National Institute for Health and Care Excellence

Draft for consultation

Neonatal parenteral nutrition

[D10] Ratio of phosphate to amino acids

NICE guideline tbc

Evidence reviews

September 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance which is part of the Royal College of Obstetricians and Gynaecologists

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Intravenous minerals for preterm and term babies

Review question

What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Introduction

Babies who are receiving parenteral nutrition (PN) require an amino acid intake of at least 1.5 g/kg/day, in order to be in positive nitrogen balance. A greater intake of amino acids is recommended in order to allow for growth and tissue accretion. Phosphate is a key substrate for growth. If not supplied in sufficient quantities in an anabolic growth environment, bone will be utilised as a source of phosphate. The release of phosphate from bone results in release of calcium. Provision of amino acids without sufficient provision of phosphate may lead to hypophosphataemia and hypercalcaemia. It is therefore important to give babies receiving recommended intakes of amino acids in PN sufficient phosphate to allow for growth and to prevent hypophosphataemia and hypercalcaemia. The aim of this review is to review what an optimal ratio of phosphate to amino acid is.

Summary of protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies)
Intervention	• Ratio of phosphate and amino acid
Comparison	• Other ratios of phosphate and amino acid

Outcomes	**Critical**
	• Metabolic bone disease of prematurity
	• Fractures
	• Growth/Anthropometric measures:
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)
	• Adverse effects of PN:
	  ○ Hypercalcaemia
	  ○ Hypercalciuria
	  ○ Hyperphospataemia (high blood level of phosphate)
	  ○ Hypophosphataemia
	Important
	• Mortality

PN: parenteral nutrition

For full details see the review protocol in appendix A.

Clinical evidence

Included studies

No randomised controlled trials (RCTs) were identified; therefore, observational studies were included to inform decision making.

Two observational studies were included in this review (Bonsante 2013 and Moe 2015).

The first study compared three different PN solutions with low phosphate intake and different amounts of amino acid intakes from day 1 to day 7 in a single hospital:

- Group 1 (LAA) received a PN nutrition solution low in levels of amino acids;
- Group 2 (MAA) received a PN nutrition solution moderate in levels of amino acids;
- Group 3 (HAA) received a PN nutrition solution high in levels of amino acids.

The second study compared three PN solutions introduced across different time periods in a single hospital:

- Group 1 received high levels of phosphate and a low content of amino acids and calcium;
- Group 2, which was the baseline group, received low levels of phosphate, a higher content of amino acids and an intermediate content of calcium;
- Group 3 received high levels of phosphate, calcium and amino acids.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E, and GRADE tables in appendix F.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusions are provided, in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention1*	Intervention 2*	Comparison*	Outcomes	Comments
Bonsante 2013* Observational study France	N=154 Preterm babies born < 33 weeks gestational age and hospitalised within 6 hours of life in the NICU	Group (MAA; n=53) Babies received PN moderate in amino acids (1.5-2 g/kg/day). Mean phosphate intake 19.9 mg/kg/day (SD 13.9). This is equivalent to 0.6 mmol/kg/day. Mean calcium intake 49.3 mg/kg/day (SD 8.6); This is equivalent to 1.23 mmol/kg/day.	Group (HAA; n=53) Babies received parenteral nutrition high in amino acids (>2 g/kg/day). Mean Phosphate intake 21.4 mg/kg/d (SD 14.6). This is equivalent to 0.64 mmol/kg/day. Mean calcium intake 50.3 mg/kg/day (SD 7.7). This is equivalent to 1,26 mmol/kg/day.	Group (LAA; n=48) Babies received PN low in amino acids (<1.5 g/kg/day). Mean phosphate intake 15.8 mg/kg/day (SD 13.6). This is equivalent to 0.47mmol/kg/day. Mean calcium intake 46.7 mg/kg/day (SD 13.1). This is equivalent to 1.16 mmol/kg/day.	• Severe hypophosphataemia • Severe hypercalcaemia	Minimal enteral feeding by breast milk was started on day one of life, and continued for at least 4 days in babies having PN. When partial PN was administered, enteral nutrition was started on day 1 at 20 ml/kg/day and increased daily over the week. Initial amount and rate of amino acid increase decided by the prescribing physician, based on a written protocol.

Study	Population	Intervention1*	Intervention 2*	Comparison*	Outcomes	Comments
Moe 2015 Observational study Denmark	N=186 Preterm babies with a gestational age of <28 weeks	Group one (n=62) high levels of phosphate (1.2 to 1.3 mmol per day) and low levels of amino acids (2 to 2.1 g per day)	Group three (n=62) high levels of both phosphate (1.08 to 1.18 mmol per day) and amino acids (2.4 to 3.1g per day)	Group two (n=62) low levels of phosphate (0.07 to 1 mmol per day) and high levels of amino acids (2.8 to 3.1 g per day) *In groups 2 and 3, phosphate intakes given are approximate, as babies were given additional phosphate supplementation in PN to correct hypophosphatae mia in this group	• Mean weight change (z-score) from day 1 to 29 • Mean weight z-score on days, 8, 15, 22 and 29	Participants were divided into three groups: Group one: PN solution prior to October 2011 Group two: new PN solution based on ESPHGAN recommendations on increased protein supplementation (October 2011) Group three: new PN solution introduced in November 2012 Fat and additives were introduced to the three different PN solutions at different time points.

**Bonsante 2013 reported phosphate as mg/kg/d which is not commonly used in as a unit measure in the UK. Therefore we have provided the conversion to mmol/kg/d in this table.*
ESPHGAN: European Society of Paediatric Gastroenterology, Hepatology and Nutrition; HAA: high amino acids; MAA: medium amino acids; NICU: neonatal intensive care unit; PN: parenteral nutrition; SD: standard deviation.

See appendix D for full evidence tables. The outcomes from the two studies could not be meta-analysed therefore there are no forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

GRADE was conducted to assess the quality of outcomes. Evidence was identified for critical outcomes, but no evidence was identified to provide data on important outcomes. The clinical evidence profiles can be found in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question. A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material D for details.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evaluations were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical Evidence statements

Medium amino acid and low phosphate versus low amino acid and low phosphate

Severe hypercalcaemia

- Very low quality evidence from 1 observational study (n=101) showed a clinically important difference in rate of severe hypercalcaemia, with greater occurrences in babies who received medium amino acid and low phosphate intake compared with low amino acid and low phosphate intake. However, there was high uncertainty around the effect: Relative risk (RR) 2.42 (95% CI 0.68 to 8.58).

Severe hypophosphataemia

- Very low quality evidence from 1 observational study (n=101) showed a clinically important difference in rate of severe hypophosphataemia, with greater occurrences in babies who received medium amino acid and low phosphate intake compared with low amino acid and low phosphate intake. However, there was uncertainty around the effect: Peto odds ratio (POR) 6.99 (95% CI 0.71 to 68.96).

High amino acid and low phosphate versus medium amino acid and low phosphate

Severe hypercalcaemia

- Very low quality evidence from 1 observational study (n=106) showed a clinically important difference in rate of severe hypercalcaemia, with greater occurrences in babies who received high amino acid and low phosphate intake compared with medium amino acid and low phosphate intake. However, there was uncertainty around the effect: RR 2.00 (95% CI 0.94 to 4.27).

Severe hypophosphataemia

- Very low quality evidence from 1 observational study (n=106) showed a clinically important different in rate of severe hypophosphataemia, with greater occurrences in babies who received high amino acid and low phosphate intake compared with medium amino acid and low phosphate intake. However, there was uncertainty around the effect: RR 3.33 (95% CI 0.97 to 11.44).

High amino acid and low phosphate versus low amino acid and low phosphate

Severe hypercalcaemia

- Very low quality evidence from 1 observational study (n=101) showed a clinically important difference in rate of severe hypercalcaemia, with greater occurrences in babies who received high amino acid and low phosphate intake compared with low amino acid and low phosphate intake: RR 4.83 (95% CI 1.50 to 15.56).

Severe hypophosphataemia

- Very low quality evidence from 1 observational study (n=101) showed a clinically important different in rate of severe hypophosphataemia, with greater occurrences in babies who received high amino acid and low phosphate intake compared with low amino acid and low phosphate intake. However, there was uncertainty around the: POR 8.12 (95%CI 2.21 to 29.82).

Low amino acid and high phosphate versus high amino acid and low phosphate

Change in weight z-score day 1 to day 29

- Very low quality evidence from 1 observational study (n=124) showed no clinically important difference in change in weight z-score between day 1 and day 29 in babies who received low amino acid and high phosphate intake compared with high amino acid and low phosphate intake: Mean difference (MD) 0.07 (95% CI -0.23 to 0.37).

Weight z-score at day 8, 15, 22 and 29

- Very low quality evidence from 1 observational study (n=124) showed no clinically important difference in weight z-score in babies who received low amino acid and high phosphate intake compared with high amino acid and low phosphate intake at day 8 (MD 0.06 [95% CI -0.25 to 0.37]), day 15 (MD -0.12 [95% CI -17.79 to 17.55]; high uncertainty around effect), day 22 (MD 0.19 [95% CI -0.11 to 0.49]; uncertainty around effect) or day 29 (MD 0.30 [95% CI -0.02 to 0.62]; uncertainty around effect).

Low amino acid and high phosphate versus high amino acid and high phosphate

Change in weight z-score day 1 to day 29

- Very low quality evidence from 1 observational study (n=124) showed no clinically important difference in change in weight z-score between day 1 and day 29 in babies who

received low amino acid and high phosphate intake compared with high amino acid and high phosphate intake. However, there was uncertainty around the effect: MD -0.16 (95% CI -0.43 to 0.11).

Weight z-score at day 8, 15, 22 and 29

- Very low quality evidence from 1 observational study (n=124) showed no clinically important difference in weight z-score in babies who received low amino acid and high phosphate intake compared with high amino acid and high phosphate intake at day 8 (MD -0.08 [95% CI -0.37 to 0.21]), day 15 (MD 0.03 [95% CI -0.25 to 0.31]), day 22 (MD 0.17 [95% CI -0.12 to 0.46]; uncertainty around effect) or day 29 (MD 0.19 [95% CI -0.01 to 0.48]; uncertainty around effect).

High amino acid and high phosphate versus high amino acid and low phosphate

Change in weight z-score day 1 to day 29

- Very low quality evidence from 1 observational study (n=124) showed no clinically important difference in change in weight z-score between day 1 and day 29 in babies who received high amino acid and high phosphate intake compared with high amino acid and low phosphate intake. However, there was uncertainty around the effect: MD 0.23 (95% CI -0.07 to 0.53).

