Aspects of protein metabolism in children in acute and chronic illness
Geukers, Vincent

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Nutritional goals, prescription and delivery in a pediatric intensive care unit

Marjorie de Neef
Vincent G. Geukers
Aafke Dral
Robert Lindeboom
Hans P. Sauerwein
Albert P. Bos

ABSTRACT

Background: Critically ill children usually receive less than the recommended protein intake, which results in deterioration of lean body mass during the admission period on a pediatric intensive care unit (PICU). This is superimposed on the fact that approximately a quarter of these children are already undernourished on admission.

Objective: The aim of this study was to compare prescription and delivery of nutrition to predefined nutritional targets, and identify risk factors associated with inadequate nutritional intake.

Design: In 84 mechanically ventilated critically ill children with length of stay on the PICU of at least 3 d, we observed prescribed and delivered percentages of predefined targets for intake of calories and macronutrients during a 10-mos study period. Factors associated with inadequate intake were identified.

Results: On the third day of admission 92.9% of the patients received nutritional therapy. The caloric goal was reached on day 5, mainly supplied by fat and carbohydrates. Mean actual daily protein delivery was about 75% of the target during the entire study period. Use of catecholamines or neuromuscular blocking agents was a risk factor for caloric undernutrition, whereas there were no specific risk factors for overnutrition.

Conclusion: Nutritional therapy should be started in the early phase of critical illness, including adequate supply of protein. In order to prevent deficits to accumulate, parenteral nutrition should be added in an early phase, if nutritional needs cannot be met by enteral nutrition.
INTRODUCTION

Despite increased awareness for adequate nutritional support during critical illness, malnutrition in pediatric intensive care (PICU) patients commonly occurs. Recent studies show that over 25% of PICU-patients are acutely or chronically malnourished at the time of admission, and that the nutritional status of these children deteriorates during hospitalization (1, 2).

The origin of malnutrition in critically ill children is multifactorial, and dependent of prescription and delivery of feeding (3). First, whereas energy demands of healthy children are well known, evidence for clear caloric goals in critically ill children is lacking, and insight in changes of protein, fat and carbohydrate metabolism in response to injury or critical illness in children is only starting to build up (4). This is also illustrated by the fact that data in critically ill children on the hypermetabolic stress response and its relationship with severity, type (e.g. post-injury or sepsis), and phase of critical illness are conflicting (5–8). Second, therapeutic interventions that are typical for the PICU setting (e.g. mechanical ventilation, administration of vasoactive or sedative agents) can have various metabolic effects that are superposed on illness-related factors (9). For example, the use of neuromuscular blocking agents in severe head trauma markedly decreases energy expenditure in patients who typically react with an increase in resting energy expenditure (REE), resulting in a lower than predicted total energy expenditure (TEE) (10). Third, it is well documented that the correlation between predictive equations for caloric requirements and actually measured energy expenditure in critically ill children is poor (11–13). Still, approximately 85% of the European intensivists have no access to expensive bedside indirect calorimetry equipment, and therefore, rely on estimations rather than measurements of daily energy requirements (14). Finally, even after thoughtful consideration of all the above mentioned factors, intensivists may be hampered in adequate nutritional prescriptions by patient-related factors. These include fluid restriction, impaired access to enteral and parenteral routes, interruptions and restrictions of delivery of nutrition. As an example, positioning and confirmation of a post-pyloric feeding tube and waiting for bowel sounds are some of the causes of delay in the initiation of enteral nutrition (EN) (15). Delivery of nutrition may be interrupted for several reasons, e.g. high residual volumes, tube displacement, routine nursing procedures and diagnostic tests (16).

All the above-mentioned factors may contribute to both over- and undernutrition (15). However, evidence is building that optimal nutritional therapy during critical illness is correlated with clinically relevant outcome parameters.

The aim of this study was to compare the amount and composition of both prescribed and actually delivered nutritional therapy to predefined nutritional requirements, and to what
extent intake was disturbed by PICU admission. We tried to identify factors on our PICU that were associated with suboptimal nutritional intake.

