National Institute for Health and Care Excellence

Draft for consultation

Neonatal parenteral nutrition

[F] Monitoring neonatal parenteral nutrition

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:

Contents

Optimal frequency of blood sampling and monitoring in babies on parenteral nutrition

Review question

In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring of glucose, calcium, phosphate, potassium, and serum triglycerides?

Introduction

Blood monitoring of babies who are on parenteral nutrition (PN) is required to ensure detection of any potential abnormalities. Frequency of testing should be performed at a rate sensitive to detect any changes in critical parameters, yet at a rate which minimises patient burden and which does not increase risk of adverse events. Currently there is variation across practice; therefore, the aim of this review is to determine the optimal frequency of blood sampling in babies on PN.

Summary of the protocol

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

Table 1: Summary of 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	• Monitoring of blood parameters, to include: glucose, calcium, phosphate, potassium, and serum triglycerides. Parameter(s) should be monitored at a particular frequency (i.e. daily).
Comparator	• Alternative frequency of monitoring (i.e. weekly).

Outcomes	**Critical**
	• Detection of:
	  ○ Abnormal calcium and phosphate levels (hypercalcaemia/hypocalcaemia, hyperphosphataemia/hypophosphataemia)
	  ○ Hyperglycaemia/hypoglycaemia
	  ○ Hypertriglyceridemia
	• Bloodstream infections
	• Alteration of PN
	• Anaemia
	
	Important
	• Mortality
	• Parental satisfaction (measured by validated scale)
	• Blood-sampling related neonatal distress (measured by validated score)

PN: parenteral nutrition

For further details see the full review protocol in appendix A.

Clinical evidence

Included studies

A systematic review of the clinical literature was conducted but no studies were identified which were applicable to this review question.

See the literature search strategy in appendix B and the study selection flow chart in appendix C.

Excluded studies

Studies excluded from this review are listed, and reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

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

Quality assessment of clinical studies included in the evidence review

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

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

This question was identified as a priority for economic modelling. However, clinical data was insufficient to inform the economic analysis.

Evidence statements

Clinical Evidence statements

No clinical studies were found which were applicable to this review question.

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

A number of critical outcomes, including abnormal levels of calcium and phosphate, bloodstream infections, anaemia, hyper/hypokalaemia, hyper/hypoglycaemia and hypertriglyceridemia were prioritised by the committee due to their clinical importance. These outcomes are likely to be affected by the frequency of blood monitoring, where more frequent blood monitoring may reduce the risk of occurrence. The alteration of PN was also included as monitoring is likely to influence whether the PN is altered or not. More frequent blood monitoring may result in reduced parenteral satisfaction and increased neonatal distress; therefore, these two outcomes were selected as important outcomes. Mortality was also selected as an important outcome but it was acknowledged that multiple factors are likely to influence mortality.

The quality of the evidence

No clinical evidence was identified for this review.

Benefits and harms

No clinical evidence was identified so all recommendations were made based on the experience and expertise of the committee by informal consensus.

General considerations

The committee agreed that there should be a balance between over sampling and under sampling of blood monitoring. Blood monitoring should occur at an optimum frequency to ensure a low risk of adverse events and minimise distress to the baby, this means taking the smallest amount of blood that is needed for the required tests. To ensure that babies would not be sampled too frequently the committee also agreed that it was important to set up a good working relationship with the laboratory supporting the neonatal unit, and to discuss how to get the most information out of the least samples. To facilitate this relationship the committee agreed that it is good practice to develop an agreed protocol with the laboratory to ensure the minimum sample can be taken that will still enable the required tests to be conducted.

The committee discussed how babies experience pain and discomfort from repeated blood sampling. Babies' heels become sore and babies may become reluctant to have their feet handled. The distress of parents was also discussed when a baby is frequently sampled, the committee acknowledge it can be upsetting for parents or carers to see their baby repeatedly tested. Therefore, sampling should be carried out in a co-ordinated manner, meaning one sample is used to conduct as many of the tests as needed, ensuring minimum frequency of sampling. Again, this co-ordination should be between those taking the bloods and the laboratory personnel.

