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Effectiveness of high vs lower enteral protein intake, considering energy intake, on clinical outcomes in critically ill children: a systematic review protocol

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ABSTRACT

Objective: The objective of this review is to evaluate the effectiveness of high vs lower enteral protein intake, considering energy intake, on clinical and nutritional outcomes in critically ill children hospitalized in the pediatric intensive care unit.

Introduction: Over- and undernutrition increases the risk of morbidity and mortality in critically ill children. The impact of high vs lower enteral protein intake on clinical outcomes, considering energy intake, still needs to be investigated in children of different ages.

Inclusion criteria: This review will consider studies of critically ill children (aged between ≥ 37 weeks gestational age and < 18 years) admitted to the pediatric intensive care unit for a minimum of 48 hours and receiving enteral nutrition. Randomized controlled trials comparing high vs lower enteral protein intake, considering energy intake, will be eligible. Primary outcomes will include clinical and nutritional outcomes, such as length of stay in the pediatric intensive care unit and nitrogen balance.

Methods: Using the JBI methodology for systematic reviews of effectiveness, we will search for randomized controlled trials published in English, French, Italian, Spanish, and German in electronic databases, including MEDLINE, CINAHL Complete, Embase, and the Cochrane Library, from database inception until the present. We will also search clinical trial registers and, if required, contact authors. Two independent reviewers will screen and select studies for inclusion, data extraction, and assessment of methodological quality. A third reviewer will be consulted if necessary. A statistical meta-analysis will be performed if feasible.

Systematic review registration number: PROSPERO CRD42022315325

Keywords: clinical outcomes; critical illness; energy; pediatrics; protein

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Introduction

Nutrition is important for health and well-being but is particularly crucial in critically ill children admitted to the pediatric intensive care unit (PICU). Most critically ill children are unable to eat orally and require enteral nutrition. PICU clinicians aim to avoid underfeeding or overfeeding, both of which increase the risk of morbidity, leading to prolonged mechanical ventilation and length of PICU stay, as well as increased mortality risk.[1–3] The negative effects of unbalanced energy intake during PICU on neurocognitive development may manifest up to 2 years after hospitalization.[4] Just as the

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optimal dose of a medication is determined based on pharmacological research, optimal energy and protein intake must be determined based on evidence-based nutritional research data. However, such data are scarce. In 2018, a Delphi study involving international experts defined energy and protein needs as 2 of the nutritional research areas that require the most investigation in PICU.[5]

For many years, the energy and protein intake recommended for critically ill children has been higher than the recommended intake for healthy children.[6] This was based on critically ill adult data, which showed that metabolic stress due to critical illness induced an increase in resting energy expenditure (hypermetabolism) and nitrogen losses (hypercatabolism).[7] A few observational studies in mechanically ventilated, critically ill children have measured their resting energy expenditure by indirect calorimetry and their urinary nitrogen loss, a surrogate for protein needs.[8–11] Strikingly, the minimum energy intake required to equilibrate the energy balance was significantly lower than the recommended intake for healthy children. Several factors may decrease energy expenditure in the PICU, including the use of sedatives and neuromuscular blocking drugs, mechanical ventilation, decreased physical activity, and eventual absence of growth. However, these studies showed that urinary nitrogen loss values in critically ill children were much higher than in healthy children.[12] In addition, the protein intake required to equilibrate nitrogen balance was significantly higher in critically ill children than in healthy children.[9–11,13]

Two systematic reviews investigated the impact of energy and/or protein intake in critically ill children.[13,14] In 2012, Bechard *et al.* examined the influence of protein and energy intake on protein balance in critically ill ventilated children.[13] The primary outcome was protein balance; no other clinical outcomes were studied. The authors included 9 studies published between 1997 and 2011 that reported both energy and protein intake, along with protein balance. Due to heterogeneity in determining the protein balance, the data could not be pooled for meta-analysis. The authors concluded that a minimum intake of 57 kcal/kg/day and 1.5 g protein/kg/day was required to achieve a positive protein balance in critically ill, ventilated children.[13]

In 2017, Hauschild *et al.* described the effects of protein intake on protein balance and clinical outcomes in critically ill children.[14] Based on 17 studies, the authors showed that the daily protein intake ranged from 0.67 to 1.5 g/kg in observational studies (n = 6) and from 2.8 to 4.7 g/kg in randomized controlled trials (n = 9). Seven studies evaluated the association between protein intake and clinical parameters other than nitrogen balance. The average daily protein intake > 1.1 g/kg, especially > 1.5 g/kg, was associated with positive protein balance and lower mortality.[14] Due to the heterogeneity of the interventions, exposures, and outcomes, no meta-analysis was performed. These results are concordant with those of Bechard *et al.*,[13] but as energy intake was not considered, no minimum energy intake was recommended in this systematic review.[14]

