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Moon K, Athalye-Jape GK, Rao U, Rao SC

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
Figure 1.	8
RESULTS	9
Figure 2.	11
Figure 3.	12
Figure 4.	13
Figure 5.	13
Figure 6.	13
DISCUSSION	15
AUTHORS' CONCLUSIONS	16
ACKNOWLEDGEMENTS	16
REFERENCES	17
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	26
Analysis 1.1. Comparison 1 Early PN versus Late PN, Outcome 1 In-hospital all-cause mortality.	27
Analysis 1.2. Comparison 1 Early PN versus Late PN, Outcome 2 Neonatal mortality (within 28 days of birth).	27
Analysis 1.3. Comparison 1 Early PN versus Late PN, Outcome 3 Death during first week of admission.	28
Analysis 1.4. Comparison 1 Early PN versus Late PN, Outcome 4 90-day mortality.	28
Analysis 1.5. Comparison 1 Early PN versus Late PN, Outcome 5 Healthcare-associated blood stream infection.	28
Analysis 1.6. Comparison 1 Early PN versus Late PN, Outcome 6 Healthcare-associated infection (any type).	28
Analysis 1.7. Comparison 1 Early PN versus Late PN, Outcome 7 Other types of hospital-acquired infection: Airway.	28
Analysis 1.8. Comparison 1 Early PN versus Late PN, Outcome 8 Other types of hospital-acquired infection: Urinary tract.	28
Analysis 1.9. Comparison 1 Early PN versus Late PN, Outcome 9 Other types of hospital-acquired infection: Central nervous system.	29
Analysis 1.10. Comparison 1 Early PN versus Late PN, Outcome 10 Other types of hospital-acquired infection: Soft tissue.	29
Analysis 1.11. Comparison 1 Early PN versus Late PN, Outcome 11 Other types of hospital-acquired infection: Others.	29
Analysis 1.12. Comparison 1 Early PN versus Late PN, Outcome 12 Other types of hospital-acquired infection: No focus identified.	29
Analysis 1.13. Comparison 1 Early PN versus Late PN, Outcome 13 Duration of hospital stay.	29
Analysis 1.14. Comparison 1 Early PN versus Late PN, Outcome 14 Duration of ICU stay.	30
Analysis 1.15. Comparison 1 Early PN versus Late PN, Outcome 15 Duration of respiratory support (mechanical ventilation or CPAP or NIPPV).	30
Analysis 1.16. Comparison 1 Early PN versus Late PN, Outcome 16 Duration of mechanical ventilation.	30
Analysis 1.17. Comparison 1 Early PN versus Late PN, Outcome 17 Hypoglycaemia.	30
Analysis 1.18. Comparison 1 Early PN versus Late PN, Outcome 18 Highest blood urea nitrogen levels during hospital stay.	30
Analysis 1.19. Comparison 1 Early PN versus Late PN, Outcome 19 Z scores for weight at discharge.	30
Analysis 1.20. Comparison 1 Early PN versus Late PN, Outcome 20 Change to Z scores for weight from baseline.	31
APPENDICES	31
CONTRIBUTIONS OF AUTHORS	34
DECLARATIONS OF INTEREST	34
SOURCES OF SUPPORT	34
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	34
INDEX TERMS	34

[Intervention Review]

Early versus late parenteral nutrition for critically ill term and late preterm infants

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ABSTRACT

Background

Recently conducted randomised controlled trials (RCTs) suggest that late commencement of parenteral nutrition (PN) may have clinical benefits in critically ill adults and children. However, there is currently limited evidence regarding the optimal timing of commencement of PN in critically ill term and late preterm infants.

Objectives

To evaluate the benefits and safety of early versus late PN in critically ill term and late preterm infants.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (5 April 2019), MEDLINE Ovid (1966 to 5 April 2019), Embase Ovid (1980 to 5 April 2019), EMCare (1995 to 5 April 2019) and MEDLINE via PubMed (1966 to 5 April 2019). We searched for ongoing or recently completed clinical trials, and also searched the grey literature and reference lists of relevant publications.

Selection criteria

We included RCTs comparing early versus late initiation of PN in term and late preterm infants. We defined early PN as commencing within 72 hours of admission, and late PN as commencing after 72 hours of admission. Infants born at 37 weeks' gestation or more were defined as term, and infants born between 34 and 36⁺⁶ weeks' gestation were defined as late preterm.

Data collection and analysis

Two review authors independently selected the trials, extracted the data and assessed the risk of bias. Treatment effects were expressed using risk ratio (RR) and risk difference (RD) for dichotomous outcomes and mean difference (MD) for continuous data. The quality of the evidence was assessed using the GRADE approach.

Main results

Two RCTs were eligible for inclusion. Data were only available from a subgroup (including 209 term infants) from one RCT in children (aged from birth to 17 years) conducted in Belgium, the Netherlands and Canada. In that RCT, children with medium to high risk of malnutrition were included if a stay of 24 hours or more in the paediatric intensive care unit (PICU) was expected. Early PN and late PN were defined as initiation of PN within 24 hours and after day 7 of admission to PICU, respectively. The risk of bias for the study was considered to be low for five domains and high for two domains.

Early versus late parenteral nutrition for critically ill term and late preterm infants (Review)

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The subgroup of term infants that received late PN had significantly lower risk of in-hospital all-cause mortality (RR 0.35, 95% confidence interval (CI) 0.14 to 0.87; RD -0.10, 95% CI -0.18 to -0.02; number needed to treat for an additional beneficial outcome (NNTB) = 10; 1 trial, 209 participants) and neonatal mortality (death from any cause in the first 28 days since birth) (RR 0.29, 95% CI 0.10 to 0.88; RD -0.09, 95% CI -0.16 to -0.01; NNTB = 11; 1 trial, 209 participants).

There were no significant differences in rates of healthcare-associated blood stream infections, growth parameters and duration of hospital stay between the two groups. Neurodevelopmental outcomes were not reported. The quality of evidence was considered to be low for all outcomes, due to imprecision (owing to the small sample size and wide confidence intervals) and high risk of bias in the included studies.

Authors' conclusions

Whilst late commencement of PN in term and late preterm infants may have some benefits, the quality of the evidence was low and hence our confidence in the results is limited. Adequately powered RCTs, which evaluate short-term as well as long-term neurodevelopmental outcomes, are needed.

PLAIN LANGUAGE SUMMARY

Early versus late intravenous nutrition in critically ill term and late preterm babies

Review question: to evaluate the benefits and risks of early (within 72 hours of admission) versus late (after 72 hours of admission) commencement of intravenous nutrition in unwell term babies (those born at 37 weeks of pregnancy or more) and late preterm babies (those born between 34 and 37 weeks of pregnancy).

Background: when very unwell term babies and late preterm babies are unable to tolerate milk feeds due to their illness, it is necessary to give nutrition (such as glucose, amino acids and fat) to these babies via an intravenous drip (a tube that is inserted directly into a vein). Recent studies in sick children and adults suggest that it is better to administer only intravenous glucose initially and to delay giving intravenous amino acids and fat by about a week.

Study characteristics: this review found two small studies that evaluated the effects of early versus late commencement of intravenous amino acids and fat in full term babies. However, relevant results were available from only one study, with evidence up to date as of 5 April 2019.

Key results: late commencement of intravenous nutrition resulted in increased survival during hospital stay and in the first 28 days of birth. The timing of intravenous nutrition was not associated with an increased risk of hospital-acquired blood stream infections, growth and duration of hospital stay. Neurodevelopmental outcomes were not reported. However, the quality of the evidence was considered to be low because the sample size was very small and the results were from only one study.

Conclusions: while there were some benefits of late commencement of intravenous nutrition in term and late preterm babies, the quality of the evidence was low and so our confidence in the results is limited. Further trials are needed which investigate the best time to start intravenous nutrition in unwell newborn babies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Late parenteral nutrition compared to early parenteral nutrition for critically ill term and late preterm infants

Late parenteral nutrition compared to early parenteral nutrition for critically ill term and late preterm infants

Patient or population: critically ill term and late preterm infants

Setting: neonatal intensive care units

Intervention: late parenteral nutrition

Comparison: early parenteral nutrition

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with early parenteral nutrition	Risk with late parenteral nutrition				
In-hospital all-cause mortality	Study population		RR 0.35 (0.14 to 0.87)	209 (1 RCT)	⊕⊕⊕⊖ LOW 1, 2, 3	
	153 per 1,000	54 per 1,000 (21 to 133)				
Neonatal mortality (within 28 days of birth)	Study population		RR 0.29 (0.10 to 0.88)	209 (1 RCT)	⊕⊕⊕⊖ LOW 1, 2, 3	
	122 per 1,000	36 per 1,000 (12 to 108)				
Healthcare-associated blood stream infection	Study population		RR 0.22 (0.05 to 1.01)	209 (1 RCT)	⊕⊕⊕⊖ LOW 1, 2, 3	
	82 per 1,000	18 per 1,000 (4 to 82)				
Healthcare-associated infection (any type)	Study population		RR 0.53 (0.32 to 0.89)	209 (1 RCT)	⊕⊕⊕⊖ LOW 1, 2, 3	
	306 per 1,000	162 per 1,000 (98 to 272)				
Mean duration of hospital stay	33.3 (SD 53.5) days	23.8 (SD 23.7) days	MD 9.5 lower (20.97 lower to 1.97 higher)	209 (1 RCT)	⊕⊕⊕⊖ LOW 1, 2, 3	
Mean duration of mechanical ventilation	7 (SD 7.5) days	3.6 (SD 3) days	MD 3.4 lower	209 (1 RCT)	⊕⊕⊕⊖ LOW 1, 2, 3	

		(4.99 lower to 1.81 lower)		
Hypoglycaemia	Study population	RR 1.64 (0.91 to 2.96)	209 (1 RCT)	⊕⊕⊕⊖ LOW 1, 2, 3
	143 per 1,000 234 per 1,000 (130 to 423)			

***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; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ The evidence was downgraded by one level due to high risk of bias for two domains (performance bias and other bias).

² The evidence was downgraded by one level due to the small sample size and wide confidence intervals.

³ The results were from the subgroup analysis of a main paediatric RCT

BACKGROUND

Description of the condition

Term and late preterm infants may suffer from various conditions that predispose them to critical illness. These include persistent pulmonary hypertension of the newborn (Jain 2015), meconium aspiration syndrome (Chettri 2016), hypoxic-ischaemic encephalopathy (Douglas-Escobar 2015), sepsis (Dong 2017; Schrag 2016), critical congenital heart disease (Strobel 2015), congenital diaphragmatic hernia (Leeuwen 2014), and other surgical conditions (Rintala 2014).

During periods of critical illness, provision of enteral nutrition is unachievable, which necessitates the use of parenteral nutrition (PN). PN is usually indicated in infants in whom enteral nutrition is either contraindicated or delivers insufficient total protein and energy requirements (Macdonald 2005). In very preterm infants (those with a gestational age of less than 32 weeks), the standard practice is early commencement of PN (Adamkin 2007; Bulbul 2012; Can 2012; Can 2013; Cleminson 2016; De Curtis 2012; Hay 2013; Liu 2015; Patel 2017; Repa 2016; Ribed 2013; Rigo 2013; Tagare 2013; Torer 2015; van Goudoever 2018). However, there is a lack of evidence regarding the optimal time to commence PN therapy in term and late preterm infants.

The nutritional reserves, requirements and morbidities of critically ill term and late preterm infants are different from those of very preterm infants. Very preterm infants have higher energy requirements than term and late preterm infants. The ratio of the minimal metabolic rate (g/kg/d) to the non-protein energy reserve (g/kg), which represents the number of days of energy reserve, is only two days at 28 weeks' gestation and increases to 20 days for term infants and 100 days for adults (Pierro 2008). The rate of protein loss in very preterm infants in the absence of amino acid intake is nearly double the rate in term infants (1.5 g/kg/d at 28 weeks' gestational age and 0.7 g/kg/d at term) (Denne 1996). Hence, the estimated protein requirements are higher in very preterm compared to term infants. Because of these differences, it is inappropriate to extrapolate nutritional recommendations for very preterm infants to term and late preterm infants.

Description of the intervention

Infants who are unable to tolerate enteral feeds always receive intravenous glucose and electrolytes. The term PN usually refers to intravenous administration of amino acids and lipids. Neonatal PN can be delivered via peripheral intravenous cannulae or central venous catheters (umbilical, percutaneous or surgically placed tunnelled catheters) (Ainsworth 2015; Cies 2014). A large RCT in adults defined early PN as administration within 48 hours of admission to the intensive care unit (ICU) (Casaer 2011), whereas a large paediatric RCT defined it as occurring within 24 hours (Fivez 2016). Both studies defined late PN as delaying the administration until day 8 of ICU admission. Studies in preterm infants have used various cutoffs between one and five days after birth (Simmer 2005; Trivedi 2013). For this Cochrane Review, we used 'within 72 hours of admission to the neonatal ICU (NICU)/paediatric ICU (PICU)' as a cutoff to define early and late PN.

How the intervention might work

Potential benefits of early parenteral amino acids

Early parenteral amino acids may:

- prevent catabolism, leading to improved growth and possibly improved neurodevelopmental outcomes (Ohnishi 2016; Roelants 2016; Schneider 2017; Singhal 2016; Yang 2016); and
- decrease the frequency and severity of neonatal hyperglycaemia and stimulate growth through enhanced secretion of insulin and insulin-like growth factors.

Potential harms of early parenteral amino acids

Early parenteral amino acids may:

- lead to hyperammonaemia, azotaemia, and metabolic acidosis (Dounousi 2015; Guellec 2015; Uthaya 2016). It may also result in slower growth of head circumference (Uthaya 2016); and
- lead to development of metabolic syndrome later in life, with detrimental effects such as insulin resistance and adiposity (Singhal 2016).