Individual components

In general the committee recommended, by informal consensus, minimum frequencies for monitoring parameters, but they also described situations when increased monitoring may be needed (for example, when there is a change in the composition of parenteral nutrition or when the baby is unstable or there are other clinical concerns).

Blood glucose

The committee agreed that glucose should be monitored when starting parenteral nutrition and at every change of the bag, for safety reasons. Initial monitoring needs to be carried out within the first 2 hours of starting PN because hypo or hyperglycaemia can occur quickly and

can be life threatening. After that, monitoring should depend on the stability of the baby – that is, an unstable glucose level should be monitored more frequently because of the risks associated with hyperglycaemia or hypoglycaemia.

Blood pH, serum potassium, chloride and calcium

The committee agreed that blood pH, serum potassium, chloride and calcium would usually need to be monitored when starting and when increasing parenteral nutrition. If the baby is stable and the maintenance dosage has been reached the committee agreed based on experience that twice weekly monitoring for these components is sufficient and safe. Blood pH is important for a number of reasons, for example, chloride levels cannot be interpreted without knowing the pH, and it is also informative when titrating acetate. More frequent monitoring may be necessary if dosages have changed or if the baby had abnormal levels in a previous blood test (to see whether levels have normalised). The committee agreed that a degree of clinical judgement is necessary when determining whether more frequent monitoring may be needed, for instance levels and needs may fluctuate when a baby is critically ill.

Serum triglycerides

The committee discussed the variability in monitoring triglycerides in clinical practice, where some neonatal units monitor more or less frequently, and some neonatal units do not monitor triglycerides at all. The committee discussed how some units work closely with the laboratory requesting that the lipaemic index of samples are measured and reported, and that if a level is demonstrated that suggests triglyceridemia, the unit is informed and a blood triglyceride test is taken. This is aimed at reducing the amount of unnecessary triglyceride testing that is undertaken. They therefore decided to recommend, by informal consensus, more frequent monitoring if high levels of serum triglycerides had already been detected or if clinical concerns were raised (one of which could be the blood sample being lipaemic). The committee agreed that recommendations would be useful to improve consistency across clinical practice. They agreed that triglycerides should be monitored when increasing dosages of lipid, because they were aware of evidence that suggests that around 10% of babies do not tolerate recommended intakes of lipids. Monitoring should continue when the maintenance dosage is reached. The committee agreed that when a baby is unstable, triglycerides should be monitored more frequently to ensure the safety of the baby.

Serum or plasma phosphate

The committee agreed that phosphate would initially require daily monitoring because amino acid intake affects phosphate levels and amino acid intake changes every day for the first 4 days of parenteral nutrition. After the maintenance dosage is reached the committee decided that monitoring at a frequency of once a week would be safe unless there are other considerations that would require more frequent monitoring such as previous abnormal levels, other clinical concerns directly relevant to phosphate levels (concerns about bone development) or the babies are below 32 weeks' gestation (because 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).

Iron status

The committee decided that iron supplementation is not needed in babies who are younger than 28 days. Therefore, they agreed that initial monitoring would not be needed. The committee noted that a number of different factors could affect iron status in babies on parenteral nutrition for longer than 28 days, including the number of transfusions administered as well as the amount of enteral nutrition achieved. It is therefore important to

measure ferritin, and iron and transferrin saturations for babies who remain on parenteral nutrition after this time.

Liver function

The committee agreed that it was important to monitor liver function for safety reasons. Abnormal liver function tests could indicate the onset of parenteral nutrition-associated liver disease, so the committee agreed it was important to carry out regular liver function tests for babies on parenteral nutrition. They agreed that it would usually be sufficient to do this on a weekly basis, but if a baby had previous abnormal levels or there are other concerns that may be related to liver function testing should be carried out more frequently.

Cost effectiveness and resource use

There was no economic evidence on the cost-effectiveness of the frequency of blood sampling and monitoring of glucose, calcium, phosphate, potassium, and serum triglycerides in babies on PN.

Too frequent blood sampling causes distress to both the baby and parents. Combining tests wherever possible is recommended and this has the potential to reduce the frequency of blood sampling and the associated blood sampling costs, and also lead to less distress to both the baby and parents (i.e. result in an increase in QALYs). Similarly, the engagement with the laboratory has the potential to lead the smaller blood sampling volumes and potentially lead to the reduction in the blood sampling costs.

