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ORIGINAL ARTICLE

Standardized feeding regimen for reducing necrotizing enterocolitis in preterm infants: an updated systematic review

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OBJECTIVE: A systematic review (2005) of observational studies has reported 87% reduction in the incidence of necrotizing enterocolitis (NEC) after introducing standardized feeding regimen (SFR) in preterm infants. Considering the many new studies in this field since 2005 and the continued health burden of NEC, we aimed to systematically review the incidence of NEC in preterm infants 'before' vs 'after' implementing a SFR.

STUDY DESIGN: PubMed, EMBASE, CINAHL and E-abstracts from the Pediatric Academic Society meetings and other pediatric and neonatal conference proceedings were searched in May 2016. Observational studies reporting incidence of NEC before and after implementing a SFR were included. Relevant data were extracted independently by two reviewers. Meta-analysis was conducted using random effects model (REM) and results rechecked with fixed effects model.

RESULTS: Pooled results from 15 observational studies ($N = 18\,160$) using REM showed that SFR significantly reduced the incidence of NEC (risk ratio 0.22; 95% confidence interval 0.13 to 0.36; $P < 0.00001$; $I^2 = 74\%$). The results remained significant after comparing studies in two epochs (1978 to 2003 vs 2004 to 2016).

CONCLUSION: SFR continues to be an important tool in prevention of NEC in preterm infants.

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INTRODUCTION

Necrotizing enterocolitis (NEC) continues to have significant mortality and morbidity, including long-term neurodevelopmental impairment in preterm neonates despite the advances in neonatal intensive care.[1,2] Apart from antenatal steroids, early preferential breast milk feeding and standardized feeding regimens (SFR), no single safe and effective strategy is available to reduce the risk of NEC.[3–5] Despite the current evidence, probiotics are still not accepted widely because of concerns over safety and lack of drug quality safe and proven products.[5–17] Lactoferrin[18] and arginine[19] have potential to reduce the risk of NEC but need evidence from large definitive randomized controlled trials.

An epidemiological study has reported that NEC has an iatrogenic component related to variations in clinical practices including feeding strategies.[20] A significant and sustained reduction in the incidence of NEC has been reported consistently following the implementation of a SFR.[21,22] We have earlier reported the benefits of SFR in reducing the incidence of definite (⩾ stage II)[23] NEC in preterm neonates by up to 87% (risk ratio (RR) 0.13; 95% confidence interval (CI) 0.03 to 0.50).[24]

The mechanisms of benefits of SFR are not clear. Adherence to SFR prevents rapid acceleration in feed volumes,[25,26] encourages earlier feeding, thereby reducing the risk of feed intolerance and NEC.[27,28] It is also possible that SFR improves consistency of care and helps in early detection of signs that may warrant actions to minimize the risk of NEC. More studies of benefits of SFR in reducing NEC have been reported since our 2005 systematic review.[26,29–35] Considering the continuing significant health burden associated with NEC and the benefits of SFR as a simple, easy and globally applicable tool, we aimed to update our previous systematic review of this strategy in preterm neonates.

METHODS

The Cochrane Handbook of Systematic Reviews of Interventions[36] and the MOOSE (Meta-analysis of Observational Studies in Epidemiology() guidelines for meta-analysis of observational studies were followed.[37] Ethics approval was not required.

Eligibility criteria

Types of studies. Studies reporting the incidence of ⩾ stage II NEC in preterm, low birth weight (birth weight < 2500 g) neonates 'before' and 'after' implementation of a SFR were considered eligible for inclusion. As in our 2005 systematic review, the presence of well-documented guidelines for enteral feeding rather than their fine details was important for inclusion of any study in the analysis. Narrative reviews, systematic reviews, case reports, letters, editorials and commentaries were excluded but read to identify potential additional studies.

