National Institute for Health and Care Excellence

Draft for consultation

Neonatal parenteral nutrition

[D6] Acetate

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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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Evidence reviews for parenteral nutrition in neonates: Intravenous acetate for parenteral nutrition in preterm and term babies

Review question

How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

Introduction

Hyperchloraemia and metabolic acidosis are potential complications of parenteral nutrition (PN). In addition, renal dysfunction of prematurity can result in failure of urinary acidification, and hence chloride retention. Acetate may be included in PN to reduce the amount of chloride administered to lower the risk of hyperchloraemia, and to help prevent acidosis by bolstering the amount of bicarbonate in blood.

Summary of the protocol

Please 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	• Any amount (mmol/L) of acetate
Comparison	• A comparison amount of acetate (as compared to intervention volume) • No acetate

Outcomes	**Critical**
	• Hyperchloraemia (>115 mmol/L)
	• Hypochloraemia (<95 mmol/L)
	• Metabolic acidosis
	• Metabolic alkalosis
	Important
	• Mortality
	• Growth measures
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)
	• Body Composition (measured as lean mass, fat-free mass, fat mass, adipose tissue, nitrogen accretion)

For further details see the review protocol in appendix A.

Clinical evidence

Included studies

As limited RCT evidence was available, we also included observational studies. Two studies were identified for inclusion in this review, one randomised controlled trial (RCT) (Richards 1993), and one observational study (Peters 1997).

The RCT (n=59) compared a standard chloride-based PN regimen to an acetate-based PN regimen, which restricted the provision of chloride up to 3mmol/kg/day (Richards 1993). The observational study (n=58) compared a standard chloride-based PN regimen to a acetate-based PN regimen (Peters 1997)

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, 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 that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Peters 1997 RCT UK	N=58 Median GA (range) Chloride: 27 weeks (24 to 31) Acetate: 28 weeks (24 to 31) Median BW (range) Chloride: 1060g (660 to 1690) Acetate: 1010g (660 to 1670)	Acetate-based PN *(n=28)* Modified PN regimen containing acetate. The maximum dose of chloride allowed was 3 mmol/kg/day and any anion requirement in excess of this was provided as acetate	Chloride-based PN (n=30) Standard PN regimen without acetate.	• Hyperchloraemia (>115mmol/L) • Mortality	PN including amino acid started on day 3 after birth. Intravenous lipid solution was added on day 5. Sodium was prescribed at standard dose of 4 mmol/kg/day. Potassium was prescribed in a basic intake of 2 mmol/kg/day.
Richards 1993 Observational study	N = 59 Mean GA	Acetate-based PN (n=31)	Chloride-based PN (n=28)	• pH* • Base excess*	Gestational age was included in the analysis as a covariate.

Study	Population	Intervention	Comparison	Outcomes	Comments
UK	Acetate: 32.5 weeks (SD 4.7) Chloride: 31 weeks (SD 4.5) Mean weight Acetate: 1.88g (SD 0.87) Chloride: 1.52g (SD 0.92)	PN formulation which included sodium acetate.	Standard PN regimen, with no acetate.		Differences in the gestational age did not significantly affect the differences between the two groups on the outcomes of interest.

** pH and base excess, even though not specifically mentioned as outcomes in the protocol, were considered as indicators (or proxy outcomes) of metabolic acidosis. pH can be considered a direct measure of acidosis, and base excess as a surrogate marker for acidosis.*
BW: birthweight; GA: gestational age; PN: parenteral nutrition; RCT: randomised controlled trial; SD: standard deviation.

See also clinical evidence tables in appendix D.

Quality assessment of clinical outcomes included in the evidence review

GRADE was conducted to assess the quality outcomes. Evidence was identified for critical and 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

Hyperchloraemia (>115mmol/L)

- Moderate quality evidence from 1 RCT (n=58) showed a clinically important difference in the incidence of hyperchloraemia in babies who received the chloride-based PN regimen as compared to those who were provided the acetate-based PN regimen, with more babies with hyperchloraemia associated with chloride-based PN: Relative risk (RR) 0.33 (95% CI 0.17 to 0.64).

Mortality

- Very low quality evidence from 1 RCT (n=58) showed a clinically important difference in mortality rate of babies who received the chloride-based PN regimen as compared to those who were provided the acetate PN regimen, with a higher mortality in those receiving the acetate PN. However, there was high uncertainty around the effect: RR 2.14 (95% CI 0.43 to 10.8).