The American Society of Parenteral and Enteral Nutrition (ASPEN) and the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) published recommendations for energy and protein intake in critically ill children in 2017 and 2020, respectively.[15,16] To determine energy requirements and guide nutritional support, the authors recommended measuring energy expenditure using a validated indirect calorimeter or an estimation based on the Schofield predictive equations.[17] For protein, it is recommended to consider a minimum enteral intake of 1.5 g/kg/day to avoid negative protein balance. The ASPEN guidelines state that the optimal protein intake required to attain a positive protein balance may be higher in critically ill infants and young children.[15] The ESPNIC guidelines state that there is insufficient evidence available to support the use of additional protein intake during the acute phase of illness.[16]

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted, and no in-progress systematic reviews on the topic were identified. A systematic review published in December 2021 examined the effectiveness of energy and/or protein dense enteral formulas on outcomes in infant cardiac surgical patients but did not assess the amount of protein and energy provided.[18] Except for the systematic review by Bechard *et al.* (2012),[13] which showed that 57 kcal/kg per day and 1.5 g/kg/day of protein were required to achieve positive protein balance, no effectiveness review has been conducted examining the impact of protein intake, and reporting energy intake, on clinical outcomes in critically ill children. Several randomized controlled trials, including recent ones, have assessed the impact of protein intake higher than 1.5 g/kg per day in

critically ill children, and reporting energy intake.[19–25] Conducting this review will improve our understanding of the impact of high vs lower protein intake on clinical outcomes, considering energy intake, in critically ill children. It may also clarify this impact on different age groups, including newborns, infants, children, and adolescents, where possible. Therefore, this review will evaluate the effectiveness of high vs lower enteral protein intake, with a clear separation between the groups, and reporting energy intake, on clinical and nutritional outcomes in critically ill children.

Review question

What is the effect of high vs lower protein intake, with a clear separation between different age groups, and reporting energy intake, on clinical and nutritional outcomes in critically ill children?

Inclusion criteria

Participants

This review will consider studies that include i) term neonates (born at ≥ 37 weeks of gestation up to 1 month of age), ii) infants (1–23 months), iii) children (2–12 years), and iv) adolescents (13–18 years) admitted to PICU. Studies involving preterm neonates will be excluded.

Interventions

This review will consider studies that evaluate high enteral protein intake compared with lower intake, with a clear separation between the high and low age groups, and reporting energy intake. For the intervention, we will consider studies that assess the impact of protein intake < 1.1 or ≥ 2 g/kg per day vs the protein intake recommended by the ASPEN and ESPNIC guidelines[15,16] (for the control group). We chose these cut-offs based on current recommended protein intakes, as there is no consensus on what constitutes low or high protein intake. We will include studies that provide enteral nutrition. Studies of children not receiving enteral nutrition; receiving exclusive oral nutrition, or combined with enteral nutrition or parenteral nutrition; or having a PICU stay lasting less than 48 hours will be excluded.

Comparators

This review will consider studies that evaluate, as a comparator, enteral protein intake between 1.1 and 2 g/kg per day vs higher or lower intake (intervention groups), and reporting energy intake. These values between 1.1 and 2 g/kg per day are based on the ASPEN and ESPNIC guidelines, which state that for critically ill infants and children on enteral nutrition, a minimum enteral protein intake of 1.5 g/kg/d can be considered to avoid negative protein balance.[15,16] These values are also based on the findings of the systematic review of Hauschild, which showed that average daily total protein intake > 1.1 g/kg, especially > 1.5 g/kg, was associated with positive protein balance and lower mortality.[14] Studies that do not have a comparison group with an intake between 1.1 and 2 g/kg per day will be excluded.

Outcomes

This review will use length of PICU stay and nitrogen balance as primary outcomes. Nitrogen balance is determined as the difference between nitrogen intake and nitrogen losses (protein balance will also be considered if provided by studies because nitrogen is simply converted into protein using the nitrogen-to-protein conversion factor of 6.25).

The secondary outcomes will include i) duration of mechanical ventilation and non-invasive ventilation, length of hospital stay, inflammatory markers (C-Reactive Protein CRP), and complications during PICU stay; and ii) nutritional outcomes, including energy target achievement, anthropometric outcomes, such as weight change and mid upper arm circumference, and relevant biochemical markers, such as serum albumin.

Types of studies

This review will consider randomized controlled trials and will exclude other study designs.

Methods

The review will be conducted in accordance with the JBI methodology for systematic reviews of effectiveness.[26] This protocol has been written in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Protocols (PRISMA-P) guidelines.[27] PRISMA[28] and the PRISMA extension for Searching (PRISMA-S)[29] will be used to report the final systematic review. This systematic review has been registered in PROSPERO (CRD42022315325).

