# National Institute for Health and Care Excellence

Draft for consultation

# Neonatal parenteral nutrition

## [D7] Ratio of non-nitrogen energy to nitrogen

*NICE guideline tbc*

*Evidence reviews*

*September 2019*

*Draft for consultation*

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

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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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# What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

## Review question

What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

### Introduction

Babies require energy in order to meet resting energy requirements, energy expenditure and to facilitate growth through new tissue formation. Nitrogen (amino acids or protein) is required for new tissue formation. If insufficient non-nitrogen energy (carbohydrates and lipids) is given then nitrogen is used for non-growth purposes and is not available to generate new tissues. An excess of non-nitrogen energy can lead to increased adiposity and may cause hyperglycaemia or hypertriglyceridemia. If an excess of nitrogen is given this results in oxidation of amino acids resulting in high levels of blood urea.

### 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)<br>• Babies born at term, up to 28 days after their birth (term babies) |
| **Intervention** | Ratio of nitrogen and non-nitrogen energy |
| **Comparison** | Other ratios of nitrogen and non-nitrogen energy |
| **Outcomes** | **Critical**<br>• Neurodevelopmental outcomes (general cognitive abilities, at two years corrected age, as measured by a validated scale)<br>• Growth/Anthropometric measures:<br>  ○ Weight gain (g/kg/d)<br>  ○ Linear growth<br>  ○ Head circumference (mm)<br>• Body composition (measured as Lean mass, fat-free mass, fat mass, adipose tissue),<br>• Adverse effects of PN<br>  ○ Infection (including sepsis)<br>  ○ Hyperglycaemia<br>  ○ Hypoglycaemia<br>  ○ Hypertriglyceridemia<br>  ○ PN associated liver disease<br>• Nitrogen balance<br>• Metabolic acidosis |

| | |
|---|---|
| | **Important**<br>• Mortality<br>• Length of hospital stay<br>• Nutritional intake (g/kg/day) (prescribed nitrogen/non-nitrogen, carbohydrates and lipids actually received) |

*PN: Parenteral nutrition.*

For further details see the review protocol in appendix A.

## Clinical evidence

### Included studies

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

Two observational studies were identified for this review (Zlotkin 1981 and Pineault 1988).

One study compared three levels of nitrogen intake, 640mg/kg/day, 480mg/kg/day and 320mg/kg/day (Zlotkin 1981), and these levels were compared giving a calorie intake of either 50kcal/kg/day or 80kcal/kg/day. Only groups with equal energy intake were compared.

One study compared a 60kcal/kg/day PN to 80kcal/kg/day PN, keeping the nitrogen intake constant at 450mg/kg/day (Pineault 1988).

See Table 2 for a summary of the included studies.

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 |
|---|---|---|---|---|---|
| Pineault 1988<br><br>Observational study<br><br>Canada | N=16<br><br>GA: 34.6 weeks<br>Age at study: 10 days | <u>High non-protein energy</u><br><br>80 kcal/kg/day<br>Plus 450 mg/kg/day nitrogen | <u>Low non-protein energy</u><br><br>60 kcal/kg/day<br>450 mg/kg/day nitrogen | • Weight gain<br>• Length<br>• Head circumference<br>• Nitrogen balance<br>• Nitrogen excretion | Every baby received two 6 day periods of high fat or low fat, (half of each group started on high fat)<br><br>The 6 day period was isocaloric (according to group) and isonitrogenous |

| Study | Population | Intervention | Comparison | Outcomes | comments |
|---|---|---|---|---|---|
| Zlotkin 1981<br><br>Observational study<br><br>Canada | N=22<br><br>GA: 29.2 weeks<br>Postnatal age: 18.7 days | <u>High nitrogen</u><br><br>Group A (n=6)<br>50 kcal/kg/day plus 640 mg/kg/day nitrogen<br><br>Group C (n=5)<br>80 kcal/kg/day plus 640 mg/kg/day nitrogen | <u>Medium nitrogen</u><br><br>Group B (n=6)<br>50 kcal/kg/day<br>480mg/kg/day nitrogen<br><br>Group D (n=8)<br>80 kcal/kg/day<br>480 mg/kg/day nitrogen<br><br><u>Low nitrogen</u><br>Group E (n=5)<br>80 kcal/kg/day<br>320 mg/kg/day nitrogen<br>high | • Weight gain<br>• Length<br>• Nitrogen retention | No data on head circumference was provided, but the article states: no difference in head circumference were observed.<br><br>3 babies died due to respiratory and or haemorrhagic complications – the authors state the babies were in different intervention groups, but do not state which group(s).<br><br>No data provided for Length in the low protein energy group |

*GA: Gestational age; RCT: randomised controlled trial.*

See appendix D for the full clinical evidence tables.

## Quality assessment of clinical outcomes included in the evidence review

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

## Economic evidence

### Included studies

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

### Excluded studies

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

## Summary of studies included in the economic evidence review

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

# Economic model

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

# Evidence statements

## Clinical evidence statements

### High non-protein energy versus low non-protein energy

#### Weight gain

- Very low quality evidence from 1 observational study (n=16) showed a clinically important difference in in weight gain over 12 days in babies who had different relative amounts of non-protein energy PN. Babies receiving low non-protein energy gained less weight than those on the high non-protein energy PN. However, there was high uncertainty around the effect: Mean difference (MD) -3.1g/kg/day (95% CI -9.08 to 2.88).

#### Length

- Very low quality evidence from 1 observational study (n=16) showed no clinically important difference in length gain over 12 days in babies who had low non-protein energy PN as compared to those who were provided with high non-protein energy PN. However, there was uncertainty around the effect: MD -0.25 (95% CI -0.79 to 0.29).

#### Head circumference

- Very low quality evidence from 1 observational study (n=16) showed a clinically important difference in head circumference over 12 days in babies who had different non-protein energy PN. Babies receiving low non-protein energy PN had a smaller head circumference than those receiving high-non-protein energy PN. However, there was uncertainty around the effect: MD -0.4cm (95% CI 0.78 to -0.02).

#### Nitrogen balance

- Very low quality evidence from 1 observational study (n=16) showed a clinically important difference in nitrogen balance in babies who had different relative amounts of non-protein energy PN. Babies receiving low non-protein energy had lower nitrogen balance compared to those who were provided with high non-protein energy. However, there was uncertainty around the effect: MD -27 (95% CI -58.84 to 4.84).

#### Nitrogen excretion

- Very low quality evidence from 1 observational study (n=16) showed a clinically important difference in nitrogen excretion in babies who had different relative amounts of non-protein energy PN. Babies receiving low non-protein energy had higher nitrogen excretion compared to those who were provided with high non-protein energy. However, there was high uncertainty around the effect: MD 23.5 (95% CI -6.08 to 53.08).

### High Nitrogen (640mg/kg/day nitrogen) versus medium nitrogen (480mg/kg/day nitrogen)

This section relates to evidence statements from one observational study with multiple arms. There were 2 comparisons: (1) high versus medium nitrogen, where energy was kept constant at 50 kcal/kg/day and (2) high versus medium nitrogen, where energy was kept constant at 80 kcal/kg/day. Arms of high versus medium were not compared when they had

different calorie intake because outcomes would be difficult to interpret (unlear whether differences would be due to levels of nitrogen or calories).

**Weight gain**

- Very low quality evidence from 1 observational study that included two comparisons for two different energy intakes showed no clinically important differences in weight gain over six days in babies who received a high nitrogen PN as compared to those who received a medium nitrogen PN at 50 kcal/kg/day intake (n=12) or at 80 kcal/kg/day intake (n=13). MD -0.7 g/kg/day (95% CI -10.74 to 9.34) and MD -0.6 g/kg/day (95% CI -4.68 to 3.48), respectively.

**Length**

- Very low quality evidence from 1 observational study that included two comparisons for two different energy intakes showed a clinically important difference in length of babies over six days between those who received a high nitrogen PN as compared to those who received a medium nitrogen PN. Babies receiving high nitrogen PN at 50 kcal/kg/day (n=12) and at 80 kcal/kg/day (n=13) had a greater length than those receiving medium nitrogen PN. However, there was high uncertainty around the effect for 50 kcal/kg/day: MD 0.3cm (95% CI -0.14 to 0.74) and there was uncertainty around the effect for 80 kcal/kg/day: MD -0.3cm (95% CI -0.86 to 0.26).

**Nitrogen retention**

- Very low quality evidence from 1 observational study that included two comparisons for two different energy intakes showed no clinically important differences in nitrogen retention over six days between babies who received a high nitrogen PN as compared to those who received a medium nitrogen PN based on 50 kcal/kg/day (n=12). MD 18mg/kg/day (95% CI -26.74 to 62.74). However there was a clinically important difference in nitrogen retention over six days between babies who received a high nitrogen as compared to those who received a medium nitrogen PN based on 80kcal/kg/day (n=13) , with increased nitrogen retention in the group of babies receiving high nitrogen PN: MD 112mg/kg/day (95% CI 67.95 to 156.05).

**High nitrogen (640mg/kg/day nitrogen) versus low nitrogen (320mg/kg/day nitrogen)**

**Weight gain**

- Very low quality evidence from 1 observational study (n=10) showed a clinically important difference in weight gain over six days in babies who received a high nitrogen PN as compared to those who received a low nitrogen PN, based on 80 kcal/kg/day, with greater weight gain in babies who received high nitrogen PN. However, there was uncertainty around the effect: MD 10.4g/kg/day (95% CI 3.28 to 17.52).

**Nitrogen retention**

- Very low quality evidence from 1 observational study (n=10) showed a clinically important differences in nitrogen retention over six days between babies who received a high nitrogen PN as compared to those who received a medium nitrogen PN based on 80kcal/kg/day, with increased nitrogen retention in the group of babies receiving high nitrogen PN: MD 247mg/kg/day (95% CI 184 to 309.51)

**Medium nitrogen (480mg/kg/day nitrogen) versus low nitrogen (320mg/kg/day nitrogen)**

**Weight gain**

- Very low quality evidence from 1 observational study (n=13) showed a clinically important difference in weight gain over six days in babies who received a medium nitrogen PN as compared to those who received a low nitrogen PN, based on 80 kcal/kg/day, with greater weight gain in the group of babies receiving medium nitrogen PN. However there was uncertainty around the effect: MD 11g/kg/day (95% CI 3.32 to 18.68).

**Nitrogen retention**

- Very low quality evidence from 1 observational study (n=13) showed a clinically important differences in nitrogen retention over six days between babies who received a medium nitrogen PN as compared to those who received a low nitrogen PN based on 80kcal/kg/day, with increased nitrogen retention in the group of babies receiving medium nitrogen PN: MD 135mg/kg/day (95% CI 85.41 to 184.59).

### Economic evidence statements

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

## Research recommendation

What is the optimal ratio of non-nitrogen energy to nitrogen in parenteral nutrition for preterm and term babies?

## The committee's discussion of the evidence

### Interpreting the evidence

#### *The outcomes that matter most*

The committee prioritised neurodevelopmental outcomes, anthropometric measures, body composition, adverse events, nitrogen balance and metabolic acidosis as the critical outcomes. These were considered critical as energy intake is key to growth and cognitive development of the baby, and differences in the relative amounts of nitrogen and non-nitrogen energy provided in PN will influence these. The relative amounts may also influence the metabolic state of the baby which could lead to adverse events, such as nitrogen imbalance and metabolic acidosis. The evidence identified only provided data on anthropometric measures and nitrogen balance.

The committee considered mortality, length of hospital stay and nutritional intake as important outcomes, as these are likely influenced by a number of complex factors, in addition to the relative amounts of nitrogen and non-nitrogen energy. Lack of sufficient nitrogen energy can lead to poor growth, which in turn can delay hospital discharge, and could be associated with increased adverse events contributing to morbidity and mortality. No evidence was identified with data on these outcomes.

#### *The quality of the evidence*

The quality of outcomes were assessed using GRADE methodology. The evidence was either very low or low quality, indicating high uncertainty in the reliability of the evidence. The data were downgraded due to serious and very serious imprecision across the different

outcomes, the 95% confidence intervals crossed either one or both default MID. There was serious risk of bias due to selection bias, the babies were allocated to treatments in one of the studies (Zlotkin 1981). There was also unclear risk of detection bias, assessors were aware of treatment allocation. In addition, the studies were old (using therefore outdated PN formulations) and included very small numbers of babies. Although the evidence was not downgraded on the basis that the studies were older (as per GRADE methodology), the committee had little confidence in this evidence both due to the quality and the generalisability of the data. Overall the committee agreed that this evidence should be regarded with caution.

***Benefits and harms***

Little evidence was identified to answer the review question, two small studies were included and these were both conducted by the same research unit in Canada over twenty years ago. The committee therefore considered this evidence, but also used their clinical knowledge and experience to make the recommendations by informal consensus.

The committee discussed how nitrogen is made up of amino acids, (and the non-nitrogen energy is made up of carbohydrate and/or lipids), and agreed they should refer to the evidence previously identified and included within the amino acid review question of this guideline. The committee considered that the studies included within the amino acid review were more relevant to current practice (more appropriate settings and more up-to-date) than the two studies retrieved for this specific review. Using these recommendations, and their clinical knowledge, the committee derived by informal consensus the recommended non-nitrogen to nitrogen ratio ranges of 20 to 30 kcal of non-nitrogen energy per gram of amino acid. The committee agreed that the recommendations made on glucose, amino acids, and lipids, (recommendations 1.4.2 to 1.4.6) respectively, should be referred to by healthcare practitioners when determining the amounts of nitrogen and non-nitrogen energy. They agreed that recommendations in the ratio section of the guideline should specifically direct the user to these key areas within the guideline. The committee agreed the amounts of amino acids, carbohydrate and lipids should then fit with the recommended ratios set out in this review.

The committee decided by informal consensus, and based on their experience and expertise, that there should be a lower and upper limit in the nitrogen to non-nitrogen energy ratios recommended, ensuring that the baby receives enough energy to grow and prevent oxidation of amino acids, but does not provide excess energy which could result in excess energy being laid down as fat mass. The committee acknowledged that there is a balance in energy provision, too much of non-nitrogen energy for amino acids will result in excess fat deposition, too little will result in ineffective utilisation of amino acids for growth. The committee discussed that the evidence included in this review was limited, and therefore also agreed it was appropriate to discuss more current research, which did not meet the inclusion criteria (i.e. did not formally provide nitrogen and non-nitrogen energy data). The committee were aware that one recent study had provided a ratio to babies of 24 kcal non-nitrogen energy per gram of amino acid, and this resulted in appropriate lean and adipose tissue development. Taking this knowledge, the evidence presented and their clinical experience, the committee felt confident in their recommendations.