Overall pH

- Very low quality evidence from 1 observational study (n=59) showed a clinically important difference in overall pH, with higher blood pH in those babies receiving acetate-based PN regimen as compared to those who received chloride-based PN regimen. However, there was uncertainty around the effect: Mean difference (MD) 0.04 (95% CI 0.02 to 0.06)

pH (mean difference, day 5)

- Low quality evidence from 1 RCT (n=58) showed a clinically important difference in the blood pH of babies receiving the acetate-based PN regimen as compared to those who received the chloride-based PN regimen, with a higher blood pH associated with the group of babies receiving acetate PN. However, there was uncertainty around the effect: MD 0.05 (95% CI 0.01 to 0.09).

pH (mean difference, day 10)

- Low quality evidence from 1 RCT (n=58) showed a clinically important difference in the blood pH of babies receiving the acetate-based PN regimen as compared to those who received the chloride-based PN regimen, with a higher blood pH associated with the group of babies receiving acetate PN. However there was uncertainty around the effect: MD 0.06 (95% CI 0.02 to 0.10).

Overall level of base excess

- Very low quality evidence from 1 observational study (n=59) showed a clinically important difference in the base excess of babies receiving the acetate-based PN regimen as compared to those who received the chloride-based PN regimen, with a higher excess associated with the group of babies receiving acetate PN: MD 3.96 (95% CI 2.54 to 5.38).

Base excess (mean difference, day 5)

- Moderate quality evidence from 1 RCT (n=58) showed a clinically important difference in the base excess of babies receiving the acetate-based PN regimen as compared to those who received the chloride-based PN regimen, with a higher excess associated with the group of babies receiving acetate PN: MD 3.60 (95% CI 2.03 to 5.17).

Base excess (mean difference, day 10)

- Moderate quality evidence from 1 RCT (n=58) showed a clinically important difference in the base excess of babies receiving the acetate-based PN regimen as compared to those who received the chloride-based PN regimen, with a higher excess associated with the group of babies receiving acetate PN: MD 9.90 (95% CI 5.98 to 13.82).

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

The outcomes that matter most

The committee identified hyperchloraemia, metabolic acidosis and metabolic alkalosis as critical outcomes. These outcomes are likely to be directly influenced by the addition of acetate in PN, as acetate is used as an alternative binding agent for cations such as sodium, thereby reducing the chloride load. However, no evidence was identified for metabolic acidosis and metabolic alkalosis. In addition, mortality, body composition, and growth measures, such as weight gain, linear growth, and head circumference were identified as important outcomes. Although chloride and acetate levels may not directly contribute to these outcomes, prolonged metabolic acidosis is of concern. Due to this, the outcomes of pH (a measure of the acidity or alkalinity of a fluid) and base excess were included where available. Base excess (and base deficit) are indicators of the overall non-respiratory acid-base blood level. It is measured in values which are usually (+) in alkalosis and (–) in acidosis and are typically defined as the amount of acid or base that would restore one litre of blood to normal acid-base composition at a Pco_2 of 40 mmHg. It is therefore a marker of acidosis or alkalosis.

The quality of the evidence

The quality of evidence was assessed using GRADE methodology. The evidence for hyperchloraemia and mean difference in base excess was considered of moderate quality; all other evidence was very low or low quality, indicating high uncertainty in the reliability of effect. The evidence drawn from the randomised controlled trial was downgraded for unclear detection and attrition bias. The evidence drawn from the observational study was downgraded for bias regarding the selection of participants, classification of interventions and missing data. Data were 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.

Benefits and harms

The evidence in this review showed that acetate was beneficial in decreasing the risk of hyperchloraemia, increasing the pH and the base excess in infants receiving PN in the first 10 days of life; however, the evidence did not provide data to determine the optimal dosages of acetate which should be provided in PN. The committee considered the evidence presented, but acknowledged it was limited. The committee therefore also used their clinical knowledge and experience, alongside the evidence to make the recommendations by informal consensus.

Data from the RCT showed that participants in the acetate-based PN regimen group had a higher mortality risk compared to the participants assigned to the chloride-based PN regimen. However, the committee agreed that this was likely not directly associated to the intervention since two out of four deaths in the acetate group occurred before, or during, the initiation of the intervention.

Data from one study (Peters, 1997) showed that participants assigned to an acetate-based PN regimen were less likely to develop hyperchloraemia and had higher levels of pH and

base excess compared to those assigned to a PN regimen with no acetate. The differences regarding the risk of hyperchloraemia between the participants were clinically meaningful, favouring the acetate-based PN regimen group. The committee acknowledged that these findings are consistent with their knowledge and experience, that adding acetate helps to balance the PN solution if there is an excess of chloride.