There is variability in the monitoring of triglycerides in clinical practice where some neonatal units monitor more or less frequently, and some neonatal units do not monitor triglycerides at all. The recommendations on triglycerides monitoring may change clinical practice in some neonatal units and result in resource implications. However, the committee expressed their view that the cost of sampling will be outweighed by the avoidance of potential adverse events e.g. the committee discussed cases of baby mortality that have previously occurred when the amounts of glucose and triglycerides were amended. The committee explained that the monitoring costs of triglycerides could be reduced by engaging laboratories. For example, the strategy where the monitoring of triglycerides is undertaken only where lipaemic index exceeds a certain threshold. The committee explained that lipaemic index is generally done for every sample (although not always routinely reported by the laboratory) and there would be no additional resource implications. However, there is uncertainty in what the trigger threshold should be. Although, each laboratory should be able to work out the correlation between lipaemic index and the level of triglycerides. Such selective strategy (engagement of laboratories) could potentially reduce the costs associated with monitoring.

In summary, the committee were of a view that blood sampling and monitoring of the specified constituents is essential in ensuring good outcomes in babies on PN. However, monitoring of these constituents is already done in neonatal units and standardising the frequency of measurements would not have significant resource implications.

Other factors the committee took into account

The committee agreed that point of care testing would be the best method to limit distress to the baby while returning the maximum amount of required measurements. It was acknowledged by the committee that not all United Kingdom neonatal units will have in-house access to blood gas machines with the necessary capability to perform point of care testing for a range of parameters. However, wherever possible, point of care testing should be implemented. The committee agreed that this would allow blood sampling for glucose, calcium, phosphate, potassium, and serum triglycerides to be combined with any other blood sampling required for the provision of neonatal intensive care. This is to minimise the number of samples and volume of blood taken. However, due to the costs associated with new point

of care testing technology and the lack of evidence for more effective testing with these kits the committee did not recommend this.

The committee acknowledge the relationship between the frequency of monitoring and the use of standardised bags (see section 1.5 of the guideline and evidence review G – standardised neonatal PN formulations). The committee discussed the higher potential risks associated with bespoke bags compared to standardised bags. In bespoke bags, macronutrients such as lipids, and other constituents such as electrolytes will all be individually prescribed, and this in turn may increase the chance of prescribing errors. In addition, as prescriptions of constituents are more varied, more frequent blood monitoring may be required when using bespoke bags. The committee acknowledged that unstable babies are the population most likely to require bespoke bags. Across most of the tests recommendations that unstable babies (i.e. those where previous high levels were identified, those where concerns were raised or those who are critically ill) should be monitored more frequently for safety reasons were made by the committee by informal consensus.

References

No studies were identified for this review.

Appendices

Appendix A – Review protocol

Review protocol for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

Table 2: Review protocol for monitoring and frequency

Field (based on PRISMA-P)	Content
Review question	In babies on parenteral nutrition, what is the optimal frequency of blood sampling for monitoring glucose, calcium, phosphate, potassium, and serum triglycerides
Type of review question	Intervention
Objective of the review	Blood monitoring of babies on PN is required to ensure detection of any potential abnormalities. Frequency of testing should be performed at a rate sensitive to detect any changes in critical parameters, yet at a rate which minimises patient burden and which does not increase risk of adverse events. Currently there is variation across practice in the frequency of blood monitoring; therefore, the aim of this review is to determine the optimal frequency of blood sampling in babies on 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)	• Monitoring of blood parameters, to include: glucose, calcium, phosphate, potassium, and serum triglycerides. Parameter(s) should be monitored at a particular frequency (i.e. daily). These parameters have been specified as they are routinely monitored in current practice.
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Alternative frequency of monitoring (i.e. weekly)

Outcomes and prioritisation	**Critical**
	• Detection of:
	  ○ Abnormal calcium and phosphate levels (hypercalcaemia/hypocalcaemia, hyperkalaemia/hypokalaemia)
	  ○ Hyperglycaemia/Hypoglycaemia
	  ○ Hypertriglyceridemia
	• Bloodstream infections
	• Alteration of PN (alteration in delivery due to findings of the monitoring)
	• Anaemia