Based on their knowledge and experience, the committee agreed by informal consensus that there is a need for some flexibility in the recommendations, as the catabolic state of the baby will influence the exact energy requirements. The committee agreed the lower ratio of 20kcal non-nitrogen energy per gram of amino acid should ensure babies do not oxidise the amino acids for fuel, and should prevent high levels of blood urea. The committee agreed on an upper limit of 30kcal non-nitrogen energy per gram of amino acid, this is lower than that suggested by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines (van Goudoever 2018), which recommend 40kcal non-nitrogen energy per gram of amino acid. The committee were concerned about

recommending 40kcal non-nitrogen energy per gram of amino acid as they agreed that this higher level risked babies putting on weight as fat mass rather than non-fat mass.

For the reasons described above, the committee agreed by informal consensus that it is important to keep the ratios within the ranges even when parenteral nutrition is altered, for instance if enteral nutrition is increased.

In light of the limited evidence identified for this review question, the committee agreed further research is required, to determine the optimal ratio of non-nitrogen to nitrogen energy; therefore, the committee have developed a research recommendation for this review question.

### 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 non-nitrogen and nitrogen components would not incur extra resource implications to the health care system.

The committee noted that optimising the relative amounts of nitrogen and non-nitrogen energy for neonatal parenteral nutrition may result in avoiding additional costs associated with adverse effects to the NHS given that incorrect relative amounts of nitrogen and non-nitrogen energy for neonatal parenteral nutrition can result in oxidation of amino acids and high blood urea, and also metabolic ill health in later life which may require resource-intensive management.

The recommendations in this area reflect clinical practice across many units and would have only modest resource implications, if any.

## References

**Pineault 1988**

Pineault, M., Chessex, P., Bisaillon, S., Brisson, G., Total parenteral nutrition in the newborn: impact of the quality of infused energy on nitrogen metabolism. Am J Clin Nutr 47, 298-304, 1988.

**Van Goudoever 2018**

Van Goudoever, J., Carnielli, V., Darmaun, D., Sainz de Pipaon, M., The ESPGHN/ESPEN/ESPRC/CSPEN working group on pediatric parenteral nutrition ESPGHAN/ESPEN/ESPR Guideline on pediatric parenteral nutrition: Amino acids. Clinical Nutrition doi:10.1016/j.clnu.2018.06.945, 2018.

**Zlotkin 1981**

Zlotkin, S, H., Anderson, G, H., Intravenous nitrogen and energy intakes required to duplicate in utero nitrogen accretion in prematurely born human infants. The Journal of Pediatrics 99, (1), 115-120, 1981.

# Appendices

## Appendix A – Review protocols

### Review protocol for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

**Table 3: Review protocol – ratio of nitrogen to non-nitrogen energy**

| Field (based on PRISMA-P) | Content |
|---|---|
| Review question | What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)? |
| Type of review question | Intervention |
| Objective of the review | What is the optimal energy ratio and daily amounts of intravenous carbohydrates and lipids? |
| Eligibility criteria – population/disease/condition/issue/domain | • Babies born preterm, up to 28 days after their due birth date (preterm babies)<br>• Babies born at term, up to 28 days after their birth (term babies) |
| Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s) | Ratio of nitrogen and non-nitrogen energy |
| Eligibility criteria – comparator(s)/control or reference (gold) standard | Other ratios of nitrogen and non-nitrogen energy |
| Outcomes and prioritisation | **Critical**<br>• Neurodevelopmental outcomes (general cognitive abilities, at two years corrected age, as measured by a validated scale)<br>• Growth/Anthropometric measures:<br>  ○ Weight gain (g/kg/d)<br>  ○ Linear growth<br>  ○ Head circumference (mm)<br>• Body composition (measured as Lean mass, fat-free mass, fat mass, adipose tissue),<br>• Adverse effects of PN |

| Field (based on PRISMA-P) | Content |
|---|---|
| | ○ Infection (including sepsis)<br>○ Hyperglycaemia<br>○ Hypoglycaemia<br>○ Hypertriglyceridemia<br>○ Other PN associated liver disease<br>• Nitrogen balance<br>• Metabolic acidosis<br><br>**Important**<br>• Mortality<br>• Length of hospital stay<br>• Nutritional intake (g/kg/day) (prescribed nitrogen/non-nitrogen, carbohydrates and lipids actually received) |
| Eligibility criteria – study design | Only published full text papers-<br>• Systematic reviews of RCTs<br>• RCTs<br>• Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making)<br>• Non-comparative studies (only if no evidence from RCTs or comparative cohort studies, limited data on critical outcomes to inform decision making)<br><br>No date restriction needed<br><br>Participant numbers (no restrictions for observational studies). For neurodevelopmental outcomes, studies with sample size of minimum 50 participants will be considered.<br><br>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 | Inclusion:<br>• Clinical settings that provide neonatal care or specialist paediatric care.<br>• UK and non-UK studies (non-UK studies from middle and high income countries according to WHO/World Bank criteria). |
| Proposed sensitivity/sub-group analysis, or meta-regression | • Parents or carers whose first language is not English<br>• Parents or carers who have learning difficulties or disabilities |

| Field (based on PRISMA-P) | Content |
|---|---|
| | There are inequalities that have been identified relating to how information is provided to them and the type of support they need.<br>• It is known that being a young woman (aged 17 years or under) or a woman with a low socioeconomic status increases the risk of giving birth to a baby preterm. These groups could require particular support and specific recommendations may be required to address their particular needs.<br><br>Stratified analysis:<br>• Babies born preterm, up to 28 days after their due birth date (preterm babies)<br>• Babies born at term, up to 28 days after their birth (term babies)<br><br>Subgroup analysis:<br><br>The following groups will be considered for subgroup analysis:<br>• Population subgroups:<br>○ Age of baby<br>○ Preterm (extremely preterm <28 weeks GA; very preterm: 28-31 weeks GA; moderately preterm: 32-36 weeks GA)<br>○ Birthweight: low birthweight (<2500g); very low birthweight (<1500g) and extremely low birthweight (<1000g)<br>○ First week of life and after first week of life<br>○ Critically ill babies or those requiring surgery (for example, inotropic support, therapeutic hypothermia or fluid restriction)<br><br>Confounders:<br><br>Important confounders (when comparative observational studies are included for interventional reviews)<br>• Age of baby<br>• Birthweight: low birthweight (<2500g); very low birthweight (<1500g) and extremely low birthweight (<1000g)<br>• Sex of baby<br>• Gestation (preterm vs. term)<br>• For neurodevelopmental outcomes:<br>○ Biological (sex, small for gestational age, ethnicity)<br>○ Neonatal (PVL, IVH, infarct, sepsis, ROP, NEC, antenatal/postnatal steroids, BPD at 36 weeks)<br>○ Social (SES, substance abuse, alcohol abuse, multiple pregnancy, chorioamnionitis, neglect, maternal age, maternal mental health disorder)<br>○ Postnatal (epilepsy, age of establishing feeding) |

| Field (based on PRISMA-P) | Content |
|---|---|
| | • Underlying diseases (Chronic lung disease)<br>• Other medications |
| 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.<br><br>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).<br><br>'GRADEpro' will be used to assess the quality of evidence for each outcome. Low income countries will be downgraded for indirectness.<br>• 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.<br><br>Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit.<br><br>Supplementary search techniques: No supplementary search techniques were used.<br><br>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<br><br>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.<br><br>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.<br><br>If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.<br><br>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. |

*BPD: Broncho pulmonary dysplasia; GA: Gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; IVH: Intraventricular haemorrhage; NEC: Necrotising enterocolitis; NICE: National Institute of Clinical Excellence; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NIHR: National Institute for Health Research; PN: Parenteral nutrition; PROSPERO: International prospective register of systematic reviews; PVL: Periventricular leukomalacia; RCT randomised controlled trial; ROBIS; risk of bias in systematic reviews; ROP: Retinopathy of prematurity; SES: socioeconomic status; UK: United Kingdom; WHO: World Health Organisation;*

# Appendix B – Literature search strategies

## Literature search strategies for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

**[Note: One combined search conducted for questions D7 and D8]**

**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 | NITROGEN/ and ratio?.ti,ab. |
| 28 | (ratio? adj10 nitrogen).mp. |
| 29 | exp PROTEINS/ and ratio?.ti,ab. |
| 30 | (ratio? adj10 (protein? or conalbumin or ovalbumin or avidin or ovomucin or phosvitin or whey or casein? or lactalbumin or lactoglobulin? or lactoferrin)).mp. |
| 31 | exp AMINO ACIDS/ and ratio?.mp. |
| 32 | (ratio? adj10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp. |
| 33 | or/27-32 |
| 34 | (nitrogen adj5 (nonnitrogen or non-nitrogen)).mp. |

| # | Searches |
|---|---|
| 35 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 nitrogen).mp. |
| 36 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (protein? or conalbumin or ovalbumin or avidin or ovomucin or phosvitin or whey or casein? or lactalbumin or lactoglobulin? or lactoferrin)).mp. |
| 37 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp. |
| 38 | or/35-37 |
| 39 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (nonnitrogen or non-nitrogen)).mp. |
| 40 | NITROGEN/ad [Administration & Dosage] |
| 41 | exp PROTEINS/ad [Administration & Dosage] |
| 42 | exp AMINO ACIDS/ad [Administration & Dosage] |
| 43 | or/40-42 |
| 44 | exp LIPIDS/ and ratio?.ti,ab. |
| 45 | exp PROSTAGLANDINS/ and ratio?.ti,ab. |
| 46 | 44 not 45 |
| 47 | ((ratio? or amount?) adj10 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp. |
| 48 | or/46-47 |
| 49 | exp CARBOHYDRATES/ and ratio?.ti,ab. |
| 50 | exp HEPARIN/ and ratio?.ti,ab. |
| 51 | exp GLYCOPEPTIDES/ and ratio?.ti,ab. |
| 52 | exp AMINOGLYCOSIDES/ and ratio?.ti,ab. |
| 53 | or/50-52 |
| 54 | 49 not 53 |

| # | Searches |
|---|---|
| 55 | ((ratio? or amount?) adj10 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp. |
| 56 | or/54-55 |
| 57 | FAT EMULSIONS, INTRAVENOUS/ and ratio?.ti,ab. |
| 58 | (ratio? adj10 macronutrient?).mp. |
| 59 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 macronutrient?).mp. |
| 60 | or/58-59 |
| 61 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp. |
| 62 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (Carbohydrate? or Amino |

| # | Searches |
|---|---|
| | Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp. |
| 63 | exp LIPIDS/ad [Administration & Dosage] |
| 64 | exp PROSTAGLANDINS/ad [Administration & Dosage] |
| 65 | 63 not 64 |
| 66 | exp CARBOHYDRATES/ad [Administration & Dosage] |
| 67 | exp HEPARIN/ad [Administration & Dosage] |
| 68 | exp GLYCOPEPTIDES/ad [Administration & Dosage] |
| 69 | exp AMINOGLYCOSIDES/ad [Administration & Dosage] |
| 70 | or/67-69 |
| 71 | 66 not 70 |
| 72 | ENERGY INTAKE/ and ratio?.ti,ab. |
| 73 | ENERGY METABOLISM/ and ratio?.ti,ab. |
| 74 | (energy adj10 ratio?).ti,ab. |
| 75 | or/72-74 |
| 76 | 14 and 26 and 33 |
| 77 | 14 and 26 and 34 |
| 78 | 14 and 26 and 38 and (39 or 61 or 62) |
| 79 | 14 and 26 and 43 and (65 or 71) |
| 80 | or/76-79 |
| 81 | 14 and 26 and 48 |
| 82 | 14 and 26 and 56 |
| 83 | 14 and 57 |
| 84 | 14 and 26 and 60 |
| 85 | 14 and 26 and 61 and 62 |
| 86 | 14 and 26 and 65 and 71 |
| 87 | or/81-86 |
| 88 | 14 and 26 and 75 |
| 89 | 80 or 87 or 88 |
| 90 | limit 89 to english language |
| 91 | LETTER/ |
| 92 | EDITORIAL/ |
| 93 | NEWS/ |
| 94 | exp HISTORICAL ARTICLE/ |
| 95 | ANECDOTES AS TOPIC/ |

| # | Searches |
|---|---|
| 96 | COMMENT/ |
| 97 | CASE REPORT/ |
| 98 | (letter or comment*).ti. |
| 99 | or/91-98 |
| 100 | RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab. |
| 101 | 99 not 100 |
| 102 | ANIMALS/ not HUMANS/ |
| 103 | exp ANIMALS, LABORATORY/ |
| 104 | exp ANIMAL EXPERIMENTATION/ |
| 105 | exp MODELS, ANIMAL/ |
| 106 | exp RODENTIA/ |
| 107 | (rat or rats or mouse or mice).ti. |
| 108 | or/101-107 |
| 109 | 90 not 108 |