Potential benefits of early parenteral lipids

Early parenteral lipids may:

- prevent essential fatty acid (EFA) deficiency. Even a short delay of three to seven days in supplying lipids to parenterally fed infants can lead to biochemical EFA deficiency (Friedman 1986; Gutcher 1991; Lee 1993);
- improve long-chain polyunsaturated fatty acid (LCPUFA) levels and probably improve neurodevelopmental outcomes (Alshweki 2015; de Jong 2015); and
- prevent the development of pulmonary arterial hypertension (PAH) and right ventricular failure (Umar 2011).

Potential harms of early parenteral lipids

Early parenteral lipids may:

- exacerbate free radical activity by providing the substrate, initiator, and catalysts for the chain reaction. Pierro 2002 and Basu 1999 have shown that parenteral nutrition is associated with increased free radical production both in critically ill infants in intensive care and in stable patients on the ward (similar findings were noted in Hasanoglu 2005);
- increase the rate of sepsis due to coagulase-negative staphylococci (Avila-Figueroa 1998; Freeman 1990) and other nosocomial infections (Gilio 2000);
- worsen respiratory function by decreasing arterial oxygenation in acute respiratory distress syndrome (Hwang 1990; Suchner 2001; Venus 1989);
- increase the risk of kernicterus in infants with hyperbilirubinaemia due to free fatty acid displacing bilirubin from albumin-binding sites (Amin 2009); and
- worsen pulmonary hypertension (Aksnes 1996; Hammerman 1989; Prasertsom 1996).

Other complications of parenteral nutrition

Administration of PN is known to be associated with an increased risk of central line-associated bloodstream infection (CLABSI), hospital-acquired bloodstream infection (HABSI), extravasation

injury, thrombosis, and many other complications (Bishay 2012; Donnell 2002; Dubbink-Verheij 2017; Gonzalez-Hernandez 2016; Kostogloudis 2015; Legeay 2015; Wilkins 2004).

Evidence from critically ill paediatric and adult populations

Results from an RCT of 4640 critically ill adults, which compared early initiation of PN (within 48 hours) versus late initiation of PN (on day 8 of admission), revealed that those in the late-initiation group had a greater chance of being discharged alive from ICU and the hospital, had fewer infectious complications, and had a shorter duration of mechanical ventilation (Casaer 2011). In a multicentre RCT of 1440 critically ill children (Favez 2016), it was reported that those children who received late PN (commenced on day 8 of ICU admission) had lower odds of new infection, shorter duration of PICU and hospital stay, higher likelihood of an earlier live discharge from the PICU, shorter duration of mechanical ventilation, and reduced need for renal replacement therapy. Hence, the overall suggestion is that early initiation of PN may worsen the outcomes of critically ill patients.

Why it is important to do this review

So far, no systematic reviews have addressed the issue of optimal timing of commencement of PN in critically ill term and late preterm infants. Evidence from systematic reviews is essential for formulating guidelines and so we conducted this Cochrane Review to help address the gap in the literature.

OBJECTIVES

To evaluate the benefits and safety of early versus late parenteral nutrition in critically ill term and late preterm infants.

- We planned to conduct separate subgroup analyses for medical and surgical infants and for each condition within those subgroups.
- We planned to conduct subgroup analyses to examine the influence of gestation (late preterm infants: 34 to 36⁺⁶ weeks' gestational age (GA) and term infants: ≥ 37 weeks' GA), given the known differences in short-term and long-term outcomes between these groups (Kugelman 2013).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), quasi-RCTs, and cluster-RCTs were eligible for inclusion.

Types of participants

We included trials enrolling critically ill term or late preterm infants (≥ 34 weeks' gestation at birth until day 28 of life) who have a high likelihood of being unable to tolerate enteral feeds for at least three to five days and hence require parenteral nutrition.

For this review, we defined critical illness as the presence of one or more of the following criteria.

- Need for mechanical ventilation.
- Use of inotropic agents.

- Persistent pulmonary hypertension of the newborn (PPHN), defined as the presence of right-to-left or bidirectional shunting of blood at the foramen ovale or the ductus arteriosus (or both), as well as high pulmonary arterial/right ventricular systolic pressure on echocardiography (Nair 2014). In settings where point-of-care echocardiogram facilities were not available, we planned to use a difference in arterial partial pressure of oxygen (PO_2) ≥ 20 mmHg or oxygen saturation $\geq 5\%$ to 10% between preductal (right upper limb) and postductal (either lower limb) to define PPHN (Nair 2014).
- Use of inhaled nitric oxide or other pulmonary vasodilators.
- Use of extracorporeal membrane oxygenation (ECMO).
- Moderate to severe hypoxic-ischaemic encephalopathy (HIE) based on modified Sarnat or Thompson classification, requiring therapeutic hypothermia (Sarnat 1976; Thompson 1997).
- Severe neonatal sepsis (early or late): early-onset sepsis to be defined as sepsis within the first 72 hours of birth (Shane 2014), and late-onset sepsis as sepsis after 72 hours of birth.
- Surgery under general anaesthesia for major cardiac, gastrointestinal or other anomalies.

If the authors of the original RCTs used validated scoring systems such as the Clinical Risk Index for Babies (CRIB), Score for Neonatal Acute Physiology II (SNAP-II), or Neonatal Therapeutic Intervention Scoring System (NTISS) to define critical illness, we planned to incorporate such information into the review (Gray 1992; International Neonatal Network 1993; Richardson 2001).

Types of interventions

We defined the early PN group as a group that receives PN within 72 hours of admission to the NICU/PICU. We chose a cutoff of 72 hours because experimental studies have shown that a delay longer than 72 hours may result in essential fatty acid and amino acid deficiency (Friedman 1976; Guther 1991; Lee 1993; Poindexter 2006). We defined the late PN group as a group that receives PN after 72 hours of admission to the NICU/PICU.

We defined parenteral nutrition as administration of any quantity of intravenous amino acids or lipids, or both. These could have been administered via peripheral intravenous cannula or through any type of central venous access.

Types of outcome measures

Primary outcomes

- In-hospital all-cause mortality: defined as death from any cause during the initial hospital stay
- Neonatal mortality: defined as death in the first 28 days since birth from any cause

Secondary outcomes

- Healthcare-associated bloodstream infection (HABSI), defined as positive culture on a blood sample drawn 48 hours after admission to the ICU
- Other types of hospital-acquired infection (e.g. ventilator-associated pneumonia, cerebrospinal fluid (CSF) infection, urinary tract infection (UTI), surgical site infection and fungal infection)
- Length of hospital stay (days)

- Duration of respiratory support (defined as mechanical ventilation via endotracheal tube, or non-invasive positive-pressure ventilation (NIPPV), or continuous positive airway pressure (CPAP), or humidified high-flow nasal prong (HFNP) therapy), in days
- Duration of ventilation (defined as mechanical ventilation via endotracheal tube or NIPPV), in days
- Duration of inhaled nitric oxide therapy, in hours
- Incidence of hypoglycaemia (plasma glucose < 45 mg/dL (2.5 mmol/L))
- Incidence of hyperglycaemia (plasma glucose > 150 mg/dL (8.3 mmol/L))
- Liver dysfunction (raised liver function tests, including total bilirubin (mg/dL), alkaline phosphatase (units/L), γ -glutamyltransferase (units/L), alanine transferase (units/L), and aspartate aminotransferase (units/L))
- Anthropometry at the time of discharge from the hospital (Z-scores)
- Anthropometry (change in Z-scores from baseline)
- Neurodevelopmental outcomes at 12, 18, and 24 months and early childhood, assessed using well-recognised scales/ tests such as Bayley Scales of Infant Development (BSID), Griffiths Mental Development Scales (GMDS), Brunet-Lézine test, Movement Assessment Battery for Children (M-ABC), and Weschler Preschool and Primary Scales of Intelligence

The following were added as additional secondary outcomes post hoc, after discussion with the Cochrane editors.

- Death during the first week of admission
- 90-day mortality
- Duration of ICU stay (days)
- Healthcare-associated infections (any type)
- Highest plasma level of total bilirubin during hospital stay (mg/dL)
- Highest plasma level of alkaline phosphatase during hospital stay (IU/L)
- Highest plasma level of γ -glutamyl-transferase during hospital stay (IU/L)
- Highest plasma level of alanine transferase (IU/L)
- Highest plasma level of aspartate aminotransferase (IU/L)
- Highest blood urea nitrogen levels during hospital stay

Search methods for identification of studies

We used the standard search strategy for the Cochrane Neonatal Group.

Electronic searches

We searched the following databases.

- Cochrane Central Register of Controlled Trials (5 April 2019) in the Cochrane Library

- MEDLINE via PubMed (1996 to 5 April 2019).
- MEDLINE via Ovid (1946 to 5 April 2019).
- Embase (1980 to 5 April 2019).
- EMCare (1995 to 5 April 2019).

We used the following search terms: (parenteral nutrition[MeSH] OR parenteral nutrition*), plus database-specific limiters for RCTs and neonates ([Appendix 1](#)). No language restrictions were applied.

We also searched for ongoing or recently completed clinical trials via the following websites.

- ClinicalTrials.gov (www.clinicaltrials.gov).
- Australia and New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au).
- World Health Organization International Clinical Trial Registry Platform (who.int/ictrp/en/).
- International Standard Randomised Controlled Trial Number (ISRCTN) Registry (www.isrctn.com).
- Clinical Trial Results (<http://www.clinicaltrialresults.org/>).

Searching other resources

We carefully read the reference lists of relevant publications, Cochrane Reviews, guidelines, and review articles to identify potentially eligible studies. We searched conference proceedings (online abstracts) for annual meetings of the Pediatric Academic Societies (2000 to present), the European Society for Pediatric Research (2009 to present), the Royal College of Paediatrics and Child Health (2009 to present), and the Perinatal Society of Australia and New Zealand (2009 to present). We also searched the grey literature via Opengrey (<http://www.opengrey.eu/>), Mednar-North Grey Literature Collection (mednar.com/mednar/desktop/en/search.html) and National Technical Reports Library (<https://ntrl.ntis.gov/NTRL/>).

Data collection and analysis

We used standard methods of the Cochrane Neonatal Group.

Selection of studies

Two review authors (KM and UR) independently searched for relevant studies by using the search strategies outlined above. We screened titles/abstracts to identify potentially relevant citations and subsequently obtained the full texts of eight potentially relevant studies to assess them for inclusion. We independently assessed the eligibility of studies by reviewing those eight full texts. When we were uncertain about the eligibility of the study for inclusion, we resolved this through discussion among all review authors.

The details of studies excluded from the review have been provided in the [Characteristics of excluded studies](#) table. The details of the study selection process are given in a PRISMA flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.

Data extraction and management

Two review authors (KM and UR) separately extracted, assessed, and coded the data from each study using a piloted form specifically developed for this review. For each included study, we collected information on design, methods, participants, interventions, outcomes, and treatment effects. We contacted the study authors of [van Puffelen 2018a](#) and [Makay 2007](#) for provision of additional data or clarification of published data. For each study, one review author (UR) entered final data into Review Manager 5.3 ([RevMan 2014](#)), and the two review authors (KM and SR) checked the data.

Assessment of risk of bias in included studies

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

- 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).
- Selection reporting (reporting bias).
- Any other bias.

See [Appendix 2](#) for a detailed description of risk of bias under each domain.

Measures of treatment effect

We reported risk ratios (RRs) and risk differences (RDs) for dichotomous data, with respective 95% confidence intervals (CIs). We determined the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD. We reported continuous data by using mean difference (MD) and associated 95% CIs.

For studies that reported medians and interquartile ranges (IQR), we calculated means and standard deviations using the formula by Wan and colleagues ([Wan 2014](#)).

Had a continuous outcome been measured using different scales, we would have calculated the standardised mean difference.

Unit of analysis issues

We planned to consider an infant only once in an analysis. We planned to exclude infants with multiple enrolments, as we would not be able to address the unit of analysis issues that may arise.

No cluster-RCT was identified for inclusion in this review. If we had identified a cluster-RCT, we would have undertaken analyses at the level of the individual infant using recalculated effective sample sizes taking into account the number of clusters in each group and intraclass correlation coefficients (ICC) ([Higgins 2011](#)).

We planned to contact the study authors of cluster RCTs to request information on ICCs from their studies. If ICCs were not available from some included studies, we planned to use the mean ICC from available ones.

Dealing with missing data

If participant dropouts lead to missing data, we planned to conduct intention-to-treat analyses. We endeavoured to obtain missing data from study authors when possible.

Assessment of heterogeneity

We planned to estimate treatment effects of individual trials and examine heterogeneity between trials by inspecting forest plots and quantifying the impact of heterogeneity using I^2 statistics. We planned to use the following criteria when describing the percentage of heterogeneity:

- < 25%: no heterogeneity;
- 25% to 49%: low heterogeneity;
- 50% to 74%: moderate heterogeneity; and
- ≥ 75%: high heterogeneity.

If we detected moderate or high statistical heterogeneity ($I^2 \geq 50\%$), we planned to explore possible causes (e.g. differences in study quality, participants, intervention regimens, or outcome assessments).

Assessment of reporting biases

We planned to assess publication bias using the funnel plot (Egger 1997) if at least 10 studies were included in the meta-analysis.

Data synthesis

We performed analyses using Review Manager 5.3, as provided by Cochrane (RevMan 2014). For estimates of relative risks and risk differences, we used the Mantel-Haenszel method. For estimates of mean differences, we used the inverse variance method. For all analyses, we used the fixed-effect model.

Had we found cluster-RCTs that reported study estimates which were unadjusted and adjusted for clustering, we would have used adjusted estimates in the meta-analyses. For cluster-RCTs that did not report post-intervention study estimates (and a relevant measure of variance) that accounted for clustering, we planned to calculate a design effect and an effective sample size using study data (number of clusters, number of participants analysed) and the ICC reported by one of the included studies.