Field (based on PRISMA-P)	Content
	Important • Mortality • Parental satisfaction (measured by validated scale) • Blood-sampling related neonatal distress (measured by validated score)
Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making). The decision to include comparative cohort studies will be determined for each parameter according to available RCTs data Conference abstracts of RCT 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 No date restriction
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analysis • 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: • Duration of PN (for example first 2 weeks *vs*. later) • Preterm (extremely preterm <28 weeks' GA; very preterm: 28-31 weeks' GA; moderately preterm: 32-36 weeks' GA) • Birth weight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) • 24hr versus 48 hour PN bag • Critically ill babies or those requiring surgery (for example, inotropic support, therapeutic hypothermia or fluid restriction) • Standardised *vs.* individualised bags Possible equality considerations

Field (based on PRISMA-P)	Content
	• Mothers aged 17 or below • Parents or carers whose first language is not English • Parents or carers who have learning difficulties Important confounders (when comparative observational studies are included for interventional reviews): • Age of baby (first 2 weeks *vs.* later) • Preterm (Very early <28 weeks' GA; 28-31 weeks' GA; 32-36 weeks' GA) • Birth weight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) • Time of day monitoring occurred
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 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 will be resolved by discussion between the two reviewers. The senior systematic reviewer or guideline lead will act as arbiter where necessary.
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).
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 https://www.nice.org.uk/guidance/indevelopment/gid-ng10037

Field (based on PRISMA-P)	Content
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.
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.
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 NGA 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

Field (based on PRISMA-P)	Content
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	The review is not registered with PROSPERO

CCTR: Cochrane controlled trials register; 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; NICE: National Institute of Clinical Excellence; NGA: National Guideline Alliance; NHS: National Health Service; PN: Parenteral nutrition; PROSPERO: International prospective register of systematic reviews; RCT: randomised controlled trial; ROBIS; risk of bias in systematic reviews;.

Appendix B – Literature search strategies

Literature search strategy for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

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/ and (nutrition$ or feed$ or fed$).ti,ab.
19	INFUSIONS, INTRAVENOUS/ and (nutrition$ or feed$ or fed$).ti,ab.
20	CATHETERIZATION, CENTRAL VENOUS/ and (nutrition$ or feed$ or fed$).ti,ab.
21	exp CATHETERIZATION, PERIPHERAL/ and (nutrition$ or feed$ or fed$).ti,ab.
22	((parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
23	((peripheral$ or central$) adj3 line? adj3 (nutrition$ or feed$ or fed$)).ti,ab.
24	(catheter$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
25	(drip? adj3 (nutrition$ or feed$ or fed$)).ti,ab.
26	or/15-25
27	BLOOD SPECIMEN COLLECTION/
28	(blood? adj5 (sampl$ or specimen? or collect$ or test$ or monitor$)).ti,ab.
29	PUNCTURES/
30	(heel adj3 (lanc$ or stick$ or prick$)).ti,ab.
31	(heellanc$ or heelstick? or heelprick$).ti,ab.
32	((arter$ or vein or venous or capillar$) adj3 punctur$).ti,ab.
33	Venepunctur$.ti,ab.
34	or/27-33
35	exp GLUCOSE/
36	(glucose or sugar? or dextrose).mp.
37	CALCIUM/
38	calcium.mp.
39	exp PHOSPHATES/
40	PHOSPHORUS/
41	PHOSPHORUS, DIETARY/
42	(Phosph$ 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.
43	exp POTASSIUM/
44	exp POTASSIUM, DIETARY/
45	potassium.mp.
46	exp TRIGLYCERIDES/
47	(triglyceride? or triacylglycerol? or triacetin or triolein).mp.
48	or/35-47
49	TIME FACTORS/ and MONITORING, PHYSIOLOGIC/
50	((frequen$ or regular$ or routine$) adj5 (sampl$ or specimen? or collect$ or test$ or monitor$ or investigat$)).ti,ab.
51	((day? or daily or hour$ or week$) adj5 (sampl$ or specimen? or collect$ or test$ or monitor$ or investigat$)).ti,ab.
52	((repetition or repeat$ or rate? or amount?) adj5 (sampl$ or specimen? or collect$ or test$ or monitor$ or investigat$)).ti,ab.
53	(number? adj5 (sampl$ or specimen? or collect$ or test$ or monitor$ or investigat$)).ti,ab.