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$)).ti,ab. |
| 22 | ((peripheral$ 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 | NITROGEN/ and ratio?.ti,ab. |
| 27 | (ratio? adj10 nitrogen).mp. |
| 28 | PROTEIN/ and ratio?.ti,ab. |
| 29 | (ratio? adj10 (protein? or conalbumin or ovalbumin or avidin or ovomucin or phosvitin or whey or casein? or lactalbumin or lactoglobulin? or lactoferrin)).mp. |
| 30 | exp AMINO ACIDS/ and ratio?.ti,ab. |
| 31 | (ratio? adj10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine |

| # | Searches |
|---|---|
| | or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp. |
| 32 | or/26-31 |
| 33 | (nitrogen adj5 (nonnitrogen or non-nitrogen)).mp. |
| 34 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 nitrogen).mp. |
| 35 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (protein? or conalbumin or ovalbumin or avidin or ovomucin or phosvitin or whey or casein? or lactalbumin or lactoglobulin? or lactoferrin)).mp. |
| 36 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp. |
| 37 | or/34-36 |
| 38 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (nonnitrogen or non-nitrogen)).mp. |
| 39 | NITROGEN/do [Drug Dose] |
| 40 | PROTEIN/do [Drug Dose] |
| 41 | exp AMINO ACIDS/do [Drug Dose] |
| 42 | or/39-41 |
| 43 | exp LIPID/ and ratio?.ti,ab. |
| 44 | exp PROSTAGLANDIN/ and ratio?.ti,ab. |
| 45 | 43 not 44 |
| 46 | ((ratio? or amount?) adj10 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp. |
| 47 | or/45-46 |
| 48 | exp CARBOHYDRATE/ and ratio?.ti,ab. |
| 49 | exp HEPARIN/ and ratio?.ti,ab. |
| 50 | exp GLYCOPEPTIDE/ and ratio?.ti,ab. |

| # | Searches |
|---|---|
| 51 | exp AMINOGLYCOSIDE/ and ratio?.ti,ab. |
| 52 | or/49-51 |
| 53 | 48 not 52 |
| 54 | ((ratio? or amount?) adj10 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp. |
| 55 | or/53-54 |
| 56 | MACRONUTRIENT/ and ratio?.ti,ab. |
| 57 | (ratio? adj10 macronutrient?).mp. |
| 58 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 macronutrient?).mp. |
| 59 | or/56-58 |
| 60 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or |

| # | Searches |
|---|---|
| | Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp. |
| 61 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj10 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp. |
| 62 | exp LIPID/do [Drug Dose] |
| 63 | exp PROSTAGLANDIN/do [Drug Dose] |
| 64 | 62 not 63 |
| 65 | exp CARBOHYDRATE/do [Drug Dose] |
| 66 | exp HEPARIN/do [Drug Dose] |
| 67 | exp GLYCOPEPTIDE/do [Drug Dose] |
| 68 | exp AMINOGLYCOSIDE/do [Drug Dose] |
| 69 | or/66-68 |
| 70 | 65 not 69 |
| 71 | CALORIC INTAKE/ and ratio?.ti,ab. |
| 72 | ENERGY METABOLISM/ and ratio?.ti,ab. |
| 73 | (energy adj10 ratio?).ti,ab. |
| 74 | or/71-73 |
| 75 | 13 and 25 and 32 |
| 76 | 13 and 25 and 33 |
| 77 | 13 and 25 and 37 and (38 or 60 or 61) |
| 78 | 13 and 25 and 42 and (64 or 70) |
| 79 | or/75-78 |
| 80 | 13 and 25 and 47 |
| 81 | 13 and 25 and 55 |
| 82 | 13 and 25 and 59 |
| 83 | 13 and 25 and 60 and 61 |
| 84 | 13 and 25 and 64 and 70 |
| 85 | or/80-84 |
| 86 | 13 and 25 and 74 |
| 87 | 79 or 85 or 86 |
| 88 | limit 87 to english language |
| 89 | letter.pt. or LETTER/ |
| 90 | note.pt. |
| 91 | editorial.pt. |

| # | Searches |
|---|---|
| 92 | CASE REPORT/ or CASE STUDY/ |
| 93 | (letter or comment*).ti. |
| 94 | or/89-93 |
| 95 | RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab. |
| 96 | 94 not 95 |
| 97 | ANIMAL/ not HUMAN/ |
| 98 | NONHUMAN/ |
| 99 | exp ANIMAL EXPERIMENT/ |
| 100 | exp EXPERIMENTAL ANIMAL/ |
| 101 | ANIMAL MODEL/ |
| 102 | exp RODENT/ |
| 103 | (rat or rats or mouse or mice).ti. |
| 104 | or/96-103 |
| 105 | 88 not 104 |

**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: [Nitrogen] this term only |
| #31 | MeSH descriptor: [Proteins] explode all trees |
| #32 | MeSH descriptor: [Amino Acids] explode all trees |
| #33 | #30 or #31 or #32 |
| #34 | ratio*:ti,ab |
| #35 | #33 and #34 |
| #36 | (ratio* near/10 nitrogen):ti,ab |
| #37 | (ratio* near/10 (protein* or conalbumin or ovalbumin or avidin or ovomucin or phosvitin or whey or casein* or lactalbumin or lactoglobulin* or lactoferrin)):ti,ab |
| #38 | (ratio* near/10 ("amino acid*" or Alanine or "Pantothenic Acid" or Lysinoalanine or Mimosine or "Chloromethyl Ketone*" or "Aspartic Acid" or "Isoaspartic Acid" or "N-Methylaspartate" or "Potassium Magnesium Aspartate" or Glutamate* or "1-Carboxyglutamic Acid" or "Glutamic Acid" or "Sodium Glutamate" or Pemetrexed or "Polyglutamic Acid" or "Pyrrolidonecarboxylic Acid" or Arginine or "Argininosuccinic Acid" or "Benzoylarginine-2-Naphthylamide" or "Benzoylarginine Nitroanilide" or Homoarginine or Nitroarginine or "omega-N-Methylarginine" or "Tosylarginine Methyl Ester" or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or "Aminoisobutyric Acids" or Isoleucine or Leucine or Valine or "2-Amino-5-phosphonovalerate" or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or "N-Formylmethionine" or "p-Fluorophenylalanine" or Thyroxine or Thyronine* or |

| # | Searches |
|---|---|
| | Diiodothyronine* or Triiodothyronine or Tryptophan or "5-Hydroxytryptophan" or Tyrosine or Betalain* or Betacyanin* or Diiodotyrosine or Melanin* or Methyltyrosine* or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine* or "Imino Acid*" or "Azetidinecarboxylic Acid" or Proline or Captopril or Fosinopril or Hydroxyproline or "Technetium Tc 99m" or Isodesmosine or "NG-Nitroarginine Methyl Ester" or Citrulline or Cystathionine or Cystine or "Diaminopimelic Acid" or Homocystine or "2-Aminoadipic Acid" or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or "Cysteic Acid" or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or "S-Adenosylhomocysteine" or "S-Adenosylmethionine" or "Buthionine Sulfoximine" or Selenomethionine or "Vitamin U" or Penicillamine or "S-Nitroso-N-Acetylpenicillamine" or Thiorphan or Tiopronin or Aminobutyrate* or "gamma-Aminobutyric Acid" or Pregabalin or Vigabatrin or Aminocaproate* or "Aminocaproic Acid" or Norleucine or Diazooxonorleucine or "Aminolevulinic Acid" or Canavanine or Creatine or Phosphocreatine or Glycine* or Allylglycine or "Glycocholic Acid" or "Glycodeoxycholic Acid" or "Glycochenodeoxycholic Acid" or Sarcosine or Homoserine or Kynurenine or "Oxamic Acid" or "Phosphoamino Acid*" or "Quisqualic Acid")):ti,ab |
| #39 | #35 or #36 or #37 #38 |
| #40 | (nitrogen near/5 (nonnitrogen or non-nitrogen)):ti,ab |
| #41 | ((Dose* or Dosage* or Regimen* or Amount* or Optimal* or Optimis* or Requir* or Target* or Rate* or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/10 nitrogen):ti,ab |
| #42 | ((Dose* or Dosage* or Regimen* or Amount* or Optimal* or Optimis* or Requir* or Target* or Rate* or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/10 (protein* or conalbumin or ovalbumin or avidin or ovomucin or phosvitin or whey or casein* or lactalbumin or lactoglobulin* or lactoferrin)):ti,ab |
| #43 | ((Dose* or Dosage* or Regimen* or Amount* or Optimal* or Optimis* or Requir* or Target* or Rate* or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/10 ("amino acid*" or Alanine or "Pantothenic Acid" or Lysinoalanine or Mimosine or "Chloromethyl Ketone*" or "Aspartic Acid" or "Isoaspartic Acid" or "N-Methylaspartate" or "Potassium Magnesium Aspartate" or Glutamate* or "1-Carboxyglutamic Acid" or "Glutamic Acid" or "Sodium Glutamate" or Pemetrexed or "Polyglutamic Acid" or "Pyrrolidonecarboxylic Acid" or Arginine or "Argininosuccinic Acid" or "Benzoylarginine-2-Naphthylamide" or "Benzoylarginine Nitroanilide" or Homoarginine or Nitroarginine or "omega-N-Methylarginine" or "Tosylarginine Methyl Ester" or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or "Aminoisobutyric Acids" or Isoleucine or Leucine or Valine or "2-Amino-5-phosphonovalerate" or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or "N-Formylmethionine" or "p-Fluorophenylalanine" or Thyroxine or Thyronine* or Diiodothyronine* or Triiodothyronine or Tryptophan or "5-Hydroxytryptophan" or Tyrosine or Betalain* or Betacyanin* or Diiodotyrosine or Melanin* or Methyltyrosine* or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine* or "Imino Acid*" or "Azetidinecarboxylic Acid" or Proline or Captopril or Fosinopril or Hydroxyproline or "Technetium Tc 99m" or Isodesmosine or "NG-Nitroarginine Methyl Ester" or Citrulline or Cystathionine or Cystine or "Diaminopimelic Acid" or Homocystine or "2-Aminoadipic Acid" or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or "Cysteic Acid" or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or "S-Adenosylhomocysteine" or "S-Adenosylmethionine" or "Buthionine Sulfoximine" or Selenomethionine or "Vitamin U" or Penicillamine or "S-Nitroso-N-Acetylpenicillamine" or Thiorphan or Tiopronin or Aminobutyrate* or "gamma-Aminobutyric Acid" or Pregabalin or Vigabatrin or Aminocaproate* or "Aminocaproic Acid" or Norleucine or Diazooxonorleucine or "Aminolevulinic Acid" or Canavanine or Creatine or Phosphocreatine or Glycine* or Allylglycine or "Glycocholic Acid" or "Glycodeoxycholic Acid" or "Glycochenodeoxycholic Acid" or Sarcosine or Homoserine or Kynurenine or "Oxamic Acid" or "Phosphoamino Acid*" or "Quisqualic Acid")):ti,ab |
| #44 | #41 or #42 or #43 |
| #45 | ((Dose* or Dosage* or Regimen* or Amount* or Optimal* or Optimis* or Requir* or Target* or Rate* or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/10 (nonnitrogen or non-nitrogen)):ti,ab |
| #46 | MeSH descriptor: [Nitrogen] this term only and with qualifier(s): [administration & dosage - AD] |
| #47 | MeSH descriptor: [Proteins] explode all trees and with qualifier(s): [administration & dosage - AD] |
| #48 | MeSH descriptor: [Amino Acids] explode all trees and with qualifier(s): [administration & dosage - AD] |
| #49 | #46 or #47 or #48 |
| #50 | MeSH descriptor: [Lipids] explode all trees |
| #51 | ratio?:ti,ab |
| #52 | #50 and #51 |
| #53 | MeSH descriptor: [Prostaglandins] explode all trees |
| #54 | ratio?:ti,ab |
| #55 | #53 and #54 |
| #56 | #52 not #55 |
| #57 | ((ratio? or amount?) near/10 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or "Fatty Acid?" or "Omega-3" or "Omega-6" or "Linolenic Acid?" or "Docosahexaenoic Acid?" or "Eicosapentaenoic Acid?" or "Ricinoleic Acid?" or Triolein or Caprylate? or "Decanoic Acid?" or Decanoate? or "Eicosanoic Acid?" or Endocannabinoid? or Eicosanoid? or "Arachidonic Acid?" or "Hydroxyeicosatetraenoic Acid?" or "eicosatetraenoic Acid?" or Isoprostane? or Neuroprostane? or Leukotriene? or "SRS-A" or Thromboxane? or "Eicosatetraynoic Acid?" or "Eicosatrienoic Acid?" or Lipoxin? or "Linoleic Acid?" or Lubiprostone or Capsaicin or "Erucic Acid?" or "Oleic Acid?" or "Undecylenic Acid?" or Gefarnate or Ionomycin or Oxylipin? or "Sorbic Acid?" or "Heptanoic Acid?" or "Atorvastatin Calcium" or Heptanoate? or "Lauric Acid?" or Laurate? or Mupirocin or "Mycolic Acid?" or "Mycophenolic Acid?" or "Myristic Acid?" or Myristate? or "Palmitic Acid?" or Palmitate? or "Palmitoyl Coenzyme A" or "Prostanoic Acid?" or "Sodium Morrhuate" or "Stearic Acid?" or Stearate? or "Thioctic Acid?" or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or "Cord Factor?" or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or |

