Nutritional support for critically ill children (Review)

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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 2
OBJECTIVES 3
METHODS 4
RESULTS 5
    Figure 1. 6
DISCUSSION 7
AUTHORS' CONCLUSIONS 7
ACKNOWLEDGEMENTS 8
REFERENCES 8
CHARACTERISTICS OF STUDIES 12
DATA AND ANALYSES 15
APPENDICES 15
HISTORY 25
CONTRIBUTIONS OF AUTHORS 25
DECLARATIONS OF INTEREST 26
SOURCES OF SUPPORT 26
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 26
INDEX TERMS 26

[**Intervention Review**]

Nutritional support for critically ill children

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ABSTRACT

Background

Nutritional support in the critically ill child has not been well investigated and is a controversial topic within paediatric intensive care. There are no clear guidelines as to the best form or timing of nutrition in critically ill infants and children.

Objectives

To assess the impact of enteral and total parenteral nutrition on clinically important outcomes for critically ill children.

Search methods

We searched: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 1); Ovid MEDLINE (1966 to February 2007); Ovid EMBASE (1988 to February 2007); OVID Evidence-Based Medicine Reviews; ISI Web of Science - Science Citation Index Expanded (1965 to February 2007); WebSPIRS Biological Abstracts (1969 to February 2007); and WebSPIRS CAB Abstracts (1972 to February 2007). We also searched trial registries; reviewed reference lists of all potentially relevant studies; handsearched relevant conference proceedings; and contacted experts in the area and manufacturers of enteral and parenteral nutrition products. We did not limit the search by language or publication status.

Selection criteria

We included studies if they were randomized controlled trials; involved paediatric patients, aged one day to 18 years of age, cared for in a paediatric intensive care unit setting (PICU) and received nutrition within the first seven days of admission; and reported data for at least one of the pre-specified outcomes (30-day or PICU mortality; length of stay in PICU or hospital; number of ventilator days; and morbid complications, such as nosocomial infections). We excluded studies if they only reported nutritional outcomes, quality of life assessments, or economic implications. Furthermore, other areas of paediatric nutrition, such as immunonutrition and different routes of delivering enteral nutrition, were not addressed in this review.

Data collection and analysis

Two authors independently screened searches, applied inclusion criteria, and performed quality assessments. We resolved discrepancies through discussion and consensus. One author extracted data and a second checked data for accuracy and completeness.

Main results

Only one trial was identified as relevant. Seventy-seven children in intensive care with burns involving > 25% of the total body surface area were randomized to either enteral nutrition within 24 hours or after at least 48 hours. No statistically significant differences were observed for mortality, sepsis, ventilator days, length of stay, unexpected adverse events, resting energy expenditure, nitrogen balance, or albumin levels. The trial was assessed as of low methodological quality (based on the Jadad scale) with an unclear risk of bias.

Authors' conclusions

There was only one randomized trial relevant to the review question. Research is urgently needed to identify best practices regarding the timing and forms of nutrition for critically ill infants and children.

PLAIN LANGUAGE SUMMARY

Nutrition for critically ill children in paediatric intensive care units

There is little evidence to support or refute the need to provide nutrition to critically ill children in a paediatric intensive care unit during the first week of their critical illness.

Giving nutrition in the form of tube feeding (enteral) or intravenous feeding (parenteral) is often considered a priority during critical illness in children. There are reasons to think this may not necessarily be true. During critical illness the body's metabolism is changed and the need for calories is reduced. There are known side effects from giving too much nutrition, such as delays in being able to take the child off a respiratory ventilator, liver problems, and worsened inflammation. We found only one small randomized controlled trial that compared early feeding (within 24 hours of injury) with conventional feeding (after at least 48 hours). The study showed no differences between the groups for any of the outcomes examined. Further research in this area is urgently needed to help guide optimal treatment of children with critical illness.

BACKGROUND

Nutritional support in the critically ill child has not been well investigated and is a controversial topic in paediatric critical care medicine. There are no clear guidelines for the optimal timing and forms of nutritional support in these children. There are several lines of evidence that suggest further investigation is required into whether any form of nutritional support is beneficial in the first week of critical illness in children, and these are discussed below.

We defined nutritional support as the provision of energy in the form of glucose, protein, or lipid to provide calories and substrate for metabolism. Some would define metabolic support as provision of these calories at basal metabolic rate, without any intention of supporting anabolic activities such as growth or activities of daily living. Accordingly, metabolic support is a form of nutritional support. For the purposes of this review, we defined critical illness as any illness requiring admission to a paediatric intensive care unit.

Metabolism during critical illness

Critical illness often results in altered cellular energy metabolism (Fink 2001; Joffe 2001; Mizock 1984; Protti 2006). Although the mechanisms and exact alterations are poorly understood, it is clear that protein catabolism and mitochondrial dysfunctions with metabolic suppression can occur (Joffe 2001; Mizock 1984). The suggestion that an increased metabolic rate occurs in adults with critical illness has been questioned (Miles 2006). Similarly, the measured metabolic rates in children with critical illness is most often at or below predicted basal metabolic rate in the first week of illness (Avitzur 2003; Briassoulis 2000; Framson 2007; Jacsik 2001; Letton 1995; Martinez 2004; Oosterveld 2006; White 2000); anabolism (with growth) does not occur (Chwals 1994).

Underfeeding and overfeeding during critical illness

Overfeeding has important adverse effects during critical illness (Chwals 1994; Zaloga 1994). Excess carbohydrate intake can increase carbon dioxide production and impede ventilator weaning (Chwals 1994). Excess protein does not prevent catabolism and can even increase catabolism of body protein (Chwals 1994; Shew 1999; Stroud 2007). High calorific intake can increase fat deposition, including in the liver (Chwals 1994; Hart 2002; Zaloga

1994). In animal models, lower calorific goals were associated with weight loss and improved survival from critical illness (Alexander 1989; Yamazaki 1986). Some adult human studies suggest that underfeeding during critical illness is associated with improved survival and reduced length of stay in hospital (Ash 2005; Boitano 2006; Dickerson 2002; Jeejeebhoy 2004; Krishnan 2003). This is compatible with the finding in many types of animals that a 30% to 50% restriction of calories increased their lifespan and resistance to diseases of aging and oxidative damage (with similar pathophysiology to critical illness inflammatory cascades) (Bordone 2005).