The committee agreed by informal consensus that generally there should be no need to add acetate to PN. However, they noted that acetate may be needed to reduce the risk of acidosis, and if hyperchloraemia occurs. The committee agreed that preventing too much chloride in the PN initially should be the priority. The committee discussed how chloride intake should be reduced as a priority over the routine provision of acetate to treat acidosis. Chloride is provided alongside sodium and phosphate as these are delivered as chloride salts. In addition, other non-PN sources of chloride may increase a baby's chloride levels, for example some trace elements are in the form of chloride salts and arterial line infusions can contain sodium chloride, or sodium chloride is used to flush intravenous lines after drug administration. The committee agreed, that chloride intake should be monitored and limited where possible by carefully controlling the intake of chloride from PN and non-PN sources. The evidence included in this review did not clearly show how chloride was given, making it difficult to determine the true benefits of acetate as a standard component in PN. The committee therefore decided that acetate should be given to decreases the risk of hyperchloraemia and disturbances occurring in pH and the base excess only if hyperchloraemia occurs despite minimising chloride from parenteral and non-PN sources.

The committee, based on informal consensus and their experience and knowledge, emphasised that these findings support the standardisation of the PN bags (see section 1.5 of the guideline). For example, standardised bags should be developed with limited chloride content, which would include a balanced solution to avoid the need for acetate. This would also decrease the risk of metabolic acidosis and improve neonatal care.

Cost effectiveness and resource use

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

The committee explained that recommendations pertaining to the acetate were unlikely to incur extra resource implications to the health care system.

The committee noted that the recommendations pertaining to the acetate and the avoidance of an excessive chloride intake in the administration of neonatal PN may result in avoiding additional costs associated with adverse effects to the NHS given that PN associated biochemical abnormalities may require more resource-intensive management, i.e. the risk of hyperchloraemia, hypochloraemia, metabolic acidosis and metabolic alkalosis are likely directly influenced by the addition of acetate in PN.

There is variation in practice. However, the committee explained that the recommendations in this area are likely to result only in negligible cost savings to the NHS, if any.

References

Peters 1997

Peters, O., Ryan, S., Matthew, L., Cheng, K., Lunn, J., Randomised controlled trial of acetate in preterm neonates receiving parenteral nutrition, Archives of disease in childhood. Fetal and neonatal edition, 77, F12-5, 1997

Richards 1993

Richards, C. E., Drayton, M., Jenkins, H., Peters, T. J., Effect of different chloride infusion rates on plasma base excess during neonatal parenteral nutrition, Acta paediatrica (Oslo, Norway : 1992), 82, 678-82, 1993

Appendices

Appendix A – Review protocols

Review protocol for review question: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 3: Review protocol – Intravenous acetate

Field (based on PRISMA-P)	Content
Review question	How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?
Type of review question	Intervention
Objective of the review	Hyperchloraemia and metabolic acidosis are potential complications with PN. Acetate may be included in PN to reduce the amount of chloride, and thus reduce the risk of PN-related metabolic acidosis. The aim of this review is to determine how much (if any) acetate, should be provided as part of parenteral nutrition in neonatal care.
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)	• Any amount (mmol/L) of acetate
Eligibility criteria – comparator(s)/control or reference (gold) standard	• A comparison amount of acetate (as compared to intervention volume) • No acetate
Outcomes and prioritisation	**Critical** • Hyperchloraemia (>115mmol/l) • Hypochloraemia (<95mmol/l) • Metabolic acidosis • Metabolic alkalosis **Important**

Field (based on PRISMA-P)	Content

	• Mortality
	• Growth measures
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)
	• Body Composition (measured as lean mass, fat-free mass, fat mass, adipose tissue, nitrogen accretion)

Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making) Conference abstracts of RCTs will only be considered if no evidence is available from full published RCTs (if no evidence from RCTs or comparative cohort studies available and are recent i.e., in the last 2 years-authors will be contacted for further information).
Other inclusion exclusion criteria	• No sample size restriction was made. • No date restriction was made.
Proposed sensitivity/sub-group analysis, or meta-regression	<u>Stratified analysis</u> • 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) Where evidence exists, consideration will be given to the specific needs of 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) Possible equality considerations: • Mothers aged 17 or below

Field (based on PRISMA-P)	Content
	• Parents or carers whose first language is not English
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 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. Low income countries will be downgraded for indirectness. • 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 a new topic for the guideline and is not an update.
Author contacts	Developer: The National Guideline Alliance 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.

Field (based on PRISMA-P)	Content
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.
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.