**MATERIALS AND METHODS**

This observational study was conducted in a 16-bed tertiary PICU of the Emma Children’s Hospital/Academic Medical Center, Amsterdam, the Netherlands. Data were collected over a 10-mos period. The study was performed by reviewing patients’ charts; therefore approval of the Medical Ethical Board was waived.

Endpoints of the study were prescribed and delivered percentages of predefined goals for energy and macronutrients (fat, protein and carbohydrates), and identification of factors associated with inadequate nutrition. Optimal nutrition was defined as reaching the predefined requirements for caloric, protein, fat, and carbohydrate intake on each day of admission.

**Patients**

All patients on the PICU with length of stay (LOS) > 3 days and mechanical ventilation were eligible for the study. Clinical patients from other wards in our hospital that were referred to the PICU, and already received EN or parenteral nutrition (PN) were excluded.

**Study procedures**

Patients’ characteristics that were recorded included sex, age, diagnosis on admission, severity of illness at admission (PIM2) (17), organ failure (PELOD) (18), ventilator days and LOS. Clinical characteristics included use of sedation, neuromuscular blocking agents and catecholamines. Probability of death was derived from the mean PIM2 score \([\text{exp} \left( \text{mean PIM} \right) / \left(1 + (\exp \text{mean PIM})\right)]\).

The amounts of prescribed and delivered calories, protein, fat and carbohydrates, and the delay between prescription and delivery of nutrition were recorded for a minimum of 3 and a maximum of 10 days. Also, side effects (e.g. vomiting, diarrhea and gastric residuals) and complications (e.g. nosocomial infections) were noted. No observations were made on the day of discharge.
Nutritional prescriptions

Predicted energy expenditure (PEE) was calculated by the WHO equation (19) adjusted for illness factor, growth factor and energy absorption coefficient (20). According to national guidelines, fat intake was set at 50 energy-% (en%) for children ≤ 1 y, and 30 en% for children > 1 y, and also protein intake was age dependent (preterm infants, 3.5 g/kg/day; 0–1 y, 2.5 g/kg/day; > 1–4 yrs, 2 g/kg/day; and > 4 yrs, 1.5 g/kg/day) (20, 21). All nutritional prescriptions were made by the attending physician, and nutrition was started as soon as possible. Consultation of the pediatric nutritionist was initiated by the physician in complex cases only.

Nutritional delivery

EN was delivered via the post-pyloric route. Feeding tubes were inserted by trained nurses; the position was confirmed by X-ray. Nutrition was delivered by feeding drip at a constant rate. Gastric residuals, defined as the aspiration of > 2 hrs-feeding, were measured via a separatenasogastric tube every 4 hrs. Diarrhea was defined as 3 or more liquid stools per day. Total intake of calories and macronutrients were calculated from EN, PN and glucose infusions.

Statistical analysis

Patients’ baseline characteristics were summarized with descriptive statistics. Adequacy of nutrition (both prescription and delivery) was calculated as the amounts of energy, fat, proteins and carbohydrates divided by the targets (percentages) for each of the initial 10 d of admission. For each day, undernutrition was defined as the actual intake per day relative to the predefined goal of < 90%, and overnutrition as > 110%, respectively.

Medians of prescribed and delivered nutrition were compared with the Wilcoxon Signed-Rank Test. Risk factors for under- and overnutrition were estimated separately by univariate analysis. Univariate associations that were significant at a 2-tailed $p < 0.05$ were entered stepwise in a multivariable logistic model with undernutrition and overnutrition as independent variables. Presence of interaction was assessed by including a cross-product term for age and weight in the logistic regression model, along with the main risk factors. The statistical significance of the coefficient for the cross-product term was evaluated by the Wald test. Statistical analysis was performed with SPSS for Windows (version 12.1, SPSS Inc., Chicago, Illinois, USA). A two-sided $p$-value < 0.05 was considered as statistically significant.
RESULTS

During the 10-mos study period 84 children were enrolled in the study (Figure 5.1), representing 631 nutrition days (median 7, inter quartile range 5–10 days). The patients’ characteristics are presented in Table 5.1.