Search strategy. The databases PubMed (www.ncbi.nlm.nih.gov, 1966 to 2016), Embase (Excerpta Medica dataBASE) via Ovid (http://ovidsp.tx.ovid.com, 1980 to 2016), Cochrane Central Register of Controlled Trials (www.thecochranelibrary.com, through May 2016), Cumulative Index of Nursing and Allied Health Literature via Ovid (http://ovidsp.tx.ovid.com, 1980 to May 2016) and E-abstracts from the Pediatric Academic Society meetings (www.abstracts2view.com/pasall, 2000 to 2016) were searched in May 2016. Abstracts of other conference proceedings such as Perinatal Society of Australia and New Zealand, European Academy of Pediatric Societies and the British Maternal and Fetal Medicine Society were searched in Embase. Google Scholar was searched for articles that might not have been cited in the standard medical databases. Gray literature was searched through the national technical information services (http://www.ntis.gov/), Open Grey (http://www.opengrey.eu/) and Trove (http://trove.nla.gov.au/).

The reference lists of eligible studies and review articles were searched to identify additional studies. Reviewers BJ and SP conducted the literature

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Table 1. Quality assessment (cohort studies)

Author, year	Selection				Comparability	Outcome		Total score (out of 9)
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Demonstration of outcome of interest not present at start of study	Comparable on basis of design/analysis (maximum score of 2)	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	
Kamitsuka[21]	*	*	*	*	*	*	*	*	8
Kuzma-O'Reilly[25]	*	*	*	*	*	*	*	*	8
Premji[42]	*	*	*	*	*	*	*	*	8
Brown[39]	*	*		*	*	*	*	*	7
Spritzer[40]	*	*	*	*	*	*	*	*	8
Patole[41]	*	*	*	*	*	*	*	*	8
Hanson[34]	*	*	*	*	*	*	*	*	8
McKallie[33]	*	*	*	*	*	*	*	*	8
Wiedmeier[31]	*	*		*	*	*	*	*	7
Street[26]	*	*	*	*	*	*	*	*	8
Patel[29]	*	*	*	*	*	*	*	*	8
Talavera[35]	*	*	*	*	*	*	*	*	8
Stefanescu[30]	*	*	*	*	*	*	*	*	8
Viswanathan[32]		*	*	*	*	*	*	*	7
Sánchez-Tamayo[38]	*	*	*	*	*	*	*	*	8

search independently. No language restriction was applied. Only published data were used for those studies, where available.

We searched PubMed for the following terms: standardised[All Fields] AND enteral[All Fields] AND feeding[All Fields] AND ('infant, newborn'[MeSH Terms] OR ('infant'[All Fields] AND 'newborn'[All Fields]) OR 'newborn infant'[All Fields] OR 'neonates'[All Fields]) AND ('necrotising enterocolitis'[All Fields] OR 'enterocolitis, necrotizing'[MeSH Terms] OR ('enterocolitis'[All Fields] AND 'necrotizing'[All Fields]) OR 'necrotizing enterocolitis'[All Fields] OR ('necrotizing'[All Fields] AND 'enterocolitis'[All Fields])). The other databases were searched for similar terms.

Study selection. Abstracts of the citations obtained from the initial broad search were read independently by two reviewers (BJ and SP) to identify potentially eligible studies. Full-text articles of these studies were obtained and assessed for eligibility by two reviewers independently (BJ and SP), under the predefined eligibility criteria. Differences in opinion were resolved by group discussion among all reviewers to reach consensus. Care was taken to ensure that multiple publications of the same study were identified and excluded to avoid duplication of the data.

Data extraction. Reviewers BJ and SP extracted the data independently by using a data collection form designed for this review. Information about the study design and outcomes was verified by all reviewers. Discrepancies during the data extraction process were resolved by discussion and consensus among all reviewers. We planned to contact authors for additional information and/or clarifications when details were not available in published manuscripts.

Quality of included studies. Quality assessment of the included studies was done independently by two authors (BJ and SP) by using the Newcastle–Ottawa scale. Maximum possible score was 9 stars and minimum was zero (Table 1). The Cochrane handbook mentions that the Newcastle–Ottawa scale is difficult to apply and hence agreement between review authors is likely to be modest. We therefore held regular group discussions to resolve differences of opinion while assessing the quality of both case–control and cohort studies. Differences of opinion were resolved by consensus after group discussion involving all authors.