| # | Searches |
|---|---|
| | Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or "Polyisoprenyl Phosphate Sugar?" or "Polyisoprenyl Phosphate Monosaccharide?" or "Polyisoprenyl Phosphate Oligosaccharide?" or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or "ATP Binding Cassette Transporter Sub-Family G Member 5" or "ATP Binding Cassette Transporter Sub-Family G Member 8" or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or "Phosphatidic Acid?" or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or "Phospholipid Ether?" or Plasmalogen? or "Platelet Activating Factor" or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or "Dihydroxyvitamin D3" or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or "19-Iodocholesterol" or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or "25-Hydroxyvitamin D2" or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)):ti,ab |
| #58 | #56 or #57 |
| #59 | MeSH descriptor: [Carbohydrates] explode all trees |
| #60 | ratio?:ti,ab |
| #61 | #59 and #60 |
| #62 | MeSH descriptor: [Heparin] explode all trees |
| #63 | MeSH descriptor: [Glycopeptides] explode all trees |
| #64 | MeSH descriptor: [Aminoglycosides] explode all trees |
| #65 | #62 or #63 or #64 |
| #66 | ratio?:ti,ab |
| #67 | #65 and #66 |
| #68 | #61 not #67 |
| #69 | ((ratio? or amount?) near/10 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or "Muramic Acid?" or "Acetylmuramyl-Alanyl-Isoglutamine" or "Neuraminic Acid?" or "Sialic Acid?" or "N-Acetylneuraminic Acid" or "Deoxy Sugar?" or Deoxyglucose or "Fluorodeoxyglucose F18" or Deoxyribose or Fucose or Rhamnose or Sucrose or "High Fructose Corn Syrup" or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or "AC133 Antigen" or "ADAM* Protein?" or Fertilin? or "Cholesterol Ester Transfer Protein?" or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or "3-O-Methylglucose" or Thioglucoside? or Glucosinolate? or "Glycosylated Hemoglobin A" or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or "Adenosine Diphosphate" or "O-Acetyl-ADP-Ribose" or "Cyclic ADP-Ribose" or "Cytidine Diphosphate Diglyceride?" or "Guanosine Diphosphate" or "Uridine Diphosphate" or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or "Quillaja Saponin?" or Solanine or "Teichoic Acid?" or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or "Imino Sugar?" or "Imino Furanose?" or "Imino Pyranose?" or "1-Deoxynojirimycin" or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or "Hypromellose Derivative?" or Methylcellulose or "Carboxymethylcellulose Sodium" or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or "Hydroxyethyl Starch Derivative?" or Trehalose or Glycosaminoglycan? or Chondroitin or "Dermatan Sulfate" or "Heparitin Sulfate" or "Hyaluronic Acid" or "Keratan Sulfate" or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or "Pentosan Sulfuric Polyester" or Bambermycin? or "Lipid A" or "O Antigen?" or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or "CD44 Antigen?" or Versican? or "Heparan Sulfate Proteoglycan?" or "Small Leucine-Rich Proteoglycan?" or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or "Sugar Acid?" or "Ascorbic Acid" or "Dehydroascorbic Acid" or "Diketogulonic Acid" or "Glucaric Acid" or Gluconate? or "Glyceric Acid?" or "Diphosphoglyceric Acid?" or Diphosphoglycerate or Tartrate? or Tartronate? or "Uronic Acid?" or Glucuronate? or "Glucuronic Acid" or "Hexuronic Acid?" or "Iduronic Acid" or "Sugar Alcohol?" or Dithioerythritol or Dithiothreitol or Erythritol or "Erythrityl Tetranitrate" or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or "Phytic Acid" or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or "Sugar Phosphate?" or "Dihydroxyacetone Phosphate" or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or "Glucose-6-Phosphate" or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or "Phosphoribosyl Pyrophosphate" or Ribosemonophosphate? or Ribulosephosphate? or "Polyisoprenyl Phosphate" or "Dolichol Monophosphate Mannose")):ti,ab |
| #70 | #68 or #69 |
| #71 | MeSH descriptor: [Fat Emulsions, Intravenous] this term only |
| #72 | ratio?:ti,ab |
| #73 | #71 and #72 |
| #74 | (ratio? near/10 macronutrient?):ti,ab |
| #75 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/10 macronutrient?):ti,ab |

| # | Searches |
|---|---|
| #76 | #74 or #75 |
| #77 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/10 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or "Fatty Acid?" or "Omega-3" or "Omega-6" or "Linolenic Acid?" or "Docosahexaenoic Acid?" or "Eicosapentaenoic Acid?" or "Ricinoleic Acid?" or Triolein or Caprylate? or "Decanoic Acid?" or Decanoate? or "Eicosanoic Acid?" or Endocannabinoid? or Eicosanoid? or "Arachidonic Acid?" or "Hydroxyeicosatetraenoic Acid?" or "eicosatetraenoic Acid?" or Isoprostane? or Neuroprostane? or Leukotriene? or "SRS-A" or Thromboxane? or "Eicosatetraynoic Acid?" or "Eicosatrienoic Acid?" or Lipoxin? or "Linoleic Acid?" or Lubiprostone or Capsaicin or "Erucic Acid?" or "Oleic Acid?" or "Undecylenic Acid?" or Gefarnate or Ionomycin or Oxylipin? or "Sorbic Acid?" or "Heptanoic Acid?" or "Atorvastatin Calcium" or Heptanoate? or "Lauric Acid?" or Laurate? or Mupirocin or "Mycolic Acid?" or "Mycophenolic Acid?" or "Myristic Acid?" or Myristate? or "Palmitic Acid?" or Palmitate? or "Palmitoyl Coenzyme A" or "Prostanoic Acid?" or "Sodium Morrhuate" or "Stearic Acid?" or Stearate? or "Thioctic Acid?" or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or "Cord Factor?" or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or "Polyisoprenyl Phosphate Sugar?" or "Polyisoprenyl Phosphate Monosaccharide?" or "Polyisoprenyl Phosphate Oligosaccharide?" or Lipofuscin or Lipopolysaccharide? or "O Antigen?" or Lipoprotein? or Apolipoprotein? or "ATP Binding Cassette Transporter Sub-Family G Member 5" or "ATP Binding Cassette Transporter Sub-Family G Member 8" or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or "Phosphatidic Acid?" or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or "Phospholipid Ether?" or Plasmalogen? or "Platelet Activating Factor" or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or "Dihydroxyvitamin D3" or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or "19-Iodocholesterol" or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or "25-Hydroxyvitamin D2" or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)):ti,ab |
| #78 | ((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/10 (Carbohydrate? or "Amino Sugar?" or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or "Muramic Acid?" or "Acetylmuramyl-Alanyl-Isoglutamine" or "Neuraminic Acid?" or "Sialic Acid?" or "N-Acetylneuraminic Acid" or "Deoxy Sugar?" or Deoxyglucose or "Fluorodeoxyglucose F18" or Deoxyribose or Fucose or Rhamnose or Sucrose or "High Fructose Corn Syrup" or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or "AC133 Antigen" or "ADAM* Protein?" or Fertilin? or "Cholesterol Ester Transfer Protein?" or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or "3-O-Methylglucose" or Thioglucoside? or Glucosinolate? or "Glycosylated Hemoglobin A" or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or "Adenosine Diphosphate" or "O-Acetyl-ADP-Ribose" or "Cyclic ADP-Ribose" or "Cytidine Diphosphate Diglyceride?" or "Guanosine Diphosphate" or "Uridine Diphosphate" or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or "Quillaja Saponin?" or Solanine or "Teichoic Acid?" or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or "Imino Sugar?" or "Imino Furanose?" or "Imino Pyranose?" or "1-Deoxynojirimycin" or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or "Hypromellose Derivative?" or Methylcellulose or "Carboxymethylcellulose Sodium" or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or "Hydroxyethyl Starch Derivative?" or Trehalose or Glycosaminoglycan? or Chondroitin or "Dermatan Sulfate" or "Heparitin Sulfate" or "Hyaluronic Acid" or "Keratan Sulfate" or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or "Pentosan Sulfuric Polyester" or Bambermycin? or "Lipid A" or "O Antigen?" or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or "CD44 Antigen?" or Versican? or "Heparan Sulfate Proteoglycan?" or "Small Leucine-Rich Proteoglycan?" or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or "Sugar Acid?" or "Ascorbic Acid" or "Dehydroascorbic Acid" or "Diketogulonic Acid" or "Glucaric Acid" or Gluconate? or "Glyceric Acid?" or "Diphosphoglyceric Acid?" or Diphosphoglycerate or Tartrate? or Tartronate? or "Uronic Acid?" or Glucuronate? or "Glucuronic Acid" or "Hexuronic Acid?" or "Iduronic Acid" or "Sugar Alcohol?" or Dithioerythritol or Dithiothreitol or Erythritol or "Erythrityl Tetranitrate" or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or "Phytic Acid" or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or "Sugar Phosphate?" or "Dihydroxyacetone Phosphate" or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or "Glucose-6-Phosphate" or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or "Phosphoribosyl Pyrophosphate" or Ribosemonophosphate? or Ribulosephosphate? or "Polyisoprenyl Phosphate" or "Dolichol Monophosphate Mannose")):ti,ab |
| #79 | MeSH descriptor: [Lipids] explode all trees and with qualifier(s): [administration & dosage - AD] |
| #80 | MeSH descriptor: [Prostaglandins] explode all trees and with qualifier(s): [administration & dosage - AD] |
| #81 | #79 not #80 |
| #82 | MeSH descriptor: [Carbohydrates] explode all trees and with qualifier(s): [administration & dosage - AD] |

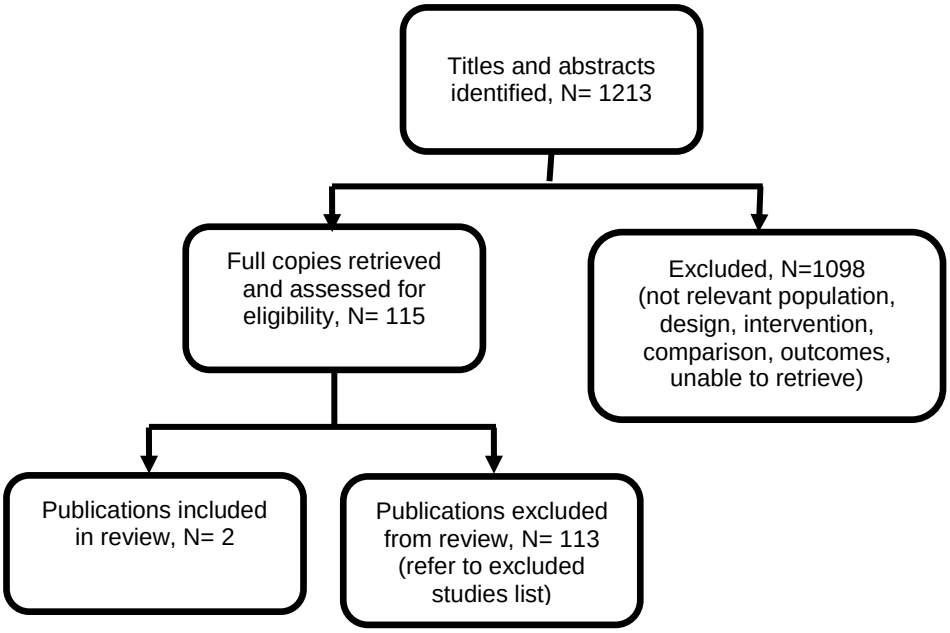
| # | Searches |
|---|---|
| #83 | MeSH descriptor: [Heparin] explode all trees and with qualifier(s): [administration & dosage - AD] |
| #84 | MeSH descriptor: [Glycopeptides] explode all trees and with qualifier(s): [administration & dosage - AD] |
| #85 | MeSH descriptor: [Aminoglycosides] explode all trees and with qualifier(s): [administration & dosage - AD] |
| #86 | #83 or #84 or #85 |
| #87 | #82 not #86 |
| #88 | MeSH descriptor: [Energy Intake] this term only |
| #89 | MeSH descriptor: [Energy Metabolism] this term only |
| #90 | #88 or #89 |
| #91 | ratio?:ti,ab |
| #92 | #90 and #91 |
| #93 | (energy near/10 ratio?):ti,ab |
| #94 | #92 or #93 |
| #95 | #14 and #29 and #39 |
| #96 | #14 and #29 and #40 |
| #97 | #14 and #29 and #44 and (#45 or #77 or #78) |
| #98 | #14 and #29 and #49 and (#81 or #87) |
| #99 | #95 or #96 or #97 or #98 |
| #100 | #14 and #29 and #58 |
| #101 | #14 and #29 and #70 |
| #102 | #14 and #73 |
| #103 | #14 and #29 and #76 |
| #104 | #14 and #29 and #77 and #78 |
| #105 | #14 and #29 and #81 and #87 |
| #106 | #100 or #101 or #102 or #103 or #104 or #105 |
| #107 | #14 and #29 and #94 |
| #108 | #99 or #106 or #107 |

1
2

# Appendix C – Clinical evidence study selection

## Clinical study selection for: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

**Figure 1: PRISMA flow chart for review question, what are the most effective amounts of nitrogen and non-nitrogen energy?**