Adult nutritional trials during critical illness

There have been several systematic reviews of nutritional support in critically ill adults. Koretz et al found no compelling evidence that enteral nutrition improved outcomes in critically ill adults when compared to no treatment or parenteral nutrition (Koretz 2007a; Koretz 2007). Koretz found no evidence that parenteral nutrition had an effect on clinical outcomes compared to not providing artificial nutrition (Koretz 2007b). A consensus statement published by the American Society for Parenteral and Enteral Nutrition, in 1997, wrote that "although it has been assumed that nutrition support is clinically beneficial in this [critically ill] patient population, this hypothesis has not been tested by well-designed clinical trials..." (Klein 1997). This was reaffirmed, in 2002, with the statement that "It appears reasonable to recommend that some form of supplemental nutritional support be started after 5 to 10 days of fasting in patients who are likely to remain unable to eat for an additional week or more" (ASPEN 2002). Canadian researchers have published systematic reviews showing that parenteral nutrition was associated with more infectious complications than with enteral nutrition (Gramlich 2004); parenteral nutrition did not improve clinically important outcomes compared to standard care (Heyland 1998a); and combined parenteral and enteral nutrition did not improve clinically important outcomes in critically ill adults compared to enteral nutrition alone (Dhaliwal 2004). Others have found poor evidence that early enteral nutrition is better than early parenteral nutrition (Peter 2005; Simpson 2005), although this is controversial (Heyland 2003). Part of the reason for controversy is that many of the trials were not of optimal quality (Preiser 2003). "The point at which 'safe' starvation ends and malnutrition-related complications begin has yet to be defined" (Preiser 2003).

Surrogate outcomes

Many clinicians have assumed that early nutritional support is required for critically ill children and adults. Malnutrition is associated with poor outcomes and nutritional support can improve surrogate nutritional outcomes, such as immune function, wound healing, and measured proteins (Briassoulis 2001; Heyland 1998b). In adult studies, however, there is a poor concordance between nutritional markers and clinical outcomes (Koretz 2005). Although it seems intuitive that providing nutrition will be of benefit, because malnutrition is harmful, it does not necessarily follow that nutritional support during the first week of illness improves a critically ill patient's outcome.

Paediatric differences

The American Society for Parenteral and Enteral Nutrition statements, from 1997 and 2002, were that no randomized controlled trials of nutritional support in children with critical illness had been found (ASPEN 2002; Klein 1997). The nutritional needs of children with critical illness may be different from adults in many ways; in terms of underlying metabolism and growth, underlying illness and co-morbidities, pre-existing energy reserves (particularly in young infants), and responses to critical illness. It would be ideal to have studies specific to children to guide nutritional support in critically ill children.

For these reasons, a systematic review is needed to identify any randomized controlled trials of nutritional support during the first week of illness in critically ill children. Evidence is needed to provide clear guidelines for how and when to initiate feedings in children requiring intensive care. We did not include premature or low birth weight neonates as their care is in a neonatal intensive care unit and their needs are very likely to be different from infants and children during the first week of critical illness.

OBJECTIVES

The objective of this review was to assess the impact of enteral and parenteral nutrition given in the first week of illness on clinically important outcomes in critically ill children. There were two primary hypotheses:

1. the mortality rate of critically ill children fed enterally or parenterally is different to that of children who are given no nutrition;

2. the mortality rate of critically ill children fed enterally is different to that of children fed parenterally.

We planned to conduct subgroup analyses, pending available data, to examine whether the treatment effect was altered by:

a. age (infants less than one year versus children greater than or equal to one-year old);

b. type of patient (medical where purpose of admission to intensive care unit (ICU) is for medical illness (without surgical intervention immediately prior to admission) versus surgical where purpose of admission to ICU is for postoperative care or care after trauma).

The following secondary hypotheses were also proposed (a priori), pending other clinical trials becoming available, to examine nutrition more distinctly:

3. the mortality rate is different in children who are given enteral nutrition alone versus enteral and parenteral combined;

4. the mortality rate is different in children who are given both enteral feeds and parenteral nutrition versus no nutrition.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomized controlled trials (RCTs), completed or ongoing.

Types of participants

We planned to include trials of paediatric patients, aged one day to 18 years, that were cared for in a paediatric intensive care setting and who received nutrition within the first seven days of admission. We also planned to include studies involving both paediatric and adult participants if data were separately available for paediatric cases cared for in a paediatric intensive care unit (PICU). Studies were to be excluded if participants were primarily adults. We planned to analyse those patients aged less than one year separately from children who were older than one year, if such data were available, given that infants are believed to have higher nutritional requirements compared to older children. Furthermore, medical patients are often studied separately from surgical, critically ill patients (including trauma patients). If there were no studies that differentiated medical from surgical patients, we planned to group these patients in the analysis.

Types of interventions

Patients must have been randomized to receive either:
1. enteral feeding versus no feeding;
2. total parenteral nutrition versus no feeding;
3. enteral versus total parenteral nutrition;
4. enteral versus enteral with supplemental parenteral nutrition.

Other areas of paediatric nutrition, such as immunonutrition versus normal nutrition and different routes of delivering enteral nutrition, were not addressed in this review.

Types of outcome measures

Primary outcome:
1. 30-day mortality. If this was not available, then paediatric intensive care unit (PICU) mortality.
Secondary outcomes:
1. length of stay in the PICU;
2. length of stay in hospital;
3. number of days on the ventilator;
4. morbid complications including nosocomial infections.
We were not interested in nutritional outcomes. Data for quality of life assessments and economic implications were to be extracted if reported in studies meeting all other criteria.