Statistical analysis. For the meta-analysis, forest plots were calculated using weighted scores and a random effects model (REM). We chose the REM over the fixed effects model because it accounts for variations between studies that we anticipated because of the inclusion of different types of intervention, different cohort designs and different ways to assess outcomes. Statistical heterogeneity was assessed with the χ^2 test and I^2 statistic and by visual inspection of the forest plot (overlap of CIs). A *P*-value of < 0.1 on the χ^2 statistic was considered to indicate heterogeneity. I^2 statistic values were interpreted according to the guidelines of Cochrane Handbook as follows: 0 to 40%, might not be important; 30 to 60%, may represent moderate heterogeneity; 50% to 90%, may represent substantial heterogeneity; 75 to 100%, considerable heterogeneity.[38] All statistical calculations were conducted using Review Manager (version 5.3.5).

Prespecified subgroup. Given the significant changes in clinical practices over time, particularly in the approach to neonatal nutrition, we aimed to compare the effects of SFR between the two epochs (1978 to 2003 vs 2004 to 2016).

RESULTS

Our literature search revealed 7515 potentially eligible studies. After removing the duplicates and reviewing full text of the original publications, we found 15 studies that met the eligibility criteria. The details of the selection process are shown in Figure 1 and the characteristics of the included studies are summarized in Table 2.[21,25,26,29–35,38–42]

Quality of included studies

The results of the quality assessment of the included studies are reported in Table 1. Majority of the studies had scores of 7 to 8 out of possible score of 9.

Meta-analysis of data from 15 studies ($N = 18\,160$) using a REM estimated a pooled RR of 0.22 (95% CI 0.13 to 0.36) (Figure 2).

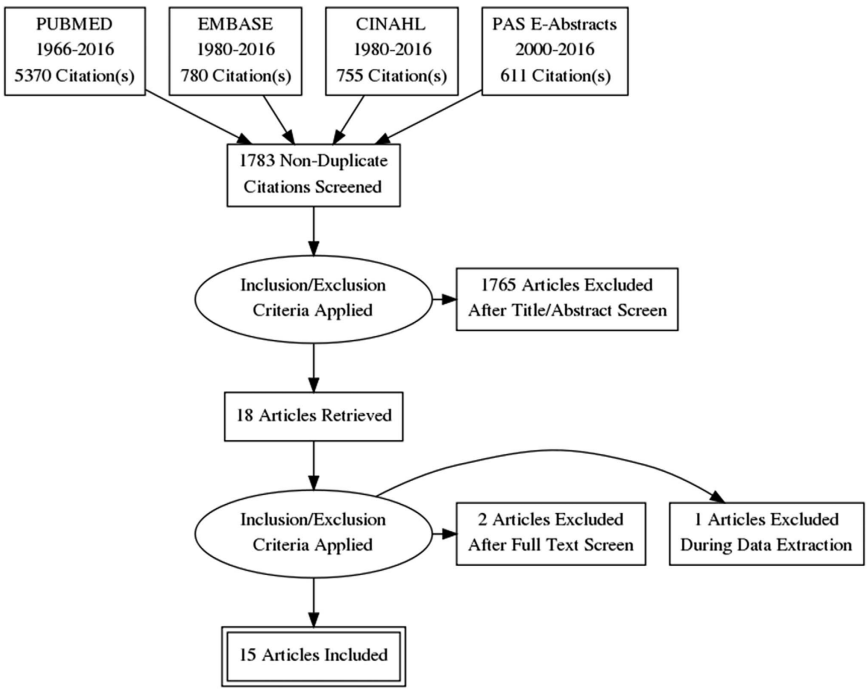


Figure 1. Flow diagram showing search strategy and study selection.

There was significant heterogeneity ($P < 0.00001$; $I^2 = 74\%$) between the studies, indicating the variations in the population characteristics and clinical practices.