We planned to enter reported post-intervention outcome data (e.g. mean and standard deviation) and author-calculated effective sample sizes into Review Manager 5.3 to calculate individual-level adjusted study estimates to enable inclusion in 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: in-hospital mortality, neonatal mortality, HABS, healthcare-associated infections (any type), length of hospital stay, duration of ventilation, and incidence of hypoglycaemia.

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

The GRADE approach yields an assessment of the quality of a body of evidence as one of the following four grades.

- High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: 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.
- Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

- Very low quality: 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

The haemodynamic and respiratory statuses of neonates with surgical conditions are usually different from those of neonates with pure medical conditions. For example, most surgical neonates are ventilated for general anaesthesia rather than lung disease, whereas infants with medical conditions usually have associated lung pathology such as hyaline membrane disease, pneumonia, or meconium aspiration syndrome. Hence we planned to conduct these subgroup analyses.

In addition, given the heterogenous nature of the individual conditions that lead to critical illness in term and late preterm infants, we planned to conduct subgroup analysis separately for each condition within medical and surgical subgroups. We will also planned to conduct subgroup analysis for term (≥ 37 weeks' GA) and late preterm (34 to 36⁺⁶ weeks' GA) infants because of the known higher risks for mortality and morbidity in late preterm infants compared to term infants (Kugelman 2013).

We were unable to conduct any of the above subgroup analyses in this review due to there being insufficient data.

Sensitivity analysis

We planned to perform sensitivity analysis to explore the influence of the following factors on effect size.

- Repeating the analysis after excluding unpublished studies.
- Repeating the analysis while taking account of risk of bias, as specified.

We planned to undertake post hoc sensitivity analyses as required based on the findings of the meta-analysis. We were unable to conduct any of the planned sensitivity analyses due to there being insufficient data.

RESULTS

Description of studies

Results of the search

Our initial broad search yielded 3695 citations. After removing 1422 duplicates and excluding 2265 studies based on titles and abstracts, we read the full texts of eight studies in detail. Finally, two studies were identified as eligible for inclusion in this review. The details of the included studies are summarised in the [Characteristics of included studies](#) table. Details of the six excluded studies are summarised in the [Characteristics of excluded studies](#) table. [Figure 1](#) illustrates the screening and the study selection process.

Included studies

We included two studies (Makay 2007; van Puffelen 2018) in this review. However, relevant information was available from only one RCT (number of participants (n) = 209 term infants) (van Puffelen 2018). This study was a secondary subgroup analysis of the Paediatric Early versus Late Parenteral Nutrition In Critical Illness (PEPANIC) multicentre paediatric trial (Fivez 2016), conducted in Belgium, the Netherlands and Canada. In that RCT, children (from

birth to 17 years of age) with medium to high risk of malnutrition (score of 2 or more on the Screening Tool for Risk on Nutritional Status and Growth) were included if a stay of 24 hours or more in PICU was expected. Early PN (the control group) was defined as initiation of PN within 24 hours after admission to the PICU. In the late PN group (the intervention group), PN was withheld until the morning of day 8 in the PICU.

The results for 209 term infants (98 of whom received early PN, and 111 of whom received late PN) from the PEPaNIC trial ([Fivez 2016](#)), reported by van Puffelen and colleagues ([van Puffelen 2018](#)), were included in this review.

Enteral nutrition was commenced early in both groups and increased according to individual unit's protocols. Macronutrient and caloric targets for the three study sites (Belgium, the Netherlands and Canada) varied. Micronutrients (trace elements, minerals, and vitamins) were started from day 2 and continued until the enteral nutrition provided reached 80% of the caloric target in all study sites. In the two study sites (Leuven and Rotterdam), insulin infusion was used to achieve tight control of blood glucose levels. In Leuven, insulin was started in both groups to achieve blood glucose levels of 2.7 mmol/L to 4.4 mmol/L. In Rotterdam, all infants received an insulin infusion designed to achieve blood glucose levels of 4 mmol/L to 8 mmol/L. In Edmonton, infants received insulin infusion when blood glucose concentrations exceeded 10 mmol/L.

The primary endpoints in [van Puffelen 2018](#) were 'incidence of PICU-acquired infections' and 'duration of PICU dependency' (number of days in the PICU) and likelihood of earlier live discharge from PICU. Secondary efficacy endpoints were 'duration of mechanical ventilatory support' (number of days and likelihood of earlier live weaning from ventilation), 'maximum plasma level of urea', 'duration of hospital stay' (number of days and likelihood of earlier live discharge from hospital), and 'direct health-care costs'. Secondary safety endpoints were 'death during the first week', '90 day mortality' and 'hypoglycaemia during the first week'.

Baseline characteristics of the infants in the early PN group were similar to the late PN group for gender, gestational age, birth weight, weight for age Z scores, Pediatric Logistic Organ Dysfunction (PELOD) score, diagnostic groups, mechanical ventilation on admission and haemodynamic support on admission. However, the Paediatric Index of Mortality 2 (PIM 2) and risk of mortality calculated based on PIM2, were significantly higher in the early PN group than in the late PN group ($P = 0.016$ and $P = 0.011$, respectively).

Additional data were provided by the authors of [van Puffelen 2018](#) for the following outcomes for this review: 'in-hospital all-cause mortality', 'neonatal mortality', 'duration of hospital stay', 'duration of respiratory support', 'highest blood urea nitrogen levels', 'Z score for weight at discharge' and 'changes to Z scores for weight from baseline'.

For the outcomes 'duration of PICU dependency' and 'duration of mechanical ventilation', authors reported the results as medians and interquartile ranges (IQRs) and were unable to provide the mean and standard deviation (SD). Hence, we calculated the mean and SD from the reported medians and IQRs using the formula by Wan and colleagues ([Wan 2014](#)).

The authors reported the results of the univariate as well as multivariable analyses. For multivariable analyses, the original investigators adjusted pre-defined risk factors such as severity of critical illness, estimated risk of mortality, diagnosis group and weight on admission.

[Makay 2007](#) was a single-centre RCT of 72 infants in Turkey. In the early PN group, amino acids (1 g/kg/day) were commenced within the first eight hours after birth and lipid emulsion (0.5 g/kg/day) was commenced from the next day. In the late PN group, 0.5 g/kg/day of amino acid and 0.5 g/kg/day of lipid emulsion were commenced after 72 hours. For both groups, amino acids and lipid emulsion were increased by 0.5 g/kg/day to a maximum 3 g/kg/day. The outcome measures were energy intake, changes in body weight, time of first stool passage, number of daily stool output, relative changes in serum bilirubin levels at 24, 48 and 72 hours, need for phototherapy and duration of phototherapy. We contacted the authors for the additional information but there was no response.

Excluded studies

We excluded six studies ([Brownlee 1993](#); [Vanhorebeek 2017](#); [van Puffelen 2018a](#); [van Puffelen 2018b](#); [Verstraete 2018](#); [Verstraete 2019](#)), of which five reports were results of the PEPaNIC trial ([van Puffelen 2018](#)), evaluating various outcomes in the paediatric population. [Brownlee 1993](#) was excluded as the study population was very preterm infants with median gestational age of 29 weeks. See [Characteristics of excluded studies](#).

Risk of bias in included studies

For [van Puffelen 2018](#), the risk of bias was considered to be low for five domains and high for two domains. For [Makay 2007](#), the risk of bias was considered to be high for all domains. Details of the risk of bias of the included studies are described in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random 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)	Other bias
Makay 2007							
van Puffelen 2018							

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

We assessed [van Puffelen 2018](#) as having a low risk of selection bias. The randomisation was done "using a central computerised randomisation, stratified in permuted blocks of 10 according to age and diagnosis". Medical and research teams were unaware of the block size. Concealment of group assignment in [van Puffelen 2018](#) was ensured by the use of a central computerised randomisation system.

We assessed [Makay 2007](#) as having a high risk of selection bias, given that the infants were "enrolled consecutively". It was unclear how allocation concealment was achieved in [Makay 2007](#). The authors stated in the manuscript that "all infants were randomly allocated to receive 1 of 2 intravenous nutrition regimen", but the exact details were not given.

Blinding

We assessed [van Puffelen 2018](#) as having a high risk of performance bias, given that healthcare workers, parents and investigators were aware of the allocation group. The study was assessed as being at low risk of detection bias as the outcome assessors and investigators who were not directly involved in ICU patient care were unaware of the treatment assignments.

We assessed [Makay 2007](#) as having high risk of performance bias and detection bias, given that the clinicians and parents were aware of the treatment assignments.

Incomplete outcome data

We assessed [van Puffelen 2018](#) as having low risk of attrition bias as the outcome data on all 209 term infants were available.

We assessed [Makay 2007](#) as having high risk of attrition bias as 18 of 72 infants were withdrawn (25%).

Selective reporting

We assessed [van Puffelen 2018](#) as having low risk of reporting bias as all the outcomes mentioned in the method section were reported in the primary analysis.

We assessed [Makay 2007](#) as having high risk of reporting bias as not all the main outcomes mentioned in the methods section were reported.

Other potential sources of bias

We assessed [van Puffelen 2018](#) as having high risk of bias because the three individual trial centres used different insulin infusion regimens and different target blood glucose levels for the study infants. The type and composition of amino acids and lipid emulsions and the caloric targets also varied across the centres. Furthermore, there were significant differences in the estimated mortality risks at the time of enrolment between the early PN and late PN group (early PN: 9.9%; late PN: 6.7%; $P = 0.011$).

Effects of interventions

See: [Summary of findings for the main comparison Late parenteral nutrition compared to early parenteral nutrition for critically ill term and late preterm infants](#)

We included only one study in our analysis ([van Puffelen 2018](#)).

Primary outcomes: mortality

In-hospital all-cause mortality (death from any cause during the initial hospital stay)

The authors of [van Puffelen 2018](#) provided additional information for this outcome. There was lower incidence of in-hospital all-cause mortality in the group that received late PN (late PN: 6/111 participants; early PN: 15/98 participants; RR 0.35, 95% CI 0.14 to 0.87; RD -0.10, 95% -0.18 to -0.02; NNTB = 10; 1 trial; 209 participants; low-quality evidence). See [Analysis 1.1](#); [Figure 4](#).

Figure 4. Forest plot of comparison: 1 Early PN versus Late PN, outcome: 1.1 In-hospital all-cause mortality.

Neonatal mortality (death in the first 28 days of birth from any cause)

The authors of [van Puffelen 2018](#) provided additional information for this outcome. The group that received late PN had lower levels

of neonatal mortality (late PN: 4/111 participants; early PN: 12/98 participants). Our analysis found that those who received late PN had significantly lower risk of neonatal mortality (RR 0.29, 95% CI 0.10 to 0.88; RD -0.09, 95% CI -0.16 to -0.01; NNTB = 11; 1 trial, 209 participants; low-quality evidence). See [Analysis 1.2](#); [Figure 5](#).

Figure 5. Forest plot of comparison: 1 Early PN versus Late PN, outcome: 1.2 Neonatal mortality (within 28 days of birth).

Secondary outcomes

Clinical outcomes

Death during the first week of admission

This outcome was added to our review as an additional secondary outcome post-hoc. [van Puffelen 2018](#) found no significant difference between the groups for this outcome (univariate analysis: odds ratio (OR) 0.28, 95% CI 0.06 to 1.43; $P = 0.15$ and multivariable analysis: OR 0.71, 95% CI 0.09 to 5.61; $P = 0.74$). Our analysis also found no significant difference between late PN and early PN (RR 0.29, 95% CI 0.06 to 1.42; RD -0.04, 95% CI -0.01 to 0.01; 1 trial, 209 participants). See [Analysis 1.3](#).

90-day mortality

This outcome was added to our review as an additional secondary outcome post-hoc. [van Puffelen 2018](#) found significantly lower mortality in the group that received late PN on univariate analysis (OR 0.32, 95% CI 0.12 to 0.85; $P = 0.018$). However, in their multivariable analysis, there was no significant difference (OR 0.41, 95% CI 0.13 to 1.30; $P = 0.13$). Our analysis found the group that received late PN had significantly lower incidence of 90-day

mortality (RR 0.35, 95% CI 0.14 to 0.87; RD -0.10, 95% CI -0.18 to -0.02; NNTB = 10; 1 trial, 209 participants). See [Analysis 1.4](#).

1. Infections

a) Healthcare-associated infection (HAI) (any type)

This outcome was added to our review as an additional secondary outcome post-hoc. [van Puffelen 2018](#) found that infants who received late PN had significantly lower risk of HAI on univariate analysis (OR 0.44, 95% CI 0.22 to 0.85; $P = 0.02$). However, in their multivariable analysis, there was no significant difference (OR 0.54, 95% CI 0.27 to 1.08; $P = 0.082$). In our analysis, those who received late PN had significantly less HAI of any type (RR 0.53, 95% CI 0.32 to 0.89; RD -0.14, 95% CI -0.26 to -0.03; NNTB = 7; 1 trial; 209 participants; low-quality evidence). See [Analysis 1.6](#).

b) Healthcare-associated bloodstream infection (HABSI)

One study found significantly lower risk of HABSI in the group that received late PN (late PN: 2/111 participants; early PN: 8/98 participants; $P = 0.048$) ([van Puffelen 2018](#)). Our analysis found no significant difference between late and early PN (RR 0.22, 95% CI 0.05 to 1.01; RD -0.06, 95% CI -0.12 to -0.00; 1 trial; 209 participants; low-quality evidence). See [Analysis 1.5](#); [Figure 6](#).