Search methods for identification of studies

We searched the following bibliographic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 1); Ovid MEDLINE (1966 to February 2007); Ovid EMBASE (1988 to February 2007); OVID Evidence-Based Medicine Reviews (includes Cochrane Database of Systematic Reviews, CENTRAL, ACP Journal Club, and Database of Abstracts of Reviews of Effectiveness (DARE)); ISI Web of Science - Science Citation Index Expanded (1965 to February 2007); WebSPIRS Biological Abstracts (1969 to February 2007); and WebSPIRS CAB Abstracts (1972 to February 2007). We also searched the following trial registries: ClinicalTrials.gov; CenterWatch Clinical Trials Listing Service; Current Controlled Trials; GlaxoSmithKline Clinical Trial Register; National Clinical Trials Registry and the National Research Register (all found at www.ualberta.ca/ARCHE/litsearch.html#trials).
We reviewed reference lists of all potentially relevant studies; handsearched relevant conference proceedings: British Association for Parenteral and Enteral Nutrition (2005 to 2007), European Society of Parenteral and Enteral Nutrition (2005 to 2007), and American Society of Parenteral and Enteral Nutrition (2005 to 2007); and contacted primary authors and experts in the area (n = 5), and manufacturers of enteral (n = 5) and parenteral (n = 2) nutritional products.
We did not limit the search by language or publication status.
The search strategies are in Appendix 1.

Data collection and analysis

Study selection
The selection of studies involved two steps. First, two authors (AJ, NA) independently screened the search results to identify citations with potential relevance. Second, we obtained the full text of selected articles. Two authors (AJ, NA) independently decided on trial inclusion using a standard form with predetermined eligibility criteria.
Assessment of quality
Two authors (NA, LH) planned to independently assess the methodological quality of all included studies using the Jadad 5-point scale (Jadad 1996). To the best of our knowledge, the Jadad scale is the only quality assessment tool that has been validated. It incorporates components that are directly related to the control of bias including randomization (0 to 2 points), double blinding (0 to 2 points), and reporting of withdrawals and dropouts (0 to 1

point). We planned to provide overall quality scores according to the Jadad scale. In addition, we planned to describe and display the quality information by individual component (that is generation of random sequence, blinding, loss to follow up, and allocation concealment (Schulz 1995)). Each component was to be classified as adequate, inadequate, unclear, or not used. We planned to examine the effect of methodological quality through sensitivity analyses, as described in the 'Data analysis' section below. In addition, we planned to record whether or not the studies used an intention-to-treat analysis and their funding sources. We also assessed risk of bias using the new Cochrane risk of bias tool, released in February 2008.

Data extraction

Two authors (NA, LL, or BV) planned to extract data from each study and resolve discrepancies through discussion and by referring to the original paper. We planned to request unpublished data from authors, when necessary. We developed a standard form to describe the following: characteristics of the study (design, method of randomization, withdrawals or dropouts); participants (age, gender); test intervention (type, dose, route of administration, timing and duration of therapy, co-interventions); control intervention (agent and dose); outcomes (types of outcome measures, timing of outcomes, adverse effects); and results.

Data analysis

We planned to conduct separate analyses for the four comparisons: enteral feeding versus standard care; total parenteral nutrition versus standard care; enteral versus total parenteral nutrition; and enteral versus enteral with supplemental parenteral nutrition. We planned to express dichotomous data (for example mortality) as relative risks (RR) and to calculate an overall RR with 95% confidence intervals (CI). We planned to express complications as risk differences, due to low event numbers. We planned to derive the number needed to treat (NNT) for dichotomous data to help clarify the degree of benefit for a range of baseline risks. We planned to convert continuous data to the mean difference and calculate an overall weighted mean difference (with 95% CI). We planned to summarize time-to-event data (for example length of stay in hospital, number of days on a ventilator) by the log hazards ratio (Parmar 1998) and to calculate an overall log hazards ratio.

We planned to calculate results using a random-effects model. We planned to quantify heterogeneity using the I^2 statistic (Higgins 2002). The I^2 statistic estimates the per cent variability due to between-study differences. If a sufficient number of trials were included in the study, we planned to assess possible sources of heterogeneity for the primary outcome using either subgroup or sensitivity analyses, or both. We identified the following clinical subgroups: age (infants less than one year, children equal to or greater than one-year old); and surgical patients (purpose of admission to PICU for postoperative care or care after trauma) versus medical patients (purpose of admission to PICU for medical illness without surgical intervention prior to admission). The subgroup for age was based on the fact that infants are at higher risk of catabolism and are generally fed more aggressively than older children. Infants may have less nutritional reserve than older children; a physiology that demonstrates rapid changes over the first year of life; different admission diagnoses and co-morbidities to older children; and accordingly they are typically managed differently from a clinical perspective. The subgroup of surgical versus medical patients was based on inherent differences between these populations and the precedence in the literature for examining these populations separately (Heyland 1998a; Heyland 2001; Marik 2001). If a study did not provide the data or results by age, or had a different age categorization to that used in this review, we planned to contact authors for additional data for the subgroups of interest. We planned to conduct the following sensitivity analyses: methodological quality of included trials; intention-to-treat status; and funding source (medical or pharmaceutical companies versus other). We also planned to calculate fixed-effect model estimates as a sensitivity analysis.

We planned to test for asymmetry: visually using the funnel plot, and quantitatively (with the rank correlation test (Begg 1994), the trim and fill method (Duval 2000), or weighted regression (Egger 1997)) depending on the number of trials included in the review. One source of asymmetry is publication bias.

