Systematic Review of the Influence of Energy and Protein Intake on Protein Balance in Critically Ill Children

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Objective To examine the influence of protein and energy intakes on protein balance in children receiving mechanical ventilation in the pediatric intensive care unit.

Study design We hypothesized that higher energy and protein intakes are correlated with positive protein balance. We performed a systematic literature search to identify studies reporting protein balance in children requiring mechanical ventilation. Factors contributing to protein balance, including protein and energy intake, age, illness severity, study design, and feeding routes, were analyzed using a qualitative approach.

Results Nine studies met the entry criteria and were included in the final analysis. Positive nitrogen balance was reported in 6 of the studies, with a wide range of associated energy and protein intakes. Measures of central tendency for daily energy and protein intakes were significantly correlated with positive protein balance. A minimum intake of 57 kcal/kg/day and 1.5 g protein/kg/day were required to achieve positive protein balance.

Conclusion We found a correlation between higher energy and protein intakes and achievement of positive protein balance in children receiving mechanical ventilation in the pediatric intensive care unit. However, there is a paucity of interventional studies, and a variety of protocols have been used to determine nitrogen balance. Larger clinical trials with uniform methodology are needed to further examine the effect of energy and protein intake on protein balance, lean body mass, and clinical outcomes in children on mechanical ventilation. (J Pediatr 2012;161:333-9).

The metabolic response to surgery, injury, or inflammation is characterized by protein catabolism and variable energy needs.1 Protein breakdown provides free amino acids, which are channeled toward tissue repair, wound healing, and the inflammatory response. This adaptive response may predispose critically ill children to substantial losses of lean body mass.2 The optimal amounts of energy and protein required during critical illness to prevent or limit loss of lean body mass are unknown.3

Although it is generally agreed that macronutrient utilization in this population differs from that in healthy children, current guidelines for energy and protein intake are based on limited evidence.4,5 Protein intake in the pediatric intensive care unit (PICU) population is estimated, with the aim of maintaining protein balance by matching the catabolism associated with the metabolic stress response. In addition to protein intake, energy intake is also thought to influence the likelihood of achieving positive protein balance during critical illness.2,6

Measurement of protein balance may be useful in clinical settings and research studies as an indicator of protein intake adequacy. However, protein balance studies are resource-intense and might be infeasible for many sites, and as a result are not widely used. In this review, we aimed to examine the influence of protein and energy intake on protein balance in children receiving mechanical ventilation in the PICU.

Methods

Clinical trials, cohort studies, and observational studies reporting energy and protein intake along with protein balance in mechanically ventilated children aged <18 years were included in this review. Studies of preterm infants, patients receiving extracorporeal membrane oxygenation support, and patients with renal insufficiency were excluded because of these patients’ unique pathophysiology and technical difficulties in measuring protein balance. Case reports, review articles, duplicate reports from the same cohort, and animal studies were excluded.

We searched the PubMed database from 1981-2011 for original articles meeting our inclusion and exclusion criteria. Search terms included were critical illness or critical care, sepsis or systemic inflammatory response syndrome, mechanical ventilation, general surgery or surgical procedures, operative or surgery, acute respiratory distress syndrome, broncho-
pulmonary dysplasia, multiple trauma, head injuries, brain injuries, spinal cord injuries, burns, neoplasms, PICU, protein-energy malnutrition or protein deficiency, nitrogen balance (NB), dietary protein, nutrition, congenital heart defects, neonatal respiratory distress, and newborns. Bibliographies of articles retrieved were also searched manually for additional studies meeting the inclusion criteria. All studies that met these criteria were published in English.

Our literature search was performed according to the guidelines of the American Dietetic Association’s Evidence Analysis Process, a framework for systematic evidence analysis modeled after work of the Institute for Clinical Systems Improvement. Grading (positive, negative, or neutral) according to quality criteria checklists was completed for each included study to assess the quality constructs and domains identified in the March 2002 Agency for Healthcare Research and Quality report on Systems to Rate the Strength of Scientific Evidence. Protein balance, protein intake, and energy intake data were abstracted from all studies that met our inclusion criteria, even when other outcomes were the primary focus of the investigation. Where necessary, the units of data described in the study were standardized, to allow comparison across reports (eg, joules converted to kilocalories, SE converted to SD, nitrogen converted to protein). Energy and protein data are presented in kilocalories per day and grams of protein per kilogram per day (assumed equivalence to gram of nitrogen *6.25), respectively, for clarity of comparisons.