Figure 6. Forest plot of comparison: 1 Early PN versus Late PN, outcome: 1.5 Healthcare-associated blood stream infection.

c) Other types of HAI

- Airway infections ([Analysis 1.7](#)): [van Puffelen 2018](#) found no significant difference between the groups for this outcome ($P = 0.42$). Our analysis found no significant difference between late and early PN (RR 0.59, 95% CI 0.22 to 1.59; RD -0.04, 95% CI -0.11 to 0.03; 1 trial, 209 participants).
- Urinary tract infections ([Analysis 1.8](#)): [van Puffelen 2018](#) found no significant difference between the groups for this outcome ($P = 0.34$). Our analysis found no significant difference between late and early PN (RR 0.29, 95% CI 0.03 to 2.78; RD -0.02, 95% CI -0.06 to 0.02; 1 trial, 209 participants).
- Central nervous system infections ([Analysis 1.9](#)): [van Puffelen 2018](#) found no significant difference between the groups for this outcome ($P = 0.47$). Our analysis found no significant difference between late and early PN (RR 0.29, 95% CI 0.01 to 7.15; RD -0.01, 95% CI -0.04 to 0.02; 1 trial, 209 participants).
- Soft tissue infection ([Analysis 1.10](#)): [van Puffelen 2018](#) found no significant difference between the groups for this outcome ($P = 1.00$). Our analysis found no significant difference between late and early PN (RR 0.88, 95% CI 0.13 to 6.15; RD -0.00, 95% CI -0.04 to 0.03; 1 trial, 209 participants).
- Other infections ([Analysis 1.11](#)): [van Puffelen 2018](#) found no significant difference between the groups for this outcome ($P = 1.00$). Our analysis found no significant difference between late and early PN (RR 2.65, 95% CI 0.11 to 64.35; RD 0.01, 95% CI -0.02 to 0.03; 1 trial, 209 participants).
- Infection with no identified focus ([Analysis 1.12](#)): [van Puffelen 2018](#) found no significant difference between the groups for this outcome ($P = 0.78$). Our analysis found no significant difference between late and early PN (RR 0.76, 95% CI 0.26 to 2.18; RD -0.02, 95% CI -0.08 to 0.05; 1 trial, 209 participants).

2. Length of hospital stay

a) Duration of hospital stay (days)

The authors of [van Puffelen 2018](#) provided additional information for this outcome by giving the mean and standard deviation. They found no significant difference between the groups on univariate analysis (hazard ratio (HR) 1.47; 95% CI 1.09 to 1.99; $P = 0.43$). However, they reported that on multivariable analysis, the group given early PN had significantly longer hospital stay than the group given late PN (HR 1.38, 95% CI 1.02 to 1.88; $P = 0.037$). Our analysis found no significant difference between late and early PN (MD -9.50, CI -20.97 to 1.97; 1 trial, 209 participants; low-quality evidence). See [Analysis 1.13](#).

b) Duration of ICU stay (days)

This outcome was added to our review as an additional secondary outcome post-hoc. [van Puffelen 2018](#) reported that the group given late PN had significantly shorter duration of ICU dependency on univariate analysis (HR 1.71, CI 1.27 to 2.30; $P = 0.0066$) and multivariable analysis (HR 1.61, 95% CI 1.19 to 2.20; $P = 0.0021$). Our analysis found that infants given late PN had significantly shorter duration of ICU stay than those given early PN (MD -3.30, 95% CI -5.27 to -1.33; 1 trial, 209 participants). We used the formula by Wan and colleagues ([Wan 2014](#)) to calculate mean and SD from median and IQR for this outcome. See [Analysis 1.14](#).

3. Respiratory outcomes

a) Duration of respiratory support (days)

The authors of [van Puffelen 2018](#) provided additional information for this outcome (late PN: mean 6.1 days, SD 8.5; early PN: mean 17, SD 44.3). Our analysis found that the infants given late PN had significantly shorter duration of respiratory support than those given early PN (MD -10.90; 95% CI -19.81 to -1.99; 1 trial, 209 participants). See [Analysis 1.15](#).

b) Duration of ventilation (days)

One study reported that the group which received late PN had significantly shorter duration of mechanical ventilation on univariate analysis (HR 1.69, 95% CI 1.26 to 2.27, $P = 0.0021$) and on multivariable analysis (HR 1.62, 95% CI 1.19 to 2.21; $P = 0.0020$) ([van Puffelen 2018](#)). Our analysis found that the infants given late PN had significantly shorter duration of mechanical ventilation than those who received early PN (MD -3.40, 95% CI -4.99 to -1.81; 1 trial, 209 participants; low-quality evidence). We used the formula by Wan and colleagues ([Wan 2014](#)) to calculate the mean and SD from the median and IQR for this outcome. See [Analysis 1.16](#).

c) Duration of inhaled nitric oxide (hours)

This outcome was not reported in the included studies.

4. Biochemical outcomes

1. Glycaemic control

a) Hypoglycaemia

One study reported no significant differences in the incidence of hypoglycaemia between the two groups on univariate analysis (OR 1.84, 95% CI 0.90 to 3.76, $P = 0.11$) ([van Puffelen 2018](#)). However, on multivariable analysis, the group who received late PN had significantly higher odds of hypoglycaemia during the first week (OR 3.05; 95% CI 1.27 to 7.35, $P = 0.013$). Our analysis found no significant difference between the two groups (RR 1.64, 95% CI 0.91 to 2.96; RD 0.09, 95% CI -0.01 to 0.20; 1 trial, 209 participants; low-quality evidence). See [Analysis 1.17](#).

b) Hyperglycaemia

This outcome was not reported in the included studies.

2. Hepatic dysfunction

Liver dysfunction was not reported in the included studies; neither were any of the additional outcomes we added post-hoc, i.e. highest plasma level of total bilirubin during hospital stay; highest plasma level of alkaline phosphatase during hospital stay; and highest plasma level of gamma-glutamyltransferase during hospital stay.

3. Blood urea nitrogen

Highest blood urea nitrogen was added as additional secondary outcome post-hoc. The authors of [van Puffelen 2018](#) provided additional information for this outcome (late PN: mean 34.0 mg/dL, SD 19.5; early PN: mean 49.7 mg/dL, SD 27.5). Our analysis found the group that received late PN had significantly lower blood urea nitrogen than the group that received early PN (MD -15.70, 95% CI -22.24 to -9.16; 1 trial, 209 participants). See [Analysis 1.18](#).

5. Growth outcomes

The following growth outcomes were not reported in the included studies: Z score for length at discharge from the hospital; Z score for head circumference at discharge from the hospital; changes to Z scores for length from baseline; changes to Z scores for head circumference from baseline.

1. Z score for weight at discharge from the hospital

The authors of [van Puffelen 2018](#) provided additional information for this outcome. Data were available from 60 infants who received early PN and 69 infants who received late PN (late PN Z score: -0.89, SD 1.39; early PN Z score: -0.96, SD 1.56). Our analysis found no significant difference between late and early PN (MD 0.07, 95% CI -0.44 to 0.58; 1 study, 209 participants). See [Analysis 1.19](#).

2. Changes to Z scores for weight from baseline

The authors of [van Puffelen 2018](#) provided additional information for this outcome. Data were available from 60 infants who received early PN and 69 infants who received late PN (late PN: -0.60, SD 1.40; early PN: -0.49, SD 1.05). Our analysis found no significant difference between late and early PN (MD -0.11, 95% CI -0.53 to 0.31; 1 trial, 209 participants). See [Analysis 1.20](#).

6. Neurodevelopmental outcomes

[Verstraete 2018](#) reported the two-year data on physical and neurocognitive outcomes for the entire cohort of children (aged 0 to 18 years) from the PEPaNIC RCT ([Fivez 2016](#)). The authors were contacted but were unable to provide neurodevelopmental outcomes of the subgroup of term infants from the trial.

DISCUSSION

Summary of main results

This Cochrane Review included data from a subgroup analysis of a paediatric RCT. It found that late PN in term and late preterm infants may be associated with decreased mortality, decreased hospital-acquired infections and reduced length of hospital stay and duration of mechanical ventilation. However, the evidence was considered to be of low quality given the various limitations of the included study. There was no effect on duration of ICU stay, incidence of hypoglycaemia and physical growth. Information on neurodevelopmental outcomes was not available.

Overall completeness and applicability of evidence

The body of evidence for this review was very limited as it was based on the results of only one RCT ([van Puffelen 2018](#)). While the included study ([van Puffelen 2018](#)) was relevant to the review question, it was a secondary subgroup analysis of the PEPaNIC multicentre paediatric trial (which included participants aged 0 to 18 years) ([Fivez 2016](#)), which makes the evidence even weaker.

In the included study, early and late PN were defined as "within 24 hours" and "after 7 days" of PICU admission, respectively ([van Puffelen 2018](#)). These extreme timings of commencement of PN are practiced only in a few paediatric and neonatal units and hence the study design is very unlikely to be applicable in term and late preterm infants ([Mehta 2018](#)). It was highlighted in the worldwide survey of nutrition of 156 PICUs that only approximately 20% of the units commence PN within 24 hours of admission and only 3.5% of the units commence PN after seven days of admission

([Kerklaan 2016](#)). Furthermore, no data exist on the current timing of commencement of PN for term and late preterm infants in NICUs.

There were variations on how glucose homeostasis in study infants was achieved across the three study sites of the included RCT ([van Puffelen 2018](#)). The use of different insulin infusion regimens, with different target blood glucose levels, for the study infants in the trial sites may have affected the clinical outcomes. In two of the study sites (Leuven and Rotterdam), insulin infusion was used to tightly control blood glucose levels. This 'tight glycaemic control' has been reported to be associated with significant increase in hypoglycaemia in critically ill infants and children admitted to PICU ([Agus 2017](#); [Chen 2018](#); [Macrae 2014](#); [Srinivasan 2014](#); [Vlasselaers 2009](#); [Zhao 2018](#)). Even though our analysis found no association between the timing of commencement of PN and the incidence of hypoglycaemia, the authors of the included RCT ([van Puffelen 2018](#)) reported higher incidence of hypoglycaemia in the first week in the late PN group on multivariable analysis ([van Puffelen 2018](#)). Potential for neonatal hypoglycaemia with the late commencement of PN is an important issue of concern, given its association with adverse neurodevelopmental outcomes ([Mahajan 2017](#); [Qiao 2019](#); [Shah 2019](#); [Tan 2017](#); [Wickstrom 2018](#)).

The types and compositions of amino acids and lipid emulsions, as well as the caloric targets, varied across the study centres in the included RCT ([van Puffelen 2018](#)). This would have led to different types and doses of amino acids and lipid emulsions being administered to infants and may have affected the clinical outcomes ([Clark 2007](#); [Jiang 2019](#)).

We found low-quality evidence that late commencement of PN reduced in-hospital all-cause mortality, neonatal mortality and 90-day mortality. However, it is important to note that these results were based on only one study ([van Puffelen 2018](#)) and that the baseline risk of mortality was lower in the group that received late PN compared to the group that received early PN (6.7% versus 9.9% respectively; $P = 0.011$). Hence it is not surprising that there was lower mortality in the group that received late PN. The authors of [van Puffelen 2018](#) also reported that there was no difference in mortality between the two groups on multivariable analysis, once the baseline risk factors were adjusted for.

In the included study ([van Puffelen 2018](#)), infection rates were 31% with early PN compared to 16% with late PN. The results of this RCT may not be generalisable to the units that have lower or higher incidences of infection.

We were unable to evaluate the long-term neurodevelopmental outcomes of early versus late PN in this review.

Based on the results of one RCT in children (aged 0 to 18 years) ([Fivez 2016](#)), the recently updated ESPGHAN/ESPEN/ESPR/CSPEN guidelines recommend that clinicians consider "withholding parenteral nutrition, including amino acids, for 1 week in critically ill term infants while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation)" ([van Goudoever 2018](#)). However, given the multiple and significant limitations to the available evidence in this Cochrane Review, we are unable to make such a recommendation. Another important reason for caution is the risk of hypoglycaemia associated with the late commencement of PN that was found on multivariable analysis of the included RCT ([van Puffelen 2018](#)).

Quality of the evidence

Overall, we considered the quality of evidence to be low on the basis of our GRADE analysis, due to the risk of bias of included studies and imprecision (the sample size was small — one study with 209 participants — and the confidence intervals were wide). We were unable to assess heterogeneity as there was only one study included in our analysis. We were unable to evaluate some of the outcomes such as liver function, duration of nitric oxide, head circumference, length and neurodevelopmental outcomes. We were unable to perform sensitivity analyses and subgroup analyses due to there being insufficient data. See [Summary of findings for the main comparison](#).

Potential biases in the review process

The review included the results from the subgroup analysis of a RCT, which was not explicitly described in the protocol methods.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no other systematic reviews comparing early versus late PN in term and late preterm infants. The only study that addressed this issue was [van Puffelen 2018](#) which has been included in this review. They concluded that withholding PN for one week of critical illness in term infants, while administering micronutrients, is superior to early initiation of PN from a short-term clinical and health-economical perspective. They also cautioned that withholding PN for one week significantly increased the risk of hypoglycaemia and hence long-term effects of hypoglycaemia need to be investigated before late PN can be confidently recommended for this population.

As highlighted in the results section of this Cochrane Review, the directions and sizes of the effect estimates from our analyses were often different to the results of the multivariable analyses in the included study ([van Puffelen 2018](#)). We found that infants given late PN had significantly lower incidence of 90-day mortality and overall incidence of HAI, but [van Puffelen 2018](#) found that the timing of PN commencement did not affect these outcomes on multivariable analyses. Furthermore, our analyses found that the timing of commencement of PN did not affect duration of hospital stay and incidence of hypoglycaemia. On the other hand, [van Puffelen 2018](#) found that late PN was associated with shorter duration of hospital stay and higher incidence of hypoglycaemia on multivariable analyses.

Our results in favour of late PN for duration of ICU stay and duration mechanical ventilation were in agreement with the results of multivariable analyses in [van Puffelen 2018](#). Furthermore, our analysis reporting no significant difference between the two groups in regards to death during first week of admission was also in agreement with the multivariable analysis results of [van Puffelen 2018](#).

For individual types of infections, [van Puffelen 2018](#) reported results from univariable analyses and they were in agreement with our review. For HABS, [van Puffelen 2018](#) reported results of univariable analysis and found that late PN was associated with

lower incidence of HABS (P = 0.048). Our analysis found that the timing of PN was not associated with incidence of HABS (P = 0.05).