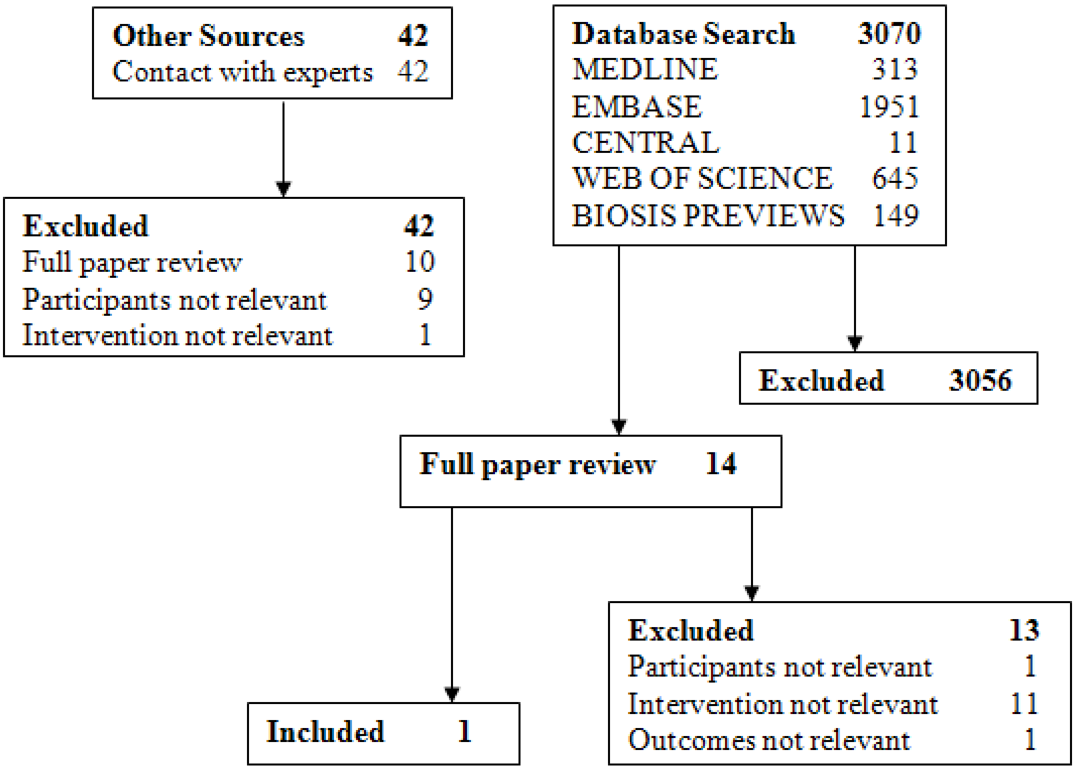
R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Our search identified 3070 studies; an additional 42 potentially relevant studies were identified through contacts with experts in the area. Following screening, 24 studies were identified as potentially relevant (see Figure 1). Upon closer review all but one of the studies were excluded, for the following reasons: different routes of delivering enteral nutrition compared (gastric versus small bowel feeding (Meert 2004); continuous versus intermittent gastric feeding (Horn 2003); immune-enhancing formula versus standard formula (Alberda 2005; Albers 2005; Barbosa 1999; Briassoulis 2005; Briassoulis 2005b; Briassoulis 2006; Gottschlich 1990; Marin 2006; Papadopoulou 2000); two regimens of early combined enteral and parenteral nutrition compared (Alexander 1980); only surrogate nutritional markers as outcomes (Chaloupecky 1994); study population was primarily adult (Hadley 1986; Hausmann 1985; Kolacinski 1993; Peng 2001; Suchner 1996; Young 1987); study population was premature neonates or newborn infants in the neonatal intensive care unit (Black 1981; Tyson 2005); and study population was not critically ill children (that is children not cared for in a PICU) (Marin 1999; Pillo-Blocka 2004).

Figure 1. Searching results



Only one relevant trial was identified. Seventy-seven children in an intensive care unit because of burns involving more than 25% of their total body surface area were randomized to enteral nutrition within 24 hours or conventional care (that is no tube feeding or oral diet for at least 48 hours) (Gottschlich 2002). Children were eligible for the study if they were older than three years and were admitted within 24 hours of the injury. Five children were excluded from the study (three protocol violations, two transferred to another hospital) leaving 36 children in each group. Children were followed up for four weeks from entry into the study. The outcomes reported are detailed in the 'Characteristics of included studies' table.

Risk of bias in included studies

The methodological quality of the one relevant study was low, based on the Jadad scale. The study scored two out of five points: one point for being randomized and one point for adequate generation of the randomization sequence. The study was not double-blinded; losses to follow up were not adequately described; and allocation concealment was unclear. The authors did not perform an intention-to-treat analysis. The authors described their funding source, which was not related to industry. We also assessed the study using the 'risk of bias' tool. The study was assessed as at low risk of bias for mortality, based on the following domains: sequence generation, blinding, incomplete outcome data, selective outcome reporting, and 'other sources of bias'. Overall, the study was assessed as at unclear risk of bias because allocation concealment was not described.

Effects of interventions

Feeding started at a mean of 15.6 hours (SE 1) in the early intervention group compared to 48.5 hours (SE 0.4) in the control group. The study groups showed no statistically significant differences in the following outcomes: mortality (early, n = 4 (11%) versus control, n = 3 (8%); P = 0.99); sepsis (early, n = 17 (47%) versus control, n = 21 (58%); P = 0.23); ventilator days (early, mean 24.5 days (SE 4.6) versus control, mean 22.5 days (SE 4.2); P = 0.75); hospital length of stay (early, mean 54.8 days (SE 5.9) versus control, mean 54.8 days (SE 4.6); P = 0.96); and unexpected adverse events (early, 8 (22%) versus control, 3 (8%); P = 0.19). Furthermore, there were no differences between groups in weekly measurements of resting energy expenditure, nitrogen balance, level of pre-albumin or albumin.

DISCUSSION

Nutritional support in children in the paediatric intensive care unit is considered important by most intensivists (van der Kuip 2004). Nevertheless, there is limited data on which to base optimal practice for nutritional support during the first week of critical illness in these children. Although it seems almost intuitively obvious that nutritional support early during critical illness would be of benefit, this has not been demonstrated in adults or children (Way 2007).

There are reasons to question the dogma that nutritional support during the first week of critical illness is a priority. These reasons include that metabolism and mitochondrial function are altered during critical illness (Fink 2001; Mizock 1984); calorie restriction has been beneficial in animal models of critical illness (Alexander 1989), and possibly in adults with critical illness (Ash 2005; Krishnan 2003); overfeeding is associated with adverse effects (Chwals 1994; Zaloga 1994); many trials in adults have given unclear evidence of benefit from early nutritional support in critical illness (Koretz 2007a; Koretz 2007; Koretz 2007b); and surrogate nutritional outcomes may not be adequate to confirm a benefit on meaningful clinical outcomes from nutritional support (Heyland 1998b; Koretz 2005). Further, it has been found that in early critical illness children do not experience hypermetabolism (Framson 2007), and energy expenditure is close to or below calculated basal metabolic rate (Briassoulis 2000; Jacsik 2001; Martinez 2004; Oosterveld 2006; White 2000). Protein catabolism during this time cannot be averted by aggressive nutritional support, and anabolism with growth cannot be induced (Chwals 1994; Shew 1999).