Protein balance was the primary outcome for this review. Based on the reported measure of central tendency for NB results, protein balance results were categorized as positive balance (>0) or negative balance (<0). For studies in which successive measurements were obtained over multiple days, protein balance on the final day of measurement was used to determine whether protein balance was achieved. Energy and protein intakes associated with corresponding NB data were considered as contributors to study outcomes, as were participant age, illness severity scores, feeding route, and type of study design.

Given the heterogeneity of measurement of the primary outcome variable among studies, aggregation of individual-level data for quantitative analysis was not possible. To facilitate qualitative comparison, intervention groups within the included clinical trials (typically “high-protein” vs “standard” groups) were separated for analysis, and the measure of central tendency reported for each group (means or medians) was abstracted. A cross-tabulation of protein balance by study characteristics was created for all studies (both clinical trials and observational studies). We hypothesized that this should result in a qualitative pattern in which a threshold for the amount of protein necessary for positive protein balance could be identified. In addition, because we believed that higher levels of protein and energy intake should be associated with a greater likelihood of positive protein balance, we hypothesized that there should be a correlation between the mean or median levels of protein and energy intake and the mean or median levels of protein balance. However, because measures of central tendency were not consistent across studies, we interpreted these measures ordinal (as more vs less) rather than as absolute measurements; thus, we performed Spearman correlations to describe relationships. We included only comparison groups (n = 11) from clinical trials (n = 6) in the correlational analysis, given that cross-sectional studies did not provide data related to a consistent time of PICU admission. SPSS version 19.0 (SPSS Inc, Chicago, Illinois) was used for the correlational analyses.

Definitions
Protein balance was defined as a general term describing the status of protein metabolism within an individual. More specifically, this includes an evaluation of protein turnover from dietary protein intake and protein breakdown, which is equivalent to protein synthesis and oxidation in steady state. A zero balance suggests protein equilibrium within an individual, a negative balance is a marker for catabolism, and a positive balance indicates anabolism.

NB was defined as a calculation of the difference between nitrogen intake and nitrogen output, measured by urinary urea nitrogen (UUN) excretion. This typically includes a correction factor for nonurinary losses (eg, stool, skin), but there is no consistently accepted correction method across studies. NB was used as a surrogate for protein balance in all studies included in this review.

Results
The number of studies screened, assessed, and included in this review are shown in Figure 1 (available at www.jpeds.com). Characteristics of the studies and abstracted findings are reported in Tables I and II. A total of 9 studies with 347 subjects were included in this review, 5 of which were randomized controlled trials comparing different levels of protein provision. Three studies included blinding of the intervention, 8–10 and 2 were open-label trials. 11,12 One noncontrolled study compared NB on the first and fifth days of the PICU stay. 13 Three studies were cross-sectional, observational reports. 1,14,15 Study populations were mixed medical and surgical patients in 5 studies (n = 231), exclusively medical patients in 2 studies (n = 39), children with severe head injury in 1 study (n = 40), and children who underwent surgery for congenital heart disease in 1 study (n = 37). Key study and group characteristics relevant to the attainment of protein balance were cross-tabulated, as shown in Table III.

Relationship of Protein and Energy Intake to NB
Positive NB was reported in 6 studies, with a wide range of associated energy intakes (57–112 kcal/kg/day) and protein intakes (1.5–3.1 g/kg/day). The central tendency for protein balance in these studies was significantly correlated with the central tendencies for protein intake (r = 0.729; P = .011) and energy intake (r = 0.721; P = .012) (Figure 2). Only groups receiving >1.5 g protein/kg/day and >57 kcal/kg/day...
Table I. Overview of protein balance studies, interventional trials (n = 6)