Weight z-score at day 8, 15, 22 and 29

- Very low quality evidence from 1 observational study (n=124) showed no clinically important difference in weight z-score in babies who received high amino acid and high phosphate intake compared with high amino acid and low phosphate intake at day 8 (MD 0.11 [95% CI -0.20 to 0.42]), day 15 (MD -0.15 [95% CI -0.49 to 0.19]), day 22 (MD 0.02 [95% CI -0.29 to 0.33]) or day 29 (MD 0.11 [95% CI -0.02 to 0.42]).

Economic Evidence statements

No studies were identified which were applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified growth parameters (weight gain, linear growth and head circumference), and complications such as fractures and metabolic bone disease of prematurity as critical outcomes. These outcomes were selected as both soft tissue growth and bone mineralisation are affected by the relative amounts of amino acids and phosphate administered. In addition, biochemical abnormalities such as hypercalcaemia, hypercalciuria, and hyper and hypophosphataemia and hypokalaemia were also identified as critical, as these outcomes may lead to important adverse effects and also directly relate to the relative amounts of amino acids and phosphate administered. Data was identified on weight-gain, hypercalcaemia and hypophosphataemia and hypokalaemia. Although the committee considered mortality as an important outcome, no data on mortality were identified.

The quality of the evidence

The studies included in this review were assessed for quality using GRADE methodology. Overall the evidence was considered of very low quality, indicating high uncertainty in the reliability of data. Only observational studies were included, and these were downgraded for bias regarding the selection of participants and the imbalance in the provision of additional co-interventions (for example, enteral feeds or glycophos) across the intervention groups. Data was downgraded due to serious or very serious risk of imprecision across the outcomes as the 95% confidence intervals crossed either one or both default MID. In one study (Moe 2015), the control group only emerged after an error in the prescription of PN. Overall, the evidence should be interpreted with caution.

Benefits and harms

Two observational studies were included in this review. The first study (Bonsante 2013) was conducted in France and was a prospective cohort study, while the second study (Moe 2015) was conducted in Denmark and followed a retrospective cohort design. Data from one study (Bonsante 2013) showed that babies assigned to PN regimen high in amino acids were more likely to develop severe hypercalcaemia and hypophosphataemia compared to those assigned to a PN regimen with low or medium amino acids, with low intakes of phosphate across all 3 groups. Similarly, babies that received medium amino acid intake were more likely to develop severe hypercalcaemia and severe hypophosphataemia than babies who received low amino acid intake. However, there was uncertainty around the effects. It should be noted that babies in this study received enteral feeding from day one after birth, and the quantity of the enteral feeding was gradually increased. The committee acknowledged that this could have a confounding effect on the observed findings. In addition, the amount of phosphate administered to infants in this study was less than currently used in clinical practice.

The second study (Moe 2015) compared three groups: PN high in phosphate but low in amino acids, PN low in phosphate and high in amino acids, and PN high in both phosphate and amino acids. All groups were assessed in terms of weight gain and no differences were found between any of the groups. The highest blood levels of phosphate and lowest levels of calcium were observed in the group receiving a high phosphate and low amino acid intake, in keeping with the evidence from Bonsante (2013).

The committee acknowledged that a sufficiently high intake of phosphate is vital for babies receiving PN in order to avoid hypercalcaemia, hypophosphataemia and hypokalaemia, especially when high intakes of amino acids are provided. The committee also discussed that the prescription of phosphate also depends on the amount of sodium intake. The committee accepted that both sodium and phosphate are very important for babies' growth. In current PN formulations, 2 mmols of sodium will be provided for every mmol of phosphate. Babies are prone to lose water during the first days of life, so the provision of too much sodium early in PN could lead to hypernatraemia (high levels of sodium in the blood).This means that the intake of phosphate in the first few days of PN provision will be limited by how much sodium can be safely administered. In addition, the amount of phosphate provided in PN should be carefully considered in conjunction with the amount of calcium that is provided. A high amino acid and phosphate intake without sufficient calcium may lead to relative hypocalcaemia. This in turn could lead to release of calcium and phosphate from bone, resulting in hyperphosphataemia, and reduced bone mineralisation. Preterm babies in particular are at risk of metabolic bone disease of prematurity where their bones become very brittle as a result of insufficient mineralisation.

Following these deliberations about the evidence the committee decided not to make a recommendation on this topic. The very low quality of the evidence and significant confounding factors gave the committee little confidence in the specific ratios that were used

in the studies. However, the committee noted that this limited evidence, does not contradict the committee's previous recommendations on the optimal intakes of amino acids and phosphate individually in which they had greater confidence. They agreed by informal consensus that following these individual recommendations would lead to a safe ratio of phosphate to amino acids.

Cost effectiveness and resource use

No economic studies were identified which were applicable to this review question.

No recommendation was made and current practice is not changed by this. Therefore there are no cost or resource implications.

References

Bonsante 2013

Bonsante, F., Iacobelli, S., Latorre, G., Rigo, J., De Felice, C., Robillard, Y. P., Gouyon, B. J. Initial Amino Acid Intake Influences Phosphorus and Calcium Homeostasis in Preterm Infants – It Is Time to Change the Composition of the Early Parenteral Nutrition, PLOS One(8), 8, 2013.

Moe 2015

Moe, K., Beck-Nielsen, S. S., Lando, A., Greisen, G., Zachariassen, G. Administering different levels of parenteral phosphate and amino acids did not influence growth in extremely preterm infants, Acta Paediatrica, 104, 894-899, 2015.

Appendices

Appendix A – Review protocols

Review protocol for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 3: Review protocol – optimal ratio of phosphate to amino acid

Field (based on PRISMA-P	Content
Review question	What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?
Type of review question	Intervention
Objective of the review	Inadequate amounts of calcium and phosphate delivered via PN may contribute to bone disease in preterm and term babies. Delivery of calcium and phosphate should be adequate to achieve retention of amounts which match those in utero, but at a concentration that does not result in adverse events. The aim of this review is to determine the optimal ratio of phosphate to amino acids in preterm and term babies who are receiving PN
Eligibility criteria – population/disease/condition/issue/domain	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies).
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Ratio of phosphate and amino acid
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Other ratios of phosphate and amino acid
Outcomes and prioritisation	**Critical** • Metabolic bone disease of prematurity • Fractures • Growth/Anthropometric measures: • Weight gain (g/kg/d) • Linear growth • Head circumference (mm) • Adverse effects of PN:

Field (based on PRISMA-P	Content
	• Hypercalcaemia • Hypercalciuria • Hyperphosphataemia (high blood level of phosphate) • Hypophosphataemia **Important** • Mortality
Eligibility criteria – study design	Only published full text papers: Systematic reviews of RCTs RCTs Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making) Conference abstracts will only be considered if related to RCTs
Other inclusion exclusion criteria	No sample size restriction No date restriction
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroup analysis: Population subgroups: Age of baby (first 2 weeks vs later) Preterm (extremely preterm <28 weeks' GA; very preterm: 28-31 weeks' GA; moderately preterm: 32-36 weeks' GA) Birthweight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) Critically ill babies or those requiring surgery (for example, inotropic support, therapeutic hypothermia or fluid restriction) First week of life and after first week of life?
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. A random sample of the references identified in the search will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identifies fewer than 1000 studies. All disagreements in

Field (based on PRISMA-P	Content
	study inclusion will be discussed and resolved between the two reviewers. The senior systematic reviewer or guideline lead will be involved if discrepancies cannot be resolved between the two reviewers.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists (ROBIS (systematic reviews and meta-analyses); Cochrane risk of bias tool (RCTs or comparative cohort studies); Cochrane risk of bias tool (Non-randomised studies); Newcastle-Ottawa scale (Non-comparative studies)).
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies.
Identify if an update	This is not an update
Author contacts	Developer: The National Guideline Alliance Guideline website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10037.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014.
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see appendix B.
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual 2014.

Field (based on PRISMA-P	Content
Methods for analysis – combining studies and exploring (in)consistency	For details of the methods please see supplementary material C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014.
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Joe Fawke (Consultant Neonatologist and Honorary Senior Lecturer, University Hospitals Leicester NHS Trust), in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from The National Guideline Alliance, undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details of the methods please see supplementary material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by The Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by The Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
PROSPERO registration number	This review is not registered with PROSPERO.

CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Controlled Trials Register; DARE: Database of Abstracts of Reviews of Effects; GA: gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; ICF: International Classification of Functioning, Disability and Health; MID: minimally important difference; NGA: National Guideline Alliance; NIHR: National Institute for Health Research; NHS: National health service; NICE: National Institute for Health and Care Excellence; PRISMA-P: preferred reporting items for systematic review and meta-analysis protocols; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	INFANT, NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURE BIRTH/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	exp INFANT, PREMATURE/
6	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
7	(pre#mie? or premie or premies).ti,ab.
8	exp INFANT, LOW BIRTH WEIGHT/
9	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
10	((LBW or VLBW) adj5 infan$).ti,ab.
11	INTENSIVE CARE, NEONATAL/
12	INTENSIVE CARE UNITS, NEONATAL/
13	NICU?.ti,ab.
14	or/1-13
15	PARENTERAL NUTRITION/
16	PARENTERAL NUTRITION, TOTAL/
17	PARENTERAL NUTRITION SOLUTIONS/
18	ADMINISTRATION, INTRAVENOUS/
19	INFUSIONS, INTRAVENOUS/
20	CATHETERIZATION, CENTRAL VENOUS/
21	exp CATHETERIZATION, PERIPHERAL/
22	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
23	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
24	drip?.ti,ab.
25	or/15-24
26	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 calcium).mp.
27	((mmol? or ml) adj3 (d or day) adj5 calcium).mp.
28	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
29	((mmol? or ml) adj3 (d or day) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
30	CALCIUM/ad [Administration & Dosage]
31	CALCIUM, DIETARY/ad [Administration & Dosage]
32	exp PHOSPHATES/ad [Administration & Dosage]
33	PHOSPHORUS/ad [Administration & Dosage]
34	PHOSPHORUS, DIETARY/ad [Administration & Dosage]
35	or/26-34
36	exp AMINO ACIDS/ and ratio?.ti,ab.
37	(ratio? adj10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or