Search strategy

A 3-step search strategy will be used to identify published and unpublished studies. First, an initial limited search of MEDLINE (Ovid) was performed to identify articles on the topic. We adapted full search strategies for MEDLINE that were previously developed for a project on nutritional guidelines for critically ill children, and specifically those on energy and protein intake.[16] The full search strategy for MEDLINE (Ovid), developed in collaboration with specialized librarians from the University of Applied Sciences of Western Switzerland (BK and MP), is shown in Appendix I. The search strategy, including all identified keywords and index terms, will be adapted for each database and/or information source.

Information sources will include electronic databases, namely, MEDLINE (Ovid), CINAHL Complete (EBSCO), Embase, and the Cochrane Library Central Register of Controlled trials, as well as trial registers such as Clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry. In addition, the reference lists of all included sources of evidence will be screened for additional studies, including references of existing systematic reviews on the topic and studies included in the systematic review.

Studies published from database inception till the present will be included. Studies published in English, French, Italian, Spanish, and German (the languages spoken by the review team) will be eligible for inclusion. The search strategy will be developed in collaboration with specialized librarians (BK and MP). Sources of unpublished studies and gray literature to be searched will include Google Scholar, ProQuest Dissertations and Theses, and MedNar, as well as contact with researchers who have recently published a paper on this topic.

Study selection

Following the search, all identified citations will be collated and uploaded into EndNote v.20.2.1 (Clarivate Analytics, PA, USA), and duplicates removed. Following a pilot test, titles and abstracts will be screened by 2 independent reviewers for assessment of the inclusion criteria using Rayyan (Qatar Computing Research Institute, Doha, Qatar). Potentially relevant studies will be retrieved in full, and their citation details will be imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).[30] The full texts of the selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers. The reasons for exclusion of full texts that do not meet the inclusion criteria will be reported in the systematic review. Any disagreements between the reviewers at each stage of the selection process will be resolved by a third reviewer. If eligible studies are published in languages that the review team does not speak (eg, Chinese), they will be excluded and the reason for exclusion will be provided. The results of the search and the study inclusion process will be reported in full in the final systematic review and presented in a PRISMA flow diagram.[29]

Assessment of methodological quality

Eligible studies will be critically appraised by 2 independent reviewers at the study level for methodological quality using standardized critical appraisal instruments from JBI for experimental studies.[26] Authors of papers will be contacted to request missing or additional data for clarification where required. Any disagreements that arise will be resolved by a third reviewer. The results of the critical appraisal will be reported in narrative format and in a table. All studies, regardless of their methodological quality, will undergo data extraction and synthesis (where possible). Sub-analysis will be performed to consider the impact of the quality of methodology on the findings.

Data extraction

Data will be extracted from studies included in the review by 2 independent reviewers using a modified version of the JBI tool,[26] which will be revised as necessary during piloting prior to data extraction (see Appendix II). Any disagreements between the reviewers will be resolved by a third reviewer. Authors of papers will be contacted to request missing or additional data, if necessary.

Data synthesis

The characteristics of the included studies will be presented narratively and in a table. Where possible, studies will be pooled in a statistical meta-analysis using JBI SUMARI. The meta-analyses will be performed by a qualified statistician. Effect sizes will be expressed in odds ratios for dichotomous outcomes and Cohen's d for continuous outcomes, and their respective 95% confidence intervals will also be

calculated for the analysis. Statistical analyses will be performed using mixed models, allowing us to include fixed effects (or population effects) and random effects (subject-specific deviations from the population effect).[31] Stratified analyses by age will be conducted where there are sufficient data to investigate the impact of protein intake on outcomes in critically ill children of different age groups (ie, term neonates, infants, children, adolescents).

Sensitivity analyses will be conducted to test the precision of decisions made regarding the type I error threshold. Clinical and methodological heterogeneity will be assessed by descriptively comparing study designs and participant characteristics between studies. Heterogeneity between groups will be assessed by visual inspection and descriptive statistics, and will be statistically tested with the standard χ^2 test for heterogeneity. A funnel plot will be generated using R statistical software v. 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) to assess publication bias if $\geq$ 10 studies are included in the meta-analysis. Where meta-analysis is not possible, the findings will be presented in narrative format, including tables and figures, to aid in data presentation, where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[32] approach for grading the certainty of evidence will be followed and a Summary of Findings (SoF) will be created using GRADEpro (McMaster University, ON, Canada). Two independent reviewers will perform these steps at the outcome level. Any disagreements between the reviewers will be resolved by a third reviewer. Authors of papers will be contacted to request missing or additional data for clarification where required. The SoF will present the following information, where appropriate: absolute risks for the treatment and control; estimates of relative risk; and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. The outcomes reported in the SoF will be our primary outcomes (ie, PICU length of stay, nitrogen balance). We will also report the duration of mechanical ventilation, length of hospital stay, and weight change, which are our main secondary outcomes.