Field (based on PRISMA-P)	Content
	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	Not registered with PROSPERO.

CCTR: Cochrane Central Register of Controlled Trials CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; GA: Gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: national guideline alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PN: Parenteral nutrition; PROSPERO: prospective register of systematic review 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: How much (if any) intravenous acetate should be provided to 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	exp ACETATES/
27	(Acetate? or Acetamide? or 2-Acetylaminofluorene or Acetoxyacetylaminofluorene or Hydroxyacetylaminofluorene or Allylisopropylacetamide or Iodoacetamide or Linezolid or Piracetam or Thioacetamide or Acetic Acidor Acetic Anhydride? or Aminooxyacetic Acid or Chloroacetate?Or Dichloroacetic Acid or Trichloroacetic Acid or Edetic Acid or Egtazic Acid or Fluoroacetate? or Trifluoroacetic Acid or Glycolate? or Phenoxyacetate? or 2,4-Dichlorophenoxyacetic Acid or Agent Orange or Ethacrynic Acid or 2-Methyl-4-chlorophenoxyacetic Acid or 2,4,5-Trichlorophenoxyacetic Acid or Halofenate or Meclofenoxate or Ticrynafen or Iodoacetate? or Iodoacetamide or Iodoacetic Acid or Nitrilotriacetic Acid or Pentetic Acid or Gadolinium DTPA or Technetium Tc 99m Pentetate or Peracetic Acid or Phosphonoacetic Acid or Foscarnet or Thioglycolate?).mp.
28	or/26-27
29	14 and 25 and 28
30	limit 29 to english language
31	LETTER/
32	EDITORIAL/
33	NEWS/
34	exp HISTORICAL ARTICLE/
35	ANECDOTES AS TOPIC/
36	COMMENT/
37	CASE REPORT/
38	(letter or comment*).ti.
39	or/31-38
40	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
41	39 not 40
42	ANIMALS/ not HUMANS/
43	exp ANIMALS, LABORATORY/
44	exp ANIMAL EXPERIMENTATION/
45	exp MODELS, ANIMAL/
46	exp RODENTIA/
47	(rat or rats or mouse or mice).ti.
48	or/41-47
49	30 not 48

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	ACETIC ACID/
26	ACETIC ACID DERIVATIVE/
27	(Acetate? or Acetamide? or 2-Acetylaminofluorene or Acetoxyacetylaminofluorene or Hydroxyacetylaminofluorene or Allylisopropylacetamide or Iodoacetamide or Linezolid or Piracetam or Thioacetamide or Acetic Acidor Acetic Anhydride? or Aminooxyacetic Acid or Chloroacetate?Or Dichloroacetic Acid or Trichloroacetic Acid or Edetic Acid or Egtazic Acid or Fluoroacetate? or Trifluoroacetic Acid or Glycolate? or Phenoxyacetate? or 2,4-Dichlorophenoxyacetic Acid or Agent Orange or Ethacrynic Acid or 2-Methyl-4-chlorophenoxyacetic Acid or 2,4,5-Trichlorophenoxyacetic Acid or Halofenate or Meclofenoxate or Ticrynafen or Iodoacetate? or Iodoacetamide or Iodoacetic Acid or Nitrilotriacetic Acid or Pentetic Acid or Gadolinium DTPA or Technetium Tc 99m Pentetate or Peracetic Acid or Phosphonoacetic Acid or Foscarnet or Thioglycolate?).mp.
28	or/25-27
29	13 and 24 and 28
30	limit 29 to english language
31	letter.pt. or LETTER/
32	note.pt.
33	editorial.pt.
34	CASE REPORT/ or CASE STUDY/
35	(letter or comment*).ti.
36	or/31-35
37	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
38	36 not 37
39	ANIMAL/ not HUMAN/
40	NONHUMAN/
41	exp ANIMAL EXPERIMENT/
42	exp EXPERIMENTAL ANIMAL/
43	ANIMAL MODEL/
44	exp RODENT/
45	(rat or rats or mouse or mice).ti.
46	or/38-45
47	30 not 46

2

3 Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic 4 Reviews; Database of Abstracts of Reviews of Effects; and Health Technology 5 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