# Appendix D – Clinical evidence tables

## Clinical evidence tables for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

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

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Full citation<br>Zlotkin, S. H., Bryan, M. H., Anderson, G. H., Intravenous nitrogen and energy intakes required to duplicate in utero nitrogen accretion in prematurely born human infants, The Journal of pediatrics, 99, 115-20, 1981<br>Ref Id<br>690255<br>Country/ies where the study was carried out<br>Canada<br>Study type<br>Observational study<br><br>Aim of the study<br>To determine nitrogen intake requirements and interaction between | Sample size<br>N=22*<br>Group A: n=6<br>Group B: n=6<br>Group C: n=5<br>Group D: n=8<br>Group E: n=5<br><br>Characteristics<br>Gestational age (weeks) - mean (range)<br>29.2 (25 to 33)<br><br>Postnatal age (days) - mean (range)<br>18.7 (4 to 55)<br><br>Infants with necrotising enterocolitis<br>n=19<br><br>Inclusion criteria | Interventions<br>High nitrogen intervention<br>Group A: Nitrogen: 640mg/kg/day with energy intake of 50 kcal/kg/day<br>Group C: Nitrogen: 640mg/kg/day with energy intake of 80kcal/kg/day<br><br>Medium nitrogen intervention<br>Group B: Nitrogen 480mg/kg/day with energy intake of 50 kcal/kg/day | Details<br>All infants received only PN; feeding periods were for 6 days. All infants were assessed for at least 4 days after surgery or after the start of treatment for nectrotising enterocolitis.<br>Infants deemed unsuitable for lipid infusion due to hyperbilirubinaemia received low energy intake.<br><br>All infants received same l-amino acid mixture in 10% dextrose and water via peripheral vein using a continuous flow infusion pump to provide a fluid intake of 160 ml/kg/day.<br><br>Statistical analyses<br>Group means compared using analysis of variance or covariance methods for unbalanced groups (Duncan's | Results<br>Weight gain (gm/kg/day) - mean ±SEM<br>Group A: 1.5 (3.2)<br>Group B: 2.2 (4.0)<br>Group C: 15.6 (1.9); p<0.05**<br>Group D: 16.2 (2.4); p<0.05**<br>Group E: 5.2 (3.1)<br><br>Linear growth (cm/6 day) - mean ±SEM<br>Group A: 0.6 (0.2)<br>Group B: 0.3 (0.1)<br>Group C: 0.7 (0.2)<br>Group D: 1.0 (0.2); p<0.05**<br>Group E: not reported<br><br>Head circumference | Limitations<br>Cochrane risk of bias tool for non-randomised trials (ROBINS-I)<br>Confounding bias: Low risk of bias<br><br>Selection of participant's bias: Serious risk of bias (infants allocated to treatments based on presence of hyperbilirubinaemia and suitability for lipid infusion)<br><br>Classification of interventions bias: Low risk of bias<br><br>Deviations from intended interventions bias: NI (8 infants were studied for two balance periods, however, none were included in the same treatment group more than once) |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| energy and nitrogen intake on growth and nitrogen retention in parenterally fed premature infants<br><br>Study dates<br>Not stated<br><br>Source of funding<br>Not stated | Premature, appropriate size for gestational age infants<br><br>Exclusion criteria<br>Infants <4 days of age | Group D: Nitrogen 480mg/kg/day with energy intake of 80 kcal/kg/day<br><br>Low nitrogen intervention<br>Group E: Nitrogen 320mg/kg/day with energy intake of 80 kcal/kg/day | multiple range test). Simple linear and multiple regression analysis used to assess the relationship between energy and nitrogen intake on nitrogen retention, weight change, and 3-methylhistidine excretion. | No statistically significant difference across Group A to D.<br><br>Nitrogen retention (mg/kg/day) - mean ±SEM<br>Group A: 274 (11)*<br>Group B: 256 (20)<br>Group C: 432 (21); p<0.05**<br>Group D: 320 (8); p<0.05**<br>Group E: 185 (24)<br><br>Nutritional intake (energy kcal/kg/day/nitrogen mg/kg/day) - mean<br>Group A: 55/655<br>Group B: 50/494<br>Group C: 80/636<br>Group D: 80/481<br>Group E: 83/310 | Missing data bias: Low risk of bias (all infants evaluable)<br><br>Measurement of outcomes bias: Serious risk of bias (outcome assessors not blinded; however, outcomes assessed using objective measures)<br><br>Selection of the reported results bias: Low risk of bias (all outcomes reported)<br><br>Other information<br>*8 infants were studied for two balance periods, however, none were included in the same treatment group more than once.<br>**effect of high vs. low energy (Group A vs. group C or Group B vs. group D) at same nitrogen intake. |
| Full citation<br>Pineault, M., Chessex, P., Bisaillon, S., Brisson, G., Total parenteral nutrition in the newborn: impact of the quality of infused energy on nitrogen | Sample size<br>N=16<br>Low fat (60 kcal/kg-1/d-1): n=4<br>Low fat (80 kcal/kg-1/d-1): n=4<br>High fat (80 kcal/kg-1/d-1): n=4 | Interventions<br>Low non-protein energy group<br>Low fat (60 kcal/kg-1/day-1): 11 g/kg/-1/day-1 glucose; 1g/kg-1/d-1 lipids. | Details<br>Each infant received two 6-day periods of isocaloric and isonitrogenous (450 mg/kg-1/day-1) infusions, differing only by the source of calories.<br><br>All infusions provided per kg per day 150 mL total fluids, 3 | Results<br>Weight gain (g/kg-1/d-1) - mean ±SEM<br>Low fat (n=8): 11.5 (2.3)<br>High fat (n=8): 14.6 (2.0) | Limitations<br>Cochrane risk of bias tool<br>Selection bias<br>Random sequence generation: Low risk. Latin-square cross-over.<br>Allocation concealment: Unclear risk. No details provided. |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| metabolism, American Journal of Clinical Nutrition, 47, 298-304, 1988<br>Ref Id<br>394278<br>Country/ies where the study was carried out<br>Canada<br>Study type<br>Observational study<br><br>Aim of the study<br>To determine the influences of the quality (level and source) of infused energy on nitrogen metabolism<br><br>Study dates<br>Not stated<br><br>Source of funding<br>Supported by the Medical Research Council of Canada by a grant-in-aid from Travenol Canada Inc and a fellowship of the Interservice Club Council | High fat (60 kcal/kg-1/d-1): n=4<br><br>Characteristics<br>Gestational age (weeks) - mean ±SEM<br>Low fat: 36 (1)<br>High fat: 34 (1)<br><br>Age at study (days) - mean ±SEM<br>Low fat: 9 (1)<br>High fat: 11 (2)<br><br>Birthweight (g) - mean ±SEM<br>Low fat: 2293 (147)<br>High fat: 2006 (169)<br><br>Weight at study (g) - mean ±SEM<br>Low fat: 2102 (153)<br>High fat: 1850 (174)<br><br>Gastroschisis<br>Low fat: 2<br>High fat: 2<br><br>Necrotising enterocolitis<br>Low fat: 3<br>High fat: 4 | Low fat (60 kcal/kg-1/day-1): 5 g/kg/-1/day-1 glucose; 3g/kg-1/d-1 lipids.<br><br>High non-protein energy group<br>High fat (80 kcal/kg-1/day-1): 11g/kg-1/day-1 glucose; 3g/kg-1/day-1 lipids<br>High fat (80 kcal/kg-1/day-1): 17g/kg-1/day-1 glucose; 1g/kg-1/day-1 lipids | mmol sodium, 2 mmol potassium, 2 mmol chloride, 1 mmol calcium, 0.125 mmol magnesium, 0.8 mmol phosphorus, 300 µg zinc, 40 µg copper and multivitamins given at 2.5 mL/day.<br>Total parenteral nutrition was delivered through a peripheral line.<br>Assisted ventilation and supplementary oxygen were not required.<br><br>Statistical analyses<br>ANOVA was used to compare results of nutrient and calorie intakes, nitrogen retention, 3-methylhistidine, glycaemia, and blood urea nitrogen. In the case of missing data from one of the periods, Student's t-test was used. | Head circumference increment (cm/week) - mean ±SEM<br>Low fat (n=8): 0.50 (0.12)<br>High fat (n=7): 0.90 (0.15); p<0.05<br><br>Length gain (cm/week) - mean ±SEM<br>Low fat (n=8): 0.67 (0.17)<br>High fat (n=8): 0.92 (0.22)<br><br>Nitrogen intake (mg/kg-1/day-1) - mean ±SEM<br>Low fat (60 kcal/kg-1/day-1): 433 (8.0)<br>Low fat (80 kcal/kg-1/day-1): 433 (4.0)<br>High fat (60 kcal/kg-1/day-1): 430 (9.0)<br>High fat (80 kcal/kg-1/day-1): 438 (6.0)<br><br>Nitrogen excretion (mg/kg-1/day-1) - mean ±SEM<br>Low fat (60 kcal/kg-1/day-1): 217 (24.0)<br>Low fat (80 kcal/kg-1/day-1): 183 (9.0) | Performance bias<br>Blinding of participants and personnel: Unclear risk. No details provided.<br><br>Detection bias<br>Blinding of outcome assessment: Unclear risk. Outcomes were objective, but not details provided on assessor blinding.<br><br>Attrition bias<br>Incomplete outcome data: Low risk. There were no study withdrawals.<br><br>Reporting bias<br>Selective reporting: Low risk. All outcomes reported.<br><br>Other bias<br>Other sources of bias: Unclear risk. Unclear wash-out period between interventions, suggesting potential for carry-over effect from one intervention to the other.<br><br>Other information |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | Feeding intolerance<br>Low fat: 0<br>High fat: 1<br><br>Inclusion criteria<br>Appropriate-for-gestational-age newborn infants demonstrating unchanging clinical conditions<br><br>Exclusion criteria<br>Not stated | | | High fat (60 kcal/kg-1/day-1): 206 (20.0)<br>High fat (80 kcal/kg-1/day-1): 193 (11.0)<br><br>Nitrogen balance (mg/kg-1/day-1) - mean ±SEM<br>Low fat (60 kcal/kg-1/day-1): 216 (27.0)<br>Low fat (80 kcal/kg-1/day-1): 250 (8.0)<br>High fat (60 kcal/kg-1/day-1): 224 (18.0)<br>High fat (80 kcal/kg-1/day-1): 245 (10.0)<br><br>Nitrogen retention (mg/kg-1/day-1) - mean ±SEM<br>Low fat (60 kcal/kg-1/day-1): 49.7 (5.8)<br>Low fat (80 kcal/kg-1/day-1): 57.1 (1.9)<br>High fat (60 kcal/kg-1/day-1): 52.0 (4.2)<br>High fat (80 kcal/kg-1/day-1): 55.9 (2.2)<br>No infant experienced proven infection. | NB: We have not combined the data from the HF and LF groups, as we would have to calculate the SD from SEM and then combine means, which we believe would introduce too much error. |

*ANOVA: analysis of variance; HF: high fat; LF; low fat; PN: parenteral nutrition; ROBINS-I: risk of bias in non-randomised studies of interventions; SD: standard deviation; SEM: standard error of the mean.*

# Appendix E – Forest plots

## Forest plots for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

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

# Appendix F – GRADE tables

## GRADE tables for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

**Table 5: Clinical evidence profile for comparison high non-protein to low non-protein PN**

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | High non-protein energy | Low non-protein energy | Relative (95% CI) | Absolute | Quality | Importance |
| **Weight gain (follow-up mean 12 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1,2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 8 | 8 | - | MD 3.1 lower (9.08 lower to 2.88 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Length (follow-up mean 12 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1,2] | no serious inconsistency | no serious indirectness | serious[4] | none | 8 | 8 | - | MD 0.25 lower (0.79 lower to 0.29 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Head circumference (follow-up mean 12 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1,2] | no serious inconsistency | no serious indirectness | serious[5] | none | 8 | 8 | - | MD 0.4 lower (0.78 to 0.02 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Nitrogen balance (follow-up mean 12 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1,2] | no serious inconsistency | no serious indirectness | serious[6] | none | 8 | 8 | - | MD 27 lower (58.84 lower to | ⊕OOO VERY LOW | CRITICAL |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **High non-protein energy** | **Low non-protein energy** | **Relative (95% CI)** | **Absolute** | **Quality** | **Importance** |
| | | | | | | | | | | 4.84 higher) | | |
| **Nitrogen excretion (follow-up mean 12 days; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | very serious[1,2] | no serious inconsistency | no serious indirectness | very serious[7] | none | 8 | 8 | - | MD 23.5 higher (6.08 lower to 53.08 higher) | ⊕OOO VERY LOW | CRITICAL |

*CI: confidence interval; MD: mean difference.*

*[1] Serious risk of bias as there is an unclear risk of carry over effects during wash out period. Unclear risk of detection bias, assessors were not blind to treatment; however most outcomes were objectively measured.*

*[2] Comparisons provide different calorie intake which could confound the outcomes.*

*[3] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-2.83 and 2.83).*

*[4] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.31).*

*[5] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.21).*

*[6] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-8.49).*

*[7] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-5.37 and 5.37).*

1

2 **Table 6: Clinical evidence profile for comparison high protein to medium protein PN**

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | High protein energy (640mg/kg/day) | Medium protein energy (480mg/kg/day) | Relative (95% CI) | Absolute | Quality | Importance |
| **Weight gain (g/kg/day) - 50kcal (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 6 | 6 | - | MD 0.7 lower (10.74 lower to 9.34 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Weight gain (g/kg/day) - 80kcal (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | very serious[3] | none | 5 | 8 | - | MD 0.6 lower (4.68 lower to 3.48 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Length - 50kcal (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | very serious[4] | none | 6 | 6 | - | MD 0.3 higher (0.14 lower to 0.74 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Length - 80kcal (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | serious[5] | none | 5 | 8 | - | MD 0.3 lower (0.86 lower to 0.26 higher) | ⊕⊕OO LOW | CRITICAL |
| **Nitrogen retention - 50kcal (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **High protein energy (640mg/kg /day)** | **Medium protein energy (480mg/kg /day)** | **Relative (95% CI)** | **Absolute** | **Quality** | **Importance** |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | very serious[6] | none | 6 | 6 | - | MD 18 higher (26.74 lower to 62.74 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Nitrogen retention - 80kcal (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 5 | 8 | - | MD 112 higher (67.95 to 156.05 higher) | ⊕OOO VERY LOW | CRITICAL |

*CI: confidence interval; MD: mean difference.*

*[1] Serious risk of bias due to high risk of selection bias, infants were allocated to treatments. Unclear risk of detection bias, assessors were not blind to treatment; however most outcomes were objectively measured.*

*[2] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (4.9).*

*[3] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (1.2).*

*[4] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.12).*

*[5] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.29).*

*[6] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (24.5).*

**Table 7: Clinical evidence profile for comparison high protein to low protein PN**

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | High protein energy (640mg/kg/day) | Low protein energy (320mg/kg/day) | Relative (95% CI) | Absolute | Quality | Importance |
| **weight gain (g/kg/day) (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious [1] | no serious inconsistency | no serious indirectness | serious[2] | none | 5 | 5 | - | MD 10.4 higher (3.28 to 17.52 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Nitrogen retention (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious [1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 5 | 5 | - | MD 247 higher (184.49 to 309.51 higher) | ⊕OOO VERY LOW | CRITICAL |

*CI: confidence interval; MD: mean difference.*

*[1] Serious risk of bias due to high risk of selection bias, infants were allocated to treatments. Unclear risk of detection bias, assessors were not blind to treatment; however most outcomes were objectively measured.*

*[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (3.47).*

**Table 8: Clinical evidence profile for comparison medium protein to low protein PN**

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Medium protein energy (480mg/kg/day) | Low protein energy (320mg/kg/day) | Relative (95% CI) | Absolute | Quality | Importance |
| **Weight gain (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 8 | 5 | - | MD 11 higher (3.32 to 18.68 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Nitrogen retention (follow-up mean 6 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 8 | 5 | - | MD 135 higher (85.41 to 184.59 higher) | ⊕OOO VERY LOW | CRITICAL |

*CI: confidence interval; MD: mean difference.*

*[1] Serious risk of bias due to high risk of selection bias, infants were allocated to treatments. Unclear risk of detection bias, assessors were not blind to treatment; however most outcomes were objectively measured.*

*[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (3.47).*

# Appendix G – Economic evidence study selection

## Economic evidence study selection for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

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

# Appendix H – Economic evidence tables

## Economic evidence tables for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

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

# Appendix I – Economic evidence profiles

## Economic evidence profiles for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

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

# Appendix J – Economic analysis

## Economic analysis for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

No economic analysis was conducted for this review question.