We were unable to compare some of our results to those of [van Puffelen 2018](#) (e.g. in-hospital all-cause mortality, neonatal mortality, duration of respiratory support, highest blood urea nitrogen and growth outcomes) as results were not reported in the manuscript of [van Puffelen 2018](#), but the raw data was kindly provided by the authors upon our request.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence from randomised controlled trials (RCTs) to determine whether early or late commencement of parenteral nutrition (PN) affects the outcomes of critically ill term and late preterm infants.

Implications for research

Adequately powered RCTs in term and late preterm infants are needed. In such trials, infants should be stratified based on the underlying condition (medical and surgical), gestation (term and late preterm) and severity of critical illness.

A prior survey of clinicians needs to be conducted to establish the current practice and beliefs. The results of such a survey should be taken into consideration while designing the trials and defining the interventions (i.e. 'early PN' and 'late PN') to ensure maximum generalisability and willingness to participate.

Given that the multivariable analyses of the included study ([van Puffelen 2018](#)) found that late PN is associated with increased risk of hypoglycaemia, blood glucose levels should be diligently monitored in the future trials.

In light of the results of a post-hoc analysis of the included study ([Vanhorebeek 2017](#); [van Puffelen 2018](#)), which suggested that early amino acids rather than lipids were associated with worse outcomes, future neonatal RCTs should analyse these interventions separately by having four arms: 1) early amino acids + early lipids; 2) early amino acids + late lipids; 3) late amino acids + early lipids; and 4) late amino acids + late lipids. It will be useful to include biochemical outcomes such as plasma amino acid and fatty acid profiles and biomarkers of oxidative stress to explore underlying pathways of benefits/harms.

In addition to the short term outcomes, long-term neurodevelopmental and growth outcomes should be evaluated in future trials.

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REFERENCES

References to studies included in this review

Makay 2007 {published data only}

Makay B, Duman N, Ozer E, Kumral A, Yesilirmak D, Ozkan H. Randomized, controlled trial of early intravenous nutrition for prevention of neonatal jaundice in term and near-term neonates. *Journal of Pediatric Gastroenterology and Nutrition* 2007;**44**(3):354-8. [DOI: [10.1097/MPG.0b013e31802b31f2](https://doi.org/10.1097/MPG.0b013e31802b31f2); PUBMED: 17325557]

van Puffelen 2018 {published data only}

van Puffelen E, Vanhorebeek I, Joosten KFM, Wouters PJ, Van den Berghe G, Verbruggen SCAT. Early versus late parenteral nutrition in critically ill, term neonates: a preplanned secondary subgroup analysis of the PEPaNIC multicentre, randomised controlled trial. *The Lancet Child & Adolescent Health* 2018;**2**(7):505-15. [DOI: [10.1016/S2352-4642\(18\)30131-7](https://doi.org/10.1016/S2352-4642(18)30131-7); PUBMED: 30169323]

References to studies excluded from this review

Brownlee 1993 {published data only}

Brownlee KG, Kelly EJ, Ng PC, Kendall-Smith SC, Dear PR. Early or late parenteral nutrition for the sick preterm infant?. *Archives of Disease in Childhood* 1993;**69**(3 Spec No):281-3. [DOI: [10.1136/adsc.69.3.spec.no.281](https://doi.org/10.1136/adsc.69.3.spec.no.281); PUBMED: 8215565]

Vanhorebeek 2017 {published data only}

Vanhorebeek I, Verbruggen S, Casaer MP, Gunst J, Wouters PJ, Hanot J, et al. Effect of early supplemental parenteral nutrition in the paediatric ICU: a preplanned observational study of post-randomisation treatments in the PEPaNIC trial. *The Lancet Respiratory Medicine* 2017;**5**(6):475-83. [DOI: [10.1016/S2213-2600\(17\)30186-8](https://doi.org/10.1016/S2213-2600(17)30186-8); PUBMED: 28522351]

van Puffelen 2018a {published data only}

van Puffelen E, Polinder S, Vanhorebeek I, Wouters PJ, Bossche N, Peers G, et al. Cost-effectiveness study of early versus late parenteral nutrition in critically ill children (PEPaNIC): preplanned secondary analysis of a multicentre randomised controlled trial. *Critical Care* 2018;**22**(1):4. [DOI: [10.1186/s13054-017-1936-2](https://doi.org/10.1186/s13054-017-1936-2); PUBMED: 29335014]

van Puffelen 2018b {published data only}

van Puffelen E, Hulst JM, Vanhorebeek I, Dulfer K, Van den Berghe G, Verbruggen SCAT, et al. Outcomes of delaying parenteral nutrition for 1 week vs initiation within 24 hours among undernourished children in pediatric intensive care: a subanalysis of the PEPaNIC randomized clinical trial. *JAMA Network Open* 2018;**1**(5):e182668. [DOI: [10.1001/jamanetworkopen.2018.2668](https://doi.org/10.1001/jamanetworkopen.2018.2668); PUBMED: 30646158]

Verstraete 2018 {published data only}

Verstraete S, Vanhorebeek I, van Puffelen E, Derese I, Ingels C, Verbruggen SC, et al. Leukocyte telomere length in paediatric critical illness: effect of early parenteral nutrition. *Critical Care* 2018;**22**(1):38. [DOI: [10.1186/s13054-018-1972-6](https://doi.org/10.1186/s13054-018-1972-6); PUBMED: 29463275]

Verstraete 2019 {published data only}

Verstraete S, Verbruggen SC, Hordijk JA, Vanhorebeek I, Dulfer K, Guiza F, et al. Long-term developmental effects of withholding parenteral nutrition for 1 week in the paediatric intensive care unit: a 2-year follow-up of the PEPaNIC international, randomised, controlled trial. *The Lancet Respiratory Medicine* 2019;**7**(2):141-53. [DOI: [10.1016/S2213-2600\(18\)30334-5](https://doi.org/10.1016/S2213-2600(18)30334-5); PUBMED: 30224325]

Additional references

Adamkin 2007

Adamkin DH. Early aggressive nutrition: parenteral amino acids and minimal enteral nutrition for extremely low birth weight (< 1000 g) infants. *Minerva Pediatrica* 2007;**59**(4):369-77. [PUBMED: 17947842]

Agus 2017

Agus MS, Wypij D, Hirshberg EL, Srinivasan V, Faustino EV, Luckett PM, et al. Tight glycemic control in critically ill children. *New England Journal of Medicine* 2017;**376**(8):729-41. [DOI: [10.1056/NEJMoa1612348](https://doi.org/10.1056/NEJMoa1612348); PUBMED: 28118549]

Ainsworth 2015

Ainsworth S, McGuire W. Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. *Cochrane Database of Systematic Reviews* 2015, Issue 10. [DOI: [10.1002/14651858.CD004219.pub4](https://doi.org/10.1002/14651858.CD004219.pub4)]

Aksnes 1996

Aksnes J, Schmidt H, Hall C, Nordstrand K. Long term lipid-based parenteral nutrition causes pulmonary hypertension in pigs. *European Journal of Surgery* 1996;**162**(8):649-56. [PUBMED: 8891624]

Alshweki 2015

Alshweki A, Munuzuri AP, Bana AM, de Castro MJ, Andrade F, Aldamiz-Echevarria L, et al. Effects of different arachidonic acid supplementation on psychomotor development in very preterm infants: a randomized controlled trial. *Nutrition Journal* 2015;**14**:101. [DOI: [10.1186/s12937-015-0091-3](https://doi.org/10.1186/s12937-015-0091-3); PUBMED: 26424477]

Amin 2009

Amin SB, Harte T, Scholer L, Wang H. Intravenous lipid and bilirubin-albumin binding variables in premature infants. *Pediatrics* 2009;**124**(1):211-7. [DOI: [10.1542/peds.2008-0846](https://doi.org/10.1542/peds.2008-0846); PUBMED: 19564302]

Avila-Figueroa 1998

Avila-Figueroa C, Goldmann DA, Richardson DK, Gray JE, Ferrari A, Freeman J. Intravenous lipid emulsions are the major determinant of coagulase-negative staphylococcal bacteremia in very low birth weight newborns. *Pediatric Infectious Disease Journal* 1998;**17**(1):10-7. [PUBMED: 9469388]

Basu 1999

Basu R, Muller DP, Papp E, Merryweather I, Eaton S, Klein N, et al. Free radical formation in infants: the effect of critical illness, parenteral nutrition, and enteral feeding. *Journal of Pediatric Surgery* 1999;**34**(7):1091-5. [PUBMED: 10442597]

Bishay 2012

Bishay M, Retrosi G, Horn V, Cloutman-Green E, Harris K, de Coppi P, et al. Septicaemia due to enteric organisms is a later event in surgical infants requiring parenteral nutrition. *European Journal of Pediatric Surgery* 2012;**22**(1):50-3. [DOI: [10.1055/s-0031-1287853](https://doi.org/10.1055/s-0031-1287853); PUBMED: 22270963]

Bulbul 2012

Bulbul A, Okan F, Bulbul L, Nuhoglu A. Effect of low versus high early parenteral nutrition on plasma amino acid profiles in very low birth-weight infants. *Journal of Maternal-Fetal & Neonatal Medicine* 2012;**25**(6):770-6. [DOI: [10.3109/14767058.2011.589873](https://doi.org/10.3109/14767058.2011.589873); PUBMED: 21770835]

Can 2012

Can E, Bulbul A, Uslu S, Comert S, Bolat F, Nuhoglu A. Effects of aggressive parenteral nutrition on growth and clinical outcome in preterm infants. *Pediatrics International* 2012;**54**(6):869-74. [DOI: [10.1111/j.1442-200X.2012.03713.x](https://doi.org/10.1111/j.1442-200X.2012.03713.x); PUBMED: 22882288]

Can 2013

Can E, Bulbul A, Uslu S, Bolat F, Comert S, Nuhoglu A. Early aggressive parenteral nutrition induced high Insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3) levels can prevent risk of retinopathy of prematurity. *Iranian Journal of Pediatrics* 2013;**23**(4):403-10. [PUBMED: 24427493]

Casaer 2011

Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. *New England Journal of Medicine* 2011;**365**(6):506-17. [DOI: [10.1056/NEJMoa1102662](https://doi.org/10.1056/NEJMoa1102662); PUBMED: 21714640]

Chen 2018

Chen L, Li T, Fang F, Zhang Y, Faramand A. Tight glycemic control in critically ill pediatric patients: a systematic review and meta-analysis. *Critical Care* 2018;**22**(1):57. [PUBMED: 29501063]

Chettri 2016

Chettri S, Bhat BV, Adhisivam B. Current concepts in the management of meconium aspiration syndrome. *Indian Journal of Pediatrics* 2016;**83**(10):1125-30. [DOI: [10.1007/s12098-016-2128-9](https://doi.org/10.1007/s12098-016-2128-9); PUBMED: 27206687]

Cies 2014

Cies JJ, Moore WS 2nd. Neonatal and pediatric peripheral parenteral nutrition: what is a safe osmolarity?. *Nutrition in Clinical Practice* 2014;**29**(1):118-24. [PUBMED: 24336401]

Clark 2007

Clark RH, Chace DH, Spitzer AR. Effects of two different doses of amino acid supplementation on growth and blood amino acid levels in premature neonates admitted to the neonatal

intensive care unit: a randomized, controlled trial. *Pediatrics* 2007;**120**(6):1286-96. [PUBMED: 18055678]

Cleminson 2016

Cleminson JS, Zalewski SP, Embleton ND. Nutrition in the preterm infant: what's new?. *Current Opinion in Clinical Nutrition and Metabolic Care* 2016;**19**(3):220-5. [PUBMED: 27504517]

De Curtis 2012

De Curtis M, Rigo J. The nutrition of preterm infants. *Early Human Development* 2012;**88**(Suppl 1):S5-7. [DOI: [10.1016/j.earlhumdev.2011.12.020](https://doi.org/10.1016/j.earlhumdev.2011.12.020); PUBMED: 22261289]

de Jong 2015

de Jong C, Kikkert HK, Seggers J, Boehm G, Decsi T, Hadders-Algra M. Neonatal fatty acid status and neurodevelopmental outcome at 9 years. *Early Human Development* 2015;**91**(10):587-91. [DOI: [10.1016/j.earlhumdev.2015.07.007](https://doi.org/10.1016/j.earlhumdev.2015.07.007); PUBMED: 26231619]

Denne 1996

Denne SC, Karn CA, Ahlrichs JA, Dorotheo AR, Wang J, Liechty EA. Proteolysis and phenylalanine hydroxylation in response to parenteral nutrition in extremely premature and normal newborns. *Journal of Clinical Investigation* 1996;**97**(3):746-54. [DOI: [10.1172/JCI118473](https://doi.org/10.1172/JCI118473); PUBMED: 8609231]

Dong 2017

Dong Y, Jiang SY, Zhou Q, Cao Y. Group B Streptococcus causes severe sepsis in term neonates: 8 years experience of a major Chinese neonatal unit. *World Journal of Pediatrics* 2017;**13**(4):314-20. [DOI: [10.1007/s12519-017-0034-5](https://doi.org/10.1007/s12519-017-0034-5); PUBMED: 28560649]

Donnell 2002

Donnell SC, Taylor N, van Saene HK, Magnall VL, Pierro A, Lloyd DA. Infection rates in surgical neonates and infants receiving parenteral nutrition: a five-year prospective study. *Journal of Hospital Infection* 2002;**52**(4):273-80. [PUBMED: 12473472]

Douglas-Escobar 2015

Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. *JAMA Pediatrics* 2015;**169**(4):397-403. [DOI: [10.1001/jamapediatrics.2014.3269](https://doi.org/10.1001/jamapediatrics.2014.3269); PUBMED: 25685948]