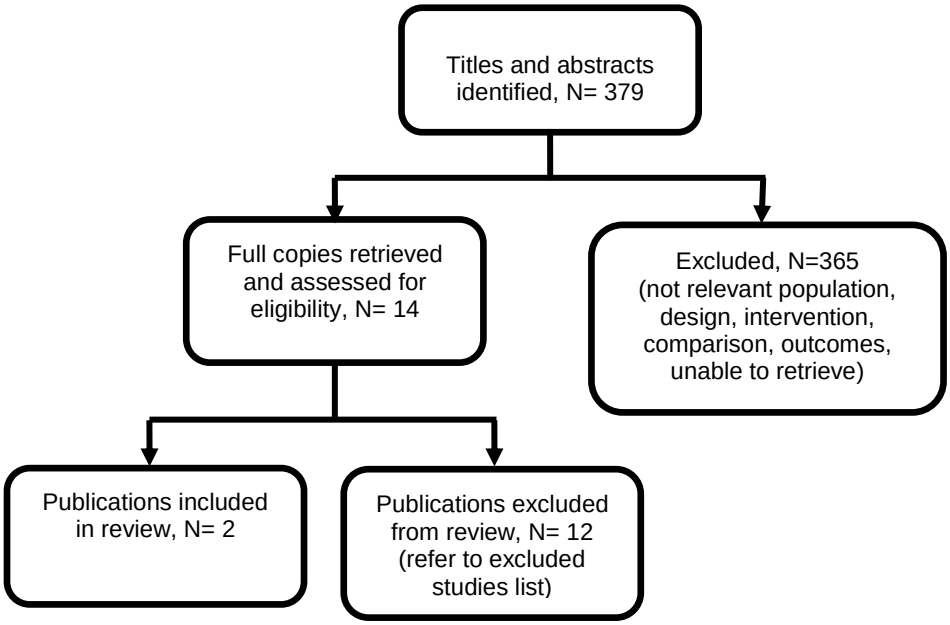
#	Searches
8	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
9	(low near/3 birth near/3 weigh* near/5 infan*):ti,ab
10	((LBW or VLBW) near/5 infan*):ti,ab
11	MeSH descriptor: [INTENSIVE CARE, NEONATAL] this term only
12	MeSH descriptor: [INTENSIVE CARE UNITS, NEONATAL] this term only
13	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
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	MeSH descriptor: [ACETATES] explode all trees
27	(Acetate? or Acetamide? or 2-Acetylaminofluorene or Acetoxyacetylaminofluorene or Hydroxyacetylaminofluorene or Allylisopropylacetamide or Iodoacetamide or Linezolid or Piracetam or Thioacetamide or Acetic Acidor Acetic Anhydride? or Aminooxyacetic Acid or Chloroacetate?Or Dichloroacetic Acid or Trichloroacetic Acid or Edetic Acid or Egtazic Acid or Fluoroacetate? or Trifluoroacetic Acid or Glycolate? or Phenoxyacetate? or 2,4-Dichlorophenoxyacetic Acid or Agent Orange or Ethacrynic Acid or 2-Methyl-4-chlorophenoxyacetic Acid or 2,4,5-Trichlorophenoxyacetic Acid or Halofenate or Meclofenoxate or Ticrynafen or Iodoacetate? or Iodoacetamide or Iodoacetic Acid or Nitrilotriacetic Acid or Pentetic Acid or Gadolinium DTPA or Technetium Tc 99m Pentetate or Peracetic Acid or Phosphonoacetic Acid or Foscarnet or Thioglycolate?):ti,ab
28	#26 or #27
29	#14 and #25 and #28

1
2

Appendix C – Clinical evidence study selection

Clinical study selection for: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

Figure 1: PRISMA flow chart of clinical article selection for review question on intravenous acetate.



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 4: Clinical evidence profiles for intravenous acetate review