# Appendix K – Excluded studies

## Excluded studies for review question: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

### Clinical studies

**Table 9: Excluded studies and reasons for their exclusion (one search was conducted for two review questions; D7 and D8)**

| Study | Reason for Exclusion |
|---|---|
| Adamkin, D. H., McClead, R. E., Jr., Desai, N. S., McCulloch, K. M., Marchildon, M. B., Comparison of two neonatal intravenous amino acid formulations in preterm infants: a multicenter study, Journal of perinatology : official journal of the California Perinatal Association, 11, 375-82, 1991 | Intervention does not fit the inclusion criteria: Different AA intakes. |
| Aiken, C. G. A., Pathogenesis of metabolic acidosis in preterm infants, Journal of Paediatrics and Child Health, 48, 135, 2012 | Conference abstract - insufficient information. |
| Altman, R. P., Randolph, J. G., Application and hazards of total parenteral nutrition in infants, Annals of Surgery, 174, 85-90, 1971 | Study design and population does not meet protocol eligibility criteria - babies aged 3 days 10 15 weeks; presented as case reports. |
| Anderson, T. L., Muttart, C. R., Bieber, M. A., Nicholson, J. F., Heird, W. C., A controlled trial of glucose versus glucose and amino acids in premature infants, Journal of Pediatrics, 94, 947-51, 1979 | Intervention does not fit the inclusion criteria: Glucose vs. Glucose AA. |
| Asch, M. J., Huxtable, R. F., Hays, D. M., High calorie parenteral therapy in infants and children, Arch.Surg., 104, 434-437, 1972 | Study intervention does not meet protocol eligibility criteria - starting and target doses not reported. |
| Bassiouny, Mohamed R., Almarsafawy, Hala, Abdel-Hady, Hesham, Nasef, Nehad, Hammad, Tarek A., Aly, Hany, A randomized controlled trial on parenteral nutrition, oxidative stress, and chronic lung diseases in preterm infants, Journal of pediatric gastroenterology and nutrition, 48, 363-9, 2009 | Intervention does not fit the inclusion criteria: Different AA intakes. |
| Biagetti, C., Bellagamba, M. P., D'Ascenzo, R., Burattini, I., Cogo, P. E., Carnielli, V. P., Increasing amino acid and non-protein energy in preterms on parenteral nutrition: Higher rate of sepsis and no benefit in short-term growth, Archives of Disease in Childhood, 99, A132, 2014 | Study design does not meet eligibility criteria - conference abstract. |
| Bonsante,F., Iacobelli,S., Chantegret,C., Martin,D., Gouyon,J.B., The effect of parenteral nitrogen and energy intake on electrolyte balance in the preterm infant, European Journal of Clinical Nutrition, 65, 1088-1093, 2011 | Intervention does not fit the inclusion criteria: Different AA intakes. |
| Bresson, J. L., Bader, B., Rocchiccioli, F., Mariotti, A., Ricour, C., Sachs, C., Rey, J., Protein-metabolism kinetics and energy-substrate utilization in infants fed parenteral solutions with different glucose-fat ratios, The American journal of clinical nutrition, 54, 370-6, 1991 | Outcome of interest does not fit the inclusion criteria: metabolism. |

| Study | Reason for Exclusion |
|---|---|
| Bulbul, Ali, Okan, Fusun, Bulbul, Lida, Nuhoglu, Asiye, Effect of low versus high early parenteral nutrition on plasma amino acid profiles in very low birth-weight infants, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 25, 770-6, 2012 | Study intervention does not meet protocol eligibility criteria - focus on high vs low amino acids; only target non-protein calories reported; lipids and carbohydrates same for all babies. |
| Callaghan, F., Morgan, C., Target parenteral protein attainment in parenterally fed preterm infants following the implementation of the concentrated macronutrients in parenteral standardised solutions (CoMPaSS) programme, Journal of Pediatric Gastroenterology and Nutrition, 64, 805, 2017 | Abstract. |
| Can, E., Bulbul, A., Uslu, S., Comert, S., Bolat, F., Nuhoglu, A., Evaluation of two different types of parenteral nutrition on early growth of preterm infants, Early Human Development, 86, S85, 2010 | Study design does not meet eligibility criteria - conference abstract. |
| Can, E., Bülbül, A., Uslu, S., Cömert, S., Bolat, F., NuhoÄŸlu, A., Effects of aggressive parenteral nutrition on growth and clinical outcome in preterm infants, Pediatrics International, 54, 869-874, 2012 | Study intervention does not meet protocol eligibility criteria - starting and target nitrogen: non-nitrogen energy not reported; target lipid: carbohydrate ratios not reported. |
| Can, Emrah, Bulbul, Ali, Uslu, Sinan, Comert, Serdar, Bolat, Fatih, Nuhoglu, Asiye, Effects of aggressive parenteral nutrition on growth and clinical outcome in preterm infants, Pediatrics international : official journal of the Japan Pediatric Society, 54, 869-74, 2012 | Intervention does not fit the inclusion criteria: Different AA and lipid intakes. |
| Chen, W. J., Oashi, E., Kasai, M., Amino acid metabolism in parenteral nutrition: with special reference to the calorie: nitrogen ratio and the blood urea nitrogen level, Metabolism: clinical and experimental, 23, 1117-23, 1974 | Intervention does not fit the inclusion criteria: Different AA intakes. |
| Chessex, P., Gagne, G., Pineault, M., Vaucher, J., Bisaillon, S., Brisson, G., Metabolic and clinical consequences of changing from high-glucose to high-fat regimens in parenterally fed newborn infants, Journal of Pediatrics, 115, 992-997, 1989 | Included study for D8: Carb/lipids. |
| Collins, C. T., Gibson, R. A., Miller, J., McPhee, A. J., Willson, K., Smithers, L. G., Makrides, M., Carbohydrate intake is the main determinant of growth in infants born <33 weeks' gestation when protein intake is adequate, Nutrition, 24, 451-7, 2008 | Study intervention does not meet protocol eligibility criteria - energy intake reported as medians for all macronutrients for parenteral and enteral nutrients; lipid: carbohydrate ratios not reported. |
| Collins, Carmel T., Gibson, Robert A., Miller, Jacqueline, McPhee, Andrew J., Willson, Kristyn, Smithers, Lisa G., Makrides, Maria, Carbohydrate intake is the main determinant of growth in infants born <33 weeks' gestation when protein intake is adequate, Nutrition (Burbank, Los Angeles County, Calif.), 24, 451-7, 2008 | Intervention does not fit the inclusion criteria: No comparator of interest. |
| Cooke, R. J., Yeh, Y. Y., Gibson, D., Debo, D., Bell, G. L., Soybean oil emulsion administration during parenteral nutrition in the preterm infant: | Outcome of interest does not meet the inclusion criteria: Metabolism. |

| Study | Reason for Exclusion |
|---|---|
| effect on essential fatty acid, lipid, and glucose metabolism, The Journal of Pediatrics, 111, 767-73, 1987 | |
| Cooke, R. J., Zee, P., Yeh, Y. Y., Safflower oil emulsion administration during parenteral nutrition in the preterm infant. 1. Effect on essential fatty acid status, Journal of Pediatric Gastroenterology and Nutrition, 4, 799-803, 1985 | Outcome of interest does not meet the inclusion criteria: Essential fatty acid. |
| D'Ascenzo, R, D'Egidio, S, Angelini, L, Bellagamba, Mp, Manna, M, Pompilio, A, Cogo, Pe, Cogo, Pe, Carnielli, Vp, Parenteral nutrition of preterm infants with a lipid emulsion containing 10% fish oil: effect on plasma lipids and long-chain polyunsaturated fatty acids, Journal of Pediatrics, 159, 33-38.e1, 2011 | Intervention does not fit the inclusion criteria: Difference in type of lipid (fish vs. soybean). |
| De Curtis, M., Dito, L., Lucchini, R., Terrin, G., Nutrition of very low birth-weight infants, Italian Journal of Pediatrics, 40, 2014 | Conference abstract. |
| Deshpande, Girish C., Simmer, Karen, Mori, Trevor, Croft, Kevin, Parenteral lipid emulsions based on olive oil compared with soybean oil in preterm (<28 weeks' gestation) neonates: a randomised controlled trial, Journal of pediatric gastroenterology and nutrition, 49, 619-25, 2009 | Intervention does not fit the inclusion criteria: Difference in lipid type (olive vs. soybean). |
| Deshpande, Girish, Simmer, Karen, Deshmukh, Mangesh, Mori, Trevor A., Croft, Kevin D., Kristensen, Judy, Fish Oil (SMOFlipid) and olive oil lipid (Clinoleic) in very preterm neonates, Journal of pediatric gastroenterology and nutrition, 58, 177-82, 2014 | Intervention does not fit the inclusion criteria: Difference in lipid type (olive vs. fish). |
| DeSilva, Shayana, Hana, Mervat, Sutija, Vesna G., Raziuddin, Khaja, Effect of amino acids on glucose tolerance and hyperkalemia in very low birth weight infants, Journal of Perinatal Medicine, 30, 128-31, 2002 | Study does not meet protocol eligibility criteria - babies received same PN regimen. |
| Dinerstein, A., Nieto, R. M., Solana, C. L., Perez, G. P., Otheguy, L. E., Larguia, A. M., Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants, Journal of Perinatology, 26, 436-42, 2006 | Intervention does not fit the inclusion criteria: Different AA and lipid intakes. |
| Dolanski, E. A., Stahlman, M. T., Meng, H. C., Parenteral alimentation of premature infants under 1,200 grams, Southern medical journal, 66, 41-6, 1973 | Study does not meet protocol eligibility criteria - PN methods/process; energy ratio and amounts of carbohydrates and lipids not reported. |
| Dudrick, S. J., Ruberg, R. L., Principles and practice of parenteral nutrition, Gastroenterology, 61, 901-10, 1971 | Study design does not meet protocol eligibility criteria - narrative review. |
| Duffy, B., Gunn, T., Collinge, J., Pencharz, P., The effect of varying protein quality and energy intake on the nitrogen metabolism of parenterally fed very low birthweight (less than 1600 g) infants, Pediatric Research, 15, 1040-4, 1981 | Intervention does not fit the inclusion criteria: Different sources of AA. |
| Filler, R. M., Eraklis, A. J., Care of the critically ill child: intravenous alimentation, Pediatrics, 46, 456-61, 1970 | Study design does not meet protocol eligibility criteria - narrative on PN. |

| Study | Reason for Exclusion |
|---|---|
| Filler, R. M., Eraklis, A. J., Rubin, V. G., Das, J. B., Long-term total parenteral nutrition in infants, The New England journal of medicine, 281, 589-94, 1969 | Study does not meet protocol eligibility criteria - babies aged 15 to 60 days (outcomes not reported separately); relative amounts of energy or carbohydrates and lipids not reported. |
| Fivez, Tom, Kerklaan, Dorian, Verbruggen, Sascha, Vanhorebeek, Ilse, Verstraete, Soren, Tibboel, Dick, Guerra, Gonzalo Garcia, Wouters, Pieter J., Joffe, Ari, Joosten, Koen, Mesotten, Dieter, Van den Berghe, Greet, Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial, Trials, 16, 202, 2015 | Study protocol. |
| Forsyth, J. S., Murdock, N., Crighton, A., Low birthweight infants and total parenteral nutrition immediately after birth. III. Randomised study of energy substrate utilisation, nitrogen balance, and carbon dioxide production, Archives of Disease in Childhood, Fetal and neonatal edition. 73, F13-6, 1995 | Comparator of interest does not meet the inclusion criteria: Population served as their own controls. Minimal change in lipid intake (difference of 0.01 g/kg/d). |
| Fosel, T. H., Uth, M., Wilhelm, W., Gruness, V., Comparison of two solutions with different glucose concentrations for infusion therapy during laparotomies in infants, Infusionstherapie und Transfusionsmedizin, 23, 80-4, 1996 | Participants do not fit the inclusion criteria: Infants aged 5-14 months. |
| Gobel, Y., Koletzko, B., Bohles, H. J., Engelsberger, I., Forget, D., Le Brun, A., Peters, J., Zimmermann, A., Parenteral fat emulsions based on olive and soybean oils: A randomized clinical trial in preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 37, 161-167, 2003 | Intervention does not fit the inclusion criteria: Difference in lipid type (olive vs. soybean). |
| Hay Jr, W. W., Intravenous nutrition of the very preterm neonate, Acta Paediatrica, International Journal of Paediatrics, 94, 47-56, 2005 | Study design not relevant to protocol - not a systematic review. |
| Hays, D. M., Kaplan, M. S., Mahour, G. H., Strauss, J., Huxtable, R. F., High-calorie infusion therapy following surgery in low-birth-weight infants: metabolic problems encountered, Surgery, 71, 834-41, 1972 | Study intervention does not meet protocol eligibility criteria - all babies received same PN; only target calories for glucose reported. |
| Heird, W. C., Driscoll, J. M., Jr., Schullinger, J. N., Grebin, B., Winters, R. W., Intravenous alimentation in pediatric patients, The Journal of pediatrics, 80, 351-72, 1972 | Study design not relevant to protocol - not a systematic review. |
| Heird, W. C., Winters, R. W., Total intravenous alimentation, American journal of diseases of children (1960), 126, 287-9, 1973 | Study design does not meet protocol eligibility criteria - narrative. |
| Hendry, P. G., James, B. E., MacMahon, R. A., Nitrogen balance studies during oral and complete intravenous feeding of small premature infants, Australian Paediatric Journal, 14, 6-10, 1978 | Intervention does not fit the inclusion criteria: Different types of AA. |
| Hirai, Y., Sanada, Y., Hasegawa, S., Fujiwara, T., Iwakiri, K., Total parenteral nutrition in low-birth-weight neonates with complicated surgical disorders; effects and difficulties, The Japanese journal of surgery, 11, 175-83, 1981 | Study does not meet protocol eligibility criteria - infants received same PN regimen. |