#	Searches
54	or/49-53
55	BLOOD GLUCOSE/
56	CALCIUM/bl [Blood]
57	exp PHOSPHATES/bl [Blood]
58	PHOSPHORUS/bl [Blood]
59	PHOSPHORUS, DIETARY/bl [Blood]
60	exp POTASSIUM/bl [Blood]
61	exp POTASSIUM, DIETARY/bl [Blood]
62	exp TRIGLYCERIDES/bl [Blood]
63	(blood? adj3 (glucose or calcium or phosph$ or potassium$ or triglyceride?)).ti,ab.
64	or/55-63
65	(sampl$ or specimen?).ti,ab.
66	BLOOD SPECIMEN COLLECTION/mt [Methods]
67	BLOOD SPECIMEN COLLECTION/ae [Adverse Effects]
68	14 and 26 and 34 and 48
69	14 and 26 and 34 and 54
70	14 and 26 and 64 and 65
71	14 and 26 and 66
72	14 and 26 and 67
73	or/68-72
74	limit 73 to english language
75	LETTER/
76	EDITORIAL/
77	NEWS/
78	exp HISTORICAL ARTICLE/
79	ANECDOTES AS TOPIC/
80	COMMENT/
81	CASE REPORT/
82	(letter or comment*).ti.
83	or/75-82
84	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
85	83 not 84
86	ANIMALS/ not HUMANS/
87	exp ANIMALS, LABORATORY/
88	exp ANIMAL EXPERIMENTATION/
89	exp MODELS, ANIMAL/
90	exp RODENTIA/
91	(rat or rats or mouse or mice).ti.
92	or/85-91
93	74 not 92

1

2 **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/ and (nutrition$ or feed$ or fed$).ti,ab.
20	exp INTRAVENOUS CATHETER/ and (nutrition$ or feed$ or fed$).ti,ab.
21	((parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj3 (nutrition$ or feed$ or fed$)).ti,ab.

#	Searches
22	((peripheral$ or central$) adj3 line? adj3 (nutrition$ or feed$ or fed$)).ti,ab.
23	(catheter$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
24	(drip? adj3 (nutrition$ or feed$ or fed$)).ti,ab.
25	or/14-24
26	BLOOD SAMPLING/
27	(blood? adj5 (sampl$ or specimen? or collect$ or test$ or monitor$)).ti,ab.
28	(heel adj3 (lanc$ or stick$ or prick$)).ti,ab.
29	(heellanc$ or heelstick? or heelprick$).ti,ab.
30	((arter$ or vein or venous or capillar$) adj3 punctur$).ti,ab.
31	Venepunctur$.ti,ab.
32	or/26-31
33	GLUCOSE/
34	(glucose or sugar? or dextrose).mp.
35	CALCIUM/
36	calcium.mp.
37	PHOSPHATE/
38	PHOSPHORUS/
39	PHOSPHATE INTAKE/
40	(Phosph$ 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.
41	POTASSIUM/
42	POTASSIUM INTAKE/
43	potassium.mp.
44	TRIACYLGLYCEROL/
45	(triglyceride? or triacylglycerol? or triacetin or triolein).mp.
46	or/33-45
47	TIME FACTOR/ and (PHYSIOLOGIC MONITORING/ or MONITORING/)
48	((frequen$ or regular$ or routine$) adj5 (sampl$ or specimen? or collect$ or test$ or monitor$ or investigat$)).ti,ab.
49	((day? or daily or hour$ or week$) adj5 (sampl$ or specimen? or collect$ or test$ or monitor$ or investigat$)).ti,ab.
50	((repetition or repeat$ or rate? or amount?) adj5 (sampl$ or specimen? or collect$ or test$ or monitor$ or investigat$)).ti,ab.
51	(number? adj5 (sampl$ or specimen? or collect$ or test$ or monitor$ or investigat$)).ti,ab.
52	or/47-51
53	GLUCOSE BLOOD LEVEL/
54	CALCIUM BLOOD LEVEL/
55	PHOSPHATE BLOOD LEVEL/
56	PHOSPHORUS BLOOD LEVEL/
57	POTASSIUM BLOOD LEVEL/
58	TRIACYLGLYCEROL BLOOD LEVEL/
59	(blood? adj3 (glucose or calcium or phosph$ or potassium$ or triglyceride?)).ti,ab.
60	or/53-59
61	(sampl$ or specimen?).ti,ab.
62	13 and 25 and 32 and 46
63	13 and 25 and 32 and 52
64	13 and 25 and 60 and 61
65	or/62-64
66	limit 65 to english language
67	letter.pt. or LETTER/
68	note.pt.
69	editorial.pt.
70	CASE REPORT/ or CASE STUDY/
71	(letter or comment*).ti.
72	or/67-71
73	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
74	72 not 73
75	ANIMAL/ not HUMAN/
76	NONHUMAN/
77	exp ANIMAL EXPERIMENT/
78	exp EXPERIMENTAL ANIMAL/
79	ANIMAL MODEL/
80	exp RODENT/
81	(rat or rats or mouse or mice).ti.
82	or/74-81
83	66 not 82