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Peters, O., Ryan, S., Matthew, L., Cheng, K., Lunn, J., Randomised controlled trial of acetate in preterm neonates receiving parenteral nutrition, Archives of disease in childhood. Fetal and neonatal edition, 77, F12-5, 1997 Ref Id 606534 Country/ies where the study was carried out UK Study type RCT	Sample size N=58 Standard: N=30 Intervention: N=28 Characteristics Gestational age (weeks) - median (range) Standard: 27 (24 to 31) Intervention: 28 (24 to 31) Birth weight (g) - median (range) Standard: 1060 (660 to 1690) Intervention: 1010 (660 to 1670) Assisted ventilation - number Standard: 29 Intervention: 28 Mortality	Interventions Standard (control): chloride-based PN regimen. Intervention: modified PN containing acetate (restriction in the provision of chloride, up to 3mmol/kg/day).	Details PN based on standard unit protocol (except for acetate and chloride). Quantity of sodium (standard dose of 4 mmol/kg/d) was varied dependent on development of hyponatraemia*. Potassium levels (2 mmol/kg/d). No large fluctuations of potassium were evident. Caloric content of solution: 97 kcal/kg/day with a standard protein intake of 2.5 g/kg/day, lipid at 3 g/kg/day, and fluid intake between 150 and 200 ml/kg/day depending on clinical circumstances. Power analysis Required sample size of 29 per treatment group to ensure 80% power to detect a significant difference in the reduction in incidence of hyperchloraemia from around 90% to 60%.	Results Hyperchloraemia (>155 mmol/l) - number (%) Standard (n=30): 23 (77) Intervention (n=28): 7 (25) Mortality - number Standard: 2 Intervention: 4	Limitations Cochrane risk of bias tool Selection bias: Random sequence generation: Low risk (Randomisation in blocks of 2 or 4, themselves randomly arranged). Allocation concealment: Low risk. (Assignment performed using sealed envelopes stratified into 2 groups; <1 kg and ≥1 kg). Performance bias: Blinding of participants and personnel: Low risk (Assignment made at a separate hospital and pharmacy staff unaware of clinical state of each child). Detection bias Blinding of outcome assessment: Unclear risk (Clinical staff could not be blinded to the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the effects of acetate on acid base status, ventilation, use of plasma volume expanders, inotropes and sodium bicarbonate therapy. Study dates Not stated Source of funding North West Regional Health authority Research Funding Scheme	Standard: 2 Intervention: 4 Inclusion criteria Preterm neonates < 32 weeks' gestation, receiving IV glucose/electrolyte solution on day 3 but not enteral nutrition. Exclusion criteria Infants with major malformations.		Statistical analyses Where continuous outcomes were normally distributed, data were presented as means (SD) and comparisons between treatment groups performed using Student's t test. Where data were not normally distributed, medians (range) were presented and comparisons made using the Mann-Whitney U test. X2 tests were used to analyse proportional data.		outcomes due to safety reasons). Attrition bias Incomplete outcome data: High risk (5 infants transferred out before end of trial (Intervention group: n=3; Standard group: n=2; <10% attrition, but suggests the trial would be underpowered: Intervention group: n=25; Standard group: n=28)). Reporting bias Selective reporting: Low risk. All outcomes reported. Other bias Other sources of bias: Low risk. Other information Treatment groups balanced across significant baseline characteristics. *There was no difference in plasma sodium concentration between the treatment groups at any time.
Full citation Richards, C. E., Drayton, M., Jenkins, H.,	Sample size N = 59	Interventions Original formulation group: PN	Details A glucose/electrolyte/trace element mixture was developed. This mixture formed	Results Original formulation group	Limitations Risk of Bias assessment (ROBINS-I)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Peters, T. J., Effect of different chloride infusion rates on plasma base excess during neonatal parenteral nutrition, Acta paediatrica (Oslo, Norway : 1992), 82, 678-82, 1993 Ref Id 797396 Country/ies where the study was carried out UK Study type Observational study (Retrospective, historical, cohort study). Aim of the study To investigate the potential benefits of reducing the chloride infusion rate in the sick parenterally fed newborn infants.	Original formulation group (chloride based PN): n=28 New formulation group (acetate based PN): n=31 Characteristics Original formulation: Chloride (50mmol/l), phosphate (5.5mmol/l), sodium (27.3mmol/l), potassium (17.6mmol/l), calcium (4.1mmol/l), magnesium (0.9mmol/l), non-metabolisable base (-4.91mmol/l, a positive concentration of non-metabolisable acid). New formulation: Chloride (32.4mmol/l), phosphate (7.3mmol/l), acetate(14.5mmol/l), gluconate (7.3mmol/l), sodium (27.3mmol/l), potassium (17.6mmol/l), calcium (7.3mmol/l), magnesium (0.9mmol/l), non-metabolisable base (8.51mmol/l, a negative concentration of non-metabolisable acid). Participants' characteristics (original formulation group): mean (SD) Weight(kg): 1.52 (0.92)	including acetate supplementary to chloride. New formulation group: PN including only chloride.	the basis of all PN regimens. Individual infant regimens were compounded by incorporating on a volume per kg basis (1) the glucose/electrolyte/trace element mixture, (2) an amino acid source and (3) water-soluble vitamins. When required, lipid-soluble vitamins were supplied in a separate syringe. The volume of parenteral feed infused per day was increased in a step-wise fashion over the nine days of life. A slight bias towards lower gestation and birth weight in the group receiving the original formulation was observed. Gestation was entered into the analysis as a covariate. Controlling for gestation, the mean plasma chloride level was 4.8mmol/l lower in the new formulation group than in the original formulation group. The 95%CI for this adjusted difference between the two groups was 2.5-7.2mmol/l. There was an inverse relationship in both groups between plasma chloride values	(control): mean (SD) pH: 7.31(0.04) Base excess: -2.79 (2.36) New formulation group (intervention): mean (SD) pH: 7.35 (0.05) Base excess: 0.99 (3.18)	Bias due to confounding: low risk (all the know confounding factors were entered into the analysis) Bias in selection of participants into the study: serious risk (start of the follow-up and start of intervention were not coincided). Bias in classification of interventions: serious risk (data of historic control participants was collected while the new intervention was being prepared). Bias due to deviations from intended interventions: low-risk Bias due to missing data: Unclear Bias in measurement of outcomes: low-risk Bias in selection of the reported results: moderate-risk Overall bias: serious-risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported Source of funding Not reported	Gestational age (weeks): 31 (4.5) Days on TPN: 10 Ventilated: unventilated: 23:5 Participants' characteristics (new formulation group): mean (SD) Weight(kg): 1.88 (0.87) Gestational age (weeks): 32.5 (4.7) Days on TPN: 8 Ventilated: unventilated: 25:6 Infants were studied from day 1 to day 7 after birth. Data of control group was collected over a 9-month period while the new formulation was being prepared. Data of the intervention group was prospectively collected. Inclusion criteria term, preterm, medical and surgical infants only infants who received TPN exclusively Exclusion criteria Not reported		and gestational age, with no statistically significant differences between the gradients. The mean base excess level was 3.1mmol/l higher in the new formulation group than in the original formulation group. The 95%CI for this adjusted difference was 1.9-4.8 mmol/l. There was a direct relationship between base excess values and gestational age, with again no statistically significant difference between the gradients in the two groups.		