| Study | Reason for Exclusion |
|---|---|
| Iacobelli, S., Bonsante, F., Vintejoux, A., Gouyon, J. B., Standardized parenteral nutrition in preterm infants: early impact on fluid and electrolyte balance, Neonatology, 98, 84-90, 2010 | Study design does not meet the inclusion criteria - cohort study. Intervention not relevant - comparison of standard versus individualised bags. |
| Ibrahim, Hassan M., Jeroudi, Majied A., Baier, R. J., Dhanireddy, Ramasubbareddy, Krouskop, Richard W., Aggressive early total parental nutrition in low-birth-weight infants, Journal of perinatology : official journal of the California Perinatal Association, 24, 482-6, 2004 | Intervention does not fit the inclusion criteria: Early vs. late PN. |
| James, B. E., Hendry, P. G., MacMahon, R. A., Total parenteral nutrition of premature infants. I. Requirement for macronutrient elements, Australian Paediatric Journal, 15, 62-66, 1979 | Study does not meet protocol eligibility criteria - relationship between sodium, potassium, calcium, magnesium, chlorine and phosphorous. |
| Janeiro, P., Cunha, M., Marques, A., Moura, M., Barroso, R., Carreiro, H., Caloric intake and weight gain in a neonatal intensive care unit, European Journal of Pediatrics, 169, 99-105, 2010 | Study intervention does not meet protocol eligibility criteria - not nitrogen vs non-nitrogen energy; starting and target dose for lipids: carbohydrates not clear. |
| Joffe, Ari, Anton, Natalie, Lequier, Laurance, Vandermeer, Ben, Tjosvold, Lisa, Larsen, Bodil, Hartling, Lisa, Nutritional support for critically ill children, Cochrane Database of Systematic Reviews, 2016 | Intervention does not fit the inclusion criteria: EN vs. PN. |
| Johnson, Patricia J., Review of macronutrients in parenteral nutrition for neonatal intensive care population, Neonatal network : NN, 33, 29-34, 2014 | Study type does not fit the inclusion criteria: Commentary review. |
| Jones, M. O., Pierro, A., Garlick, P. J., McNurlan, M. A., Donnell, S. C., Lloyd, D. A., Protein metabolism kinetics in neonates: effect of intravenous carbohydrate and fat, Journal of pediatric surgery, 30, 458-62, 1995 | Included study for D8: Carb/lipids. |
| Jones, M. O., Pierro, A., Hammond, P., Nunn, A., Lloyd, D. A., Glucose utilization in the surgical newborn infant receiving total parenteral nutrition, Journal of pediatric surgery, 28, 1121-5, 1993 | Ratio of carbohydrate to lipid not clear and no comparison group. Outcomes not relevant to protocol - correlation to glucose intake. |
| Kaemmer, A., Miller, J. D., Hyperalimentation in infancy. Experiences at the Maine Medical Center, The Journal of the Maine Medical Association, 63, 200-passim, 1972 | Study does not meet protocol eligibility criteria - case reports; energy and carbohydrate: lipid ratios not reported. |
| Kanarek, K. S., Williams, P. R., Curran, J. S., Total parenteral nutrition in infants and children, Advances in pediatrics, 29, 151-81, 1982 | Not relevant to protocol - not a systematic review. |
| Kandil, H., Darwish, O., Hammad, S., Zagloul, N., Halliday, D., Millward, J., Nitrogen balance and protein turnover during the growth failure in newly born low-birth-weight infants, The American journal of clinical nutrition, 53, 1411-7, 1991 | Conference abstract. |
| Kesiak, M., Nowiczewski, M., Talar, T., Gulczynska, E., Early use of intravenous lipids in two different doses in the group of very low birth weight newborns - RCT, Early Human Development, 86, S86, 2010 | Conference abstract. |

| Study | Reason for Exclusion |
|---|---|
| Khan, Z., Morris, N., Unterrainer, H., Haiden, N., Holasek, S. J., Urlesberger, B., Effect of standardized feeding protocol on nutrient supply and postnatal growth of preterm infants: A prospective study, Journal of Neonatal-Perinatal MedicineJ Neonatal Perinatal Med, 11, 11-19, 2018 | Study intervention does not meet protocol eligibility criteria - relative amounts of nitrogen: non-nitrogen or carbohydrates: lipids not reported. |
| Kotiya, P., Zhao, X., Cheng, P., Zhu, X., Xiao, Z., Wang, J., Fish oil- and soy oil-based lipid emulsions in neonatal parenteral nutrition: a systematic review and meta-analysis, European journal of clinical nutrition, 70, 1106-1115, 2016 | Intervention type does not meet the inclusion criteria: Fish vs. Soy oil. |
| Lenclen, R., Crauste-Manciet, S., Narcy, P., Boukhouna, S., Geffray, A., Guerrault, M. N., Bordet, F., Brossard, D., Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants, European Journal of Pediatrics, 165, 512-518, 2006 | Study design does not meet inclusion criteria - retrospective study. Interventions not relevant, comparison of standardised versus individualised PN (additionally the lipid intake is the same across interventions). |
| Lindblad, B. S., Settergren, G., Feychting, H., Persson, B., Total parenteral nutrition in infants. Blood levels of glucose, lactate, pyruvate, free fatty acids, glycerol, d-beta-hydroxybutyrate, triglycerides, free amino acids and insulin, Acta paediatrica Scandinavica, 66, 409-19, 1977 | Includes ineligible infants (aged 2 to 10 months) and outcomes are not reported separately in eligible infants. |
| Lindblad, B. S., Settergren, G., Feychting, H., Persson, B., Total parenteral nutrition in infants. Blood levels of glucose, lactate, pyruvate, free fatty acids, glycerol, D beta hydroxybutyrate, triglycerides, free amino acids and insulin, Acta Paediatrica Scandinavica, 66, 409-419, 1977 | Study population does not meet protocol eligibility criteria - babies aged 2 days to 10 months; caloric intake not reported for 1 treatment group. |
| Malloy, M. H., Rassin, D. K., Richardson, C. J., Total parenteral nutrition in sick preterm infants: effects of cysteine supplementation with nitrogen intakes of 240 and 400 mg/kg/day, Journal of Pediatric Gastroenterology and Nutrition, 3, 239-44, 1984 | Comparison not relevant to protocol - high versus low nitrogen. |
| Martin, Camilia R., Brown, Yolanda F., Ehrenkranz, Richard A., O'Shea, T. Michael, Allred, Elizabeth N., Belfort, Mandy B., McCormick, Marie C., Leviton, Alan, Extremely Low Gestational Age Newborns Study, Investigators, Nutritional practices and growth velocity in the first month of life in extremely premature infants, Pediatrics, 124, 649-57, 2009 | Data provided does not present outcomes for different lipid to carbohydrate ratios. |
| Mayes, K., Tan, M. J., Morgan, C., Hyperalimentation results in paradoxical fall in tyrosine levels in very preterm infants receiving parenteral nutrition, Archives of disease in childhood., 97, A51, 2012 | Study design does not meet eligibility criteria - conference abstract. |
| McIntosh, N., Mitchell, V., A clinical trial of two parenteral nutrition solutions in neonates, Archives of Disease in Childhood, 65, 692-9, 1990 | Intervention type does not meet the inclusion criteria: Different types of AA. |
| Morgan, C, Herwitker, S, Badhawi, I, Hart, A, Tan, M, Mayes, K, Newland, P, Turner, Ma, SCAMP: standardised, concentrated, additional | Study protocol. |

| Study | Reason for Exclusion |
|---|---|
| macronutrients, parenteral nutrition in very preterm infants: a phase IV randomised, controlled exploratory study of macronutrient intake, growth and other aspects of neonatal care, BMC Pediatrics, 11, 53, 2011 | |
| Morgan, C., Burgess, L., Grosdenier, M., Green, J., McGowan, P., Turner, M. A., Hyperalimentation and blood glucose control in very preterm infants: A randomised controlled parenteral nutrition study, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A2-A3, 2014 | Conference abstract - insufficient information. |
| Morgan, C., Burgess, L., Grosdenier, M., McGowan, P., Turner, M. A., Hyperalimentation and blood glucose control in very preterm infants: The randomised controlled scamp nutrition study, Archives of Disease in Childhood, 99, A208, 2014 | Conference abstract - insufficient information. |
| Morgan, C., McGowan, P., Herwitker, S., Hart, A. E., Turner, M. A., Early postnatal head growth in very preterm infants: The randomised controlled scamp nutrition study, Journal of Neonatal-Perinatal Medicine, 6, 197, 2013 | Abstract. |
| Morgan, C., McGowan, P., Herwitker, S., Hart, A. E., Turner, M. A., Preventing early postnatal head growth failure in very preterm infants: The randomised controlled scamp nutrition study, Archives of Disease in Childhood: Education and Practice Edition, 98, 2013 | Conference abstract. |
| Morgan, C., Parry, S., Tan, M., Neurodevelopmental outcome at 2.5 years in very preterm infants randomised to receive two different parenteral nutrition regimens at birth: The SCAMP nutrition study, Journal of Pediatric Gastroenterology and Nutrition, 64, 764, 2017 | Conference abstract - insufficient information. |
| Morgan, C., Parry, S., Tan, M., Neurodevelopmental outcome in very preterm infants randomized to receive two different parenteral nutrition regimens: The scamp nutrition study, Journal of Neonatal-Perinatal Medicine, 10, 220-221, 2017 | Study design does not meet eligibility criteria - conference abstract. |
| Morgan, Colin, Herwitker, Shakeel, Badhawi, Isam, Hart, Anna, Tan, Maw, Mayes, Kelly, Newland, Paul, Turner, Mark A., SCAMP: standardised, concentrated, additional macronutrients, parenteral nutrition in very preterm infants: a phase IV randomised, controlled exploratory study of macronutrient intake, growth and other aspects of neonatal care, BMC pediatrics, 11, 53, 2011 | Study design does not meet protocol eligibility criteria - study protocol. |
| Morgan, Colin, McGowan, Patrick, Herwitker, Shakeel, Hart, Anna E., Turner, Mark A., Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study, Pediatrics, 133, e120-8, 2014 | Intervention does not meet inclusion criteria – high AA and lipids vs. low AA and lipids. |
| Murdock, N., Crighton, A., Nelson, L. M., Forsyth, J. S., Low birthweight infants and total parenteral nutrition immediately after birth. II. Randomised study of biochemical tolerance of intravenous glucose, amino acids, and lipid, Archives of | Intervention type does not meet the inclusion criteria: Glucose vs. glucose AA/lipid. |

| Study | Reason for Exclusion |
|---|---|
| disease in childhood. Fetal and neonatal edition, 73, F8-12, 1995 | |
| Najm, S., Lofqvist, C., Hellgren, G., Engstrom, E., Lundgren, P., Hard, A. L., Lapillonne, A., Savman, K., Nilsson, A. K., Andersson, M. X., Smith, L. E. H., Hellstrom, A., Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial, Clinical Nutrition ESPEN, 20, 17-23, 2017 | Intervention type does not meet the inclusion criteria: Compares different types of lipid solutions. |
| O'Neill Jr, J. A., Meng, H. C., Caldwell, M. D., Stahlman, M. T., Metabolic evaluation of a synthetic amino acid mixture for parenteral nutrition in infants and children, Journal of Pediatric Surgery, 11, 979-985, 1976 | Study population does not meet protocol eligibility criteria - includes neonates and children aged 1 month to 15 years; unclear whether neonates pre-term or term babies aged up to 28 days. |
| O'Neill, J. A., Caldwell, M. D., Meng, H. C., Otten, A., Stahlman, M. T., Use of a 10% l-amino acid solution with glucose in pediatric parenteral nutrition, Acta chirurgica Scandinavica. Supplementum, 466, 106-7, 1976 | Study does not meet protocol eligibility criteria - unclear whether neonates eligible for inclusion; starting and target amounts for nitrogen: non-nitrogen energy and lipids: carbohydrates not reported. |
| Ong, E. G., Eaton, S., Wade, A. M., Horn, V., Losty, P. D., Curry, J. I., Sugarman, I. D., Klein, N. J., Pierro, A., Randomized clinical trial of glutamine-supplemented versus standard parenteral nutrition in infants with surgical gastrointestinal disease, British journal of surgery, 99, 929-938, 2012 | Study does not meet protocol eligibility criteria - relative amounts of nutrition provided at start of study not reported; energy intake reported as an outcome. |
| Osborn, D. A., Schindler, T., Jones, L. J., Sinn, J. K. H., Bolisetty, S., Higher versus lower amino acid intake in parenteral nutrition for newborn infants, Cochrane Database of Systematic Reviews, 2018, CD005949, 2018 | Systematic review - references checked. |
| Pawlik, Dorota, Lauterbach, Ryszard, Walczak, Maria, Hurkala, Joanna, Sherman, Michael P., Fish-oil fat emulsion supplementation reduces the risk of retinopathy in very low birth weight infants: a prospective, randomized study, JPEN. Journal of parenteral and enteral nutrition, 38, 711-6, 2014 | Intervention type does not meet the inclusion criteria: Fish vs. Soy/olive oil. |
| Peden, V. H., Karpel, J. T., Total parenteral nutrition in premature infants, The Journal of pediatrics, 81, 137-44, 1972 | Study intervention does not meet protocol eligibility criteria - relative amounts of starting does for nitrogen: non-nitrogen energy and carbohydrates: lipids not reported. |
| Pencharz, P., Beesley, J., Sauer, P., Van Aerde, J., Canagarayar, U., Renner, J., McVey, M., Wesson, D., Swyer, P., Total-body protein turnover in parenterally fed neonates: Effects of energy source studied by using [15N]glycine and [1-13C]leucine, American Journal of Clinical Nutrition, 50, 1395-1400, 1989 | Study intervention does not meet protocol eligibility criteria - starting and target doses not reported. |
| Quan, M., Wang, D., The early-life nutritional status and progress in nutritional support strategy of extremely low birth weight infants in China, Journal of Pediatric Gastroenterology and Nutrition, 62, 819, 2016 | Abstract. |
| Ribed Sanchez, A., Romero Jimenez, R. M., Sanchez De Orgaz, M. C., De Juan, A., Tovar | Abstract. |