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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
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	#18 or #19 or #20 or #21
23	(nutrition* or feed* or fed*):ti,ab
24	#22 and #23
25	((parenteral* or intravenous* or intra-venous* or IV or venous* or infusion?) near/3 (nutrition* or feed* or fed*)):ti,ab
26	((peripheral* or central*) near/3 line? near/3 (nutrition* or feed* or fed*)):ti,ab
27	(catheter* near/3 (nutrition* or feed* or fed*)):ti,ab
28	(drip? near/3 (nutrition* or feed* or fed*)):ti,ab
29	#15 or #16 or #17 or #24 or #25 or #26 or #27 or #28
30	MeSH descriptor: [BLOOD SPECIMEN COLLECTION] this term only
31	(blood? near/5 (sampl* or specimen? or collect* or test* or monitor*)):ti,ab
32	MeSH descriptor: [PUNCTURES] this term only
33	(heel near/3 (lanc* or stick* or prick*)):ti,ab
34	(heellanc* or heelstick? or heelprick*):ti,ab
35	((arter* or vein or venous or capillar*) near/3 punctur*):ti,ab
36	Venepunctur*:ti,ab
37	#30 or #31 or #32 or #33 or #34 or #35 or #36
38	MeSH descriptor: [GLUCOSE] explode all trees
39	(glucose or sugar? or dextrose):ti,ab
40	MeSH descriptor: [CALCIUM] this term only
41	calcium:ti,ab
42	MeSH descriptor: [PHOSPHATES] explode all trees
43	MeSH descriptor: [PHOSPHORUS] this term only
44	MeSH descriptor: [PHOSPHORUS, DIETARY] this term only
45	(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
46	MeSH descriptor: [POTASSIUM] explode all trees
47	MeSH descriptor: [POTASSIUM, DIETARY] explode all trees
48	potassium:ti,ab
49	MeSH descriptor: [TRIGLYCERIDES] explode all trees
50	(triglyceride? or triacylglycerol? or triacetin or triolein):ti,ab
51	#38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
52	MeSH descriptor: [TIME FACTORS] this term only
53	MeSH descriptor: [MONITORING, PHYSIOLOGIC] this term only
54	#52 and #53
55	((frequen* or regular* or routine*) near/5 (sampl* or specimen? or collect* or test* or monitor* or investigat*)):ti,ab
56	((day? or daily or hour* or week*) near/5 (sampl* or specimen? or collect* or test* or monitor* or investigat*)):ti,ab
57	((repetition or repeat* or rate? or amount?) near/5 (sampl* or specimen? or collect* or test* or monitor* or investigat*)):ti,ab
58	(number? near/5 (sampl* or specimen? or collect* or test* or monitor* or investigat*)):ti,ab
59	#54 or #55 or #56 or #57 or #58
60	MeSH descriptor: [BLOOD GLUCOSE] this term only