<table>
<thead>
<tr>
<th>Study, Design, Class/Rating</th>
<th>Number of subjects, Age group, Feeding route</th>
<th>Intervention</th>
<th>Energy intake, kcal/kg/day</th>
<th>Protein intake, g/kg/day</th>
<th>Protein balance, g/kg/day</th>
<th>Other significant outcomes</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botran et al, 2011</td>
<td>Randomized controlled trial, Class A/rating +</td>
<td>n = 41, 73% postcardiac surgery, Median age 7 months (75% &lt; 1 year) EN</td>
<td>Protein-enriched vs standard age-appropriate formula over 5 days</td>
<td>Day 1 median S, 61.9; median HP, 65.1</td>
<td>Day 1* median S, 1.5; median HP, 2.6</td>
<td>Day 1 median S, −1.2; median HP, 0.6</td>
<td>Significantly higher serum retinol-binding protein with higher-protein diet at 1 day and 5 days</td>
</tr>
<tr>
<td>Briassoulis et al, 2005</td>
<td>Randomized controlled trial, Class A/rating +</td>
<td>n = 50, Respiratory failure, sepsis, severe head injury, Median age 103 (48) months EN</td>
<td>EN with glutamine, L-arginine, ω-3 fatty acids, fiber, vitamin E, beta-carotene, Zn, Cu, Se, protein vs standard formula</td>
<td>After 5 days: HP, 58 (38); S, 64 (30)</td>
<td>After 5 days: HP, 2.6 (2); S, 2.2 (0.8)</td>
<td>After 5 days: HP, 0.44 (2.19); S, −0.38 (1.25)</td>
<td>Higher rate of diarrhea in HP,* higher rate of gastric colonization and distention in S*</td>
</tr>
<tr>
<td>Briassoulis et al, 2006</td>
<td>Randomized controlled trial, Class A/rating +</td>
<td>n = 40, Severe head injury, Median age 120 (51) months EN</td>
<td>EN with glutamine, L-arginine, ω-3 fatty acids, fiber, vitamin E, beta-carotene, Zn, Cu, Se, protein vs standard formula</td>
<td>Mean after 5 days: HP, 57; S, 62</td>
<td>Mean after 5 days: HP, 2.5; S, 2.2</td>
<td>Mean after 5 days: HP, 0.44; S, −0.38</td>
<td>Less positive gastric cultures and lower IL-8 levels in HP*</td>
</tr>
<tr>
<td>Chaloupecky et al, 1997</td>
<td>Randomized controlled trial, Class A/rating +</td>
<td>n = 37, Congenital heart disease for surgical repair, Median age 6.7 (3.4) months PN</td>
<td>PN at postoperative day 1 vs standard IV fluids</td>
<td>Nonprotein kcal: PN, 33 (9); S, 25 (15)</td>
<td>PN, 0.8 (0.1); S, 0</td>
<td>At postoperative day 1*: PN, −0.71 (0.51); S, −1.53 (0.54)</td>
<td>Higher plasma levels of isoleucine, valine, leucine, proline, and threonine at day 2*</td>
</tr>
<tr>
<td>Van Waardenburg et al, 2009</td>
<td>Randomized controlled trial, Class A/rating +</td>
<td>n = 20, RSV, Median age 2.9 (1.7) months EN</td>
<td>Protein-enriched infant formula vs standard formula over 5 days</td>
<td>On day 5*: HP, 112 (37); S, 82 (13)</td>
<td>On day 5*: HP, 2.8 (0.8); S, 1.5 (0.3)</td>
<td>On day 5*: HP, 1.86 (0.73); S, 0.77 (0.46)</td>
<td>Higher plasma essential and branched chain amino acids with HP*</td>
</tr>
<tr>
<td>Briassoulis et al, 2002</td>
<td>Noncontrolled trial, Class D/rating +</td>
<td>n = 71, 25% sepsis, 41% brain injury, 13% respiratory failure, 10% neuromuscular disease, 11% burns, Median age 54 months (range, 2-204 months) EN</td>
<td>EN starting within 12 hours after admission</td>
<td>Paired samples*: day 1, 22 (9.3); day 5, 66 (22.8)</td>
<td>Paired samples*: day 1, 0.69 (0.25); day 5, 1.9 (0.59)</td>
<td>Paired samples*: day 1, −1.63 (1.06); day 5, 0.19 (1.06)</td>
<td>On day 5, protein intake (RDA) and energy intake (BMR) positively correlated with NB; MOSF negatively correlated with NB</td>
</tr>
</tbody>
</table>

8 BM1, estimated basal metabolic rate; EN, enteral nutrition; HP, high protein; MOSF, multiple organ system failure; RDA, recommended daily allowance; RSV, respiratory syncytial virus; S, standard group. Class and rating were determined using methodology from the American Dietetic Association’s Evidence Analysis Manual 2010. All values are presented as mean (SD), except where noted otherwise. *P < .05.
achieved positive protein balance. Patients received nutrient intake through the enteral route alone (n = 5), parenteral route alone (n = 3), or both the enteral and parenteral routes (n = 1). Energy expenditure was measured by indirect calorimetry in 6 of the studies, although energy intake was not adjusted or prescribed to meet measured expenditure in any of the studies.

