [DOI: 10.1002/14651858.CD001241.pub4; PUBMED: 23543511]

Morgan 2015

Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *The Cochrane Database of Systematic Reviews* 2015;**10**:CD001241. [PUBMED: 26469124]

* 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	Feed advancement at 20 mL/kg/d (n = 84) vs 30 mL/kg/d (n = 74)
Outcomes	NEC (Bell stage 2 or 3) Time to regain birth weight Time to achieve full enteral feeds Time to hospital discharge

Caple 2004 *(Continued)*

Notes	Feeds were ceased if the residual gastric aspirate was more than one-third of the previous feed volume, or if frequent vomiting, abdominal distention, or bloody stools (including occult blood) were noted We were unable 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 the study
Blinding (performance bias and detection bias) Clinical assessments	High risk	Caregivers 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	3 infants excluded after enrolment because of protocol violations were included in this review and meta-analysis. 2 infants (1 in each group) were excluded because they were determined not eligible for enrolment as the result of an in utero gastrointestinal perforation and foetal alcohol syndrome; these infants were not included in the meta-analysis

Jain 2016

Methods	Randomised controlled trial
Participants	Preterm infants (birth weight 1000-1249 grams and gestational age > 30 weeks at birth) who have antenatal evidence of absent end-diastolic flow velocities (presumed in umbilical artery) Setting: Department of Paediatrics, Postgraduate Institute of Medical Education & Research, Chandigarh, India
Interventions	Feed advancement at 20 mL/kg/d (n = 15) vs 30 mL/kg/d (n = 15)
Outcomes	NEC (all stages and stage 2 or 3) Late-onset bloodstream (culture-positive) infection In-hospital mortality Time to achieve full enteral feeds
Notes	Prespecified subgroup of a larger trial that enrolled infants with birth weight > 1250 grams and compared feed advancement at 30 mL/kg/d vs 40 mL/kg/d Additional data courtesy of Dr. Mukhopadhyay (September 2014)

Risk of bias

Bias	Authors' judgement	Support for judgement

Jain 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias) Clinical assessments	High risk	Caregivers and investigators were not blinded to the interventions
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up for primary outcomes

Karagol 2013

Methods	Randomised controlled trial
Participants	Preterm infants < 32 weeks' gestation with birth weight of 750-1250 grams 32% of infants weighed < 1000 grams Exclusion criteria included major congenital malformations, severe respiratory distress, presence of umbilical vessel catheters, contraindications to enteral feeding, perinatal asphyxia, and cardiovascular compromise Setting: Division of Neonatology, Dr. Sami Ulus Maternity, Children's Education and Research Hospital, Ankara, Turkey
Interventions	Slow advancement at 20 mL/kg/d (n = 46) vs rapid advancement at 30 mL/kg/d (n = 46)
Outcomes	NEC (Bell stage 2 or 3) All-cause mortality Time to regain birth weight Time to reach full enteral feeds Feed intolerance 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

Karagol 2013 *(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	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 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 Setting: Department of Paediatrics, University College of Medical Sciences, Delhi, India
Interventions	Feed advancement at 20 mL/kg/d (n = 50) vs 30 mL/kg/d (n = 50)
Outcomes	NEC (Bell stage 2 or 3) Incidence of invasive infection In-hospital mortality Time to regain birth weight Time to achieve full enteral feeds Time to hospital discharge
Notes	All feeds were delivered by gavage via nasogastric tube at 2-hour intervals Feeds were ceased if any of the following occurred: residual gastric contents > 50% of previous feed volume (delayed if volume was 25% to 50%), > 3 episodes of apnoea in the preceding hour, abdominal distension 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

Krishnamurthy 2010 *(Continued)*

Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes
Blinding (performance bias and detection bias) Clinical assessments	High risk	Caregivers and investigators were not blinded to interventions
Blinding (performance bias and detection bias) Radiological assessments	Low risk	Radiologist interpreting x-rays was blinded to the intervention group
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up