Dounousi 2015

Dounousi E, Zikou X, Koulouras V, Katopodis K. Metabolic acidosis during parenteral nutrition: pathophysiological mechanisms. *Indian Journal of Critical Care Medicine* 2015;**19**(5):270-4. [DOI: [10.4103/0972-5229.156473](https://doi.org/10.4103/0972-5229.156473); PUBMED: 25983433]

Dubbink-Verheij 2017

Dubbink-Verheij GH, Bekker V, Pelsma ICM, van Zwet EW, Smits-Wintjens VEJ, Steggerda SJ, et al. Bloodstream infection incidence of different central venous catheters in neonates: a descriptive cohort study. *Frontiers in Pediatrics* 2017;**5**:142. [DOI: [10.3389/fped.2017.00142](https://doi.org/10.3389/fped.2017.00142); PUBMED: 28676849]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629-34. [DOI: [10.1136/bmj.315.7109.629](https://doi.org/10.1136/bmj.315.7109.629); PUBMED: 9310563]

Fivez 2016

Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. *New England Journal of Medicine* 2016;**374**(12):1111-22. [DOI: [10.1056/NEJMoa1514762](https://doi.org/10.1056/NEJMoa1514762); PUBMED: 26975590]

Freeman 1990

Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *New England Journal of Medicine* 1990;**323**(5):301-8. [DOI: [10.1056/NEJM199008023230504](https://doi.org/10.1056/NEJM199008023230504); PUBMED: 2082952]

Friedman 1976

Friedman Z, Danon A, Stahlman MT, Oates JA. Rapid onset of essential fatty acid deficiency in the newborn. *Pediatrics* 1976;**58**(5):640-9. [PUBMED: 824608]

Friedman 1986

Friedman Z. Essential fatty acid consideration at birth in the premature neonate and the specific requirement for preformed prostaglandin precursors in the infant. *Progress in Lipid Research* 1986;**25**(1-4):355-64. [PUBMED: 3321088]

Gilio 2000

Gilio AE, Stape A, Pereira CR, Cardoso MF, Silva CV, Troster EJ. Risk factors for nosocomial infections in a critically ill pediatric population: a 25-month prospective cohort study. *Infection Control and Hospital Epidemiology* 2000;**21**(5):340-2. [DOI: [10.1086/501770](https://doi.org/10.1086/501770); PUBMED: 10823571]

Gonzalez-Hernandez 2016

Gonzalez-Hernandez J, Daoud Y, Styers J, Journeycake JM, Channabasappa N, Piper HG. Central venous thrombosis in children with intestinal failure on long-term parenteral nutrition. *Journal of Pediatric Surgery* 2016;**51**(5):790-3. [DOI: [10.1016/j.jpedsurg.2016.02.024](https://doi.org/10.1016/j.jpedsurg.2016.02.024); PUBMED: 26936289]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 14 September 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2014.

Gray 1992

Gray JE, Richardson DK, McCormick MC, Workman-Daniels K, Goldmann DA. Neonatal therapeutic intervention scoring system: a therapy-based severity-of-illness index. *Pediatrics* 1992;**90**(4):561-7. [PUBMED: 1408510]

Guellec 2015

Guellec I, Gascoin G, Beuchee A, Boubred F, Tourneux P, Ramful D, et al. Biological impact of recent guidelines on parenteral nutrition in preterm infants. *Journal of Pediatric*

Gastroenterology and Nutrition 2015;**61**(6):605-9. [DOI: [10.1097/MPG.0000000000000898](https://doi.org/10.1097/MPG.0000000000000898); PUBMED: 26147627]

Gutcher 1991

Gutcher GR, Farrell PM. Intravenous infusion of lipid for the prevention of essential fatty acid deficiency in premature infants. *American Journal of Clinical Nutrition* 1991;**54**(6):1024-8. [DOI: [10.1093/ajcn/54.6.1024](https://doi.org/10.1093/ajcn/54.6.1024); PUBMED: 1957817]

Hammerman 1989

Hammerman C, Aramburo MJ, Hill V. Intravenous lipids in newborn lungs: thromboxane-mediated effects. *Critical Care Medicine* 1989;**17**(5):430-6. [DOI: [10.1097/00003246-198905000-00011](https://doi.org/10.1097/00003246-198905000-00011); PUBMED: 2707013]

Hasanoglu 2005

Hasanoglu A, Dalgic N, Tumer L, Atalay Y, Cinasal G, Biberoglu G, et al. Free oxygen radical-induced lipid peroxidation and antioxidant in infants receiving total parenteral nutrition. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 2005;**73**(2):99-102. [DOI: [10.1016/j.plefa.2005.04.015](https://doi.org/10.1016/j.plefa.2005.04.015); PUBMED: 15961302]

Hay 2013

Hay WW Jr. Aggressive nutrition of the preterm infant. *Current Pediatrics Reports* 2013;**1**(4). [DOI: [10.1007/s40124-013-0026-4](https://doi.org/10.1007/s40124-013-0026-4); PUBMED: 24386613]

Higgins 2011

Higgins JP, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hwang 1990

Hwang TL, Huang SL, Chen MF. Effects of intravenous fat emulsion on respiratory failure. *Chest* 1990;**97**(4):934-8. [DOI: [10.1378/chest.97.4.934](https://doi.org/10.1378/chest.97.4.934); PUBMED: 2108849]

International Neonatal Network 1993

International Neonatal Network. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. *Lancet* 1993;**342**(8865):193-8. [PUBMED: 8100927]

Jain 2015

Jain A, McNamara PJ. Persistent pulmonary hypertension of the newborn: advances in diagnosis and treatment. *Seminars in Fetal & Neonatal Medicine* 2015;**20**(4):262-71. [DOI: [10.1016/j.siny.2015.03.001](https://doi.org/10.1016/j.siny.2015.03.001); PUBMED: 25843770]

Jiang 2019

Jiang W, Chen G, Zhang J, Lv X, Lu C, Chen H, et al. The effects of two mixed intravenous lipid emulsions on clinical outcomes in infants after gastrointestinal surgery: a prospective, randomized study. *Pediatric Surgery International* 2019;**35**(3):347-55. [DOI: [10.1007/s00383-018-4422-2](https://doi.org/10.1007/s00383-018-4422-2); PUBMED: 30474700]

Kerklaan 2016

Kerklaan D, Fivez T, Mehta NM, Mesotten D, van Rosmalen J, Hulst JM, et al. Worldwide survey of nutritional practices in

PICUs. *Pediatric Critical Care Medicine* 2016;**17**(1):10-8. [DOI: [10.1097/PCC.0000000000000542](https://doi.org/10.1097/PCC.0000000000000542); PUBMED: 26509815]

Kostogloudis 2015

Kostogloudis N, Demiri E, Tsimponis A, Dionyssiou D, Ioannidis S, Chatziioannidis I, et al. Severe extravasation injuries in neonates: a report of 34 cases. *Pediatric Dermatology* 2015;**32**(6):830-5. [DOI: [10.1111/pde.12664](https://doi.org/10.1111/pde.12664); PUBMED: 26337780]

Kugelman 2013

Kugelman A, Colin AA. Late preterm infants: near term but still in a critical developmental time period. *Pediatrics* 2013;**132**(4):741-51. [DOI: [10.1542/peds.2013-1131](https://doi.org/10.1542/peds.2013-1131); PUBMED: 24062372]

Lee 1993

Lee EJ, Simmer K, Gibson RA. Essential fatty acid deficiency in parenterally fed preterm infants. *Journal of Paediatrics and Child Health* 1993;**29**(1):51-5. [PUBMED: 8461181]

Leeuwen 2014

Leeuwen L, Fitzgerald DA. Congenital diaphragmatic hernia. *Journal of Paediatrics and Child Health* 2014;**50**(9):667-73. [DOI: [10.1111/jpc.12508](https://doi.org/10.1111/jpc.12508); PUBMED: 24528549]

Legeay 2015

Legeay C, Bourigault C, Lepelletier D, Zahar JR. Prevention of healthcare-associated infections in neonates: room for improvement. *Journal of Hospital Infection* 2015;**89**(4):319-23. [DOI: [10.1016/j.jhin.2015.02.003](https://doi.org/10.1016/j.jhin.2015.02.003); PUBMED: 25748794]

Liu 2015

Liu MY, Chen YY, Hu SH, Chen YK, Chang SJ. The influence of aggressive parenteral nutrition to preterm and very low birth weight infants. *Global Pediatric Health* 2015;**2**:1-6. [DOI: [10.1177/2333794X14567192](https://doi.org/10.1177/2333794X14567192); PUBMED: 27335933]

Macdonald 2005

Macdonald MG, Seshia MM, Mullett MD. Avery's Neonatology. 6th Edition. Baltimore (MD): Lippincott Williams and Wilkins, 2005.

Macrae 2014

Macrae D, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, et al. CHiP Investigators. A randomized trial of hyperglycemic control in pediatric intensive care. *New England Journal of Medicine* 2014;**370**(2):107-18. [DOI: [10.1056/NEJMoa1302564](https://doi.org/10.1056/NEJMoa1302564); PUBMED: 24401049]

Mahajan 2017

Mahajan G, Mukhopadhyay K, Attri S, Kumar P. Neurodevelopmental outcome of asymptomatic hypoglycemia compared with symptomatic hypoglycemia and euglycemia in high-risk neonates. *Pediatric Neurology* 2017;**74**:74-9. [DOI: [10.1016/j.pediatrneurol.2017.05.028](https://doi.org/10.1016/j.pediatrneurol.2017.05.028); PUBMED: 28739364]

Mehta 2018

Mehta NM, Tasker RC. Nutrition for term neonates in the paediatric intensive care unit. *The Lancet Child & Adolescent Health* 2018;**2**(7):469-71. [DOI: [10.1016/S2352-4642\(18\)30147-0](https://doi.org/10.1016/S2352-4642(18)30147-0); PUBMED: 30169311]

Nair 2014

Nair J, Lakshminrusimha S. Update on PPHN: mechanisms and treatment. *Seminars in Perinatology* 2014;**38**(2):78-91. [DOI: [10.1053/j.semperi.2013.11.004](https://doi.org/10.1053/j.semperi.2013.11.004); PUBMED: 24580763]

Ohnishi 2016

Ohnishi S, Ichiba H, Tanaka Y, Harada S, Matsumura H, Kan A, et al. Early and intensive nutritional strategy combining parenteral and enteral feeding promotes neurodevelopment and growth at 18 months of corrected age and 3 years of age in extremely low birth weight infants. *Early Human Development* 2016;**100**:35-41. [DOI: [10.1016/j.earlhumdev.2016.03.014](https://doi.org/10.1016/j.earlhumdev.2016.03.014); PUBMED: 27391871]

Patel 2017

Patel P, Bhatia J. Total parenteral nutrition for the very low birth weight infant. *Seminars in Fetal & Neonatal Medicine* 2017;**22**(1):2-7. [DOI: [10.1016/j.siny.2016.08.002](https://doi.org/10.1016/j.siny.2016.08.002); PUBMED: 27576106]

Pierro 2002

Pierro A. Metabolism and nutritional support in the surgical neonate. *Journal of Pediatric Surgery* 2002;**37**(6):811-22. [PUBMED: 12037742]

Pierro 2008

Pierro A, Eaton S. Metabolism and nutrition in the surgical neonate. *Seminars in Pediatric Surgery* 2008;**17**(4):276-84. [DOI: [10.1053/j.sempedsurg.2008.07.006](https://doi.org/10.1053/j.sempedsurg.2008.07.006); PUBMED: 19019296]

Poindexter 2006

Poindexter BB, Langer JC, Dusick AM, Ehrenkranz RA. Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome. *Journal of Pediatrics* 2006;**148**(3):300-5. [DOI: [10.1016/j.jpeds.2005.10.038](https://doi.org/10.1016/j.jpeds.2005.10.038); PUBMED: 16615955]

Prasertsom 1996

Prasertsom W, Phillipos EZ, Van Aerde JE, Robertson M. Pulmonary vascular resistance during lipid infusion in neonates. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 1996;**74**(2):F95-8. [DOI: [10.1136/fn.74.2.f95](https://doi.org/10.1136/fn.74.2.f95); PUBMED: 8777674]

Qiao 2019

Qiao LX, Wang J, Yan JH, Xu SX, Wang H, Zhu WY, et al. Follow-up study of neurodevelopment in 2-year-old infants who had suffered from neonatal hypoglycemia. *BMC Pediatrics* 2019;**19**(1):133. [DOI: [10.1186/s12887-019-1509-4](https://doi.org/10.1186/s12887-019-1509-4); PUBMED: 31023291]

Repa 2016

Repa A, Lochmann R, Unterasinger L, Weber M, Berger A, Haiden N. Aggressive nutrition in extremely low birth weight infants: impact on parenteral nutrition associated cholestasis and growth. *PeerJ* 2016;**4**:e2483. [DOI: [10.7717/peerj.2483](https://doi.org/10.7717/peerj.2483); PUBMED: 27688976]

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ribed 2013

Ribed SA, Romero Jimenez RM, Sanchez Gomez de Orgaz MC, Sanchez Luna M, Sanjurjo Saez M. Aggressive parenteral nutrition and growth velocity in preterm infants. *Nutricion Hospitalaria* 2013;**28**(6):2128-34. [DOI: [10.3305/nutr.hosp.v28in06.6961](https://doi.org/10.3305/nutr.hosp.v28in06.6961); PUBMED: 24506392]

Richardson 2001

Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. *Journal of Pediatrics* 2001;**138**(1):92-100. [DOI: [10.1067/mpd.2001.109608](https://doi.org/10.1067/mpd.2001.109608); PUBMED: 11148519]

Rigo 2013

Rigo J, Senterre T. Intrauterine-like growth rates can be achieved with premixed parenteral nutrition solution in preterm infants. *Journal of Nutrition* 2013;**143**(12 Suppl):2066S-70S. [DOI: [10.3945/jn.113.177006](https://doi.org/10.3945/jn.113.177006); PUBMED: 24108133]

Rintala 2014

Rintala RJ, Pakarinen MP, Koivusalo AI. Neonatal surgery: towards evidence-based practice and management. *Seminars in Pediatric Surgery* 2014;**23**(5):303-8. [DOI: [10.1053/j.sempedsurg.2014.09.012](https://doi.org/10.1053/j.sempedsurg.2014.09.012); PUBMED: 25459016]

Roelants 2016

Roelants JA, Vlaardingerbroek H, van den Akker CH, de Jonge RC, van Goudoever JB, Vermeulen MJ. Two-year follow-up of a randomized controlled nutrition intervention trial in very low-birth-weight infants. *Journal of Parenteral and Enteral Nutrition* 2016; Vol. 42, issue 1:122-31. [DOI: [10.1177/0148607116678196](https://doi.org/10.1177/0148607116678196); PUBMED: 27875287]

Sarnat 1976

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Archives of Neurology* 1976;**33**(10):696-705. [PUBMED: 987769]

Schneider 2017

Schneider N, Garcia-Rodenas CL. Early nutritional interventions for brain and cognitive development in preterm infants: a review of the literature. *Nutrients* 2017;**9**(3):187. [DOI: [10.3390/nu9030187](https://doi.org/10.3390/nu9030187); PUBMED: 28241501]

Schrag 2016

Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. *Pediatrics* 2016;**138**(6):e20162013. [DOI: [10.1542/peds.2016-2013](https://doi.org/10.1542/peds.2016-2013); PUBMED: 27940705]

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.gradeapro.org/app/handbook/handbook.html.