| Study | Reason for Exclusion |
|---|---|
| Pozo, M., Diaz Garzon, J., Sanjurjo Saez, M., Early aggressive parenteral nutrition in preterm infants, International Journal of Clinical Pharmacy, 35, 983, 2013 | |
| Ribed Sanchez, Almudena, Romero Jimenez, Rosa Ma, Sanchez Gomez de Orgaz, Ma Carmen, Sanchez Luna, Manuel, Sanjurjo Saez, Maria, Aggressive parenteral nutrition and growth velocity in preterm infants, Nutricion hospitalaria, 28, 2128-34, 2013 | No comparison of interest. |
| Riskin, Arieh, Hartman, Corina, Shamir, Raanan, Parenteral Nutrition in Very Low Birth Weight Preterm Infants, The Israel Medical Association journal : IMAJ, 17, 310-5, 2015 | Study design does not meet protocol eligibility criteria - narrative review. |
| Roelants, Jorine A., Vlaardingerbroek, Hester, van den Akker, Chris H. P., de Jonge, Rogier C. J., van Goudoever, Johannes B., Vermeulen, Marijn J., Two-Year Follow-up of a Randomized Controlled Nutrition Intervention Trial in Very Low-Birth-Weight Infants, JPEN. Journal of parenteral and enteral nutrition, 42, 122-131, 2018 | Study intervention does not meet protocol eligibility criteria - focus on lipids amino acids; ratios not clearly reported. |
| Rubecz, I., Mestyan, J., Soltesz, G., Horvath, M., Metabolic and hormonal effects of alternate infusion of hypertonic glucose and aminosol-glucose in premature infants, Acta paediatrica Academiae Scientiarum Hungaricae, 15, 301-21, 1974 | Study does not meet protocol eligibility criteria - no comparator group; all babies received the same PN regimen. |
| Rubin, M., Moser, A., Naor, N., Merlob, P., Pakula, R., Sirota, L., Effect of three intravenously administered fat emulsions containing different concentrations of fatty acids on the plasma fatty acid composition of premature infants, The Journal of pediatrics, 125, 596-602, 1994 | Intervention type does not meet the inclusion criteria: Compares different types of lipids. |
| Salas-Salvado, J., Molina, J., Figueras, J., Masso, J., Marti-Henneberg, C., Jimenez, R., Effect of the quality of infused energy on substrate utilization in the newborn receiving total parenteral nutrition, Pediatric research, 33, 112-7, 1993 | Included study for D8: Carb/lipids. |
| Schanler, R. J., Shulman, R. J., Prestridge, L. L., Parenteral nutrient needs of very low birth weight infants, Journal of Pediatrics, 125, 961-8, 1994 | Intervention type does not meet the inclusion criteria: Differ in calcium gluconate and potassium monobasic-dibasic phosphate. |
| Simmer, K., Rao, S. C., Early introduction of lipids to parenterally-fed preterm infants, Cochrane Database of Systematic Reviews, 2005 | Systematic review - relevant references checked. |
| Stensvold, H. J., Lang, A. M., Strommen, K., Abrahamsen, T. G., Ogland, B., Pripp, A. H., Ronnestad, A. E., Strictly controlled glucose infusion rates are associated with a reduced risk of hyperglycaemia in extremely low birth weight preterm infants, Acta Paediatrica, International Journal of Paediatrics, 107, 442-449, 2018 | Study intervention does not meet protocol eligibility criteria - babies received same intake of carbohydrates and lipids during 2 study periods. |
| Tan, M. J., Cooke, R. W., Improving head growth in very preterm infants - A randomised controlled trial I: Neonatal outcomes, Archives of Disease in Childhood: Fetal and Neonatal Edition, 93, f337-f341, 2008 | Intervention does not meet protocol - Hyperalimented PN vs. standard PN. |

| Study | Reason for Exclusion |
|---|---|
| Tan, M., Parry, S., Morgan, C., Neurodevelopmental outcome in very preterm infants randomised to receive two different parenteral nutrition regimens: The SCAMP nutrition study, Archives of Disease in Childhood, 101, A5, 2016 | Conference abstract. |
| te Braake, F. W., van den Akker, C. H., Wattimena, D. J., Huijmans, J. G., van Goudoever, J. B., Amino acid administration to premature infants directly after birth, Journal of Pediatrics, 147, 457-461, 2005 | Study intervention does not meet protocol eligibility criteria - babies received same amounts of glucose and lipids; focus on amino acids delivered early or late. |
| Thakur, A., Kansal, B. K., Saini, A., Kler, N., Garg, P., Modi, M., Soni, A., Saluja, S., Effect of aggressive versus standard nutritional regime on growth of extremely low birth weight infants-A randomized controlled trial, Journal of Pediatric Gastroenterology and Nutrition, 66, 1089, 2018 | Study design does not meet eligibility criteria - conference abstract. |
| Torer, Birgin, Hanta, Deniz, Ozdemir, Zeliha, Cetinkaya, Bilin, Gulcan, Hande, An aggressive parenteral nutrition protocol improves growth in preterm infants, The Turkish journal of pediatrics, 57, 236-41, 2015 | Study intervention does not meet protocol eligibility criteria - focus on high dose lipids and amino acids vs low dose lipids and amino acids; ratios not clearly reported. |
| Tottman, A. C., Bloomfield, F. H., Cormack, B. E., Harding, J. E., Mohd Slim, M. A., Weston, A. F., Alsweiler, J. M., Relationships between Early Nutrition and Blood Glucose Concentrations in Very Preterm Infants, Journal of Pediatric Gastroenterology and Nutrition, 66, 960-966, 2018 | Study intervention does not meet protocol eligibility criteria - starting and target lipids: carbohydrates not clear. |
| Uthaya, S., Liu, X., Babalis, D., Dore, C., Warwick, J., Bell, J., Thomas, L., Ashby, D., Durighel, G., Ederies, A., Yanez-Lopez, M., Modi, N., Nutritional Evaluation and Optimisation in Neonates (NEON) trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double-blind controlled trial, Efficacy and Mechanism Evaluation, 3, 2016 | Intervention type does not meet the inclusion criteria: High AA vs low AA. |
| Uthaya, Sabita, Liu, Xinxue, Babalis, Daphne, Dore, Caroline J., Warwick, Jane, Bell, Jimmy, Thomas, Louise, Ashby, Deborah, Durighel, Giuliana, Ederies, Ash, Yanez-Lopez, Monica, Modi, Neena, Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition, The American journal of clinical nutrition, 103, 1443-52, 2016 | Intervention type does not meet the inclusion criteria: High AA vs low AA. |
| Uthaya, Sabita, Liu, Xinxue, Babalis, Daphne, Dore, Caroline, Warwick, Jane, Bell, Jimmy, Thomas, Louise, Ashby, Deborah, Durighel, Giuliana, Ederies, Ash, Yanez-Lopez, Monica, Modi, Neena, 2016 | Study interventions do not meet protocol eligibility criteria - starting energy for non-nitrogen: nitrogen not reported; same amount of carbohydrates: lipids administered. |
| Van Aerde, J. E., Sauer, P. J., Pencharz, P. B., Smith, J. M., Heim, T., Swyer, P. R., Metabolic consequences of increasing energy intake by adding lipid to parenteral nutrition in full-term infants, The American journal of clinical nutrition, 59, 659-62, 1994 | Ineligible intervention - comparison of lipid and non-lipid containing parenteral nutrition. |

| Study | Reason for Exclusion |
|---|---|
| van den Akker, C. H., te Braake, F. W., Schierbeek, H., Rietveld, T., Wattimena, D. J., Bunt, J. E., van Goudoever, J. B., Albumin synthesis in premature neonates is stimulated by parenterally administered amino acids during the first days of life, American Journal of Clinical NutritionAm J Clin Nutr, 86, 1003-8, 2007 | Study intervention does not meet protocol eligibility criteria - glucose vs glucose amino acids (lipids withheld; only nonprotein energy reported as an outcome). |
| van den Akker, C. H., te Braake, F. W., Weisglas-Kuperus, N., van Goudoever, J. B., Observational outcome results following a randomized controlled trial of early amino acid administration in preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 59, 714-719, 2014 | Study intervention does not meet protocol eligibility criteria - glucose vs amino acid; starting and target energy not reported; amount of lipid not reported. |
| van Puffelen, E., Vanhorebeek, I., Joosten, K. F. M., Wouters, P. J., Van den Berghe, G., Verbruggen, S. C. A. T., Early versus late parenteral nutrition in critically ill, term neonates: a preplanned secondary subgroup analysis of the PEPaNIC multicentre, randomised controlled trial, The Lancet Child and Adolescent Health, 2, 505-515, 2018 | Study intervention does not meet protocol eligibility criteria - babies receive same PN regimen but early vs late administration. |
| Vlaardingerbroek, H., Roelants, J. A., Rook, D., Dorst, K., Schierbeek, H., Vermes, A., Vermeulen, M. J., van Goudoever, J. B., van den Akker, C. H., Adaptive regulation of amino acid metabolism on early parenteral lipid and high-dose amino acid administration in VLBW infants - a randomized, controlled trial, Clinical nutrition (Edinburgh, Scotland), 33, 982-990, 2014 | Study intervention does not meet protocol eligibility criteria - amino acids lipids vs high amino acids lipids; ratios not clearly reported. |
| Vlaardingerbroek, H., Rook, D., Van Den Akker, C. H. P., Vermeulen, M. J., Van Goudoever, J. B., Can early parenteral lipid and high dose amino acid administration improve growth in VLBW infants?, Archives of Disease in Childhood, 97, A397, 2012 | Study design does not meet eligibility criteria - conference abstract. |
| Vlaardingerbroek, H., Vermeulen, M. J., Rook, D., van den Akker, C. H., Dorst, K., Wattimena, J. L., Vermes, A., Schierbeek, H., van Goudoever, J. B., Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants, Journal of Pediatrics, 163, 638-44.e1-5, 2013 | Study intervention does not meet protocol eligibility criteria - amino acids lipids vs high amino acids lipids; ratios not clearly reported. |
| Wagner, J. V., Moe-Byrne, T., Grover, Z., McGuire, W., Glutamine supplementation for young infants with severe gastrointestinal disease, Cochrane database of systematic reviews (Online), 7, CD005947, 2012 | Systematic review - references checked. |
| Wolf, H., Melichar, V., von Berg, W., Kerstan, J., Intravenous alimentation with a mixture of fat, carbohydrates and amino acids in small immature newborn infants--a preliminary report, Die Infusionstherapie, 1, 479-81, 1974 | Not relevant to protocol - does not assess different carbohydrate to lipid ratios. |
| Xie, E., Sun, J., Shen, Y., Ju, H., Li, J., Zhang, G., Huang, P., Influence of early rapidly increased amino acid dosaging on nitrogen balance and growth in preterm infants, Chinese journal of clinical nutrition, 22, 136-140, 2014 | Study does not meet protocol eligibility criteria - non-English language (Chinese). |

| Study | Reason for Exclusion |
|---|---|
| Yu, V. Y. H., James, B., Hendry, P., MacMahon, R. A., Total parenteral nutrition in very low birthweight infants: A controlled trial, Archives of Disease in Childhood, 54, 653-661, 1979 | Intervention type does not meet the inclusion criteria: PN vs. EN. |
| Zhao, Yiyang, Wu, Yang, Pei, Jiao, Chen, Zude, Wang, Qi, Xiang, Bo, Safety and efficacy of parenteral fish oil-containing lipid emulsions in premature neonates, Journal of pediatric gastroenterology and nutrition, 60, 708-16, 2015 | Study does not meet protocol eligibility criteria - comparison of different lipid emulsions. |
| Zlotkin, S. H., Intravenous nitrogen intake requirements in full-term newborns undergoing surgery, Pediatrics, 73, 493-6, 1984 | Outcome of interest does not fit the inclusion 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: What are the most effective relative amounts of nitrogen and non-nitrogen energy (starting and target dose)?

What is the optimal ratio of non-nitrogen energy to nitrogen in parenteral nutrition for preterm and term babies?

### Why this is important

Babies require energy in order to meet resting energy requirements, energy expenditure and to facilitate growth. If insufficient non-nitrogen energy (carbohydrates and lipids) is given then nitrogen (protein energy) is used for non-growth purposes and is not available to generate new tissues. An excess of non-nitrogen energy can lead to increased adiposity and may cause hyperglycaemia or hypertriglyceridemia. Determining an optimal ratio of nitrogen to non-nitrogen energy to provide in parenteral nutrition is critical.

**Table 10: Research recommendation rationale**

| **Research question** | **What is the optimal ratio of nitrogen to non-nitrogen energy in parenteral nutrition for preterm and term babies?** |
|---|---|
| **Why is this needed** | |
| **Importance to 'patients' or the population** | High: An excess of either non-nitrogen or nitrogen energy can result in adverse consequences; therefore, determining the optimal ratio is crucial. Early nutritional interventions can have long term consequences including into childhood and adulthood. |
| **Relevance to NICE guidance** | High: Only two, non-randomised studies were identified for inclusion in this review. The evidence that was identified was limited in quality, inconclusive and out of date. The review included studies did not provide any data to determine the optimal ratio of nitrogen to non-nitrogen energy. |
| **Relevance to the NHS** | High: Improving the nutritional quality of parenteral nutrition provided to pre-term and term babies is critical for optimal growth, development and survival |
| **National priorities** | The NHS Long term plan (launched in January 2019) for the next 10 years highlights 'enabling everyone to get the best start in life' as one of the main areas to improve the quality of patient care and health outcomes. |
| **Current evidence base** | The guideline identified that there is a gap in the evidence base. The two identified studies were non-randomised, were published from one research unit, and were published over 30 years ago. Furthermore, the studies were very small, (36 babies included across two studies). The evidence was considered very low quality, with a high risk of bias and imprecision. |
| **Equality** | The research aims to ensure all babies are provided with optimum care. |

| Research question | What is the optimal ratio of nitrogen to non-nitrogen energy in parenteral nutrition for preterm and term babies? |
|---|---|
| **Feasibility** | This would require NRES research ethics and MHRA approval but would be feasible and safe to conduct. |
| **Other comments** | The comparative ratios for the study are based on the ranges recommended in this guideline. |

*MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NRES: National Research Ethics Service*

**Table 11: Research recommendation modified PICO table**

| Criterion | Explanation |
|---|---|
| **Population** | • Babies born preterm, up to 28 days after their birth date (preterm babies)<br>• Babies born at term, up to 28 days after their birth (term babies) |
| **Intervention** | Low ratio of non-nitrogen energy to and nitrogen energy: for example, 20 kcal of non-nitrogen energy per gram of amino acid |
| **Comparator** | High ratio non-nitrogen energy to nitrogen energy: For example, 30 kcal of non-nitrogen energy per gram of amino acid |
| **Outcomes** | Growth<br>Body composition<br>Neurodevelopmental outcomes<br>Metabolic disturbances (e.g. blood urea nitrogen, hyperglycaemia metabolic acidosis)<br>Nitrogen balance |
| **Study design** | Randomised controlled trial |
| **Timeframe** | From birth to measurement of outcomes (e.g. expected date of delivery, discharge, age at 2 years) |
| **Additional information** | None |