Modi 2015

Methods	Randomised controlled trial
Participants	Newborn infants with birth weight of 750 to 1250 grams who commenced enteral feeds within 4 days after birth. Mean gestational age of participants was 31 weeks Exclusion criteria were "gross congenital malformation and anomalies of gastrointestinal tract (intestinal atresia, imperforated anus etc)" Setting: Department of Neonatology, Maulana Azad Medical College, New Delhi, India
Interventions	Feed advancement at 15-20 mL/kg/d (n = 65) vs 30-40 mL/kg/d (n = 66)
Outcomes	NEC (Bell stage 2 or 3) Incidence of feed intolerance Invasive infection In-hospital (all cause) mortality Mean daily weight gain Time to achieve full enteral feeds
Notes	Published as abstract only Further information available from www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=5289

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stratified block randomisation
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed, opaque envelopes
Blinding (performance bias and detection bias)	High risk	Unblinded

Modi 2015 *(Continued)*

Clinical assessments		
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up

Raban 2014a

Methods	Randomised controlled trial (2 × 2 factorial design with Raban 2014b)
Participants	Infants with birth weight ≤ 1000 grams Setting: Groote Schuur Hospital, in Cape Town, South Africa (2011-2013)
Interventions	Feed advancement (from 12 mL/kg/d on day 2) in daily increments of 24 mL/kg (n = 51) vs 36 mL/kg (n = 47) until enteral feeds of 200 mL/kg/d were attained
Outcomes	Time to attain 1500 grams of weight Time to regain birth weight Mortality Feed intolerance NEC (Bell stage 2 or 3) Invasive infection
Notes	Factorial design also randomised to commencing feeds on day 1 (24 mL/kg) or day 2 (12 mL/kg) Infants received maternal expressed breast milk or donor breast milk Trial registration: ISRCTN96923718

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) Clinical assessments	High risk	Caregivers and investigators were not blinded to the interventions
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	Not stated

Raban 2014a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up for primary outcomes

Raban 2014b

Methods	Randomised controlled trial (2 × 2 factorial design with Raban 2014a)
Participants	Infants with birth weight ≤ 1000 grams Setting: Groote Schuur Hospital, in Cape Town, South Africa (2011-2013)
Interventions	Feed advancement (from 24 mL/kg/d on day 1) in daily increments of 24 mL/kg (n = 52) vs 36 mL/kg (n = 50) until enteral feeds of 200 mL/kg/d were attained
Outcomes	Time to attain 1500 grams of weight Time to regain birth weight Mortality Feed intolerance NEC (Bell stage 2 or 3) Invasive infection
Notes	Factorial design also randomised to commencing feeds on day 1 (24 mL/kg) or day 2 (12 mL/kg) Infants received maternal expressed breast milk or donor breast milk Trial registration: ISRCTN96923718

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) Clinical assessments	High risk	Caregivers and investigators were not blinded to the interventions
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up for primary outcomes

Rayyis 1999

Methods	Randomised controlled trial
Participants	Very low birth weight infants of gestational age < 34 weeks at birth Setting: Neonatal Unit, Department of Pediatrics, University of Alabama, Birmingham, Alabama, USA
Interventions	Feed advancement at 15 mL/kg/d (n = 98) vs 35 mL/kg/d (n = 87)
Outcomes	NEC (Bell stage 2 or 3) Time to regain birth weight Time to achieve full enteral feeds Time to hospital discharge
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 was switched to nutrient-enriched 'preterm' formula when full enteral feeding had been achieved. Feeds were ceased if any of the following occurred: residual gastric contents > 30% of previous feed volume, abdominal distension 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	Caregivers and investigators were not blinded to the intervention groups
Blinding (performance bias and detection bias) Radiological assessments	Low risk	Radiologist interpreting 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 in the final data analysis