Shah 2019

Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and

meta-analysis. *Neonatology* 2019; Vol. 115, issue 2:116-26. [DOI: [10.1159/000492859](https://doi.org/10.1159/000492859); PUBMED: 30408811]

Shane 2014

Shane AL, Stoll BJ. Neonatal sepsis: progress towards improved outcomes. *Journal of Infection* 2014;**68** (Suppl 1):S24-32. [DOI: [10.1016/j.jinf.2013.09.011](https://doi.org/10.1016/j.jinf.2013.09.011); PUBMED: 24140138]

Simmer 2005

Simmer K, Rao SC. Early introduction of lipids to parenterally-fed preterm infants. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: [10.1002/14651858.CD005256](https://doi.org/10.1002/14651858.CD005256)]

Singhal 2016

Singhal A. Optimizing early protein intake for long-term health of preterm infants. *Nestle Nutrition Institute Workshop Series* 2016;**86**:129-37. [DOI: [10.1159/000442735](https://doi.org/10.1159/000442735); PUBMED: 27336311]

Srinivasan 2014

Srinivasan V, Agus MS. Tight glucose control in critically ill children--a systematic review and meta-analysis. *Pediatric Diabetes* 2014;**15**(2):75-83. [PUBMED: 24783254]

Strobel 2015

Strobel AM, Lu le N. The critically ill infant with congenital heart disease. *Emergency Medicine Clinics of North America* 2015;**33**(3):501-18. [DOI: [10.1016/j.emc.2015.04.002](https://doi.org/10.1016/j.emc.2015.04.002); PUBMED: 26226862]

Suchner 2001

Suchner U, Katz DP, Furst P, Beck K, Felbinger TW, Senftleben U, et al. Effects of intravenous fat emulsions on lung function in patients with acute respiratory distress syndrome or sepsis. *Critical Care Medicine* 2001;**29**(8):1569-74. [DOI: [10.1097/00003246-200108000-00012](https://doi.org/10.1097/00003246-200108000-00012); PUBMED: 11505129]

Tagare 2013

Tagare A, Walawalkar M, Vaidya U. Aggressive parenteral nutrition in sick very low birth weight babies: a randomized controlled trial. *Indian Pediatrics* 2013;**50**(10):954-6. [PUBMED: 23798635]

Tan 2017

Tan JK, Minutillo C, McMichael J, Rao S. Impact of hypoglycaemia on neurodevelopmental outcomes in hypoxic ischaemic encephalopathy: a retrospective cohort study. *BMJ Paediatrics Open* 2017;**1**(1):e000175. [DOI: [10.1136/bmjpo-2017-000175](https://doi.org/10.1136/bmjpo-2017-000175); PUBMED: 29637170]

Thompson 1997

Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteni CD, et al. The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. *Acta Paediatrica* 1997;**86**(7):757-61. [PUBMED: 9240886]

Torer 2015

Torer B, Hanta D, Ozdemir Z, Cetinkaya B, Gulcan H. An aggressive parenteral nutrition protocol improves growth in preterm infants. *Turkish Journal of Pediatrics* 2015;**57**(3):236-41. [PUBMED: 26701941]

Trivedi 2013

Trivedi A, Sinn JK. Early versus late administration of amino acids in preterm infants receiving parenteral nutrition. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: [10.1002/14651858.CD008771.pub2](https://doi.org/10.1002/14651858.CD008771.pub2)]

Umar 2011

Umar S, Nadadur RD, Li J, Maltese F, Partownavid P, van der Laarse A, et al. Intralipid prevents and rescues fatal pulmonary arterial hypertension and right ventricular failure in rats. *Hypertension* 2011;**58**(3):512-8. [DOI: [10.1161/HYPERTENSIONAHA.110.168781](https://doi.org/10.1161/HYPERTENSIONAHA.110.168781); PUBMED: 21747043]

Uthaya 2016

Uthaya S, Liu X, Babalis D, Dore C, Warwick J, Bell J, et al. Efficacy and mechanism avaluation. Nutritional Evaluation and Optimisation in Neonates (NEON) Trial of Amino Acid Regimen and Intravenous Lipid Composition in Preterm Parenteral Nutrition: A Randomised Double-blind Controlled Trial. Southampton (UK): NIHR Journals Library, 2016. [PUBMED: 27030860]

van Goudoever 2018

van Goudoever JB, Carnielli V, Darmaun D, Sainz de Pipaon M. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: amino acids. *Clinical Nutrition* 2018;**37**(6 Pt B):2315-23. [DOI: [10.1016/j.clnu.2018.06.945](https://doi.org/10.1016/j.clnu.2018.06.945); PUBMED: 30100107]

Venus 1989

Venus B, Smith RA, Patel C, Sandoval E. Hemodynamic and gas exchange alterations during Intralipid infusion in patients with adult respiratory distress syndrome. *Chest* 1989;**95**(6):1278-81. [DOI: [10.1378/chest.95.6.1278](https://doi.org/10.1378/chest.95.6.1278); PUBMED: 2721266]

Vlasselaers 2009

Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, et al. Intensive insulin therapy for patients in

paediatric intensive care: a prospective, randomised controlled study. *The Lancet* 2009;**373**(9663):547-56. [DOI: [10.1016/S0140-6736\(09\)60044-1](https://doi.org/10.1016/S0140-6736(09)60044-1); PUBMED: 19176240]

Wan 2014

Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014;**14**:135. [DOI: [10.1186/1471-2288-14-135](https://doi.org/10.1186/1471-2288-14-135); PUBMED: 25524443]

Wickstrom 2018

Wickstrom R, Skiold B, Petersson G, Stephansson O, Altman M. Moderate neonatal hypoglycemia and adverse neurological development at 2-6 years of age. *European Journal of Epidemiology* 2018;**33**(10):1011-20. [DOI: [10.1007/s10654-018-0425-5](https://doi.org/10.1007/s10654-018-0425-5); PUBMED: 30030683]

Wilkins 2004

Wilkins CE, Emmerson AJ. Extravasation injuries on regional neonatal units. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2004;**89**(3):F274-5. [DOI: [10.1136/adc.2003.028241](https://doi.org/10.1136/adc.2003.028241); PUBMED: 15102736]

Yang 2016

Yang J, Chang SS, Poon WB. Relationship between amino acid and energy intake and long-term growth and neurodevelopmental outcomes in very low birth weight infants. *Journal of Parenteral and Enteral Nutrition* 2016;**40**(6):820-6. [DOI: [10.1177/0148607115572833](https://doi.org/10.1177/0148607115572833); PUBMED: 25690346]

Zhao 2018

Zhao Y, Wu Y, Xiang B. Tight glycemic control in critically ill pediatric patients: a meta-analysis and systematic review of randomized controlled trials. *Pediatric Research* 2018;**84**(1):22-7. [DOI: [10.1038/s41390-018-0002-3](https://doi.org/10.1038/s41390-018-0002-3); PUBMED: 29795449]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Makay 2007

Methods	Single-centre RCT conducted in Turkey
Participants	72 infants with gestational age 35 ≥ weeks
Interventions	<p>Early PN: 1 g/kg/day of amino acid (TrophAmine 6%) started within the first 8 hours after birth and 1 g/kg/day lipid emulsion</p> <p>(Intralipid 20%) the next day</p> <p>Late PN: start on solution containing 10% glucose and electrolyte in the first 72 hours of life followed by 0.5 g/kg/day of amino acid and lipid</p> <p>Amino acids and lipid were increased by 0.5 g/kg/day to a maximum 3 g/kg/day.</p> <p>PIVC used for PN infusions</p>

Makay 2007 (Continued)

Outcomes	Energy intake, changes in body weight, time of first stool passage, number of daily stool output, relative changes in serum bilirubin levels at 24, 48 and 72 hours, need for phototherapy and duration of phototherapy
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"All singleton newborns with a gestational age of ≥ 35 weeks and whose clinical condition seemed to preclude oral feeding for a period of ≥ 3 days consecutively enrolled after informed parental consent"
Allocation concealment (selection bias)	Unclear risk	It is not clear how allocation concealment was achieved. The authors stated that "All infants were randomly allocated to receive 1 of 2 intravenous nutrition regimen".
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was no blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	High risk	From the 72 infants who entered the study, "18 were withdrawn for several reasons". Outcomes of remaining infants (n = 30 in early PN and n = 24 in late PN) were available and analysed.
Selective reporting (reporting bias)	High risk	The main outcomes (including changes in body weight, time of first stool passage and number of daily stool output) were not fully reported in the results section.
Other bias	High risk	Eligibility criteria were applied after randomisation. This lead to withdrawal of infants from the study after the randomisation and unequal number of infants in each study arm.

van Puffelen 2018

Methods	Multicentre RCT conducted in Belgium, the Netherlands and Canada
Participants	1440 children aged 0 to 17 years, of which 209 were term neonates (published separately in van Puffelen 2018)
Interventions	Early parenteral nutrition within 24 hours of admission to paediatric ICU. Late parenteral nutrition: parenteral nutrition not provided until the 8th day of ICU admission
Outcomes	Fivez 2016 Primary

van Puffelen 2018 (Continued)

PICU-acquired infections (airway, bloodstream, urinary tract, central nervous system, soft tissue, other focus, no focus identified), total duration of antibiotic treatment for patients with new infection (days), total duration of stay in paediatric ICU (days), patients requiring ≥ 8 days in paediatric ICU (number (%))

Secondary

Highest plasma level of urea

Direct healthcare costs

Duration of hospital stay

Safety

Death (within 8 days of admission to paediatric ICU, during stay in paediatric ICU, during hospital stay, within 90 days after enrolment)

Hypoglycaemia, defined as glucose < 40 mg/dl during first 7 days in paediatric ICU

Hypoglycaemia refractory to treatment for ≥ 2 hr

Readmission to paediatric ICU within 48 hours after discharge

Efficacy

Duration of mechanical ventilatory support

Duration of haemodynamic support

Kidney failure with renal-replacement therapy

Liver dysfunction during first 7 days in paediatric ICU

- Highest plasma level of total bilirubin
- Highest plasma level of alkaline phosphatase
- Highest plasma level of γ -glutamyltransferase
- Highest plasma level of alanine aminotransferase
- Highest plasma level of aspartate aminotransferase

Highest plasma level of C-reactive protein during first 7 days in paediatric ICU, as measure of inflammation (mg/litter)

Duration of hospital stay

Index hospital

Index and transfer hospital

van Puffelen 2018

Primary

Incidence of infection acquired in the paediatric ICU

Duration of paediatric ICU dependency (number of days in the paediatric ICU and likelihood of earlier live discharge from ICU)

Secondary

Efficacy

Duration of mechanical ventilatory support

Highest plasma level of urea

Duration of hospital stay

van Puffelen 2018 (Continued)

Direct healthcare costs

Safety

Death during first week

90-day mortality

Hypoglycaemia, defined as blood glucose < 40 mg/dL (< 2.2 mmol/L) during first week

Notes	van Puffelen 2018 is a report of a secondary subgroup analysis of Fivez 2016, involving 209 term infants.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was stratified in permuted blocks of 10 according to age (< 1 year or ≥ 1 year) and diagnosis on admission (medical–neurologic, medical–other, surgical–cardiac, or surgical–other). The block size was unknown to the medical and research teams.
Allocation concealment (selection bias)	Low risk	Concealment of group assignment was ensured by the use of a central computerised randomisation system.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Healthcare workers, parents and investigators were aware of the allocation group. Given the nature of interventions, blinding of participants and personnel was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors and other personnel such as statisticians, infectious disease specialists and laboratory personnel were fully blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary outcome data for the original RCT on all 209 term infants were available
Selective reporting (reporting bias)	Low risk	All outcomes written in the Methods section of the article were reported in the Results section.
Other bias	High risk	Three individual trial centres used different insulin infusion regimens and different target blood glucose levels for the study infants. The type and composition of amino acids and lipid emulsions and the caloric targets also varied across the centres. Furthermore, there were significant differences between groups in the estimated mortality risks at the time of enrolment (early PN: 9.9%; late PN: 6.7%; $P = 0.011$).