The study by Viswanathan *et al.*[32] was unusual considering the extremely conservative feeding regimen selectively in extremely low birth weight (birth weight < 1000 g) infants. Given its unique characteristics, we decided to repeat the analysis after excluding this study. The results still showed the benefits of SFR in reducing the incidence of NEC (RR 0.20; 95% CI 0.11 to 0.34; $P < 0.00001$; $I^2 = 76\%$).

Comparison between the two epochs showed that the benefits of SFR were as significant for the epoch 2004 to 2016 compared with 1978 to 2004 (RR 0.26; 95% CI 0.19 to 0.35; $P < 0.00001$, $I^2 = 7\%$ versus RR 0.13; 95% CI 0.03, 0.51, $P = 0.004$, $I^2 = 88\%$) respectively (Figures 3a and b).

DISCUSSION

Our systematic review of 15 observational studies ($N = 18\,160$) showed that SFR was associated with a significant decrease in the risk of NEC in preterm infants born at < 37 weeks or with birth weight < 2500 g. Our results are consistent with the previous systematic review by Patole and de Klerk,[24] although the number of studies and infants included are significantly more than the previous review.

The study by Viswanathan *et al.*[32] needs to be discussed considering it enrolled extremely low birth weight infants, and used an extremely conservative feeding regimen. Infants in the standardized slow enteral feeding (SSEF: $n = 125$) group were compared with 294 historical controls. The day of starting feeds was delayed, and the time to full feeds, duration of parenteral nutrition and central line usage were longer in the SSEF vs control group. The incidence of stage II NEC (5.6% vs 11.2%, respectively; $P = 0.10$) or surgical/stage III NEC (1.6% vs 4.8%, respectively; $P = 0.17$) was not significantly different between the two groups. In infants with birth weight < 750 g, the incidence of NEC (2.1% vs 16.2%, respectively; $P < 0.01$) and 'NEC/death' (12.8% vs 29.5%, respectively; $P = 0.03$) was significantly less in the SSEF vs control group. The observational design and possibility of changes in practice over the study duration (control: 79 vs SSEF: 40 months) make it difficult to interpret their results. The subgroup that showed the benefits was not pre-stated, had small sample size (control: 129 vs SSEF: 47) and long-term neurodevelopment was not reported.

Prevention of preterm birth, the single most high-risk factor for NEC, remains difficult. Except for the well-established interventions such as antenatal steroids, and early preferential feeding with breast milk, no other strategies were available till recently for reducing the burden of $\geqslant$ stage II NEC. The results of our updated meta-analysis indicate that despite its limitations SFR should continue as a simple, effective and universally available tool to reduce NEC. Other investigators have also supported the use of SFR for this purpose.[4,43–45] We acknowledge the limitations of our study that no randomized controlled trials of SFR have been conducted, and that the current data are based only on non-randomized controlled trials, not adjusted for various confounders, not large enough and may not be representative of clinical practice/outcomes in different settings. However, considering the number of studies, total sample size, diverse settings of the studies, effect size, narrow confidence intervals and consistency of results after analysis by REM and fixed effects model, we believe that the results of our updated meta-analysis are significant. As per our previously shared view the heterogeneity should be considered as the strength rather than weakness of this intervention as it reflects the efficacy of SFR across a range of population characteristics, clinical practices and, importantly, the contents of the feeding protocols. Considering the difficulties in conducting a large definitive randomized controlled trial (for example, difficulty with blinding the intervention, ethics in the context of current evidence) and the fact that there are no potential significant adverse effects (unless the regimen is unduly conservative to compromise nutrition), there is no reason why SFR should not continue as an important tool to reduce the risk of NEC. SFR can also help in assessing different feeding protocols for enteral nutrition in high-risk preterm infants.