Salhotra 2004

Methods	Randomised controlled trial
Participants	Preterm infants of birth weight < 1250 grams (> 95% of 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	Feed advancement at 15 mL/kg/d (n = 26) vs 30 mL/kg/d (n = 27)

Salhotra 2004 *(Continued)*

Outcomes	NEC (Bell stage 2 or 3) Neonatal mortality Time to regain birth weight Time to achieve full enteral feeds Time to hospital discharge
Notes	Feeds were ceased if residual gastric content was > 30% of previous feed volume or if abdominal distension was noted Mortality data courtesy of Dr. Namasivayam Ambalavanan

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 were blinded at allocation stage, but it is unclear whether they remained blinded thereafter. Caregivers were 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

SIFT 2016

Methods	Randomised controlled trial
Participants	Very preterm or very low birth weight infants (subgroup data for gestational age and birth weight categories reported)
Interventions	Feeds advancement at 18 mL/kg/d (n = 1404) vs 30 mL/kg/d (n = 1400)
Outcomes	Death Neurodisability by 18 to 24 months post term (yet to be reported) Late-onset invasive infection from trial entry to discharge home NEC (Bell stage 2 or 3) from trial entry to discharge home Time taken to reach full milk feeds (tolerating 150 mL/kg/d for 3 consecutive days) Growth (change in z-score - weight and head circumference for gestational age) from birth to discharge home

SIFT 2016 *(Continued)*	
	Duration of parenteral feeding
	Length of time in intensive care
	Length of hospital stay to discharge home
Notes	Published in abstract form (for hospital outcomes only to date)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Computer-based random allocation
Blinding (performance bias and detection bias) Clinical assessments	High risk	Unblinded
Blinding (performance bias and detection bias) Radiological assessments	Unclear risk	Clinicians likely to be unblinded; radiologists may have been blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete outcome data for in-hospital outcomes (2789/2804 = 99.5%)

ELBW: extremely low birth weight; n: number of infants; NEC: necrotising enterocolitis

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

Study	Reason for exclusion
Berseth 2003	Infants were randomly allocated to a stable (not progressively increased) trophic feeding volume or to feed volume advancement at 20 mL/kg/d
Book 1976	Enteral feeding volumes were advanced at 10 mL/kg/d vs 20 mL/kg/d, that is, both groups received 'slow' advancement of feed volumes
Gray 2017	RCT of different feeding intervals (not different rates of feed volume advancement) in very preterm infants
Ibrahim 2017	RCT of different feeding intervals (not different rates of feed volume advancement) in very preterm infants
Jayaraman 2017	RCT examining the effect on breast milk feeding of early vs delayed kangaroo mother care in low birth weight infants (no intention to advance enteral feed volumes at different rates)
Tewari 2017	RCT of early vs delayed initiation of progressive enteral feeding in very preterm infants (feeds were advanced at 10 to 15 mL/kg/d in both groups)