ICU: intensive care unit

PICU: paediatric intensive care unit

PVC: peripheral intravenous catheter

PN: parenteral nutrition

n = number

RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brownlee 1993	Study population was very preterm infants with median gestational age of 29 weeks
van Puffelen 2018a	Substudy of PEPaNIC RCT (Fivez 2016). Cost-effectiveness analysis
van Puffelen 2018b	Subanalysis of PEPaNIC RCT (Fivez 2016). Clinical outcomes of undernourished patients were compared via multivariable logistic regression and Cox proportional hazard analyses, adjusted for risk factors
Vanhorebeek 2017	Secondary analysis of PEPaNIC RCT (Fivez 2016). Analysed independent associations between clinical outcomes and average daily total doses of each macronutrient
Verstraete 2018	Two-year follow-up study of PEPaNIC RCT. Assessed physical and neurocognitive development. Authors contacted for the neurodevelopmental outcomes of term infants but unable to obtain
Verstraete 2019	Substudy of PEPaNIC RCT. Leukocyte telomere length was the outcome measure.

DATA AND ANALYSES

Comparison 1. Early PN versus Late PN

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 In-hospital all-cause mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Neonatal mortality (within 28 days of birth)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Death during first week of admission	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 90-day mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Healthcare-associated blood stream infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Healthcare-associated infection (any type)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Other types of hospital-acquired infection: Airway	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Other types of hospital-acquired infection: Urinary tract	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Other types of hospital-acquired infection: Central nervous system	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Other types of hospital-acquired infection: Soft tissue	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Other types of hospital-acquired infection: Others	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12 Other types of hospital-acquired infection: No focus identified	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Duration of hospital stay	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Duration of ICU stay	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15 Duration of respiratory support (mechanical ventilation or CPAP or NIPPV)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16 Duration of mechanical ventilation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17 Hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18 Highest blood urea nitrogen levels during hospital stay	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19 Z scores for weight at discharge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20 Change to Z scores for weight from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Early PN versus Late PN, Outcome 1 In-hospital all-cause mortality.

Study or subgroup	Late PN n/N	Early PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
van Puffelen 2018	6/111	15/98		0.35[0.14,0.87]

Analysis 1.2. Comparison 1 Early PN versus Late PN, Outcome 2 Neonatal mortality (within 28 days of birth).

Study or subgroup	Late PN n/N	Early PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
van Puffelen 2018	4/111	12/98		0.29[0.1,0.88]

Analysis 1.3. Comparison 1 Early PN versus Late PN, Outcome 3 Death during first week of admission.

Study or subgroup	Late PN n/N	Early PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
van Puffelen 2018	2/111	6/98		0.29[0.06,1.42]
Favours [Late PN]				Favours [Early PN]

Analysis 1.4. Comparison 1 Early PN versus Late PN, Outcome 4 90-day mortality.

Study or subgroup	Late PN n/N	Early PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
van Puffelen 2018	6/111	15/98		0.35[0.14,0.87]
Favours [Late PN]				Favours [Early PN]

Analysis 1.5. Comparison 1 Early PN versus Late PN, Outcome 5 Healthcare-associated blood stream infection.

Study or subgroup	Late PN n/N	Early PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
van Puffelen 2018	2/111	8/98		0.22[0.05,1.01]
Favours Late PN				Favours Early PN

Analysis 1.6. Comparison 1 Early PN versus Late PN, Outcome 6 Healthcare-associated infection (any type).

Study or subgroup	Late PN n/N	Early PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
van Puffelen 2018	18/111	30/98		0.53[0.22,1.29]
Favours Late PN				Favours Early PN

Analysis 1.7. Comparison 1 Early PN versus Late PN, Outcome 7 Other types of hospital-acquired infection: Airway.

Study or subgroup	Late PN n/N	Early PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
van Puffelen 2018	6/111	9/98		0.59[0.22,1.59]
Favours [Late PN]				Favours [Early PN]

Analysis 1.8. Comparison 1 Early PN versus Late PN, Outcome 8 Other types of hospital-acquired infection: Urinary tract.

Study or subgroup	Late PN n/N	Early PN n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
van Puffelen 2018	1/111	3/98		0.29[0.03,2.78]
Favours [Late PN]				Favours [Early PN]

Analysis 1.9. Comparison 1 Early PN versus Late PN, Outcome 9 Other types of hospital-acquired infection: Central nervous system.

Analysis 1.10. Comparison 1 Early PN versus Late PN, Outcome 10 Other types of hospital-acquired infection: Soft tissue.

Analysis 1.11. Comparison 1 Early PN versus Late PN, Outcome 11 Other types of hospital-acquired infection: Others.

Analysis 1.12. Comparison 1 Early PN versus Late PN, Outcome 12 Other types of hospital-acquired infection: No focus identified.

Analysis 1.13. Comparison 1 Early PN versus Late PN, Outcome 13 Duration of hospital stay.

Analysis 1.14. Comparison 1 Early PN versus Late PN, Outcome 14 Duration of ICU stay.

Study or subgroup	Late PN		Early PN		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
van Puffelen 2018	111	5.7 (4.5)	98	9 (9)	+	-3.3[-5.27,-1.33]
					Favours [Late PN] -100 -50 0 50 100 Favours [Early PN]	

Analysis 1.15. Comparison 1 Early PN versus Late PN, Outcome 15 Duration of respiratory support (mechanical ventilation or CPAP or NIPPV).

Study or subgroup	Late PN		Early PN		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
van Puffelen 2018	111	6.1 (8.5)	98	17 (44.3)	→	-10.9[-19.81,-1.99]
					Favours [Late PN] -100 -50 0 50 100 Favours [Early PN]	

Analysis 1.16. Comparison 1 Early PN versus Late PN, Outcome 16 Duration of mechanical ventilation.

Study or subgroup	Late PN		Early PN		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
van Puffelen 2018	111	3.6 (3)	98	7 (7.5)	+	-3.4[-4.99,-1.81]
					Favours Late PN -100 -50 0 50 100 Favours Early PN	

Analysis 1.17. Comparison 1 Early PN versus Late PN, Outcome 17 Hypoglycaemia.

Study or subgroup	Late PN		Early PN		Risk Ratio	Risk Ratio
	n/N		n/N		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
van Puffelen 2018	26/111		14/98		+	1.64[0.91,2.96]
					Favours Late PN 0.01 0.1 1 10 100 Favours Early PN	

Analysis 1.18. Comparison 1 Early PN versus Late PN, Outcome 18 Highest blood urea nitrogen levels during hospital stay.

Study or subgroup	Late PN		Early PN		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
van Puffelen 2018	111	34 (19.5)	98	49.7 (27.5)	→	-15.7[-22.24,-9.16]
					Favours [Late PN] -100 -50 0 50 100 Favours [Early PN]	

Analysis 1.19. Comparison 1 Early PN versus Late PN, Outcome 19 Z scores for weight at discharge.

Study or subgroup	Late PN		Early PN		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
van Puffelen 2018	69	-0.9 (1.4)	60	-1 (1.6)		0.07[-0.44,0.58]
					Favours Late PN -100 -50 0 50 100 Favours Early PN	

Analysis 1.20. Comparison 1 Early PN versus Late PN, Outcome 20 Change to Z scores for weight from baseline.

Study or subgroup	Late PN		Early PN		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
van Puffelen 2018	69	-0.6 (1.4)	60	-0.5 (1.1)		-0.11[-0.53,0.31]
					Favours late	Favours early

APPENDICES

Appendix 1. Standard search methods

PubMed search strategy

#1

("parenteral nutrition, total"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields] AND "total"[All Fields]) OR "total parenteral nutrition"[All Fields] OR ("parenteral"[All Fields] AND "nutrition"[All Fields]) OR "parenteral nutrition"[All Fields] OR "parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields])) AND (((("infant, premature"[MeSH Terms] OR ("infant"[All Fields] AND "premature"[All Fields]) OR "premature infant"[All Fields] OR ("preterm"[All Fields] AND "infant"[All Fields]) OR "preterm infant"[All Fields]) OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR ("newborn"[All Fields] AND "infant"[All Fields])) OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonate"[All Fields]))): 5211

#2

("Infant, Premature, Diseases"[Mesh] OR "Infant, Premature"[Mesh] OR "Infant, Postmature"[Mesh] OR "Infant, Newborn, Diseases"[Mesh] OR "Infant, Newborn"[Mesh]) AND ("Parenteral Nutrition, Total"[Mesh] OR "Parenteral Nutrition"[Mesh]): 3747

#3: #1 OR #2: 5267

#4: #3 with limits

((("parenteral nutrition, total"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields] AND "total"[All Fields]) OR "total parenteral nutrition"[All Fields] OR ("parenteral"[All Fields] AND "nutrition"[All Fields]) OR "parenteral nutrition"[All Fields] OR "parenteral nutrition"[MeSH Terms] OR ("parenteral"[All Fields] AND "nutrition"[All Fields])) AND (((("infant, premature"[MeSH Terms] OR ("infant"[All Fields] AND "premature"[All Fields]) OR "premature infant"[All Fields] OR ("preterm"[All Fields] AND "infant"[All Fields]) OR "preterm infant"[All Fields]) OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR ("newborn"[All Fields] AND "infant"[All Fields])) OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonate"[All Fields])))) OR ((("Infant, Premature, Diseases"[Mesh] OR "Infant, Premature"[Mesh] OR "Infant, Postmature"[Mesh] OR "Infant, Newborn, Diseases"[Mesh] OR "Infant, Newborn"[Mesh]) AND ("Parenteral Nutrition, Total"[Mesh] OR "Parenteral Nutrition"[Mesh])) AND (randomised Controlled Trial[ptyp] OR Multicenter Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Clinical Trial Protocol[ptyp] OR Clinical Trial[ptyp]) = 905

Embase search strategy

1 parenteral nutrition.mp. or exp parenteral nutrition/ (47463)

2 exp infant/ (862157)

3 exp newborn/ (458119)

4 2 or 3 (862157)

5 1 and 4 (7557)

6 limit 5 to (clinical trial or randomised controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) (610)

MEDLINE via Ovid

Early versus late parenteral nutrition for critically ill term and late preterm infants (Review)

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1 parenteral nutrition.mp. or exp Parenteral Nutrition/ (28818)

2 infant.mp. or exp Infant, Newborn/ or exp Infant, Newborn, Diseases/ or exp Infant, Premature/ or exp Infant, Premature, Diseases/ or Infant Nutrition Disorders/ or exp Infant/ or exp Infant Welfare/ or Infant, Postmature/ (1179624)

3 neonate.mp. or exp Infant, Newborn/ (588572)

4 2 or 3 (1185533)

5 1 and 4 (6624)

6 limit 5 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv) (487)

EMCare via ovid

1 parenteral nutrition.mp. or exp parenteral nutrition/ (12913)

2 exp infant/ or infant.mp. (195204)

3 1 and 2 (2369)

4 limit 3 to (clinical trial or randomised controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) (263)

Cochrane CENTRAL

#1 parenteral nutrition 5491

#2 MeSH descriptor: [Parenteral Nutrition] explode all trees 1599

#3 infant 46575

#4 MeSH descriptor: [Infant] explode all trees 15207

#5 neonate 2299

#6 MeSH descriptor: [Infant, Newborn] explode all trees 14968

#7 #1 OR #2 5491

#8 #3 OR #4 OR #5 OR #6 47504

#9 #7 AND #8 854

Trial 687

Mednar

Parenteral nutrition limit to clinical trials: 71

Clinicaltrials.gov

Parenteral nutrition

Limit to 0-17

154

Appendix 2. Risk of bias tool

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:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- 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:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- 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:

- low risk, high risk or unclear risk for participants; and
- 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 class of outcomes. We categorised the methods as:

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

- low risk (< 20% missing data);
- high risk ($\geq$ 20% missing data); or
- 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. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all 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
- unclear risk.

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

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

- low risk;
- high risk; or
- unclear risk.

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

CONTRIBUTIONS OF AUTHORS

KM contributed to all stages of protocol and review preparation, performed the literature search, entered characteristics of studies, performed the 'Risk of bias' assessment, extracted data and wrote the review.

SR contributed to all stages of protocol and review preparation, assessed studies for eligibility, checked characteristics of studies, checked final data, checked the 'Risk of bias' assessment and wrote the review.

UR reviewed protocol, performed the literature search, entered characteristics of studies, performed the 'Risk of bias' assessment, extracted data and reviewed the manuscript.

GJ reviewed the protocol, assessed studies for eligibility, checked final data and reviewed the manuscript.

DECLARATIONS OF INTEREST

KM has no interests to declare.

SR has no interests to declare.

UR has no interests to declare.

GJ has no interests to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Vermont Oxford Network, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following outcomes were added as additional secondary outcomes post hoc:

- Death during the first week of admission
- 90-day mortality
- Duration of ICU stay (days)
- Healthcare-associated infections (any types)
- Highest plasma level of total bilirubin during hospital stay (mg/dl)
- Highest plasma level of alkaline phosphatase during hospital stay (IU/L)
- Highest plasma level of γ -glutamyl-transferase during hospital stay (IU/L)
- Highest plasma level of alanine transferase (IU/L)
- Highest plasma level of aspartate aminotransferase (IU/L)
- Highest blood urea nitrogen levels during hospital stay

The following changes to the list of 7 outcomes for GRADE assessment were made post hoc.

- We replaced 'incidence of hyperglycaemia' to 'neonatal mortality' given that we should be adding the primary outcome as one of the most important outcomes.
- We replaced 'Other types of hospital acquired infection' to 'healthcare-associated infections (any type)' as we have reported 'other types of hospital acquired infection' as individual type of infection rather than combined.

INDEX TERMS

Medical Subject Headings (MeSH)

Amino Acids [administration & dosage] [adverse effects]; Bias; Critical Illness [*therapy]; Cross Infection [epidemiology]; Fat Emulsions, Intravenous [administration & dosage] [adverse effects]; Hospital Mortality; Hypoglycemia [epidemiology]; Infant Mortality; Infant, Premature; Length of Stay; Lipids [administration & dosage] [adverse effects]; Parenteral Nutrition [adverse effects] [mortality] [*statistics & numerical data]; Parenteral Nutrition Solutions [administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]; Term Birth; Time Factors

MeSH check words

Humans; Infant; Infant, Newborn