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Author contributions

CJC, LNT, and FVV designed the study in collaboration with the research team and wrote the first draft of the protocol, which was reviewed and approved by all authors.

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Appendix I: Search strategy

MEDLINE(R) (Ovid) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to 4 November, 2022>

Search conducted on November 4, 2022.

The full search strategy was developed by combining population and intervention terms and excluding animal studies and editorials. We did not include terms related to outcomes to avoid limiting the results.

#	Searches	Results retrieved
1	"Nutritional Support"/ or "Enteral Nutrition"/ or ((enteric* or enteral* or tube* or gastric* or support*) adj3 (nutrition* or feeding*)).ab,ti. or ("Percutaneous endoscopic gastrostomy" or "Percutaneous endoscopic transgastric jejunostomy" or nasogastric or nasojejunal or PEG or PEG-J).ab,ti.	101,866
2	exp "Child"/ or "Infant"/ or "Infant, Newborn"/ or "Adolescent"/ or exp "Pediatrics"/ or "Hospitals, Pediatric"/ or (child* or infant* or newborn* or pediatr* or paediatr*).ab,ti.	4,463,991
3	(exp "Intensive Care Units"/ or exp "Critical Care"/ or "Critical Illness"/ or "Critical Care Nursing"/ or exp "Intensive Care Units, Pediatric"/ or "Intensive Care, Neonatal"/ or (((intensive or critical*) adj3 (care or ill*)) or ICU* or PICU* or "high risk*").ab,ti.)	655,271
4	2 AND 3	173,249
5	"Proteins"/ or "Amino Acids"/ or ((protein* or "amino acid" or "amino acids") adj4 (optimal* or high* or low* or requir* or deliver* or administ* or intake* or feeding* or metabol* or suppl* or infusion* or dos*)).ab,ti. or ("Eating"/ or ((diet* or food* or feed* or macronutri* or micronutri* or nutri*) adj4 (requir* or deliver* or administ* or intake* or consumpt* or metabol* or suppl* or infusion* or dos*)).ab,ti.)	1,052,783
6	1 AND 4 AND 5	911
7	(("Nutritional Support"/ or "Enteral Nutrition"/ or ((enteric* or enteral* or tube* or gastric* or support*) adj3 (nutrition* or feeding*)).ab,ti. or ("Percutaneous endoscopic gastrostomy" or "Percutaneous endoscopic transgastric jejunostomy" or nasogastric or nasojejunal or PEG or PEG-J).ab,ti.) and (exp "Child"/ or "Infant"/ or "Infant, Newborn"/ or "Adolescent"/ or exp "Pediatrics"/ or "Hospitals, Pediatric"/ or (child* or infant* or newborn* or pediatr* or paediatr*).ab,ti.) and (exp "Intensive Care Units"/ or exp "Critical Care"/ or "Critical Illness"/ or "Critical Care Nursing"/ or exp "Intensive Care Units, Pediatric"/ or "Intensive Care, Neonatal"/ or (((intensive or critical*) adj3 (care or ill*)) or ICU* or PICU* or "high risk*").ab,ti.) and ("Proteins"/ or "Amino Acids"/ or ((protein* or "amino acid" or "amino acids") adj4 (optimal* or high* or low* or requir* or deliver* or administ* or intake* or feeding* or metabol* or suppl* or infusion* or dos*)).ab,ti. or ("Eating"/ or (("diet*" or food* or feed* or macronutri* or micronutri* or nutri*) adj4 (requir* or deliver* or administ* or intake* or consumpt* or metabol* or suppl* or infusion* or dos*)).ab,ti.))) not (exp animals/ not humans/) not "editorial".pt.	908

Appendix II: Data extraction instrument

First author's last name	
Publication year	
Study design	
Review objectives/questions	
Inclusion criteria	
Participants • Age • Gender • Diagnosis • Severity of disease	
Setting/context	
Sample • Sample size • Drop-out rate	
Description of intervention • Amount of protein • Amount of energy • Type of feeding formula • Days (follow-up)	
Description of comparator • Amount of protein • Amount of energy • Type of feeding formula • Days (follow-up)	
Primary outcomes	
Other outcomes	
Outcome measures • Clinical outcomes • Nutritional outcomes	
Results	
Bias and main limitations	
Funding	
Conflict of interest	
Appraisal rating	