IV: intravenous; PN: parenteral nutrition; RCT: randomised controlled trial; ROBINS-I: risk of bias in non-randomised studies of interventions; SD: standard deviation; TPN: total parenteral nutrition; UK: United Kingdom.

Appendix E – Forest plots

Forest plots for review question: Evidence review for IV acetate: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

No meta-analysis was conducted for this review; therefore there are no forest plots

Appendix F – GRADE tables

GRADE tables for review question: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 5: Clinical evidence profile for comparison of chloride-based only PN regimen versus acetate-based PN regimen.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetate	Chloride	Relative (95% CI)	Absolute	Quality	Importance
Hyperchloraemia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/28 (25%)	23/30 (76.7%)	RR 0.33 (0.17 to 0.64)	514 fewer per 1000 (from 276 fewer to 636 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Mortality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/28 (14.3%)	2/30 (6.7%)	RR 2.14 (0.43 to 10.8)	76 more per 1000 (from 38 fewer to 653 more)	⊕OOO VERY LOW	IMPORTANT
pH (Better indicated by lower values)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	31	28	-	MD 0.04 higher (0.02 to 0.06 higher)	⊕OOO VERY LOW	CRITICAL
Mean Difference (pH) - Day 5 (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	28	30	-	MD 0.05 higher (0.01 to 0.09 higher)	⊕⊕OO LOW	CRITICAL
Mean Difference (pH) - Day 10 (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	28	30	-	MD 0.06 higher (0.02	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetate	Chloride	Relative (95% CI)	Absolute	Quality	Importance
										to 0.1 higher)		
Base excess (Better indicated by lower values)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31	28	-	MD 3.96 higher (2.54 to 5.38 higher)	⊕OOO VERY LOW	CRITICAL
Mean difference (base excess) - Day 5 (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28	30	-	MD 3.6 higher (2.03 to 5.17 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean difference (base excess) - Day 10 (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28	30	-	MD 9.9 higher (5.98 to 13.82 higher)	⊕⊕⊕O MODERATE	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio.

[1] *Serious risk of bias due to unclear risk of detection bias, and unclear risk of attrition bias.*

[2] *Evidence was downgraded due to very serious imprecision, 95% confidence interval crosses both default MID for dichotomous outcomes (0.8 and 1.25).*

[3] *Evidence downgraded due to serious risk of bias, unclear missing data bias, and moderate risk of reporting bias, selection of participants and classification of interventions.*

[4] *Evidence was downgraded due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.02).*

[5] *Evidence was downgraded due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.04).*

[6] *Evidence was downgraded due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.04).*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: How much (if any) intravenous acetate should be provided to 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: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

No evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

No evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic analysis for review question: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 6 Excluded studies for intravenous acetate review