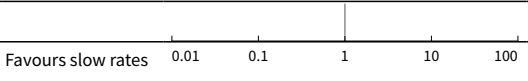
DATA AND ANALYSES

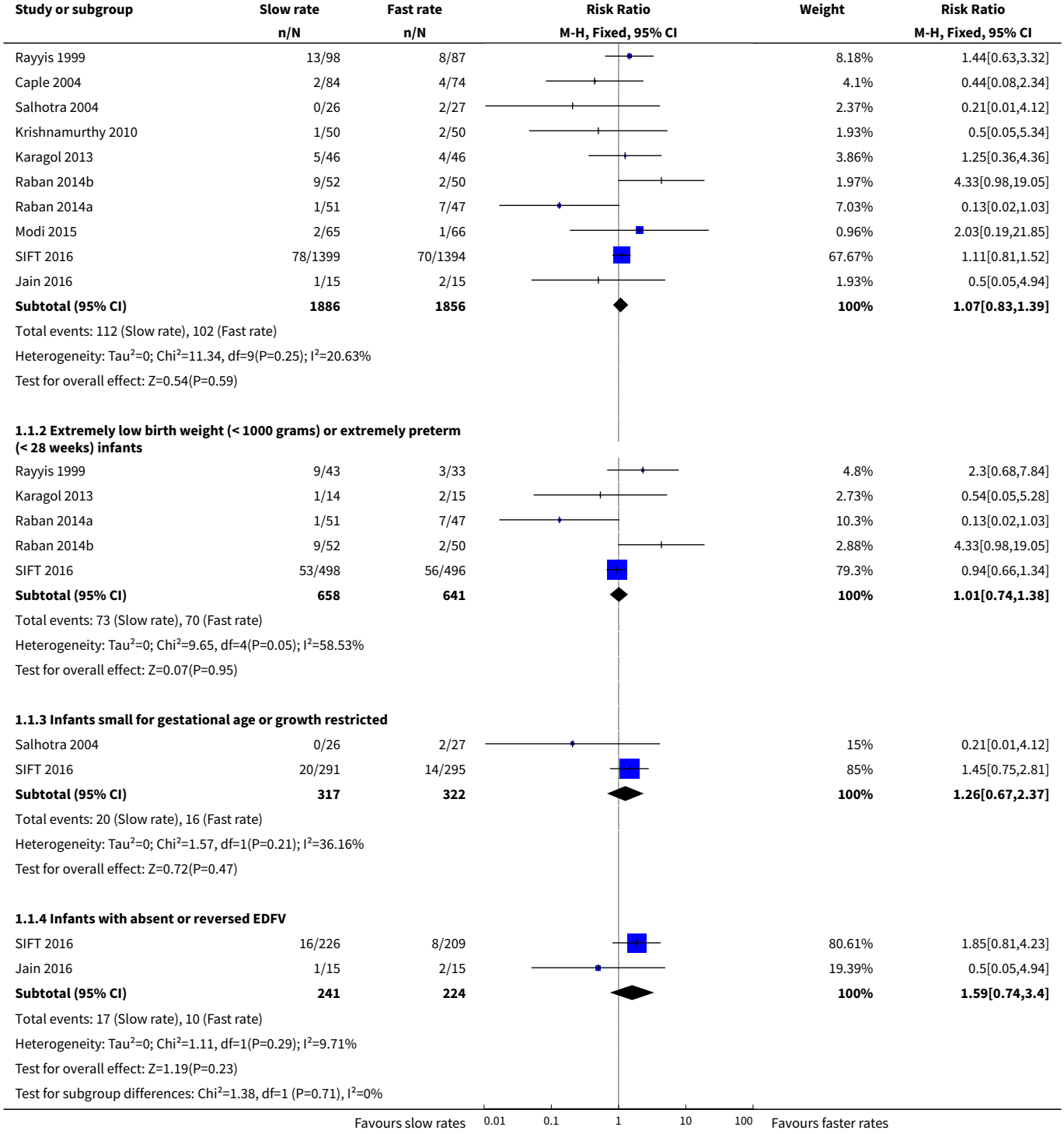
Comparison 1. Slow versus faster rates of feed advancement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of necrotising enterocolitis	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All infants	10	3742	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.83, 1.39]
1.2 Extremely low birth weight (< 1000 grams) or extremely preterm (< 28 weeks) infants	5	1299	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.74, 1.38]
1.3 Infants small for gestational age or growth restricted	2	639	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.67, 2.37]
1.4 Infants with absent or reversed EDFV	2	465	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.74, 3.40]
2 Mortality	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 All infants	9	3576	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.42]
2.2 Extremely low birth weight (< 1000 grams) or extremely preterm (< 28 weeks) infants	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.55, 1.25]
2.3 Infants small for gestational age or growth restricted	1	53	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.83, 3.81]
2.4 Infants with absent or reversed EDFV	1	30	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.39, 124.83]
3 Weight z-score at hospital discharge	1	2602	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.08, 0.08]
4 Head circumference z-score at hospital discharge	1	2286	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.13, 0.13]
5 Feed intolerance (causing interruption of enteral feeding)	7	606	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.95, 1.50]
6 Incidence of invasive infection	8	3392	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.00, 1.32]

Analysis 1.1. Comparison 1 Slow versus faster rates of feed advancement, Outcome 1 Incidence of necrotising enterocolitis.