#	Searches
61	MeSH descriptor: [CALCIUM] this term only and with qualifier(s): [Blood - BL]
62	MeSH descriptor: [PHOSPHATES] this term only and with qualifier(s): [Blood - BL]
63	MeSH descriptor: [PHOSPHORUS] this term only and with qualifier(s): [Blood - BL]
64	MeSH descriptor: [PHOSPHORUS, DIETARY] this term only and with qualifier(s): [Blood - BL]
65	MeSH descriptor: [POTASSIUM] this term only and with qualifier(s): [Blood - BL]
66	MeSH descriptor: [POTASSIUM, DIETARY] this term only and with qualifier(s): [Blood - BL]
67	MeSH descriptor: [TRIGLYCERIDES] this term only and with qualifier(s): [Blood - BL]
68	(blood? near/3 (glucose or calcium or phosph* or potassium* or triglyceride?)):ti,ab
69	#60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68
70	(sampl* or specimen?):ti,ab
71	MeSH descriptor: [BLOOD SPECIMEN COLLECTION] this term only and with qualifier(s): [Methods - MT]
72	MeSH descriptor: [BLOOD SPECIMEN COLLECTION] this term only and with qualifier(s): [Adverse effects - AE]
73	#14 and #29 and #37 and #51
74	#14 and #29 and #37 and #59
75	#14 and #29 and #69 and #70
76	#14 and #29 and #71
77	#14 and #29 and #72
78	#73 or #74 or #75 or #76 or #77

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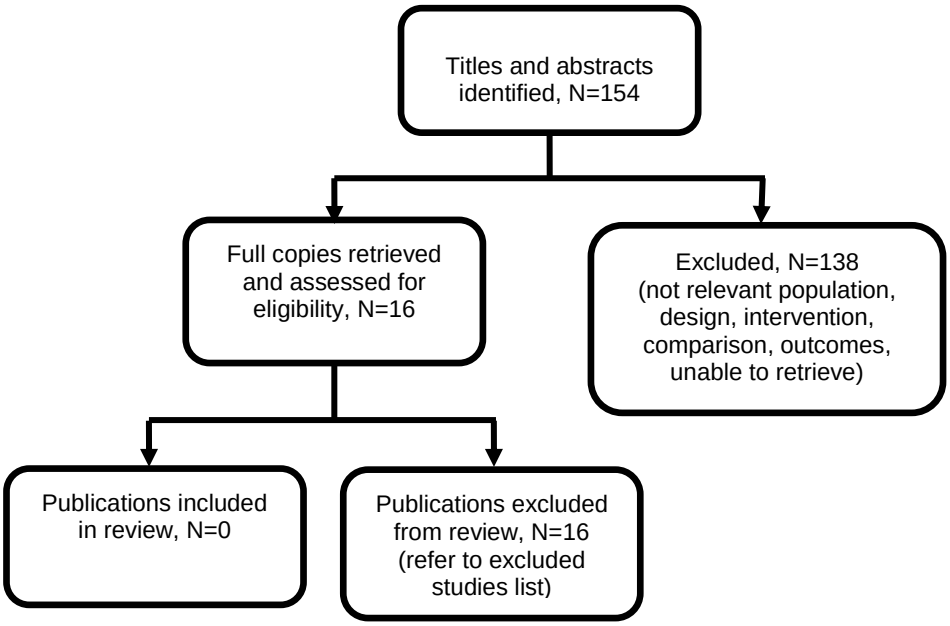
Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

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

Appendix E – Forest plots

Clinical evidence forest plots for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

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

Appendix F – GRADE tables

Clinical evidence GRADE tables for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

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

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

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: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