#	Searches
	Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
38	exp PHOSPHATES/ and ratio?.ti,ab.
39	PHOSPHORUS/ and ratio?.ti,ab.
40	PHOSPHORUS, DIETARY/ and ratio?.ti,ab.
41	(ratio? adj10 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
42	(percent$ adj10 (Phosph$ or amino acid?)).mp.
43	(percent$ adj5 feed$).ti,ab.
44	or/36-43
45	exp AMINO ACIDS/ and (exp PHOSPHATES/ or PHOSPHORUS/ or PHOSPHORUS, DIETARY/)
46	((amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
47	or/45-46
48	14 and 25 and 35
49	14 and 25 and 44
50	14 and 25 and 47
51	or/48-50
52	limit 51 to english language
53	LETTER/
54	EDITORIAL/
55	NEWS/
56	exp HISTORICAL ARTICLE/
57	ANECDOTES AS TOPIC/
58	COMMENT/
59	CASE REPORT/
60	(letter or comment*).ti.
61	or/53-60
62	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
63	61 not 62
64	ANIMALS/ not HUMANS/
65	exp ANIMALS, LABORATORY/
66	exp ANIMAL EXPERIMENTATION/
67	exp MODELS, ANIMAL/
68	exp RODENTIA/
69	(rat or rats or mouse or mice).ti.
70	or/63-69
71	52 not 70

1

1 **Databases: Embase; and Embase Classic**

#	Searches
1	NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURITY/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
6	(pre#mie? or premie or premies).ti,ab.
7	exp LOW BIRTH WEIGHT/
8	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
9	((LBW or VLBW) adj5 infan$).ti,ab.
10	NEWBORN INTENSIVE CARE/
11	NEONATAL INTENSIVE CARE UNIT/
12	NICU?.ti,ab.
13	or/1-12
14	PARENTERAL NUTRITION/
15	TOTAL PARENTERAL NUTRITION/
16	PERIPHERAL PARENTERAL NUTRITION/
17	PARENTERAL SOLUTIONS/
18	INTRAVENOUS FEEDING/
19	INTRAVENOUS DRUG ADMINISTRATION/
20	exp INTRAVENOUS CATHETER/
21	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
22	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
23	drip?.ti,ab.
24	or/14-23
25	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 calcium).mp.
26	((mmol? or ml) adj3 (d or day) adj5 calcium).mp.
27	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
28	((mmol? or ml) adj3 (d or day) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
29	CALCIUM/ad, do [Drug Administration, Drug Dose]
30	CALCIUM INTAKE/
31	PHOSPHATE/ad, do [Drug Administration, Drug Dose]
32	PHOSPHORUS/ad, do [Drug Administration, Drug Dose]
33	PHOSPHATE INTAKE/
34	or/25-33
35	exp *AMINO ACIDS/ and ratio?.ti,ab.
36	(ratio? adj10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
37	PHOSPHATE/ and ratio?.ti,ab.
38	PHOSPHORUS/ and ratio?.ti,ab.
39	PHOSPHATE INTAKE/ and ratio?.ti,ab.
40	(ratio? adj10 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.

#	Searches
41	(percent$ adj10 (Phosph$ or amino acid?)).mp.
42	(percent$ adj5 feed$).ti,ab.
43	or/35-42
44	exp AMINO ACIDS/ and (PHOSPHATE/ or PHOSPHORUS/ or PHOSPHATE INTAKE/)
45	((amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
46	or/44-45
47	13 and 24 and 34
48	13 and 24 and 43
49	13 and 24 and 46
50	or/47-49
51	limit 50 to english language
52	letter.pt. or LETTER/
53	note.pt.
54	editorial.pt.
55	CASE REPORT/ or CASE STUDY/
56	(letter or comment*).ti.
57	or/52-56
58	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
59	57 not 58
60	ANIMAL/ not HUMAN/
61	NONHUMAN/
62	exp ANIMAL EXPERIMENT/
63	exp EXPERIMENTAL ANIMAL/
64	ANIMAL MODEL/
65	exp RODENT/
66	(rat or rats or mouse or mice).ti.
67	or/59-66
68	51 not 67

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

#	Searches
1	MeSH descriptor: [INFANT, NEWBORN] this term only
2	(neonat* or newborn* or new-born* or baby or babies):ti,ab
3	MeSH descriptor: [PREMATURE BIRTH] this term only
4	((preterm* or pre-term* or prematur* or pre-matur*) near/5 (birth? or born)):ti,ab
5	MeSH descriptor: [INFANT, PREMATURE] explode all trees
6	((preterm* or pre-term* or prematur* or pre-matur*) near/5 infan*):ti,ab
7	(pre#mie? or premie or premies):ti,ab
8	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
9	(low near/3 birth near/3 weigh* near/5 infan*):ti,ab
10	((LBW or VLBW) near/5 infan*):ti,ab
11	MeSH descriptor: [INTENSIVE CARE, NEONATAL] this term only
12	MeSH descriptor: [INTENSIVE CARE UNITS, NEONATAL] this term only
13	NICU?:ti,ab
14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#	Searches
15	MeSH descriptor: [PARENTERAL NUTRITION] this term only
16	MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only
17	MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only
18	MeSH descriptor: [ADMINISTRATION, INTRAVENOUS] this term only
19	MeSH descriptor: [INFUSIONS, INTRAVENOUS] this term only
20	MeSH descriptor: [CATHETERIZATION, CENTRAL VENOUS] this term only
21	MeSH descriptor: [CATHETERIZATION, PERIPHERAL] explode all trees
22	(parenteral* or intravenous* or intra-venous* or IV or venous* or infusion?):ti,ab
23	((peripheral* or central*) near/3 (line? or catheter*)):ti,ab
24	drip?:ti,ab
25	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 calcium):ti,ab
27	((mmol? or ml) near/3 (d or day) near/5 calcium):ti,ab
28	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 (Phosph* or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)):ti,ab
29	((mmol? or ml) near/3 (d or day) near/5 (Phosph* or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)):ti,ab
30	MeSH descriptor: [CALCIUM] this term only and with qualifier(s): [Administration & dosage - AD]
31	MeSH descriptor: [CALCIUM, DIETARY] this term only and with qualifier(s): [Administration & dosage - AD]
32	MeSH descriptor: [PHOSPHATES] explode all trees and with qualifier(s): [Administration & dosage - AD]
33	MeSH descriptor: [PHOSPHORUS] this term only and with qualifier(s): [Administration & dosage - AD]
34	MeSH descriptor: [PHOSPHORUS, DIETARY] this term only and with qualifier(s): [Administration & dosage - AD]
35	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
36	MeSH descriptor: [AMINO ACIDS] explode all trees
37	ratio?:ti,ab
38	#36 and #37
39	(ratio? near/10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)):ti,ab
40	MeSH descriptor: [PHOSPHATES] explode all trees
41	MeSH descriptor: [PHOSPHORUS] this term only
42	MeSH descriptor: [PHOSPHORUS, DIETARY] this term only
43	#40 or #41 or #42
44	ratio?:ti,ab
45	#43 and #44
46	(ratio? near/10 (Phosph* or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)):ti,ab
47	(percent* near/10 (Phosph* or amino acid?)):ti,ab
48	(percent* near/5 feed*):ti,ab
49	#38 or #39 or #45 or #46 or #47 or #48
50	MeSH descriptor: [AMINO ACIDS] explode all trees
51	MeSH descriptor: [PHOSPHATES] explode all trees
52	MeSH descriptor: [PHOSPHORUS] this term only
53	MeSH descriptor: [PHOSPHORUS, DIETARY] this term only
54	#51 or #52 or #53
55	#50 and #54

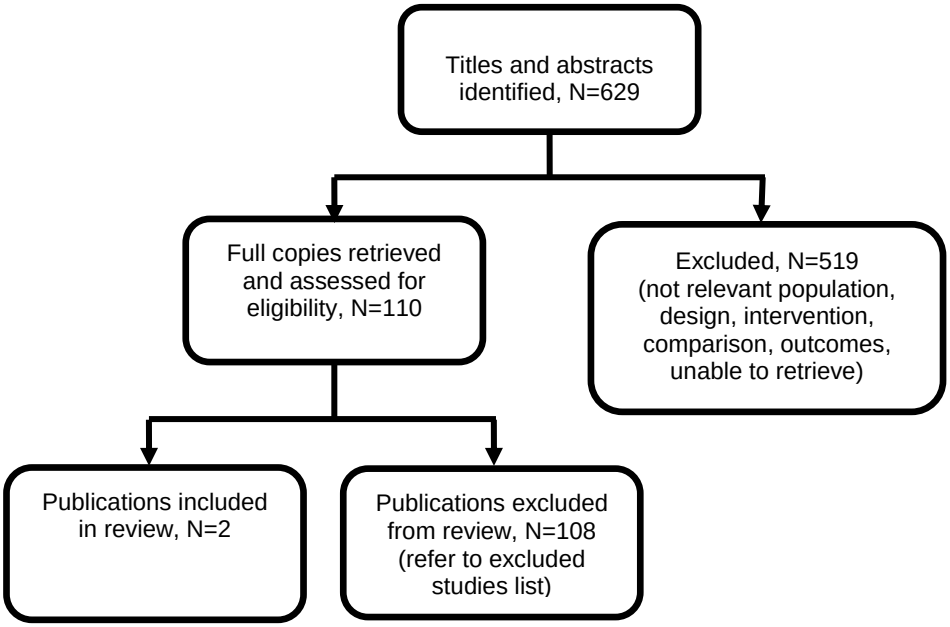
#	Searches
56	((amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid) near/5 (Phosph* or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)):ti,ab
57	#55 or #56
58	#14 and #25 and #35
59	#14 and #25 and #49
60	#14 and #25 and #57
61	#58 or #59 or #60

1

Appendix C – Clinical evidence study selection

Clinical study selection for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Figure 1: Flow diagram of clinical article selection for review question, what is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?



1 Appendix D – Clinical evidence tables

2 Clinical evidence tables for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies 3 who are receiving parenteral nutrition and neonatal care?