Factors Associated with NB
The Pediatric Risk of Mortality score was assessed in 8 studies. Pediatric Risk of Mortality score, PICU length of stay, mortality, and duration of mechanical ventilation were significantly negatively correlated with NB in 1 noncontrolled trial of early enteral feeding. The remaining studies did not report significant associations between protein balance and measures of illness severity. Two studies reported an association between NB and age. A negative correlation between protein balance and age in 1 study suggested either inadequate protein intake or poorer nitrogen retention in older children, and a larger study of 71 patients with a wide range of ages found that older children were more likely to achieve NB. There were no significant differences in important clinical outcomes in these investigations.

Measurement of NB
The protocol for measuring NB was inconsistent among studies. Studies used a 24-hour urine collection, although 1 study included 13 of 36 patients with a shorter urine collection interval. Various correction factors for skin and stool losses were reported in 5 studies; the remaining studies did not specify a correction factor used for calculating NB results. Nitrogen losses were estimated from measurements of total urinary nitrogen (TUN) using the Kjeldahl method in 2 studies, and from analysis of UUN measured by high-resolution liquid chromatography in 3 studies.

Other studies did not specify the analytic technique for measurements of UUN, which was then converted to an estimate of TUN using an adjustment factor of 1.2-1.25.

**Discussion**

Maintaining positive protein balance, as a surrogate measure of lean body mass preservation, is an important goal of nutrition therapy during critical illness. In our review of the literature, we noted a paucity of well-conducted prospective studies describing factors associated with positive protein balance in children on mechanical ventilation. Methodologies for determining protein balance varied among these studies. Both protein intake and energy intake were correlated with protein balance in this selection of studies. Positive protein balance was achieved only in those patients with protein intake >1.5 g/kg/day and energy intake >57 kcal/kg/day.

In general, protein balance improved as protein intake increased. Although the lowest protein intake associated with a positive balance was 1.5 g/kg/day, individual and grouped thresholds for protein intake associated with achieving a positive protein balance varied. In parenterally fed, hypermetabolic subjects, a protein intake of 2.8 g/kg/day was required to achieve positive NB, whereas positive balance was achieved in enterally fed infants with viral bronchiolitis with as little as 1.5 g protein/kg/day.

**Table II. Overview of protein balance studies, observational reports (n = 3)**

<table>
<thead>
<tr>
<th>Study, Class/Rating</th>
<th>Number of subjects, Population, Age group, Feeding route</th>
<th>Energy intake, kcal/kg/day</th>
<th>Protein intake, g/kg/day</th>
<th>Protein balance, g/kg/day</th>
<th>Other significant outcomes</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-Bu et al. 1998</td>
<td>n = 19, 68% sepsis, 8 (6) years, PN</td>
<td>49 (22)</td>
<td>1.74 (0.78)</td>
<td>−0.75 (0.96)</td>
<td>NB positively correlated with energy intake (r = 0.74)* and negatively correlated with age (r = −0.62)*; REE 46% higher than BMR</td>
<td>Single observation day, small heterogeneous sample</td>
</tr>
<tr>
<td>Cross-Bu et al. 2001</td>
<td>n = 33, 61% sepsis, 21% postoperative, 5.5 (5.3) years, PN</td>
<td>60 (33)</td>
<td>2.1 (1)</td>
<td>−0.56 (1.04)</td>
<td>NB positively correlated with energy intake and REE (r = 0.51)* and negatively correlated with protein oxidation (r = −0.72)</td>
<td>Urinary NB not a precise measure of substrate oxidation</td>
</tr>
<tr>
<td>Joosten et al. 1999</td>
<td>n = 36, 31% heart disease, 22% sepsis, 22% bronchiolitis or pneumonia, 19% subglottic stenosis or upper airway obstruction, Median age 10 months (range, 1 week-13 years), 28 received EN, 2 PN, 3 EN + PN, 3 fluids alone</td>
<td>62.3 (28.6)</td>
<td>1.62 (1.2)</td>
<td>0.1 (1.1)</td>
<td>NB positively correlated with energy intake and REE (r = 0.69)<em>; energy and protein intake higher with NB</em></td>
<td>Heterogenous group, inconsistent methods of NB</td>
</tr>
</tbody>
</table>

REE, measured resting energy expenditure.
Class and rating were determined using methodology from the American Dietetic Association’s Evidence Analysis Manual 2010. All values are presented as mean (SD), except where noted otherwise.

*P < .05.
ill, catabolic patients may be unable to maintain protein balance even with increasing amounts of protein and energy intake during the early and most critical stages of illness. Provision of nutrients during this time is often technically challenged by fluid restriction, interruptions or intolerance to feeding, and difficulty obtaining access for enteral or parenteral feeding. This results in cumulative negative energy and protein balance and resulting anthropometric deterioration. Lean body mass loss from cumulative negative protein balance is particularly concerning in children with preexisting malnutrition, those with compromised respiratory reserves and muscle function, and preterm infants with low reserves. Based on our review, protein intake for critically ill infants and children should reach a minimum of 1.5 g/kg/day, which is consistent with the recommendation in the recent American Society for Parenteral and Enteral Nutrition’s pediatric critical care nutrition guidelines.