Table 2. Characteristics of included studies

Variable/ authors	*Timing to start feeds*	*Feeding method*	*Feeding type*	*Feed volume at start*	*Increment volume*	*Total maximum volume*	*Minimal enteral feeds (volume and duration)*	*Definition of 'feed intolerance'*	*Plan of action for sepsis*	*Plan of action for PDA and indomethacin*	*Plan of action for 'large" gastric aspirates*	*Plan of action for bile-stained gastric aspirates*	*Policy for umbilical catheters*
Patole *et al.*[41]	No respiratory assistance or MAP < 10, no PDA or sepsis, no need for cardiovascular support	Intermittent bolus gavage feeds by nasogastric tube	Expressed breast milk (preferred) or 20 kcal oz^{-1} formula (later increased to 24 kcal oz^{-1})	0.5 ml h^{-1} (< 28 weeks) or 1 ml h^{-1} (>28 weeks)	Start with 0.5 ml per 12 h for < 28 weeks, and 1 ml per 12 h for >28 weeks. Increase by 1 ml 8 hourly after reaching 100 ml kg^{-1} day^{-1}(maximum: 24 ml $kg^{-1}day^{-1}$)	170 ml kg^{-1} day^{-1}	Not used	Specified	Stop feeds for 48 h or until hemodynamic stability	Stop feeds until 24 h after completing indomethacin therapy	Stop feeds if such aspirates are persistent	Stop feeds if such aspirates are persistent	Catheters were retained as long as they were needed
Kamitsuka *et al.*[21]	Days 4, 3, 2 (or longer if needed) for neonates weighing 1250–1500 g (A), 1502–2000 g (B) and 2001–2500 g (C), respectively	Intermittent bolus gavage feeds by nasogastric tube	Expressed breast milk (preferred) or half strength formula (later increased to full strength)	Group A and B: 3 ml 3 hourly. Group C: 4 ml 3 hourly	Not more than 20 ml kg^{-1} day^{-1}	150 ml kg^{-1} day^{-1}	Not used	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
O'Reilly *et al.*[25]	1–8 days	Intermittent bolus gavage feeds, by gastric tube	Expressed breast milk (preferred) or 20 kcal oz^{-1} iron-fortified formula	Started as minimal enteral feeds (10–20 ml kg^{-1} day^{-1}) for 3–4 days and then upgraded by 10–20 ml kg^{-1} day^{-1}	10–20 ml kg^{-1} day^{-1}	150 ml kg^{-1} day^{-1} or 120 kcal kg^{-1} day^{-1}	10–20 ml kg^{-1} day^{-1}, continued for 3–4 days (breast milk or preterm formula)	Specified	Not specified	Not specified	Stop feeds	Stop feeds	Not specified
Premji *et al.*[42,44]	Started at days 5–6 of life	Intermittent bolus gavage feeds by nasogastric tube	Expressed breast milk (preferred) or 24 kcal oz^{-1} formula	Maximum >24 ml kg^{-1} day^{-1}. For < 750 g: 1 ml per 2 h For >750–<1000 g: 2 ml per 2 h. For >1000–<1500 g: 1 ml every 2 h	Maximum: (30 ml kg^{-1} day^{-1}. For < 750 g: 1 ml every 24 h. For >750–1000 g: 1 ml every 24 h. For >1000– 1500 g: 1 ml every 12 h	Not clear	Used only for neonates,1 kg at,24 ml kg^{-1} day^{-1}, Start within 48 h of birth, and continued for 5–6 days	Specified	Not specified	Not specified	Guidelines provided for contacting clinician for decision making	Guidelines provided for contacting clinician for decision making	Not specified
Brown *et al.*[39]	Feeds delayed for 5–7 days or longer in complicated deliveries with fetal distress	Intermittent 3 hourly bolus feeds by nasogastric tube	Sterile water followed by formula (0.45 cal ml^{-1} graded up to 0.80 cal ml^{-1})	For < 1250 g: 2 ml per 2 h. For 1250–1500 g: 3 ml per 2 h. For >1500 g: 4 ml per 2 h	Detailed plan provided for reaching 20 ml per 8 h (< 1250 g), 25 ml per 8 h (1250–1500 g), 29 ml per 8 h (>1500 g)	See above	Not used	Not specified Plan of action given for apnea, bradycardia, abdominal distension, gastric retention of formula, occult blood in stools and for 'NEC' or 'shock'	Not specified	Not specified	Stop feeds 'for a week or two or more till resolution of the problem'	Not specified	Not specified
Spritzer *et al.*[40]	As soon as possible in well neonates. Delayed by 1 week in presence of ventilation, IUGR or complicated labor/delivery	Not specified	Dilute formula, graded gradually to full strength	20 ml kg^{-1}	20 ml kg^{-1} day^{-1}	Not specified	Not used	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Talavera *et al.*[35]	As early as possible	Not specified	Expressed breast milk (preferred) or banked human milk if EBM not available	For < 28 weeks: 10 ml kg^{-1} day^{-1} 6 hourly × 3 days	10–20 ml kg^{-1} day^{-1}	150 ml kg^{-1} day^{-1}	< 28 weeks: 10 ml kg^{-1} day^{-1} 6 hourly × 3 days	Not specified	Not specified	Specified	Not specified	Not specified	Not specified
McCallie *et al.*[33]	Started at day 3 of life	Not specified	Expressed breast milk (preferred)	For ⩽ 1000 g: 10 ml kg^{-1} day^{-1} For 1001–1500 g: 20 ml kg^{-1} day^{-1}	10–20 ml kg day	160 ml $kg^{-1}day^{-1}$	< 1000 g: 10 ml kg^{-1} day^{-1} for 4 days 1001–1500 g: 20 ml kg^{-1} day^{-1} for 6 days	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified

Table 2. (Continued)

Variable/ authors	*Timing to start feeds*	*Feeding method*	*Feeding type*	*Feed volume at start*	*Increment volume*	*Total maximum volume*	*Minimal enteral feeds (volume and duration)*	*Definition of 'feed intolerance'*	*Plan of action for sepsis*	*Plan of action for PDA and indomethacin*	*Plan of action for 'large" gastric aspirates*	*Plan of action for bile-stained gastric aspirates*	*Policy for umbilical catheters*
Hanson *et al.*[34]	Enteral feeding by day of life 3	Not specified	Expressed breast milk (preferred) or 20 kcal oz^{-1} preterm formula (later increased to 24 kcal oz^{-1})	Started as minimal enteral feeds (<20 ml kg^{-1} day^{-1}) for 5–7 days	20 ml kg^{-1} day^{-1}	150 ml kg^{-1} day^{-1}	<20 ml kg^{-1} day^{-1} for 5–7 days	Specified	Not specified	Not specified	Specified	Specified	Not specified
Viswanathan *et al.*[32]	Days 7, 14 of life for neonates weighing 750–1000 g, <750 g, respectively	Not specified	Expressed breast milk (preferred) or 24 kcal oz^{-1} preterm formula	0.5 ml per 2 hourly (<750 g) or 1 ml per 2 hourly (750–1000 g)	0.5 ml/feed every other day (<750 g) 0.5 ml/feed every day (750–1000 g)	150 ml kg^{-1} day^{-1}	Volume: 0.5 ml per 2 hourly (<750 g) or 1 ml per 2 hourly (750–1000 g) Duration: 7 days	Specified	Not specified	Not specified	Not specified	Not specified	Not specified
Wiedmeier *et al.*[31]	Not specified	Not specified	Expressed breast milk (preferred) or banked human milk if EBM not available.	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Patel *et al.*[29]	4–9 Days	Not specified	Expressed breast milk (preferred) or 20 kcal oz^{-1} preterm formula.	1 ml q4hr (400–750 g) 1 ml q2hr (750–1000 g) 1 ml q2hr (1001–1250 g) 3 ml q3hr (1251–1500 g)	Not more than 20 ml kg^{-1} day^{-1}	140 ml kg^{-1} day^{-1}	1 ml q4hr $\times$5d (400–750 g) 1 ml q2hr $\times$4d (750–1000 g) 1 ml q2hr $\times$3d (1001–1250 g) 3 ml q3hr $\times$3d (1251–1500 g)	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Stefanescu *et al.*[30]	Not specified	Not specified	Expressed breast milk (preferred) or banked human milk if EBM not available	Not clear	23–25 weeks: Increase by 10 ml kg^{-1} day^{-1} 26–28 weeks: 10–15 ml kg^{-1} day^{-1} 29–31 weeks:15–20 ml kg^{-1} day^{-1} 32–34 weeks: 20–35 ml kg^{-1} day^{-1}.	150 ml kg^{-1} day^{-1}		Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Street *et al.*[26]	Not specified	Intermittent 3 hourly feeds	Expressed breast milk (preferred) or 20 kcal oz^{-1} preterm formula (later increased to 24 kcal oz^{-1})	1.5 ml kg^{-1} 3 hourly $\times$3 days (1001–1250 g)	1.5–18.5 ml kg^{-1}	Not specified	1.5 ml kg^{-1} 3 hourly $\times$3 days (1001–1250 g)	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
Sanchez-Tamayo *et al.*[38]	Hemodynamically stable	Continuous /bolus feeds	Expressed breast milk (preferred) or banked human milk if EBM not available.		10 ml kg^{-1} every 12 h at <1000 g (20 ml kg^{-1} day^{-1}) 15 ml kg^{-1} every 12 h in >1000 g (30 ml kg^{-1} day^{-1})	160 ml kg^{-1} day^{-1}	As per protocol For 5–7 days High risk for NEC 0.3 ml kg^{-1} h^{-1} $\times$3 days 0.5 ml kg^{-1} h^{-1} $\times$3 days 1 ml kg^{-1} h^{-1} $\times$1 day 750–1000 g 0.5 ml kg^{-1} h^{-1} $\times$3 days 1 ml kg^{-1} h^{-1} $\times$3 days 1000–1500 g 1 ml kg^{-1} h^{-1} $\times$5 days	Specified	Not specified	Not specified	Not specified	Not specified	Not specified