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

Appendix J – Economic analysis

Economic analysis for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

Clinical studies

Study	Reason for Exclusion
Anonymous,, Total intravenous feeding, The Medical letter on drugs and therapeutics, 14, 73-4, 1972	Narrative paper describing total intravenous feeding.
Chace, D. H., De Jesus, V. R., Lim, T. H., Hannon, W. H., Clark, R. H., Spitzer, A. R., Detection of TPN contamination of dried blood spots used in newborn and metabolic screening and its impact on quantitative measurement of amino acids, Clinica Chimica Acta, 412, 1385-1390, 2011	Intervention does not meet the inclusion criteria - the study examined markers of contamination of blood by TPN.
Chen,C., Management guidelines of premature infants, Chinese Journal of Contemporary Pediatrics, 7, 1-7, 2005	Guideline paper, not specifically related to PN.
Chowdhary, S. K., Parashar, K., Central venous access in neonates through the peripheral route, Current Opinion in Clinical Nutrition and Metabolic Care, 3, 217-219, 2000	Narrative paper describing central venous access. References checked for relevance.
DeSilva, S., Hana, M., Sutija, V. G., Raziuddin, K., Effect of amino acids on glucose tolerance and hyperkalemia in very low birth weight infants, Journal of Perinatal Medicine, 30, 128-131, 2002	Intervention does not meet the inclusion criteria - all infants have glucose monitored every 1 to 2 hours.
Evans, Charity H., Lee, Jane, Ruhlman, Melissa K., Optimal glucose management in the perioperative period, The Surgical clinics of North America, 95, 337-54, 2015	Narrative review on glucose management. References checked for relevance.
Fox, M., Molesky, M., Van Aerde, J. E., Muttitt, S., Changing parenteral nutrition administration sets every 24 h versus every 48 h in newborn infants, Journal canadien de gastroenterologie [Canadian journal of gastroenterology], 13, 147-51, 1999	Intervention not relevant - comparison of changing the fluid line at different time periods. No difference in monitoring procedures.
Gutcher, G., Cutz, E., Complications of parenteral nutrition, Seminars in Perinatology, 10, 196-207, 1986	Narrative review.
Hitrova-Nikolova, S., Vakrilova, L., Slancheva, B., Nikolov, A., Popivanova, A., Pramatarova, T., Yarakova, N., Radulova, P., Jekova, N., Emilova, Z., Osteopenia of prematurity-predictive biochemical markers, Journal of Perinatal Medicine. Conference: 11th World Congress of Perinatal Medicine, 41, 2013	Conference abstract - not an RCT.
Horvath, M., Mestyan, I., Mestyan, J., Iatrogenic hyperosmolality in critically ill low-birth-weight infants, Acta paediatrica Academiae Scientiarum Hungaricae, 16, 231-42, 1975	Study outcomes do not meet protocol eligibility criteria - plasma osmolality.

Study	Reason for Exclusion
Mack, E., Consolidating blood draws in children as a blood conservation technique, Critical Care Medicine, 41, A173, 2013	Conference abstract - not an RCT.
Martin, R. G., Fenton, L. J., Leonardson, G., Reid, T. J., Consistency of care in an intensive care nursery staffed by nurse clinicians, American Journal of Diseases of Children, 139, 169-172, 1985	Study design not relevant to protocol - retrospective chart review (not an RCT or comparative cohort study). Not specifically PN.
McVea, S., Cassidy, K., Carville, C., Hogan, M., Improving neonatal hypoglycaemia management compliance on a district general postnatal ward, European Journal of Pediatrics, 175, 1791, 2016	Conference abstract - not an RCT (retrospective chart review).
Meites, S., Glassco, K. M., Studies on the quality of specimens obtained by skin-puncture of children. 2. An analysis of blood-collecting practices in a pediatric hospital, Clinical chemistry, 31, 1669-72, 1985	Intervention does not meet inclusion criteria - study determines blood collecting practices for clinical chemistry; not specifically PN and includes ineligible population.
Mizumoto, H., Honda, Y., Iki, Y., Ueda, K., Uchio, H., Hata, D., Hyperinsulinemic hypoglycemia in tube fed preterm infants, Pediatric Diabetes, 13, 355, 2012	Full text is a conference abstract - not an RCT.
Rhoton, B., Annibale, D. J., Southgate, W. M., Salgado, C., Chase, K. E., Beardsley, W. E., Driggers, T. L., NICU Journey to zero central line-associated bloodstream infections: Incremental interventions lead to sustainable outcomes, American Journal of Infection Control, 38, E113-E114, 2010	Conference abstract - not an RCT.

Economic studies

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

Appendix K – Research recommendations

Research recommendation for review question: In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

No research recommendation was made for this topic.