Groups with a positive protein balance reported a minimum energy intake of 57 kcal/kg/day. The association between energy intake and protein balance in these studies might be independent of protein intake. Predicting energy expenditure is difficult in critically ill patients. Predicting energy expenditure is difficult in critically ill patients. Predicting energy expenditure is difficult in critically ill patients. Therefore, longitudinal studies including measurements of both protein and energy balance in critically ill children are needed.

Enteral nutrition is the preferred manner of feeding critically ill children; however, when the gastrointestinal tract is nonfunctional or unavailable, parenteral nutrition (PN) is often necessary to provide nutrients until enteral feeding can be safely resumed. On average, subjects receiving PN did not achieve positive NB. Children receiving PN tend to have more severe illness or injury. The high degree of catabolism in more severely ill children may preclude achievement of protein balance despite the provision of seemingly adequate amounts of parenteral nutrients.

Two methods of measuring protein balance–urinary nitrogen excretion and stable isotope analysis–are available for use in research studies. Substantial disagreement and controversy exists regarding the validity and feasibility of these methods for the clinical setting.
within the diverse and challenging PICU setting.\textsuperscript{20} Stable isotopic quantitation of protein metabolism has been used in a few studies of critically ill neonates supported by extracorporeal membrane oxygenation support and PN.\textsuperscript{17,21,22} However, the applicability of this method is limited due to its cost, invasiveness, and necessary extra resources and expertise. No studies using a stable isotope technique met our inclusion criteria for this evidence analysis.

Although clinically more feasible, measurements of nitrogen loss through urinary excretion are variable and thus might be not be comparable across studies. In the studies in our review, TUN was measured directly,\textsuperscript{1,14} calculated from UUN with a correction factor for nonurea nitrogen,\textsuperscript{10-12,15} or estimated directly from UUN without a correction factor.\textsuperscript{8,9,12,13} The differences in modeling and assumptions of these techniques, particularly in critically ill patients, can contribute to substantial differences in results.\textsuperscript{23} Various estimations were used to account for extraurinary nitrogen losses. Details of the correction factor used for skin and stool losses were reported in 5 studies and varied widely.\textsuperscript{8,9,11,13,14} No correction factor for nonurinary nitrogen losses was specified in the other studies.\textsuperscript{1,10,12,15} PICU populations are typically heterogeneous, with a wide variety of ages, diagnoses, sizes, and clinical conditions, contributing important physiological variations to balance calculations. The reliability of UUN as an estimate of nitrogen losses may be questionable in this cohort, and TUN measurement, although a more accurate measure of urinary nitrogen losses,\textsuperscript{23} is not readily available. Future studies comparing urinary nitrogen excretion methods with the stable isotope technique for NB determination might be desirable.

Because we were able to identify patterns in the research findings using categorical comparisons and simple correlational statistics, we caution against using the statistical values reported in this review as estimates of population parameters. Our approach in this systematic review should not be confused with a standard meta-analysis. Because of study heterogeneity, we could not aggregate individual-level data across studies; thus, different measures of central tendency across comparison groups among the different studies were used for qualitative comparison, rather than quantitative analysis.

The present review has several limitations. Protein balance investigations in critically ill children are scarce, generally include small samples, and often do not examine significant clinical outcomes. Subgroup analyses for specific disease groups were not possible. In the absence of measured energy expenditure, true energy balance could not be ascertained, and its role in achieving protein balance remains unclear. Multicenter randomized trials ideally would provide larger, more homogenous samples and also facilitate consistency in methods and design. Uniform methodology and standard definitions for the measurement of NB in the PICU are currently lacking.

In our review of the literature, higher energy and protein intakes were associated with positive protein balance in mechanically ventilated children. However, existing studies lack uniform study design, consistent methodology for measuring protein balance, and as such do not allow meaningful interpretation from pooled data. There is a strong need for studies with clearly defined interventions, larger samples, uniform and reproducible methodology, and longitudinal data points. Future research should consider the effect of increased protein provision on measures of lean body mass, while accounting for energy balance.\textsuperscript{\textbullet}

Submitted for publication Sep 14, 2011; last revision received Jan 5, 2012; accepted Jan 20, 2012.
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