4 **Table 4: Clinical evidence tables for included studies**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bonsante, F., Iacobelli, S., Latorre, G., Rigo, J., de Felice, C., Robillard, P. Y., Gouyon, J. B., Initial Amino Acid Intake Influences Phosphorus and Calcium Homeostasis in Preterm Infants - It Is Time to Change the Composition of the Early Parenteral Nutrition, PLoS ONE, 8, e72880, 2013 Ref Id 688561 Country/ies where the study was carried out France Study type Observational study.	Sample size N=154 Low amino acid intake (LAA): N=48 Medium amino acid intake (MAA): N=53 High amino acid intake (HAA): N=53 Characteristics Birth weight (g) - mean ±SD LAA: 1595 (284) MAA: 1210 (295) HAA: 1143 (332) Gestational age (weeks) - mean ±SD LAA: 31.2 (1.4) MAA: 29.2 (1.9) HAA: 29.2 (1.6) Small for gestational age - % LAA: 12	Interventions LAA: <1.5 g/kg/day: MAA: 1.5-2.0 g/kg/day HAA: >2 g/kg/day Nutritional intake: LAA group intake (mean, SD) amino acid: 1.2 (0.6) g/kg/d, energy: 55 (21) Kcal/kg/d, calcium: 46.7 (13.1) mg/kg/d, phosphate: 15.8 (13.6) mg/kg/d, enteral feeding: 39 mL/kg/d MAA group intake (mean, SD) amino acid: 1.8 (0.7) g/kg/d, energy: 58 (22) Kcal/kg/d, calcium: 49.3 (8.6) mg/kg/d, phosphate: 19.9 (13.9) mg/kg/d, enteral feeding: 16.5 ml/kg/d	Details PN on central venous line or peripheral venous line administered according to clinical decision. Administered by individualised formulations prepared into the unit or by standardised batch-produced bags. Minimal enteral feeding by human milk was started on day one of life, and continued for at least 4 days in babies having total PN. When partial PN was administered, enteral nutrition was started on day one at 20 ml/kg/day and increased daily over the week. Standardised procedure: Amino acid intake started on day one and increased daily up to 3.5 g/kg at the end of the first week.	Results Severe hypophosphataemia - number of infants (%) LAA: 0/48 (0.0) MAA: 3/53 (5.7) HAA: 10/53 (18.9); ANOVA <0.001 Severe hypercalcaemia - number of infants (%) LAA: 3/48 (6.2) MAA: 8/53 (15.1) HAA: 16/53 (30.2); ANOVA 0.05	Limitations ROBINS-I Confounding bias: Moderate risk of bias Selection of participant's bias: Low risk of bias Classification of interventions bias: Low risk of bias (intervention groups clearly defined and information recorded at start of intervention) Deviations from intended interventions bias: Moderate risk of bias (no deviations reported; co-interventions (mean enteral feeding) not balanced across intervention groups) Missing data bias: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the effect of early nutrition on calcium and phosphate homeostasis in preterm infants and to estimate the optimal amount of phosphorus added to parenteral nutrition, in accordance with amino acid intake administered. Study dates June 2006 to September 2007. Source of funding Supported by the University Hospital of Dijon.	MAA: 13 HAA: 17 Oxygen dependency at 36 weeks - % LAA: 4.3 MAA: 13 HAA: 19 Necrotising enterocolitis - % LAA: 2.1 MAA: 1.9 HAA: 1.9 Several abnormal cerebral ultrasound* - % LAA: 2.1 MAA: 1.9 HAA: 1.9 Mean daily nutritional intakes - mean ±SD Amino acids (g/kg/day) LAA: 1.2 (0.6) MAA: 1.8 (0.7) HAA: 2.3 (0.8); p<0.001	HAA group intake (mean, SD) amino acid: 2.3 (0.8) g/kg/d, energy: 65 (25) Kcal/kg/d, calcium: 50.3 (7.7) mg/kg/d, phosphate: 21.4 (14.6) mg/kg/d, enteral feeding: 11.1 ml/kg/d	Individualised procedure: initial amount and rate of amino acid increase decided by the prescribing physician, based on a written protocol. Phosphate infusion started on 2nd and 3rd day, with wide variations among infants depending on the prescribing physician. Statistical analyses Continuous outcomes were expressed as mean ±SD. Differences between groups were assessed using analysis of variance test, adjusted for gestational age using analysis of covariance test. Linear regression procedures were used to correlate the cumulative calculated deficit of phosphate intake with calcium and phosphate plasma levels.		Measurement of outcomes bias: NI (unclear whether outcome assessors were blinded, but unlikely due to safety reasons) Selection of the reported results bias: Low risk of bias (all outcomes reported) Other information *Intraventricular haemorrhage grade 3 or 4 and/or periventricular leukomalacia.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Energy (kcal/kg/day) LAA: 55 (21) MAA: 58 (22) HAA: 65 (25); p<0.001 Calcium (mg/kg/day) LAA: 46.7 (13.1) MAA: 49.3 (8.6) HAA: 50.3 (7.7); p=not significant Phosphate (mg/kg/day) LAA: 15.8 (13.6) MAA: 19.9 (13.9) HAA: 21.4 (14.6); p=0.04 Enteral feeding (mL/kg/day) - mean LAA: 39.0 MAA: 16.5 HAA: 11.1; p<0.001 Inclusion criteria Infants born <33 weeks gestational age and hospitalised within 6 hours of life in the Neonatal Intensive Care Unit of the				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Dijon University Hospital. Exclusion criteria Infants with major congenital anomalies.				
Full citation Moe, K., Beck-Nielsen, S. S., Lando, A., Greisen, G., Zachariassen, G., Administering different levels of parenteral phosphate and amino acids did not influence growth in extremely preterm infants, Acta Paediatrica, International Journal of Paediatrics, 104, 894-899, 2015 Ref Id 689499 Country/ies where the study was carried out Denmark Study type Observational study Aim of the study To analyse the impact of three different PN	Sample size N=186 N= 62 (group 1) N=62 (group 2, baseline) N=62 (group 3) Characteristics Birthweight (SDS), mean (SD) Group 1: -1.20 (0.92) Group 2: -1.21 (1.34) Group 3: -1.20 (1.14); p=0.997 Small for gestational age, n (%) Group 1: 11 (18) Group 2: 13 (21) Group 3: 9 (15); p=0.643 Gestational age (weeks), mean (SD)	Interventions Group one: high content of phosphate (Day 1-3 without fat: 1.3 mmol); Day 4 with fat: 1.3 mmol); Day 4 with fat and additives: 1.2 mmol), a low content of amino acids (Day 1-3 without fat: 2.1 g; Day 4 with fat: 2.1 g; Day 4 with fat and additives: 2.0 g) and a low content of calcium (Day 1-3 without fat: 0 mmol; Day 4 with fat: 0 mmol; Day 4 with fat and additives: 0.7 mmol). Group two (baseline): lower content of phosphate (Day 1-3 with fat: 0.07 mmol; Day 1-3 without fat: 1.0 mmol; Day 4 with fat: 0.75 mmol), higher content of amino acids (Day 1-3 with fat: 3.1 g; Day 1-3 without fat: 3.3 g; Day 4 with fat: 2.8 g) and an intermediate content of calcium (Day 1-	Details Infants were treated with one type of PN solution from day 1-3 and then changed to another PN solution from day four. From day 7-10, fortification with a human milk fortifier was added to the mothers' own milk or donor milk if the mothers' milk was not available. When low levels of plasma phosphate (<1.5 mmol/L) were detected, infants were given additional phosphate supplementation using Glycophos, (1 mmol phosphate and 2 mmol sodium per mL). Glycophos was added to a maximum of what the three-in-one PN allowed, with the aim of reaching a plasma phosphate level of >1.50 mmol/L. Infants received oral phosphate	Results Weight change (z-score) from day 1 to 29 - mean ±SD Group 1: -1.30 ± 0.78 Group 2: -1.37 ± 0.93 group 3: -1.14 ± 0.77 ΔZ-score, p = 0.497 From day one to 29, there was a significant difference in weight Z-score changes between the SGA infants and the non-SGA infants SGA infants: -0.36 ± 0.52 non-SGA infants: -1.50 ± 0.71 ΔZ-score, p < 0.001 SDS, day 8, mean (SD) (z-score) Group 1: -2.31 (0.77) Group 2: -2.37 (0.99) Group 3: -2.23 (0.86) p = 0.689 SDS, day 15, mean (SD) (z-score)	Limitations ROBINS-I Confounding bias: Low risk of bias Selection of participant's bias: Moderate risk of bias (retrospective study; start and follow-up of the three cohorts differ as different PN solutions introduced over different time periods; no adjustments techniques used) Classification of interventions bias: Low risk of bias (intervention groups clearly defined and information recorded at start of intervention) Deviations from intended interventions bias: Moderate risk of bias (no deviations reported; co-interventions (glycophos supplementation) not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
solutions on plasma phosphate, plasma calcium and weight increases on extremely preterm infants during the first month of life. Study dates From late September 2010 until February 2014 Source of funding Not reported	Group 1: 26.5 (7.45) Group 2: 26.6 (6.98) Group 3: 26.4 (7.35); p=0.705 Duration of parenteral nutrition intake (days), median (range) Group 1: 12.50 (28) Group 2: 13 (29) Group 3: 13.18 (28); p=0.707 Inclusion criteria Extremely preterm infants, with a gestational age of <28 weeks, and who received parenteral nutrition during hospitalisation. Exclusion criteria Infants who were transferred to another hospital within the first week of life or died before one month of age.	3 with fat: 0.49 mmol; Day 1-3 without fat: 0.47 mmol; Day 4: 1.47 mmol). Group three: higher content of phosphate (Day 1-3 with fat: 1.08 mmol; Day 4 with fat: 1.18 mmol; Day 4 without fat: 1.0 mmol), calcium (Day 1-3 with fat: 1.19 mmol; Day 4 with fat: 1.2 mmol; Day 4 without fat: 1.2 mmol) and amino acids (Day 1-3 with fat: 3.1 g; Day 4 with fat: 2.8 g; Day 4 without fat: 2.4 g).	supplementation when they could tolerate small amounts of enteral feeding. Statistical analysis Body weight was converted to a standard deviation score (Z-score) using an intrauterine foetal growth reference (Marsal et al). SGA was defined as a birthweight of <-2 Z-scores. The birthweight (Z-score) and gestational age were compared between the three groups using ANOVA. A two-way ANOVA was used to compare the differences in the lowest plasma phosphate levels between groups and between SGA and non-SGA infants. The Kruskal–Wallis test was used to compare plasma calcium levels between groups and between SGA and non-SGA infants, and to compare the duration of	Group 1: -2.43 (0.71) Group 2: -2.31 (1.04) Group 3: -2.46 (0.87) p = 0.673 SDS, day 22, mean (SD) (z-score) Group 1: -2.51 (0.8) Group 2: -2.70 (0.91) Group 3: -2.68 (0.85) p = 0.541 SDS, day 29, mean (SD) (z-score) Group 1: -2.46 (0.87) Group 2: -2.76 (0.97) group 3: -2.65 (0.79) p = 0.400	balanced across intervention groups) Missing data bias: Low risk of bias Measurement of outcomes bias: NI (unclear whether outcome assessors were blinded, but unlikely due to safety reasons) Selection of the reported results bias: Low risk of bias (all outcomes reported) Other information Supplementary phosphate All infants with plasma phosphate levels below 1.50 mmol/L received supplementary phosphate. Group 1: No infants received Glycophos as it had not yet been introduced at the Rigshospitalet at that time. Group 2:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			PN intake between the three groups. The change in weight Z-score from birth until 29 days of age was also compared between the three groups using ANOVA, with group affiliation, SGA status and use of Glycophos as independent categorical variables. Statistical significance was defined as $p < 0.05$.		13 infants (21%) received Glycophos (6.2% of the infants receiving Glycophos were SGA) Glycophos duration (days): 8.15 Glycophos day of start-up, mean 11.77 Group 3: 16 infants (26%) received Glycophos (12.5% of the infants receiving Glycophos were SGA) Glycophos duration (days): 8.12 Glycophos day of start-up, mean 8.69 Glycophos recipients: $p < 0.001$

ANOVA: analysis of variance analysis; HAA: High amino acid intake; LAA: Low amino acid intake; MAA: Medium amino acid intake; N: number; NI: no information; PN: parenteral nutrition; ROBINS-I: risk of bias in non-randomised studies of interventions; SD: standard deviation; SDS: standard deviation score; SGA: small for gestational age.