Study	Reason for Exclusion
Blanco, C. L., Falck, A., Green, B. K., Cornell, J. E., Gong, A. K., Metabolic Responses to Early and High Protein Supplementation in a Randomized Trial Evaluating the Prevention of Hyperkalemia in Extremely Low Birth Weight Infants, Journal of Pediatrics, 153, 535-540, 2008	Study intervention does not meet protocol eligibility criteria - Sodium acetate infusion levels recorded as outcomes for the two intervention groups (high amino acid group versus standard amino acid group), but not clear how this impacted on the outcomes.
Ekblad, H., Kero, P., Takala, J., Slow sodium acetate infusion in the correction of metabolic acidosis in premature infants, American journal of diseases of children (1960), 139, 708-10, 1985	Study design does not meet protocol eligibility criteria - non-comparative study; case series.
Friedman, C. A., Wender, D. F., Temple, D. M., Parks, B. R., Rawson, J. E., Serum alpha-tocopherol concentrations in preterm infants receiving less than 25 mg/kg/day alpha-tocopherol acetate supplements, Developmental pharmacology and therapeutics, 11, 273-80, 1988	Does not meet protocol's eligibility criteria for being included in this review: - it's not a comparative study - enteral feeding was received - addresses none of the outcomes of interest.
Gutcher, G. R., Farrell, P. M., Early intravenous correction of vitamin E deficiency in premature infants, Journal of Pediatric Gastroenterology and Nutrition, 4, 604-9, 1985	Study design does not meet protocol eligibility criteria - non-comparative study; includes children aged up to 16 years.
Janjua, Halima S., Mahan, John D., Patel, Hiren P., Mentser, Mark, Schwaderer, Andrew L., Continuous infusion of a standard combination solution in the management of hyperkalemia, Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 26, 2503-8, 2011	Study design not relevant to protocol. Study outcomes do not meet protocol eligibility criteria.
Janssen, Lisanne M. A., Tostmann, Alma, Hopman, Joost, Liem, Kian D., 0.2% chlorhexidine acetate as skin disinfectant prevents skin lesions in extremely preterm infants: a preliminary report, Archives of disease in childhood. Fetal and neonatal edition, 103, F97-F100, 2018	Study intervention does not meet protocol eligibility criteria - skin disinfectant; not acetate administered as part of PN.
Laine, L., Shulman, R. J., Pitre, D., Lifschitz, C. H., Adams, J., Cysteine usage increases the need for acetate in neonates who receive total parenteral	Study outcomes do not meet protocol eligibility criteria - pH levels assessed in vitro; baseline acetate levels similar in both treatment groups (cysteine vs no cysteine groups).

nutrition, American Journal of Clinical Nutrition, 54, 565-567, 1991	
Larsson, L. E., Nilsson, K., Niklasson, A., Andreasson, S., Ekstrom-Jodal, B., Influence of fluid regimens on perioperative blood-glucose concentrations in neonates, British Journal of Anaesthesia, 64, 419-424, 1990	Study intervention does not meet protocol eligibility criteria - all infants receive Ringer-acetate at different time points, difference in addition or not of glucose at different time points.
Obara, H., Maekawa, N., Hoshino, H., Plasma levels of vitamin E and lipoperoxide during paediatric anaesthesia, Canadian Anaesthetists Society Journal, 32, 358-363, 1985	Study intervention does not meet protocol eligibility criteria - acetate not provided as part of PN.
Ricci, Zaccaria, Haiberger, Roberta, Pezzella, Chiara, Garisto, Cristiana, Favia, Isabella, Cogo,	Study intervention does not meet protocol eligibility criteria - does not include acetate infusion.
Sandstrom, K., Nilsson, K., Andreasson, S., Niklasson, A., Larsson, L. E., Metabolic consequences of different perioperative fluid therapies in the neonatal period, Acta Anaesthesiologica Scandinavica, 37, 170-5, 1993	Study intervention does not meet protocol eligibility criteria - Ringer acetate administered at different time points; doesn't appear to be infused as part of PN; assessed none of the outcomes of interest.
Schwalbe, P., Buttner, P., Elmadfa, I., Development of vitamin-E-status of premature infants after intravenous application of all-rac-alpha-tocopheryl acetate, International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition, 62, 9-14, 1992	Study outcomes do not meet protocol eligibility criteria.

Economic studies

No economic evidence was identified for this review. See supplementary material D for further information.

Appendix L – Research recommendations

Research recommendations for review question: How much (if any) intravenous acetate should be provided to preterm and term babies who are receiving parenteral nutrition and neonatal care?

No research recommendations were made for this review.