Therefore, we conducted this systematic review of the evidence for nutritional support during the first week of critical illness in children. With our exhaustive search strategy we found only one small, randomized controlled trial that met our criteria (Gottschlich 2002). This trial evaluated early enteral feeding (that is within 24 hours of injury) versus conventional feeding (that is feeding withheld for at least 48 hours) among children with burns over 25% of their body surface area. The study found no differences between groups in clinically important outcomes including infection, length of stay, and mortality.

We found eight trials of an immune-enhancing formula versus a standard formula for feeding critically ill children, without consistent benefit on clinically important outcomes. This was, however, not a systematic review of immune-enhancing formulae in critically ill children. It would be of interest to conduct a systematic review of immune-enhancing formulae in paediatric critical illness. The immune-enhancing components may best be considered as pharmacologic interventions, rather than nutritional support, in which case they should be studied separately from the need for nutritional support (Heyland 2006). One trial of gastric versus small-bowel feeding found that more calories were provided in the small bowel-fed group, with trends toward increased mortality, ventilator days, intensive care unit days, and hospital days in the small bowel-fed group (Meert 2004).

Randomized controlled trials are needed to help guide optimal nutritional support of critically ill children during the first week of critical illness. We found little evidence to support or refute the suggested need for nutritional support in these children. While more research is needed, there are a number of challenges that researchers face in this area. These include the small number of children available for study, fewer funding opportunities for non-pharmacological nutritional interventions, and ethical concerns related to experimental protocols among this critically ill population. Further, methodological challenges exist, including difficulty in blinding due to the nature of the intervention, heterogeneity of the patient population (comorbidities, admission diagnosis, age), and the large sample size required to show a change because of the low mortality rate in paediatric intensive care. Nevertheless, future multicentre trials are urgently needed. These must ensure methodological rigour by examining potential risks for bias at the design stage (for example in blinding outcome assessors or using objective outcomes, such as organ dysfunction scores, that are less prone to biased assessments or reporting).

AUTHORS' CONCLUSIONS

Implications for practice

Only one small randomized controlled trial was identified. This review does not provide evidence for or against the need for nutritional support in children during the first week of critical illness; nor does it provide evidence for or against the optimal route of nutritional support in children during the first week of critical illness. Further evidence from randomized controlled trials is needed to support statements regarding the importance or lack of importance of early nutritional support in critically ill children.

Implications for research

Research is needed to guide nutritional support in critically ill children (excluding premature or low birth weight neonates). We suggest that randomized trials of nutritional support in critically ill children during the first week of critical illness should include a control arm in which no nutritional support is administered or hypocaloric goals (below basal metabolic rate) for nutritional support are used.

A C K N O W L E D G E M E N T S

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gottschlich 2002

Methods	Randomized trial using random numbers table; no blinding
Participants	77 children over a 10-year period; inclusion criteria: greater than 3-years old; burns to greater than 25% total body surface area; admitted within 24 hours after burn
Interventions	Early enteral feeding beginning within 24 hours of injury versus conventional treatment (tube feeding and oral diet withheld for at least 48 hours after injury); all children received routine clinical management based on published practices and supervised by one physician to ensure uniformity of care
Outcomes	The following outcomes were reported weekly for four weeks: metabolic rate, caloric intake, anabolism indices (nitrogen balance, 3-methylhistidine); hormone levels (insulin, glucagon, cortisol, gastrin, epinephrine, norepinephrine, dopamine, T_3, T_4); clinical nutrition (albumin, transferrin, pre-albumin, retinol-binding protein, glucose). Clinical outcome data included: incidence of sepsis and wound infection; number of patients requiring parenteral nutrition, experiencing diarrhea, or requiring growth hormone; days on tube feed; number of diarrhoea days; days receiving antibiotics; ventilator days; number of surgeries; unexpected adverse events (bowel necrosis, acute respiratory distress syndrome, renal failure, multisystem organ failure, death); medical and wound length of stay; discharge weight Primary outcome was not specified; no sample size calculation reported
Notes	Jadad score=2; generation of randomization sequence=adequate; double-blinding=inadequate; losses to follow up=not described; allocation concealment=unclear; intention-to-treat analysis not performed; funding source: Shriners of North America

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random numbers table.
Allocation concealment?	Unclear	No description.
Blinding? All outcomes	Yes	For mortality.
Incomplete outcome data addressed? All outcomes	Yes	Five patients excluded from analysis; reasons described (3 protocol violations, 2 transferred to another hospital). Exclusions unlikely to change the results
Free of selective reporting?	Yes	All outcomes listed in the methods section appear in the results section of the pub-

Gottschlich 2002 (*Continued*)

		lished report
Free of other bias?	Yes	No risk of bias due to inappropriate influence of study sponsors or baseline imbalances

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alberda 2005	Comparison: immune-enhancing versus standard formula
Albers 2005	Comparison: immune-enhancing versus standard formula
Alexander 1980	Comparison: two forms of early combined enteral and parenteral nutrition
Barbosa 1999	Comparison: immune-enhancing versus standard formula
Black 1981	Study population: premature neonates or newborns in the neonatal intensive care unit
Briassoulis 2005	Comparison: immune-enhancing versus standard formula
Briassoulis 2005b	Comparison: immune-enhancing versus standard formula
Briassoulis 2006	Comparison: immune-enhancing versus standard formula
Chaloupecky 1994	Outcomes: only surrogate nutritional markers
Gottschlich 1990	Comparison: immune-enhancing versus standard formula
Hadley 1986	Study population: predominantly adults
Hausmann 1985	Study population: predominantly adults
Horn 2003	Comparison: two routes of delivering enteral nutrition (continuous versus intermittent gastric feeding)
Kolacinski 1993	Study population: predominantly adults
Marin 1999	Study population: children not in PICU
Marin 2006	Comparison: immune-enhancing versus standard formula
Meert 2004	Comparison: two routes of delivering enteral nutrition (gastric versus small bowel feeding)

(*Continued*)

Papadopoulou 2000	Comparison: immune-enhancing versus standard formula
Peng 2001	Study population: predominantly adults
Pillo-Blocka 2004	Study population: children not in PICU
Suchner 1996	Study population: predominantly adults
Tyson 2005	Study population: premature neonates or newborns in the neonatal intensive care unit
Young 1987	Study population: predominantly adults