Appendix E – Forest plots

Forest plots for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No meta-analysis was carried out for this review; therefore, there are no forest plots.

Appendix F – GRADE tables

GRADE table for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 5: Clinical evidence profile for medium amino acid and low phosphate versus low amino acid and low phosphate

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medium AA and low Ph	Low AA and low Ph	Relative (95% CI)	Absolute	Quality	Importance
Severe hypercalcaemia												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/53 (15.1%)	3/48 (6.3%)	RR 2.42 (0.68 to 8.58)	89 more per 1000 (from 20 fewer to 474 more)	⊕OOO VERY LOW	CRITICAL
Severe hypophosphataemia												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/53 (5.7%)	0/48 (0%)	Peto OR 6.99 (0.71 to 68.96)	-	⊕OOO VERY LOW	CRITICAL

AA: amino acid; CI: confidence interval; OR: odds ratio; Ph: phosphate; RR: risk ratio

[1] Very serious risk of bias due to observational cohort design, study groups were not adjusted on potential confounding factors (nutritional intake, enteral feeding, birth-weight, and gestational age), outcome assessors were not blinded, and the type and amount of PN prescribed was not based in a pre-specified protocol (i.e. it was prescribed by a physician and the outcome assessors were not blinded).

[2] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.80 and 1.25).

[3] Evidence was downgraded for risk of serious imprecision due to low event rate

Table 6: Clinical evidence profile for high amino acid and low phosphate versus medium amino acid and low phosphate

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High AA and low Ph	Medium AA and low Ph	Relative (95% CI)	Absolute	Quality	Importance
Severe hypercalcaemia												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/53 (30.2%)	8/53 (15.1%)	RR 2 (0.94 to 4.27)	151 more per 1000 (from 9 fewer to 494 more)	⊕OOO VERY LOW	CRITICAL
Severe hypophosphataemia												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/53 (18.9%)	3/53 (5.7%)	RR 3.33 (0.97 to 11.44)	132 more per 1000 (from 2 fewer to 591 more)	⊕OOO VERY LOW	CRITICAL

AA: amino acid; CI: confidence interval; Ph: phosphate; RR: risk ratio.

[1] Very serious risk of bias due to observational cohort design, study groups were not adjusted on potential confounding factors (nutritional intake, enteral feeding, birth-weight, and gestational age), outcome assessors were not blinded, and the type and amount of PN prescribed was not based in a pre-specified protocol (i.e. it was prescribed by a physician and the outcome assessors were not blinded).

[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.80 or 1.25).

Table 7: Clinical evidence profile for high amino acid and low phosphate versus low amino acid and low phosphate

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High AA and low Ph	Low AA and low Ph	Relative (95% CI)	Absolute	Quality	Importance
Severe hypercalcaemia												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/53 (30.2%)	3/48 (6.3%)	RR 4.83 (1.5 to 15.56)	239 more per 1000 (from 31 more to 910 more)	⊕OOO VERY LOW	CRITICAL
Severe hypophosphataemia												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/53 (18.9%)	0/48 (0%)	Peto OR 8.12 (2.21 to 29.82)	-	⊕OOO VERY LOW	CRITICAL

AA: amino acid; CI: confidence interval; OR: odds ratio; Ph: phosphate; RR: risk ratio.

[1] Very serious risk of bias due to observational cohort design, study groups were not adjusted on potential confounding factors (nutritional intake, enteral feeding, birth-weight, and gestational age), outcome assessors were not blinded, and the type and amount of PN prescribed was not based in a pre-specified protocol (i.e. it was prescribed by a physician and the outcome assessors were not blinded).

Evidence was downgraded for risk of serious imprecision due to low event rate

Table 8: Clinical evidence profile for low amino acid and high phosphate versus high amino acid and low phosphate

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low AA and high Ph	High AA and low Ph	Relative (95% CI)	Absolute	Quality	Importance
Weight change (z-score) from day 1 to 29 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 0.07 higher (0.23 lower to 0.37 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 8 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 0.06 higher (0.25 lower to 0.37 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 15 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	62	62	-	MD 0.12 lower (17.79 lower to 17.55 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 22 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	62	62	-	MD 0.19 higher (0.11 lower to 0.49 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 29 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	62	62	-	MD 0.3 higher (0.02 lower to 0.62 higher)	⊕OOO VERY LOW	CRITICAL

AA: amino acid; CI: confidence interval; MD: mean difference; Ph: phosphate

[1] *Very serious risk of bias due to retrospective observational study design; co-interventions (glycophos supplementation) not balanced across three groups); unclear whether outcome assessors were blinded, but unlikely due to safety reasons).*
[2] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.52, 0.52).*
[3] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.46).*
[4] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.49).*

Table 9: Clinical evidence profile for low amino acid and high phosphate versus high amino acid and high phosphate

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low AA and high Ph	High AA and high Ph	Relative (95% CI)	Absolute	Quality	Importance
Weight change (z-score) from day 1 to 29 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	62	62	-	MD 0.16 lower (0.43 lower to 0.11 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 8 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 0.08 lower (0.37 lower to 0.21 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 15 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 0.03 higher (0.25 lower to 0.31 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 22 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	62	62	-	MD 0.17 higher (0.12 lower to 0.46 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 29 (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low AA and high Ph	High AA and high Ph	Relative (95% CI)	Absolute	Quality	Importance
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	62	62	-	MD 0.19 higher (0.1 lower to 0.48 higher)	⊕OOO VERY LOW	CRITICAL

AA: amino acid; CI: confidence interval; MD: mean difference; Ph: phosphate.
[1] Very serious risk of bias due to retrospective observational study design; co-interventions (glycophos supplementation) not balanced across three groups); unclear whether outcome assessors were blinded, but unlikely due to safety reasons).
[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.39).
[3] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.43).
[4] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.40).

Table 10: Clinical evidence profile for high amino acid and high phosphate versus high amino acid and low phosphate

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High AA and high Ph	High AA and low Ph	Relative (95% CI)	Absolute	Quality	Importance
Weight change (z-score) from day 1 to 29 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	62	62	-	MD 0.23 higher (0.07 lower to 0.53 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 8 (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High AA and high Ph	High AA and low Ph	Relative (95% CI)	Absolute	Quality	Importance
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 0.11 higher (0.2 lower to 0.42 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 15 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 0.15 lower (0.49 lower to 0.19 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 22 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 0.02 higher (0.29 lower to 0.33 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score - Day 29 (Better indicated by higher values)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	62	-	MD 0.11 higher (0.2 lower to 0.42 higher)	⊕OOO VERY LOW	CRITICAL

AA: amino acid; CI: confidence interval; MD: mean difference; Ph: phosphate.

[1] Very serious risk of bias due to retrospective observational study design; co-interventions (glycophos supplementation) not balanced across three groups); unclear whether outcome assessors were blinded, but unlikely due to safety reasons).

[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.47).

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

One global search was conducted for all review questions. See supplementary material D for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No economic studies were identified which were applicable to this review question.

Appendix I – Economic evidence profiles

Health economic evidence profiles for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No economic studies were identified which were applicable to this review question.

Appendix J – Economic analysis

Health economic analysis for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded studies for review question: What is the optimal ratio of 3 phosphate to amino acid in preterm and term babies who are 4 receiving parenteral nutrition and neonatal care?

5 Clinical studies

6 **Table 11: Excluded clinical studies and reasons for exclusion**

Study	Reason for Exclusion
Aiken, G., Lenney, W., Calcium and phosphate content of intravenous feeding regimens for very low birthweight infants, Archives of disease in childhood, 61, 495-501, 1986	Included in review of optimal calcium and phosphate doses.
Aiken, C. G., Sherwood, R. A., Kenney, I. J., Furnell, M., Lenney, W., Mineral balance studies in sick preterm intravenously fed infants during the first week after birth. A guide to fluid therapy, Acta paediatrica Scandinavica. Supplement, 355, 1-59, 1989	Study does not provide adequate data for analysis.
Aiken, C. G., Sherwood, R. A., Lenney, W., Role of plasma phosphate measurements in detecting rickets of prematurity and in monitoring treatment, Annals of clinical biochemistry, 30 (Pt 5), 469-75, 1993	Intervention does not meet review protocol eligibility criteria - participants also received enteral feeding.
Aladangady, N., Coen, P. G., White, M. P., Rae, M. D., Beattie, T. J., Urinary excretion of calcium and phosphate in preterm infants, Pediatric Nephrology, 19, 1225-1231, 2004	Intervention does not meet review protocol eligibility criteria - participants also received enteral nutrition.
Allwood, M. C., The compatibility of calcium phosphate in paediatric TPN infusions, Journal of Clinical Pharmacy and Therapeutics, 12, 293-301, 1987	Intervention does not meet review protocol eligibility criteria - objectives of the review are not relevant to the protocol (solubility)
Andronikou, S., Rothberg, A. D., Pettifor, J. M., Thomson, P. D., Early introduction of parenteral nutrition in premature infants and its effect on calcium and phosphate homeostasis, South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 64, 349-51, 1983	Study design and outcomes do not meet review protocol eligibility criteria - prospective comparative study but the allocation was made arbitrarily. Compared AA against Ca-dextrose.
Ardicli, B., Karnak, I., Ciftci, A. O., Ozen, H., Tanyel, F. C., Senocak, M. E., Composition of parenteral nutrition solution affects the time of occurrence but not the incidence of cholestasis in surgical infants, Turkish Journal of Pediatrics, 56, 500-506, 2014	Study design does not meet review protocol eligibility criteria - retrospective case control design.
Atkinson, S. A., Calcium and phosphorus requirements of low birth weight infants: a nutritional and endocrinological perspective, Nutrition reviews, 41, 69-78, 1983	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Awad, H. A., Fand, T. M., Khafagy, S. M., Nofal, R. I., Bone mineral content measured by DEXA scan in preterm neonates receiving total parentral nutrition with and without phosphorus	Study design and outcomes do not meet review protocol eligibility criteria - case-control design - compares phosphorous to non-phosphorous control; unable to assess optimal dosage.