Abbreviations: EBM, expressed breast milk; IUGR, intrauterine growth restriction; MAP, mean airway pressure; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.

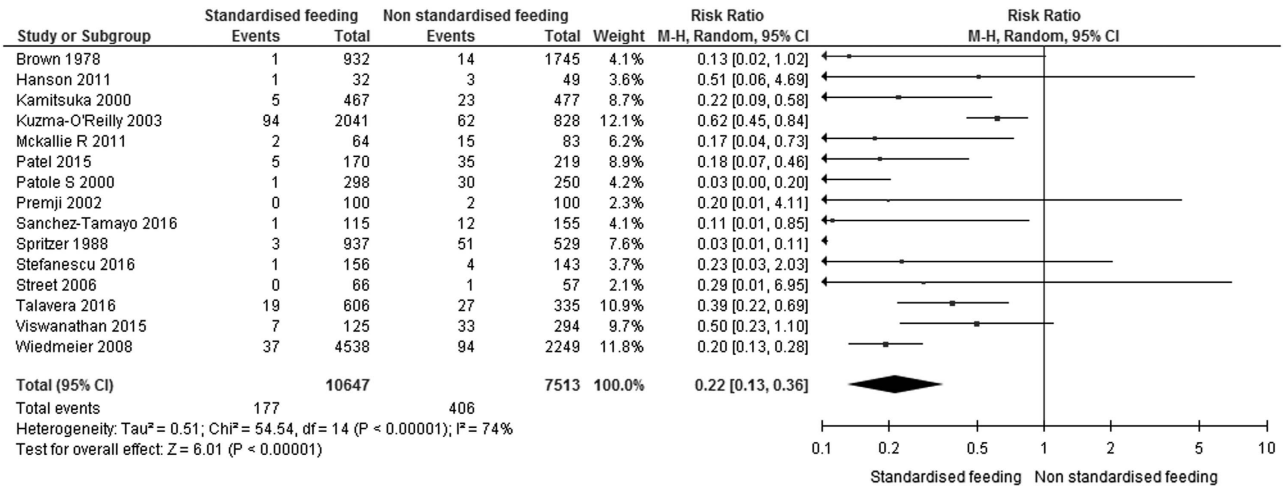
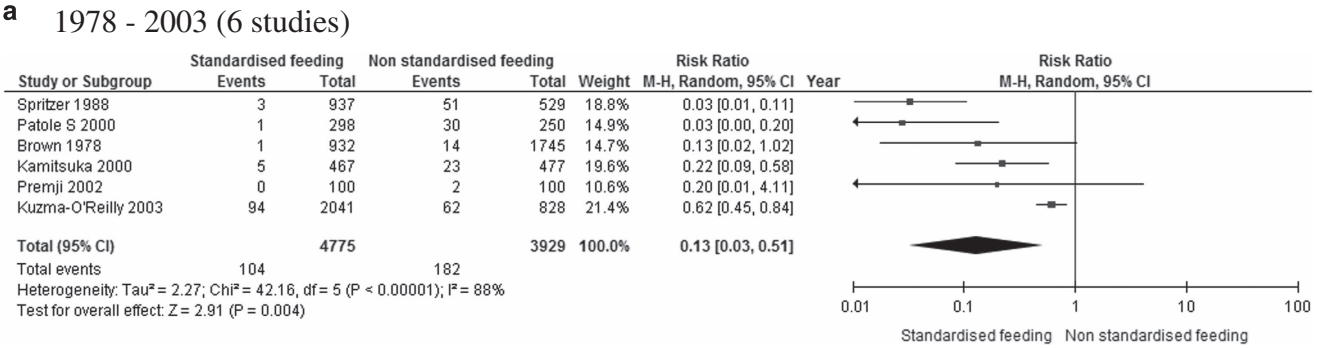