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search Strategies

Ovid MEDLINE(R) <1950 to February Week 1 2007>

#1. ((artificial$ or enteric$ or naso-gastric$ or nasogastric$ or nose$ or tube$ or ng or intravenous$ or iv$ or parenteral$ or enteral$ or jejunal$ or naso-jejunal$ or nasojejunal$) adj5 (nutrition$ or feed$ or food$ or refeed$ or re-feed$ or refed$ or re-fed$ or fasting or fasts or immunonutrition$ or immuno-nutrition$ or diet$ or hyperalimentation$ or alimentation$ or fluid$ or liquid$)).mp.
#2. tpn.ti,ab.
#3. food intake/
#4. infant nutrition/
#5. child nutrition/
#6. diet/
#7. exp parenteral nutrition, total/
#8. intravenous feeding/
#9. feeding methods/
#10. or/1-9
#11. (picu or icu).mp.
#12. ((critical$ or intensive$) adj5 (care$ or ill$)).mp.
#13. exp intensive care units, pediatric/
#14. or/11-13
#15. #10 and #14
#16. child/
#17. infant/
#18. adolescence/
#19. exp infant, newborn/
#20. exp child, preschool/
#21. or/16-20
#22. (pediatric or paediatric).tw.
#23. (child$ or newborn$ or adolescen$ or infan$).tw.
#24. preschool$.tw.
#25. teen$.tw.
#26. kindergarten$.tw.
#27. elementary school$.tw.
#28. nursery school$.tw.
#29. youth$.tw.
#30. (baby$ or babies$).tw.
#31. schoolchild$.tw.
#32. toddler$.tw.
#33. or/22-32
#34. 21 or 33
#35. 15 and 34
#36. “neonatal intensive care”.ti.
#37. “very low birth weight”.ti.
#38. (preterm or prematur$).ti.
#39. or/36-38

#40. #35 not #39
#41. clinical trial.pt.
#42. randomi?ed.ti,ab.
#43. placebo.ti,ab.
#44. dt.fs.
#45. randomly.ti,ab.
#46. trial.ti,ab.
#47. groups.ti,ab.
#48. or/41-47
#49. animals/
#50. humans/
#51. #49 not (#49 and #50)
#52. #48 not #51
53. #40 and #52
EMBASE <1988 to 2007 Week 06>
Date searched: 15 February 2007
#1. exp Intensive Care/ or exp Intensive Care Unit/
#2. ((critical$ or intensive$) adj5 (care$ or ill$)).mp.
#3. (picu or icu).ti,ab.
#4. or/1-3
#5. (early or earlier or late$ or delay$ or postoperati$ or post-operati$ or time$ or timing$).ti,ab.
#6. exp TOTAL PARENTERAL NUTRITION/
#7. exp PARENTERAL NUTRITION/
#8. exp Intravenous Feeding/
#9. exp enteric feeding/
#10. exp Food Intake/
#11. exp nutritional support/
#12. exp Child Nutrition/
#13. exp Infant Nutrition/
#14. exp nasogastric tube/
#15. exp DIET/
#16. exp DIET RESTRICTION/
#17. tpn.ti,ab.
#18. ((artificial$ or enteric$ or naso-gastric$ or nasogastric$ or nose$ or tube$ or ng or intravenous$ or iv$ or parenteral$ or enteral$ or jejunal$ or naso-jejunal$ or nasojejunal$) adj5 (nutrition$ or feed$ or food$ or refeed$ or re-feed$ or refed$ or re-fed$ or fasting or fasts or immunonutrition$ or immuno-nutrition$ or diet$ or hyperalimentation$ or alimentation$ or fluid$ or liquid$)).mp.
#19. or/6-15
#20. Child/
#21. Infant/
#22. Newborn/
#23. Adolescent/
#24. or/20-23
#25. (pediatric$ or paediatric$ or child$ or neonat$ or newborn$ or adolescen$ or infan$ or preschool$ or pre-school$ or teen$ or kindergarden$ or elementary school$ or nursery school$ or youth$ or baby$ or babies$ or schoolchild$ or toddler$).tw.
#26. #24 or #25
#27. and/4,19,26
#28. ("neonatal intensive care" or NICU).ti.
#29. (preterm or prematur$).ti.
#30. or/28-29
#31. exp clinical trial/
#32. randomi?ed.ti,ab.
#33. placebo.ti,ab.
#34. (ae or dt or to).fs.

#35. randomly.ti,ab.
#36. trial.ti,ab.
#37. groups.ti,ab.
#38. or/31-37
#39. animal/ or nonhuman/
#40. human/
#41. 39 not (39 and 40)
#42. 38 not 41
#43. (27 and 42) not 30

EBM Reviews - Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects <Issue 4, 2006>

Date Searched: 13th February 2007

1. ((artificial$ or enteric$ or naso-gastric$ or nasogastric$ or nose$ or tube$ or ng or intravenous$ or iv$ or parenteral$ or enteral$ or jejunal$ or naso-jejunal$ or nasojejunal$) adj5 (nutrition$ or feed$ or food$ or refeed$ or re-feed$ or refed$ or re-fed$ or fasting or fasts or immunonutrition$ or immuno-nutrition$ or diet$ or hyperalimentation$ or alimentation$ or fluid$ or liquid$)).mp.
#2. tpn.ti,ab.
#3. food intake.sh.
#4. infant nutrition.sh.
#5. child nutrition/
#6. diet.sh.
#7. parenteral nutrition, total.sh.
#8. food intake.sh.
#9. intravenous feeding.sh.
#10. feeding methods/
#11. or/1-10
#12. (picu or icu or nicu).mp.
#13. ((critical$ or intensive$) adj5 (care$ or ill$)).mp.
#14. intensive care units, pediatric/
#15. or/12-14
#16. and/11,15
#17. child/
#18. infant/
#19. adolescence/
#20. infant, newborn/
#21. child, preschool/
#22. or/17-21
#23. (pediatric$ or paediatric$ or child$ or newborn$ or adolescen$ or infan$ or preschool$ or pre-school$ or teen$ or kindergarden$ or elementary school$ or nursery school$ or youth$ or baby$ or babies$ or neonat$ or schoolchild$ or toddler$).tw.
#24. #22 or #23
#25. #16 and #24

EBM Reviews - Cochrane Central Register of Controlled Trials <Issue 4, 2006>

Date searched: 16th February 2007

#1. exp parenteral nutrition, total/
#2. feeding methods/
#3. exp TOTAL PARENTERAL NUTRITION/
#4. exp PARENTERAL NUTRITION/
#5. exp Intravenous Feeding/
#6. exp Food Intake/
#7. exp nutritional support/
#8. exp Child Nutrition/
#9. exp Infant Nutrition/
#10. exp DIET/
#11. tpn.ti,ab.