Study	Reason for Exclusion
supplementation, Pakistan Journal of Biological Sciences, 13, 891-895, 2010	
Bentur, L., Alon, U., Berant, M., Bone and mineral homeostasis in the preterm infant: A review, Pediatric Reviews and Communications, 1, 291-310, 1987	Study design does not meet review protocol eligibility criteria - Not a systematic review of RCTs.
Berg, G., Recommendations for parenteral nutrition, Zeitschrift fur Ernahrungswissenschaft. Journal of nutritional sciences. Supplementa, 9, 1-40, 1970	Study design does not meet review protocol eligibility criteria - recommendations of practice.
Berry, M. A., Conrod, H., Usher, R. H., Growth of very premature infants fed intravenous hyperalimentation and calcium-supplemented formula, Pediatrics, 100, 647-653, 1997	Study design does not meet review protocol eligibility criteria - Not an RCT or comparative cohort study.
Bloomfield, F. H., Crowther, C. A., Harding, J. E., Conlon, C. A., Jiang, Y., Cormack, B. E., The ProVIDe study: The impact of protein intravenous nutrition on development in extremely low birthweight babies, BMC Pediatrics, 15, 2015	Study design and outcomes do not meet review protocol eligibility criteria - protocol of RCT - the arms of the RCT do not accommodate the objectives of the review (AA vs placebo).
Bolisetty, S., Osborn, D., Sinn, J., Lui, K., Kent, A., Trivedi, A., Yaacou, D., Morris, S., Marshall, P., Birch, P., Corban, J., Natthondan, V., Ching, S. K., Wake, C., Vaidya, U., Tobiansky, R., Pazanin, N., Tan, K., Downe, L., Deshpande, G., Paoli, T. D., Colvin, J., Ravindranathan, H., Gupta, N., Gibney, D., Luig, M., Ng, K., Pham, T., McPhee, A., Standardised neonatal parenteral nutrition formulations - an Australasian group consensus 2012, BMC Pediatrics, 14, 48, 2014	Study design and outcomes do not meet review protocol eligibility criteria - literature review - consensus group - refers to optimal dosages of Ca and P.
Boubred, F., Herlenius, E., Bartocci, M., Jonsson, B., Vanpee, M., Extremely preterm infants who are small for gestational age have a high risk of early hypophosphatemia and hypokalemia, Acta Paediatrica, International Journal of Paediatrics, 104, 1077-1083, 2015	Study design does not meet review protocol eligibility criteria - observational cohort design not a RCT.
Boullata, J. I., Gilbert, K., Sacks, G., Labossiere, R. J., Crill, C., Goday, P., Kumpf, V. J., Mattox, T. W., Plogsted, S., Holcombe, B., Compher, C., A.S.P.E.N. Clinical guidelines: Parenteral nutrition ordering, order review, compounding, labeling, and dispensing, Journal of Parenteral and Enteral Nutrition, 38, 334-377, 2014	Study design does not meet review protocol eligibility criteria - clinical guidelines.
Brener Dik, P. H., Galletti, M. F., Bacigalupo, L. T., Jonusas, S. F., Mariani, G. L., Hypercalcemia and hypophosphatemia among preterm infants receiving aggressive parenteral nutrition, Archivos Argentinos de Pediatria, 116, e371-e377, 2018	Study design does not meet review protocol eligibility criteria - non-randomised comparative study.
Brown, D. R., Salsburey, D. J., Short-term biochemical effects of parenteral calcium treatment of early-onset neonatal hypocalcemia, The Journal of pediatrics, 100, 777-81, 1982	Study design does not meet review protocol eligibility criteria - cross-sectional study.
Brown, D. R., Steranka, B. H., Taylor, F. H., Treatment of early-onset neonatal	Does not address any of the outcomes specified in the protocol.

Study	Reason for Exclusion
hypocalcemia. Effects on serum calcium and ionized calcium, American journal of diseases of children (1960), 135, 24-8, 1981	
Bustos Lozano, Gerardo, Soriano-Ramos, Maria, Pinilla Martin, Maria Teresa, Chumillas Calzada, Silvia, Garcia Soria, Carmen Elia, Pallas-Alonso, Carmen Rosa, Early Hypophosphatemia in High-Risk Preterm Infants: Efficacy and Safety of Sodium Glycerophosphate From First Day on Parenteral Nutrition, JPEN. Journal of parenteral and enteral nutrition, 43, 419-425, 2019	Study design does not meet review protocol eligibility criteria - non-randomised comparative study.
Castillo, Salinas F, Clinical efficacy of organic phosphorus in newborns who require parenteral nutrition, Revista espanola de pediatria, 69, 312-318, 2013	Non-English publication (full text in Spanish).
Changaris, D. G., Purohit, D. M., Balentine, J. D., Levkoff, A. H., Holden, A. E., Dean, D. L., Jr., Biggs, P. J., Brain calcification in severely stressed neonates receiving parenteral calcium, The Journal of pediatrics, 104, 941-6, 1984	Study does not meet review protocol eligibility criteria.
Chessex, P., Pineault, M., Brisson, G., Delvin, E. E., Glorieux, F. H., Role of the source of phosphate salt in improving the mineral balance of parenterally fed low birth weight infants, The Journal of pediatrics, 116, 765-72, 1990	Study outcomes do not meet review protocol eligibility criteria - testing solubility of plasma for Ca and P.
Chessex, P., Pineault, M., Zebiche, H., Ayotte, R. A., Calciuria in parenterally fed preterm infants: role of phosphorus intake, The Journal of pediatrics, 107, 794-6, 1985	Study design does not meet review protocol eligibility criteria - non-comparative prospective cohort.
Chetta, K. E., Hair, A. B., Hawthorne, K. M., Abrams, S. A., Serum phosphorus levels in premature infants receiving a donor human milk derived fortifier, Nutrients, 7, 2562-2573, 2015	Study design does not meet review protocol eligibility criteria - observational cohort study - does not directly compare Ca and P.
Christmann, V., De Grauw, A. M., Visser, R., Matthijsse, R. P., Van Goudoever, J. B., Van Heijst, A. F. J., Early postnatal calcium and phosphorus metabolism in preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 58, 398-403, 2014	Study design does not meet review protocol eligibility criteria - non-comparative prospective cohort study.
Christmann, V., Gradussen, C. J. W., Kornmann, M. N., Roeleveld, N., van Goudoever, J. B., van Heijst, A. F. J., Changes in biochemical parameters of the calcium-phosphorus homeostasis in relation to nutritional intake in very-low-birth-weight infants, Nutrients, 8 (12) (no pagination), 2016	Intervention does not meet review protocol eligibility criteria - participants receive both enteral and parenteral nutrition.
Christmann, V., van der Putten, M. E., Rodwell, L., Steiner, K., Gotthardt, M., van Goudoever, J. B., van Heijst, A. F. J., Effect of early nutritional intake on long-term growth and bone mineralization of former very low birth weight infants, Bone, 108, 89-97, 2018	Study design does not meet review protocol eligibility criteria - not RCT (observational cohort study)
Colonna, F., Candusso, M., De Vonderweid, U., Marinoni, S., Gazzola, A. M., Calcium and phosphorus balance in very low birth weight	Study outcomes do not meet review protocol eligibility criteria - assesses

Study	Reason for Exclusion
babies on total parenteral nutrition, Clinical Nutrition, 9, 89-95, 1990	maturation/tolerability/ and retention of Ca and P in PN patients.
Cooper, L. J., Anast, C. S., Circulating immunoreactive parathyroid hormone levels in premature infants and the response to calcium therapy, Acta Paediatrica Scandinavica, 74, 669-673, 1985	There is no randomisation. prospective comparative study - does not address the outcomes reported to the protocol.
De Schepper, J., Cools, F., Vandenplas, Y., Louis, O., Whole body bone mineral content is similar at discharge from the hospital in premature infants receiving fortified breast milk or preterm formula, Journal of Pediatric Gastroenterology and Nutrition, 41, 230-234, 2005	Study intervention does not meet review protocol eligibility criteria - oral feeding.
Dear, P. R. F., Total parenteral nutrition of the newborn, Care of the Critically Ill, 8, 252-257, 1992	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Dilena, B. A., White, G. H., The responses of plasma ionised calcium and intact parathyrin to calcium supplementation in preterm infants, Acta Paediatrica Scandinavica, 80, 1098-1100, 1991	Study outcomes do not meet review protocol eligibility criteria - assesses whole blood ionised.
Dreyfus, Lelia, Fischer Fumeaux, Celine Julie, Remontet, Laurent, Essomo Megnier Mbo Owono, Murielle Christine, Laborie, Sophie, Maucort-Boulch, Delphine, Claris, Olivier, Low phosphatemia in extremely low birth weight neonates: A risk factor for hyperglycemia?, Clinical nutrition (Edinburgh, Scotland), 35, 1059-65, 2016	Study design and intervention do not meet review protocol eligibility criteria - retrospective cohort - EN and PN.
Enomoto, M., Minami, H., Takano, T., Katayama, Y., Lee, Y. K., High-dose calcium reduces early-onset hyperkalemia in extremely preterm neonates, Pediatrics International, 54, 918-922, 2012	Study design does not meet review protocol eligibility criteria - retrospective cohort not an RCT.
Forsythe, R. M., Wessel, C. B., Billiar, T. R., Angus, D. C., Rosengart, M. R., Parenteral calcium for intensive care unit patients, Cochrane Database of Systematic Reviews, (4) (no pagination), 2008	Study design does not meet review protocol eligibility criteria - narrative review.
Gaio, P., Fantinato, M., Daverio, M., Nardo, D., Favero, V., Meneghelli, M., De Terlizzi, F., Verlato, G., Bone status in preterm infants: Influences of maternal factors and nutritional regimens, Journal of Pediatric Gastroenterology and Nutrition, 62, 707, 2016	Study design and objectives do not meet review protocol eligibility criteria - not an RCT (prospective, experimental study) - other than reviews' objectives.
Genoni, G., Binotti, M., Monzani, A., Bernascone, E., Stasi, I., Bona, G., Ferrero, F., Nonrandomised interventional study showed that early aggressive nutrition was effective in reducing postnatal growth restriction in preterm infants, Acta Paediatrica, International Journal of Paediatrics, 106, 1589-1595, 2017	Study design and intervention do not meet review protocol eligibility criteria - prospective, non-randomised study - PN and EN.
Giapros, V., Vantziou, S., Cholevas, V., Challa, A., Andronikou, S., Effect of intravenous phosphate on the red cell phosphate metabolites	Study comparator does not meet review protocol eligibility criteria - control group was enterally fed.