Figure 2. Association of standardized feeding regimen (SFR) and necrotizing enterocolitis (NEC) in preterm neonates.



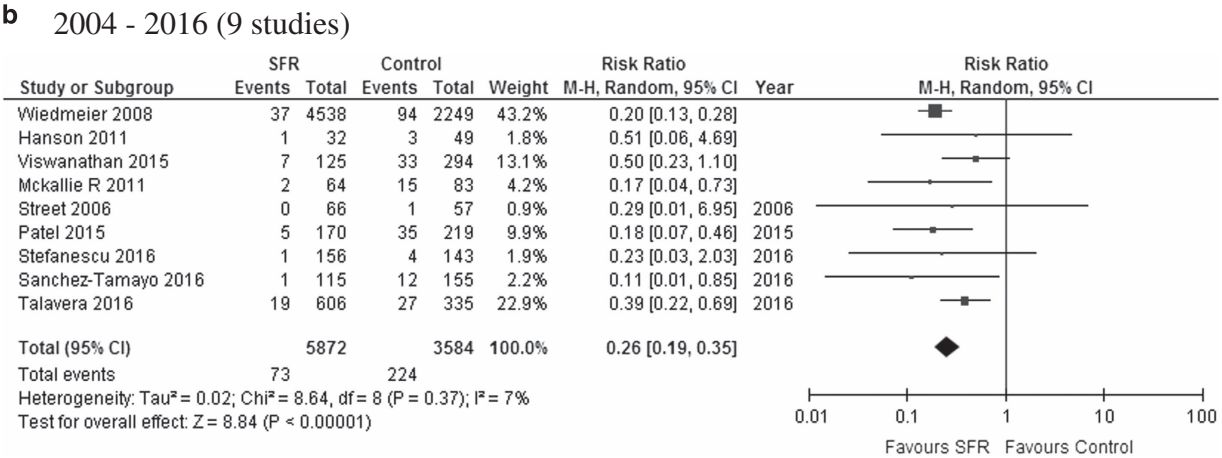


Figure 3. Association of standardized feeding regimen (SFR) and necrotizing enterocolitis (NEC) in two epochs (1978 to 2003 vs 2004 to 2016).

In summary, the results of our updated systematic review and meta-analysis indicate the significant benefits of SFR in reducing ⩾stage II NEC in preterm infants. This simple, easily available and 'no cost' intervention is important in our efforts to reduce the significant mortality and morbidity associated with NEC, a potentially disastrous condition with poorly understood pathogenesis, and no cure.[2,46–48]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed toward the design, concept and preparation of the manuscript. BJ and SP conducted literature search, included the eligible trials, analyzed the data and prepared the initial manuscript. SP was responsible for the intellectual content, concept of the study and finalized the manuscript.

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