#12. ((artificial$ or enteric$ or naso-gastric$ or nasogastric$ or nose$ or tube$ or ng or intravenous$ or iv$ or parenteral$ or enteral$ or jejunal$ or naso-jejunal$ or nasojejunal$) adj5 (nutrition$ or feed$ or food$ or refeed$ or re-feed$ or refed$ or re-fed$ or fasting or fasts or immunonutrition$ or immuno-nutrition$ or diet$ or hyperalimentation$ or alimentation$ or fluid$ or liquid$)).mp.
#13. or/1-12
#14. exp Intensive Care/
#15. exp intensive care units, pediatric/
#16. (picu or icu).mp.
#17. ((critical$ or intensive$) adj5 (care$ or ill$)).mp.
#18. or/14-17
#19. child/
#20. exp child, preschool/
#21. infant/
#22. exp infant, newborn/
#23. Adolescent/
#24. (pediatric$ or paediatric$ or child$ or neonat$ or newborn$ or adolescen$ or infan$ or preschool$ or pre-school$ or teen$ or kindergarden$ or elementary school$ or nursery school$ or youth$ or baby$ or babies$ or schoolchild$ or toddler$).mp.
#25. or/19-24
#26. #13 and #18 and #25
#27. "neonatal intensive care".ti.
#28. "very low birth weight".ti.
#29. (preterm or prematur$).ti.
#30. or/27-29
#31. #26 not #30

Web Of Science <1900 to 2007>

Date of Search: 15th February 2007

#1 TS=((critical$ or intensive$) SAME (care$ or ill$))
#2 TS=(PICU OR ICU OR NICU)
#3 TS=(pediatric* or paediatric* or child* or newborn* or neonat* or adolescen* or infan* or preschool* or pre-school* or teen* or kindergarden* or elementary school* or nursery school* or youth* or baby* or babies* or schoolchild* or toddler*)
#4 TS=(PARENTERAL NUTRITION OR Intravenous Feeding OR Food Intake OR Child Nutrition OR Infant Nutrition OR DIET OR tpn)
#5 TS=(naso gastric* or nasogastric* or nose* or tube* or ng or intravenous* or iv or parenteral* or enteral* or jejunal* or naso jejunal* or nasojejunal* or artificial* or enteric*)
#6 TS=(nutrition* or feed* or food* or refeed* or re feed* or refed* or re fed* or fasting or fasts or immunonutrition* or immuno-nutrition* or diet* or hyperalimentation* or alimentation* or fluid* or liquid*)
#7 (#1 OR #2) AND #3 AND (#4 OR #5 OR #6)
#8 TS=clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS= follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) OR TS=groups
#9 #7 AND #8

BIOSIS Previews <1969 to 2007>

Date of Search: 16th February 2007

#1 TS=((critical$ or intensive$) SAME (care$ or ill$))
#2 TS=(PICU OR ICU)
#3 TS=(pediatric* or paediatric* or child* or newborn* or adolescen* or infan* or preschool* or pre-school* or teen* or kindergarden* or elementary school* or nursery school* or youth* or baby* or babies* or schoolchild* or toddler*)
#4 TS=(PARENTERAL NUTRITION OR Intravenous Feeding OR Food Intake OR Child Nutrition OR Infant Nutrition OR DIET OR tpn)
#5 TS=(naso gastric* or nasogastric* or nose* or tube* or ng or intravenous* or iv or parenteral* or enteral* or jejunal* or naso jejunal* or nasojejunal* or artificial* or enteric*)
#6 TS=(nutrition* or feed* or food* or refeed* or re feed* or refed* or re fed* or fasting or fasts or immunonutrition* or immuno-nutrition* or diet* or hyperalimentation* or alimentation* or fluid* or liquid*)
#7 (#1 OR #2) AND #3 AND (#4 OR #5 OR #6)

#8 TS=clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS= follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) OR TS=groups
#9 #7 AND #8
#10 TI=(preterm OR prematur* OR "neonatal intensive care" OR NICU)
#11 #9 NOT #10
#12 #9 NOT #11
TRIALS REGISTRIES
Dates of Searches: 14th February 2007
Current Controlled Trials
(critical% or icu or picu) AND (nutrition% or feed% or food% or refeed% OR PN or EN or TPN) NOT adult%
Clinicaltrials.gov
("parenteral nutrition" OR "enteral nutrition" OR nutritional OR nutritionally OR feed or feeding OR feedings OR food OR refeed OR refeeding OR PN OR EN OR TPN) [TREATMENT] AND "Child" [AGE-GROUP] AND (ICU OR picu OR critical OR "critically ill" OR serious) [CONDITION]
Medline Plus Searching Of Clinicaltrials.gov
parenteral nutrition [TREATMENT]
"nutritional support" [TREATMENT]
National Research Register
#1. (nutritional next support)
#2. (nutrition* or feed* or refeed* or tubefeed* or tubefed* or en or pn or tpn)
#3. (critical* or intensive or icu or picu)
#4. (#1 or #2)
#5. (#3 and #4)
#6. (enteral or parenteral)
#7. ((#1 or #6) and #3)
#8. picu
#9. ((#1 or #6) and #8)
#10. (pediatric next intensive next care)
#11. (paediatric next intensive next care)
#12. ((#10 or #11 or #8) and (#4 or #6))

Appendix 2. Inclusion Form

Please assess each study with reference to the criteria below. Place a check mark beside the statement that best describes the study. A study will be excluded even if has only one "NO" answer.
Reviewer ____
Reference number_________________________

STUDY DESIGN:
1. Was the study a randomized controlled trial? Yes[] No[]

POPULATION:
2. Was the population studied children/youth (age 1 day to 18 years) that are cared for in a paediatric intensive care setting and who receive nutrition within the first seven days of admission? [Studies that involve both paediatric and adult participants will be included.] Yes[] No[]

INTERVENTIONS:
3. Were patients randomized during the first week of admission to receive either: Yes [] No[]
a) enteral feeding versus no feeding;
b) total parenteral nutrition versus no feeding;
c) enteral versus total parenteral nutrition;

d) enteral versus enteral with supplemental parenteral nutrition.