Study	Reason for Exclusion
of the preterm infant, Nutrition Research, 21, 71-79, 2001	
Glenn, S. R., Finch, C., DellaValle, D. M., Taylor, S., Parenteral nutrition in extremely low birth weight infants: Increased phosphorus and early potassium delivery, Journal of Investigative Medicine, 67, 518-519, 2019	Abstract only.
Green, J., Burgess, L., Morgan, C., Insulin treated hyperglycaemia, hyperalimentation and metabolic changes associated with growth in very preterm infants receiving parenteral nutrition, Archives of Disease in Childhood, 99, A208, 2014	Study does not meet review protocol eligibility criteria - other than the objectives of the review.
Green, J., McGowan, P., Hyperalimentation and electrolyte requirements in very preterm infants: A randomised controlled parenteral nutrition study, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A6, 2014	Abstract only. Did not assess outcomes of interest.
Green, J., McGowan, P., Morgan, C., Hyperalimentation and electrolyte requirements in very preterm infants: The randomised controlled scamp nutrition study, Archives of Disease in Childhood, 99, A58, 2014	Study does not meet review protocol eligibility criteria - other than the objectives of the review.
Guellec, I., Gascoin, G., Beuchee, A., Boubred, F., Tourneux, P., Ramful, D., Zana-Taieb, E., Baud, O., Biological Impact of Recent Guidelines on Parenteral Nutrition in Preterm Infants, Journal of Pediatric Gastroenterology & Nutrition, 61, 605-9, 2015	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Hair, A. B., Chetta, K. E., Bruno, A. M., Hawthorne, K. M., Abrams, S. A., Delayed introduction of parenteral phosphorus is associated with hypercalcemia in extremely preterm infants, Journal of Nutrition, 146, 1212-1216, 2016	Study design does not meet review protocol eligibility criteria - not an RCT; addresses some of the outcomes of interest and the different ratios between Ca and P, however, this is not a comparison/balanced study.
Hanning, R. M., Atkinson, S. A., Whyte, R. K., Efficacy of calcium glycerophosphate vs conventional mineral salts for total parenteral nutrition in low-birth-weight infants: a randomized clinical trial, The American journal of clinical nutrition, 54, 903-8, 1991	Study outcomes do not meet review protocol eligibility criteria - does not compare directly Ca and phosphate.
Hay Jr, W. W., Intravenous nutrition of the very preterm neonate, Acta Paediatrica, International Journal of Paediatrics, 94, 47-56, 2005	Study design does not meet review protocol eligibility criteria - expert/narrative/guidance review.
Heird, W. C., Winters, R. W., Total intravenous alimentation, American journal of diseases of children (1960), 126, 287-9, 1973	Study design does not meet review protocol eligibility criteria - practice report.
Hicks, W., Hardy, G., Phosphate supplementation for hypophosphataemia and parenteral nutrition, Current opinion in clinical nutrition and metabolic care, 4, 227-233, 2001	Study design does not meet review protocol eligibility criteria -expert/narrative/guidance review.
Hoehn, G. J., Carey, D. E., Rowe, J. C., Horak, E., Raye, J. R., Alternate day infusion of calcium and phosphate in very low birth weight infants: wasting of the infused mineral, Journal of	Study outcomes do not meet review protocol eligibility criteria - assessed sequence not different dosages.

Study	Reason for Exclusion
pediatric gastroenterology and nutrition, 6, 752-7, 1987	
Iacobelli, S., Bonsante, F., Vintejoux, A., Gouyon, J. B., Standardized parenteral nutrition in preterm infants: early impact on fluid and electrolyte balance, Neonatology, 98, 84-90, 2010	Study design does not meet review protocol eligibility criteria - not an RCT (prospective comparative but does not meet the eligibility criteria).
Ichikawa, G., Watabe, Y., Suzumura, H., Sairenchi, T., Muto, T., Arisaka, O., Hypophosphatemia in small for gestational age extremely low birth weight infants receiving parenteral nutrition in the first week after birth, Journal of Pediatric Endocrinology and Metabolism, 25, 317-321, 2012	Study design does not meet review protocol eligibility criteria - retrospective review; not an RCT.
Jain, Ashish, Agarwal, Ramesh, Sankar, M. Jeeva, Deorari, Ashok K., Paul, Vinod K., Hypocalcemia in the newborn, Indian Journal of Pediatrics, 75, 165-9, 2008	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Johnston, I. D., Management of prolonged intravenous feeding, Proceedings of the Royal Society of Medicine, 66, 770-1, 1973	Study design does not meet review protocol eligibility criteria - expert/opinion review.
Kamali, K., Pishva, N., Deireh, E., The effects of low and high dose oral calcium and phosphor supplementation on nephrocalcinosis diagnosed by sonography in premature and low birth weight neonates, Iranian Journal of Medical Sciences, 39, 559-64, 2014	Study outcomes do not meet review protocol eligibility criteria.
Kashyap, Sudha, Is the early and aggressive administration of protein to very low birth weight infants safe and efficacious?, Current opinion in pediatrics, 20, 132-6, 2008	Study design does not meet review protocol eligibility criteria - narrative review.
Khan,M.A.G., Upadhyay,A., Chikanna,S., Jaiswal,V., Efficacy of prophylactic intravenous calcium administration in first 5 days of life in high risk neonates to prevent early onset neonatal hypocalcaemia: A randomised controlled trial, Archives of Disease in Childhood: Fetal and Neonatal Edition, 95, F462-F463, 2010	Study outcomes do not meet review protocol eligibility criteria - hypocalcaemia measured.
Knight, P., Heer, D., Abdenour, G., CaxP and Ca/P in the parenteral feeding of preterm infants, Journal of Parenteral and Enteral Nutrition, 7, 110-114, 1983	Study does not meet review protocol eligibility criteria.
Koo, W. W., Parenteral nutrition-related bone disease, JPEN. Journal of parenteral and enteral nutrition, 16, 386-94, 1992	Study does not meet review protocol eligibility criteria.
Koo, W. W., Calcium, phosphorus, and vitamin D requirements of infants receiving parenteral nutrition, Journal of perinatology : official journal of the California Perinatal Association, 8, 263-268, 1988	Study design does not meet review protocol eligibility criteria - narrative/expert review.
Koo, W. W., Tsang, R. C., Mineral requirements of low-birth-weight infants, Journal of the American College of Nutrition, 10, 474-86, 1991	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.

Study	Reason for Exclusion
Koo, W. W., Tsang, R. C., Poser, J. W., Laskarzewski, P., Buckley, D., Johnson, R., Steichen, J. J., Elevated serum calcium and osteocalcin levels from calcitriol in preterm infants. A prospective randomized study, American journal of diseases of children (1960), 140, 1152-8, 1986	Study outcomes do not meet review protocol eligibility criteria - assesses calcitrol only.
Koo, W. W., Tsang, R. C., Steichen, J. J., Succop, P., Babcock, D., Oestreich, A. E., Noseworthy, J., Horn, J., Farrell, M. K., Parenteral nutrition for infants: effect of high versus low calcium and phosphorus content, Journal of pediatric gastroenterology and nutrition, 6, 96-104, 1987	Included in review of optimal calcium and phosphate doses,
Koo, W. W., Tsang, R. C., Succop, P., Krug-Wispe, S. K., Babcock, D., Oestreich, A. E., Minimal vitamin D and high calcium and phosphorus needs of preterm infants receiving parenteral nutrition, Journal of pediatric gastroenterology and nutrition, 8, 225-33, 1989	Included in review of optimal calcium and phosphate doses,
Koren,G., Zarfin,Y., Maresky,D., Spiro,T.E., MacLeod,S.M., Pharmacokinetics of intravenous clindamycin in newborn infants, Pediatric Pharmacology, 5, 287-292, 1986	Study design and outcomes do not meet review protocol eligibility criteria.
Kreuder, J, Otten, A, Reiter, Hl, Klingmüller, V, Wolf, H, Efficacy and side effects of differential calcium and phosphate administration in prevention of osteopenia in premature infants, Monatsschrift Kinderheilkunde, 138, 775-779, 1990	Non-English publication (full text in German).
Lenclen, R., Crauste-Manciet, S., Narcy, P., Boukhouna, S., Geffray, A., Guerrault, M. N., Bordet, F., Brossard, D., Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants, European Journal of Pediatrics, 165, 512-518, 2006	Study interventions do not meet review protocol eligibility criteria - compares Standard PN with individualised PN.
MacMahon, P., Blair, M. E., Treweeke, P., Kovar, I. Z., Association of mineral composition of neonatal intravenous feeding solutions and metabolic bone disease of prematurity, Archives of Disease in Childhood, 64, 489-93, 1989	Included in review of optimal calcium and phosphate doses.
MacMahon, P., Mayne, P. D., Blair, M., Pope, C., Kovar, I. Z., Acid-base state of the preterm infant and the formulation of intravenous feeding solutions, Archives of Disease in Childhood, 65, 354-6, 1990	Study interventions do not meet review protocol eligibility criteria - not different dosages of Ca and P.
Marks, K. E., Crill, C. M., Calcium and phosphorous in pediatric parenteral nutrition, Journal of Pharmacy Practice, 17, 432-446, 2004	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Mazouri, Ali, Khosravi, Nastaran, Bordbar, Arash, Khalesi, Nasrin, Saboute, Maryam, Taherifard, Pegah, Mirzababaee, Marjan, Ebrahimi, Mehran, Does Adding Intravenous Phosphorus to Parenteral Nutrition Has Any	Included in review of optimal calcium and phosphate doses.