Study or subgroup	Slow rate n/N	Fast rate n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 All infants					





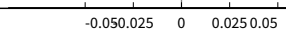
Analysis 1.2. Comparison 1 Slow versus faster rates of feed advancement, Outcome 2 Mortality.

Study or subgroup	Slow rate n/N	Fast rate n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 All infants					
Rayyis 1999	0/98	0/87			Not estimable
Raban 2014a	13/51	19/47		15.42%	0.63[0.35,1.13]
SIFT 2016	65/1393	60/1392		46.79%	1.08[0.77,1.53]
Raban 2014b	16/52	14/50		11.13%	1.1[0.6,2.01]
Karagol 2013	4/46	3/46		2.34%	1.33[0.32,5.63]
Modi 2015	28/65	20/66		15.47%	1.42[0.9,2.25]
Krishnamurthy 2010	6/50	4/50		3.12%	1.5[0.45,4.99]
Salhotra 2004	12/26	7/27		5.35%	1.78[0.83,3.81]
Jain 2016	3/15	0/15		0.39%	7[0.39,124.83]
Subtotal (95% CI)	**1796**	**1780**		**100%**	**1.15[0.93,1.42]**
Total events: 147 (Slow rate), 127 (Fast rate)					
Heterogeneity: Tau^2=0; Chi^2=8.03, df=7(P=0.33); I^2=12.82%					
Test for overall effect: Z=1.25(P=0.21)					
1.2.2 Extremely low birth weight (< 1000 grams) or extremely preterm (< 28 weeks) infants					
Raban 2014a	13/51	19/47		58.08%	0.63[0.35,1.13]
Raban 2014b	16/52	14/50		41.92%	1.1[0.6,2.01]
Subtotal (95% CI)	**103**	**97**		**100%**	**0.83[0.55,1.25]**
Total events: 29 (Slow rate), 33 (Fast rate)					
Heterogeneity: Tau^2=0; Chi^2=1.68, df=1(P=0.19); I^2=40.58%					
Test for overall effect: Z=0.9(P=0.37)					
1.2.3 Infants small for gestational age or growth restricted					
Salhotra 2004	12/26	7/27		100%	1.78[0.83,3.81]
Subtotal (95% CI)	**26**	**27**		**100%**	**1.78[0.83,3.81]**
Total events: 12 (Slow rate), 7 (Fast rate)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.49(P=0.14)					
1.2.4 Infants with absent or reversed EDFV					
Jain 2016	3/15	0/15		100%	7[0.39,124.83]
Subtotal (95% CI)	**15**	**15**		**100%**	**7[0.39,124.83]**
Total events: 3 (Slow rate), 0 (Fast rate)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.32(P=0.19)					
Test for subgroup differences: Chi^2=5.07, df=1 (P=0.17), I^2=40.8%					

Analysis 1.3. Comparison 1 Slow versus faster rates of feed advancement, Outcome 3 Weight z-score at hospital discharge.

Study or subgroup	Slow rate N	Slow rate Mean(SD)	Fast rate N	Fast rate Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
SIFT 2016	1295	-1.5 (1.1)	1307	-1.5 (1.1)		100%	0[-0.08,0.08]
Total ***	**1295**		**1307**			**100%**	**0[-0.08,0.08]**

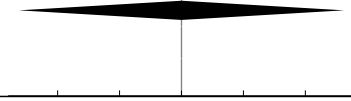
Study or subgroup	Slow rate N	Slow rate Mean(SD)	Fast rate N	Fast rate Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Favours slow rates | Favours faster rates

Analysis 1.4. Comparison 1 Slow versus faster rates of feed advancement, Outcome 4 Head circumference z-score at hospital discharge.