[This review will not address other areas of paediatric nutrition, such as Immunonutrition versus normal nutrition, or different routes of delivering enteral nutrition.]

OUTCOME S:
4. Are data reported for one of the following outcomes: Yes[] No[]

- 30-day mortality or PICU mortality []

- length of stay in PICU []

- length of stay in hospital []

- number of days on ventilator []

- morbid complications, including nosocomial infections []

DECISION:
Should this study be included in this systematic review?

Yes [] (questions 1-4 must ALL be answered "Yes")
No [] (any of questions 1-4 answered with "No")
Unsure [] (will need to be reviewed and decided by consensus)

If disagreement; final consensus decision: Yes[] No []
Reason:

Appendix 3. Data Extraction Form

The Cochrane Anaesthesia Review Group 02.01
APPENDIX IV, DATA EXTRACTION FORM

Study ID:				
Authors:				
Medline Journal ID:				
Year of Publication:				
Language:			**Country:**	
Type of Study:	**RCT_____**	**CCT_____**	**Non-randomized_____**	
Comments on Study Design:				
QUALITY OF CONCEALMENT OF ALLOCATION				**POINTS**

(*Continued*)

Allocation was not concealed (e.g. quasi-randomized)	0
Allocation concealment was not stated or was unclear	1
Disclosure of allocation was a possibility	2
Allocation was concealed (e.g. numbered, sealed opaque envelopes drawn NON consecutively)	3
Inclusion and exclusion criteria were not clearly defined in the text	0
Inclusion and exclusion criteria were clearly defined in the text	1
Outcomes of patients who withdrew or were excluded after allocation were NEITHER detailed separately NOR included in an intention to treat	0
Outcomes of patients who withdrew or were excluded after allocation were EITHER detailed separately OR included in an intention to treat analysis **OR** the text stated there were no withdrawals	1
Treatment and control groups were NOT adequately described at entry	0
Treatment and control groups were adequately described at entry A minimum of 4 admission details were described (e.g. age, sex, mobility, type of surgery, ASA grade, function score, mental test score)	1
The text stated that the care programmes other than trial options were NOT identical	0
The text stated that the care programmes other than trial options were identical	1
Outcome measures were NOT clearly defined in the text	0
Outcome measures were clearly defined in the text	1
Outcome assessors were NOT blind to the allocation of patients	0
Outcome assessors were blind to the allocation of patients	1

(*Continued*)

The timing of the measurement of the outcomes was NOT appropriate	0
The timing of the measurement of the outcomes was appropriate	1
TOTAL NUMBER OF POINTS: / 10	
METHODS:	
Subject -Blinded Yes_____ No_____ Unclear_____	
Physician - Blinded Yes_____ No_____ Unclear_____	
Intention-to-treat analysis: Planned Yes_____ No_____ Unclear_____ Performed Yes_____ No_____ Unclear_____ N/A_____	
Method of randomization:	
PARTICIPANTS:	
Number of eligible participants: Number enrolled in study:	
Number of males: Number of females:	
Age of participants: Type of patients: surgical_____ medical_____ Specify: < 1 yr ___ >= 1 yr ___ no stratification ___	
Severity of illness:	

INTERVEN-TION:	Intervention	Duration
Study Group 1:		
Study Group 2:		
Study Group 3:		
Study Group 4:		
COMMENT ON TREATMENT:		

(*Continued*)

Withdrawals: Yes_____ No_____ Unclear_____ Indicate number by group: study group 1 _____ study group 2 _____ study group 3 _____ Indicate reasons for withdrawals:				
OUTCOMES: (specify units and measures, e.g. mean, SD, SE median, range, IQR)	Study Group 1	Study Group 2	Study Group 3	Study Group 4
30-day mortality (n, %)				
PICU Mortality (n, %)				
LOS in PICU (days)				
LOS in hospital (days)				
Ventilator days (days)				

(*Continued*)

Infection (n, %)				
Other complications (list)				
Side effects (list)				

Was a time to event analysis performed: **no_____** **yes_____**
If yes:
List outcomes:
Are data available for individual cases: **no _____** **yes_____**

CHANGES IN PROTOCOL:

CONTACT WITH AUTHOR:

OTHER COMMENTS ON THIS STUDY:

SUBGROUPS:

Age <1 year	Study Group 1	Study Group2	Study Group 3	Study Group 4
30-day mortality (n, %)				
PICU mortality (n, %)				

Age ? 1 year	Study Group 1	Study Group 2	Study Group 3	Study Group 4
30-day mortality (n, %)				
PICU mortality (n, %)				

Medical patients	Study Group 1	Study Group 2	Study Group 3	Study Group 4

(*Continued*)

30-day mortality (n, %)				
PICU mortality (n, %)				
Surgical patients	Study Group 1	Study Group 2	Study Group3	Study Group 4
30-day mortality (n, %)				
PICU mortality (n, %)				

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 2, 2009

Date	Event	Description
11 December 2007	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Ari Joffe (AJ)

Co-ordinating the review: AJ, Lisa Hartling (LH)

Undertaking manual searches: AJ

Screening search results: AJ, Natalie Anton (NA)

Organizing retrieval of papers: Lisa Tjosvold (LT), AJ

Screening retrieved papers against inclusion criteria: AJ, NA

Appraising quality of papers: LH, NA

Abstracting data from papers: AJ, LH, NA

Writing the review: AJ, NA, LH, Ben Vandermeer (BV), Laurance Lequier (LL), Bodil Larsen (BL)

Guarantor for the review (one author): AJ

Person responsible for reading and checking review before submission: AJ, LH

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Alberta Research Centre for Child Health Evidence (ARCHE), University of Alberta, Edmonton, Canada.

External sources

- Alberta Heritage Foundation for Medical Research, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Background updated

INDEX TERMS

Medical Subject Headings (MeSH)

Burns [complications]; Critical Illness [*therapy]; Enteral Nutrition [*methods]; Intensive Care Units, Pediatric; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans; Infant