Study	Reason for Exclusion
Effects on Calcium and Phosphorus Metabolism and Bone Mineral Content in Preterm Neonates?, Acta medica Iranica, 55, 395-398, 2017	
McCarthy, R., Segurado, R., Crealey, M., Twomey, A., Standardised versus individualised parenteral nutrition. Further food for thought, Irish Medical Journal, 109, 388, 2016	Study design does not meet review protocol eligibility criteria - non RCT - prospective comparative but it does not assess the objectives of the review.
McNelis, K., Viswanathan, S., Effects of parenteral phosphorus dose restriction in preterm infants, Journal of Neonatal-Perinatal Medicine, 9, 153-158, 2016	Study design does not meet review protocol eligibility criteria - retrospective case control.
Mimouni, F. B., Mandel, D., Lubetzky, R., Senterre, T., Calcium, phosphorus, magnesium and vitamin D requirements of the preterm infant, World review of nutrition and dietetics, 110, 140-151, 2014	Study design does not meet review protocol eligibility criteria - literature review (book chapter).
Morgan, C., Green, J., Hyperalimentation and electrolyte requirements in very preterm infants: A randomised controlled parenteral nutrition study, Clinical Nutrition, 33, S7, 2014	Study design does not meet review protocol eligibility criteria - conference abstract and does not accommodate reviews objectives.
Mulla, S., Stirling, S., Cowey, S., Close, R., Pullan, S., Howe, R., Radbone, L., Clarke, P., Severe hypercalcaemia and hypophosphataemia with an optimised preterm parenteral nutrition formulation in two epochs of differing phosphate supplementation, Archives of Disease in Childhood, 2017	Study design does not meet review protocol eligibility criteria - retrospective cohort study.
Narendra, A., White, M. P., Rolton, H. A., Alloub, Z. I., Wilkinson, G., McColl, J. H., Beattie, J., Nephrocalcinosis in preterm babies, Archives of Disease in Childhood, Fetal and neonatal edition. 85, F207-213, 2001	Study design and outcomes do not meet review protocol eligibility criteria - non RCT (prospective observational cohort). Outcome measured is nephrocalcinosis.
Nehra,D., Carlson,S.J., Fallon,E.M., Kalish,B., Potemkin,A.K., Gura,K.M., Simpser,E., Compher,C., Puder,M., A.S.P.E.N. clinical guidelines: Nutrition support of neonatal patients at risk for metabolic bone disease, Journal of Parenteral and Enteral Nutrition, 37, 570-578, 2013	Study design does not meet review protocol eligibility criteria - clinical guidelines.
Orimadegun, Adebola Emmanuel, Akingbola, Titilola Stella, Routine administration of intravenous calcium during exchange blood transfusion for treatment of severe neonatal hyperbilirubinaemia: a systematic review of quantitative evidence protocol, JBI database of systematic reviews and implementation reports, 13, 134-45, 2015	Study design does not meet review protocol eligibility criteria - study protocol.
O'Shea, T. M., Kothadia, J. M., Klinepeter, K. L., Goldstein, D. J., Jackson, B., Dillard, R. G., Follow-up of preterm infants treated with dexamethasone for chronic lung disease, American Journal of Diseases of Children, 147, 658-61, 1993	Study design does not meet review protocol eligibility criteria - not an RCT (Longitudinal follow-up using historic controls).
Pajak, A., Krolak-Olejnik, B., Szafranska, A., Early hypophosphatemia in very low birth weight	Study design does not meet review protocol eligibility criteria - non-randomised study.

Study	Reason for Exclusion
preterm infants, Advances in Clinical and Experimental Medicine, 27, 841-847, 2018	
Pelegano, J. F., Rowe, J. C., Carey, D. E., LaBarre, D. J., Edgren, K. W., Lazar, A. M., Horak, E., Effect of calcium/phosphorus ratio on mineral retention in parenterally fed premature infants, Journal of pediatric gastroenterology and nutrition, 12, 351-5, 1991	Does not assess any of the outcomes reported in the protocol.
Pelegano, J. F., Rowe, J. C., Carey, D. E., LaBarre, D. J., Raye, J. R., Edgren, K. W., Horak, E., Simultaneous infusion of calcium and phosphorus in parenteral nutrition for premature infants: use of physiologic calcium/phosphorus ratio, The Journal of pediatrics, 114, 115-9, 1989	Study does not meet review protocol eligibility criteria.
Pereira-Da-Silva, L, Costa, Ab, Pereira, L, Filipe, Af, Vierella, D, Moreira, Ac, Rosa, Ml, Mendes, L, Serelha, M, Short-Term Effect Of Two Different Parenteral Calcium And Phosphorus Regimens On Bone Strength In Preterm Infants, 50th annual meeting of the European society for paediatric research; 2009 October 9-12; hamburg, germany, 2009	Study outcomes do not meet review protocol eligibility criteria.
Pereira-Da-Silva, L., Costa, A. B., Pereira, L., Filipe, A. F., Virella, D., Leal, E., Moreira, A. C., Rosa, M. L., Mendes, L., Serelha, M., Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 52, 203-209, 2011	Study outcomes do not meet review protocol eligibility criteria - plasma concentrations, solubility, precipitation.
Pereira-da-Silva, Luis, Nurmamodo, Abdurrachid, Amaral, Joao M. Videira, Rosa, Maria L., Almeida, Maria C., Ribeiro, Maria L., Compatibility of calcium and phosphate in four parenteral nutrition solutions for preterm neonates, American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists, 60, 1041-4, 2003	Study intervention does not meet review protocol eligibility criteria - composition.
Pohlandt, F., Prevention of postnatal bone demineralization in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus, Pediatric Research, 35, 125-9, 1994	Study intervention does not meet review protocol eligibility criteria - includes enteral feeding.
Porcelli, P. J., Jr., Oh, W., Effects of single dose calcium gluconate infusion in hypocalcemic preterm infants, American Journal of Perinatology, 12, 18-21, 1995	Does not assess any of the outcomes reported to the protocol.
Prestridge, L. L., Schanler, R. J., Shulman, R. J., Burns, P. A., Laine, L. L., Effect of parenteral calcium and phosphorus therapy on mineral retention and bone mineral content in very low birth weight infants, Journal of Pediatrics, 122, 761-8, 1993	Included in review of optimal calcium and phosphate doses.

Study	Reason for Exclusion
Prince, A., Groh-Wargo, S., Nutrition management for the promotion of growth in very low birth weight premature infants, Nutrition in Clinical Practice, 28, 659-68, 2013	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Ronchera-oms, C. L., Allwood, M. C., Hardy, G., Organic phosphates in parenteral nutrition: pouring fresh water into an old bucket, Nutrition (Burbank, Los Angeles County, Calif.), 12, 388-9, 1996	Study design does not meet review protocol eligibility criteria - expert review.
Salle, B. L., David, L., Chopard, J. P., Grafmeyer, D. C., Renaud, H., Prevention of early neonatal hypocalcemia in low birth weight infants with continuous calcium infusion: Effect on serum calcium, phosphorus, magnesium, and circulating immunoreactive parathyroid hormone and calcitonin, Pediatric Research, 11, 1180-1185, 1977	Study design does not meet review protocol eligibility criteria - non-randomised comparative study.
Salsburey, D. J., Brown, D. R., Effect of parenteral calcium treatment on blood pressure and heart rate in neonatal hypocalcemia, Pediatrics, 69, 605-9, 1982	Study outcomes do not meet review protocol eligibility criteria.
Schanler, R. J., Shulman, R. J., Prestridge, L. L., Parenteral nutrient needs of very low birth weight infants, Journal of Pediatrics, 125, 961-8, 1994	Study outcomes do not meet review protocol eligibility criteria.
Scott, S. M., Ladenson, J. H., Aguanna, J. J., Walgate, J., Hillman, L. S., Effect of calcium therapy in the sick premature infant with early neonatal hypocalcemia, Journal of Pediatrics, 104, 747-751, 1984	Study outcomes do not meet review protocol eligibility criteria - reports only ionised and total calcium and comparisons are for bolus vs drip.
Senterre, T., Zahirah, I. A., Pieltain, C., De Halleux, V., Rigo, J., Electrolyte and mineral homeostasis after optimizing early macronutrient intakes in VLBW infants on parenteral nutrition, Journal of Pediatric Gastroenterology and Nutrition, 61, 491-498, 2015	Study design does not meet review protocol eligibility criteria - not an RCT (prospective cohort).
Stein, J., Boehles, H. J., Blumenstein, I., Goeters, C., Schulz, R., Amino acids - Guidelines on Parenteral Nutrition, Chapter 4, German medical science : GMS e-journal, 7, 2009	Study design does not meet review protocol eligibility criteria - not an RCT (practice review).
Thowladda, N., Siritientong, T., Compatibility of calcium and sodium glycerophosphate in parenteral nutrition solutions, Thai Journal of Pharmaceutical Sciences, 40, 176-179, 2016	Study does not meet review protocol eligibility criteria.
Trindade, C. E. P., Minerals in the nutrition of extremely low birth weight infants, Jornal de Pediatria, 81, S43-S51, 2005	Study design does not meet review protocol eligibility criteria - literature review.
Trotter, A., Pohlandt, F., Calcium and phosphorus retention in extremely preterm infants supplemented individually, Acta paediatrica (Oslo, Norway : 1992), 91, 680-3, 2002	Study intervention does not meet review protocol eligibility criteria - includes enteral feeding.

Study	Reason for Exclusion
Tsang, R. C., Demarini, S., Rickets and calcium and phosphorus requirements in very low birth weight infants, Monatsschrift fur Kinderheilkunde, 143, S125-S129, 1995	Study design does not meet review protocol eligibility criteria - not an RCT (practice-literature review).
Uthaya, S., Liu, X., Babalis, D., Dore, C. J., Warwick, J., Bell, J., Thomas, L., Ashby, D., Durighel, G., Ederies, A., Yanez-Lopez, M., Modi, N., Nutritional Evaluation and Optimisation in Neonates: A randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition, American Journal of Clinical Nutrition, 103, 1443-1452, 2016	Study interventions do not meet review protocol eligibility criteria - does not compare dosages of AA and phosphate.
van den Akker, Chris H. P., te Braake, Frans W. J., Weisglas-Kuperus, Nynke, van Goudoever, Johannes B., Observational outcome results following a randomized controlled trial of early amino acid administration in preterm infants, Journal of pediatric gastroenterology and nutrition, 59, 714-9, 2014	Study does not meet review protocol eligibility criteria.
Vileisis, R. A., Effect of phosphorus intake in total parenteral nutrition infusates in premature neonates, The Journal of pediatrics, 110, 586-90, 1987	Included in review of optimal calcium and phosphate doses.
Vileisis, R. A., Furosemide effect on mineral status of parenterally nourished premature neonates with chronic lung disease, Pediatrics, 85, 316-22, 1990	Study outcomes do not meet review protocol eligibility criteria.
Virella, D., Pereira-Da-Silva, L., Papoila, A. L., Parenteral phosphate and amino acids supply effect on the growth of extremely preterm infants: Accurate measurements and optimized statistical analysis are important, Acta Paediatrica, International Journal of Paediatrics, 104, e537, 2015	Study design does not meet review protocol eligibility criteria - letter to editor.
Watts, S., Mactier, H., Grant, J., Cameron Nicol, E., Mullen, A. B., Is additional oral phosphate supplementation for preterm infants necessary: An assessment of clinical audit, European Journal of Pediatrics, 172, 1313-1319, 2013	Study intervention does not meet review protocol eligibility criteria - oral feeding.
Yeung, M. Y., Smyth, J. P., Maheshwari, R., Shah, S., Evaluation of standardized versus individualized total parenteral nutrition regime for neonates less than 33 weeks' gestation, Journal of paediatrics and child health, 39, 613-7, 2003	Study design and interventions do not meet review protocol eligibility criteria - non RCT. Assesses standard vs total PN.

1 Economic studies

2 No economic evidence was identified for this review question. See
3 supplementary document D for further information.

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal ratio of phosphate to amino acid in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No research recommendations were made for this review question.