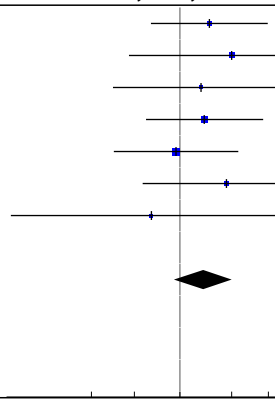
Study or subgroup	Slow rate N	Slow rate Mean(SD)	Fast rate N	Fast rate Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
SIFT 2016	1156	-0.8 (1.7)	1130	-0.8 (1.5)		100%	0[-0.13,0.13]
Total ***	**1156**		**1130**			**100%**	**0[-0.13,0.13]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Favours slow rates | Favours faster rates

Analysis 1.5. Comparison 1 Slow versus faster rates of feed advancement, Outcome 5 Feed intolerance (causing interruption of enteral feeding).

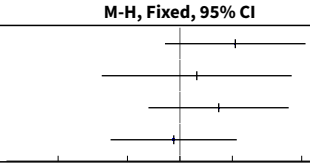
Study or subgroup	Slow rate n/N	Fast rate n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Salhotra 2004	17/26	14/27		15.47%	1.26[0.8,1.99]
Krishnamurthy 2010	12/50	8/50		9.01%	1.5[0.67,3.35]
Karagol 2013	13/46	11/46		12.39%	1.18[0.59,2.36]
Raban 2014b	24/52	19/50		21.82%	1.21[0.77,1.92]
Raban 2014a	20/51	19/47		22.27%	0.97[0.6,1.58]
Modi 2015	17/65	12/66		13.41%	1.44[0.75,2.77]
Jain 2016	4/15	5/15		5.63%	0.8[0.27,2.41]
Total (95% CI)	**305**	**301**		**100%**	**1.2[0.95,1.5]**
Total events: 107 (Slow rate), 88 (Fast rate)					
Heterogeneity: Tau^2=0; Chi^2=1.89, df=6(P=0.93); I^2=0%					
Test for overall effect: Z=1.55(P=0.12)					



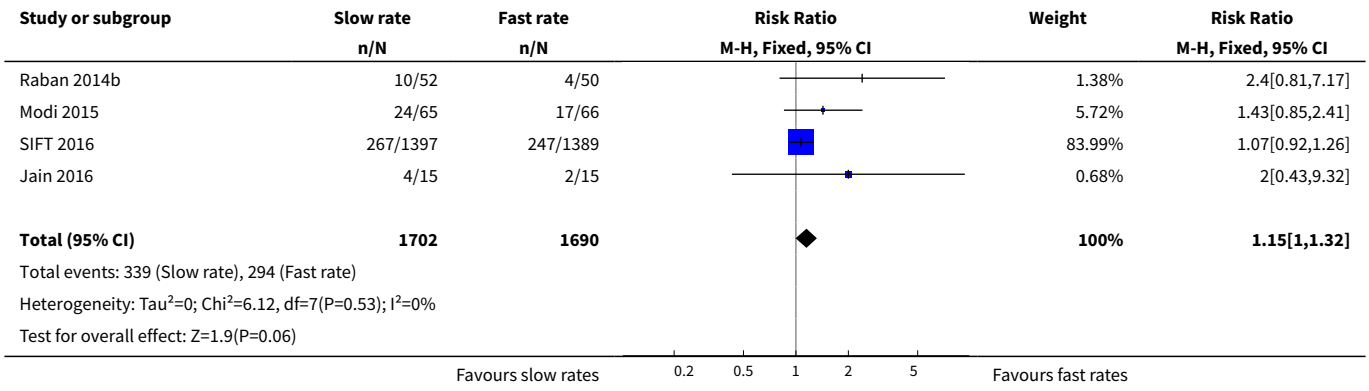
Favours slow rate | Favours faster rate

Analysis 1.6. Comparison 1 Slow versus faster rates of feed advancement, Outcome 6 Incidence of invasive infection.

Study or subgroup	Slow rate n/N	Fast rate n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Salhotra 2004	10/26	5/27		1.66%	2.08[0.82,5.26]
Krishnamurthy 2010	5/50	4/50		1.36%	1.25[0.36,4.38]
Karagol 2013	10/46	6/46		2.03%	1.67[0.66,4.21]
Raban 2014a	9/51	9/47		3.18%	0.92[0.4,2.12]



Favours slow rates | Favours fast rates



APPENDICES

Appendix 1. Standard search methods

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Risk of bias tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality (to meet the validity criteria) of trials. For each trial, we sought information regarding the method of randomisation and blinding and reporting of all outcomes of all infants enrolled in the trial. We assessed each criterion as low, high, or unclear risk. Two review authors separately assessed each study. We resolved any disagreement by discussion. We added this information to the table 'Characteristics of included studies'. We evaluated the following issues and entered the findings into the risk of bias table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

a. Low risk (any truly random process, e.g. random number table; computer random number generator);

b. High risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or

c. Unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

a. Low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

b. High risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or

c. Unclear risk

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

a. Low risk, high risk, or unclear risk for participants; and

b. Low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods as:

a. Low risk for outcome assessors;

b. High risk for outcome assessors; or

c. Unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion when reported, and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported or supplied by trial authors, we re-included missing data in the analyses. We categorised the methods as:

a. Low risk (< 20% missing data);

b. High risk (≥ 20% missing data); or

c. Unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

a. Low risk (when it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);

b. High risk (when not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or

c. Unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether a potential source of bias was related to the specific study design, whether the trial was stopped early owing to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

a. Low risk;

b. High risk; or

c. Unclear risk.

If needed, we explored the impact of the level of bias by undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
27 April 2017	New citation required but conclusions have not changed	The updated search identified 1 new trial for inclusion (SIFT 2016). New data and an increased total number of participating infants (from 949 to 3753) narrowed confidence intervals for the estimates of effect and modified implications for practice and research
27 April 2017	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 2015)

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	New data and an increased total number of participating infants (to 496) narrowed confidence intervals for the estimates of effect and modified 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", which was published in the *Cochrane Database of Systematic Reviews*, Issue 2, 2008 (McGuire 2008) We updated the search in December 2010 and included 1 new trial (Krishnamurthy 2010) We included new co-authors on the review team: Jessie Morgan and Lauren Young
13 February 2008	New citation required but conclusions have not changed	We added new review authors: Sarah Bombell and William McGuire
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, which was published in the *Cochrane Database of Systematic Reviews*, Issue 2, 2000 (Kennedy 2000) We modified the title to read "Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants", and we added new review authors: Sarah Bombell and William McGuire. We have outlined below changes made to the original protocol • We defined "slow" rate of feed advancement as daily increments up to 24 mL/kg (body weight) • We restricted the population to very low birth weight and very preterm infants • We added mortality, adverse neurodevelopment, growth parameters, and infection rates as outcomes of interest

Date	Event	Description
		We updated the search in December 2007. We included 1 new trial (Salhotra 2004) and excluded 1 previously included trial (Book 1976) Findings and implications for practice and research of this review have not changed overall
11 January 2008	Amended	We converted the review to new review format

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

WM and SO are investigators for the largest included trial (SIFT 2016).

SOURCES OF SUPPORT

Internal sources

- Centre for Reviews and Dissemination, Hull York Medical School, UK.
- Bradford Neonatal, Bradford Royal Infirmary, UK.

External sources

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

  This report is independent research funded by a UK NIHR Grant Cochrane Programme Grant (13/89/12). The views expressed in this publication are those of the review authors and are not necessarily those of the National Health Service, the NIHR, or the UK Department of 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. HHSN275201600005C.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans; Infant, Newborn