![Flow chart eligible patients.](image)

**Prescription and delivery**

In approximately 40% of the patients, nutritional therapy in any form was started on the day of admission, stepwise increasing to more than 90% on the third day, predominantly via the enteral route (Figure 5.2). PN was prescribed to 5–15% of the patients in the study group, and only a small minority of patients received a combination of EN and PN.

The mean caloric goal was reached on day 5, mainly supplied by fat and carbohydrates (Figures 5.3A–C). The highest mean protein intake was approximately 75% of the goal during the 10-day study period (Figure 5.3D). However, some patients did reach their nutritional goals on individual days. Table 5.2 shows the amount of patient days with respective adequate, under-, and overnutrition of calories and macronutrients. Generally, underfeeding occurred most frequently on the initial 4 days of admission.
Table 5.1  Patients’ characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>4.7 [0.9 to 18.9]</td>
</tr>
<tr>
<td>Male (%)</td>
<td>53</td>
</tr>
<tr>
<td>Weight at admission (kg)</td>
<td>6.1 [3.6 to 11.8]</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>8 [6 to 13]</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>6.8 [4.0 to 10.3]</td>
</tr>
<tr>
<td>PELOD score</td>
<td>11 [1 to 11]</td>
</tr>
<tr>
<td>PIM score</td>
<td>-3.52 [-4.35 to 1.96]</td>
</tr>
<tr>
<td>Probability of death (%)</td>
<td>4.30</td>
</tr>
<tr>
<td>Primary diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>38.8</td>
</tr>
<tr>
<td>Post surgical</td>
<td>20</td>
</tr>
<tr>
<td>Trauma</td>
<td>3.5</td>
</tr>
<tr>
<td>Neurology</td>
<td>3.5</td>
</tr>
<tr>
<td>Cardiology</td>
<td>10.6</td>
</tr>
<tr>
<td>Other</td>
<td>23.5</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>7.1</td>
</tr>
</tbody>
</table>

* Values given as median (inter quartile range), unless otherwise noted.

Figure 5.2  Percentages of patients receiving nutrition. EN, enteral nutrition; PN, parenteral nutrition; Combi, combination of EN and PN.
Figure 5.3  Prescribed (squares) and delivered (triangles) percentages of targets for energy (A) and macronutrients (B–D). Targets are represented as dotted lines. *Wilcoxon signed-rank test for prescribed and delivered nutrition is significant at \( p \leq 0.05 \) level. Targets are represented as dotted lines. Values are means ± SD.

Table 5.2  Percentages of patient days with adequate, under-, and over-nutrition of calories and macronutrients

<table>
<thead>
<tr>
<th>Percentage of target</th>
<th>&lt;90%</th>
<th>90–110%</th>
<th>&gt;110%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>49.9</td>
<td>23.6</td>
<td>26.5</td>
</tr>
<tr>
<td>Fat</td>
<td>66.0</td>
<td>14.6</td>
<td>19.4</td>
</tr>
<tr>
<td>Protein</td>
<td>84.5</td>
<td>10.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>56.1</td>
<td>18.7</td>
<td>25.1</td>
</tr>
</tbody>
</table>
**DISCUSSION**

In this observational study, we found that malnutrition also occurs on our PICU. The predefined caloric goal was reached as late as day 5 of admission, and calories were mainly supplied by fat and carbohydrates (Figures 5.3A–C). We have underfed our patients in approximately 50% of patient days, and overfed in 25% (Table 5.2). Moreover, the mean actual daily protein delivery stagnated at around 75% of the target from day 5 on, after an initial increase (Figure 5.3D), resulting in protein malnutrition in almost 85% of the patient days.

These findings are similar to a recently published study in PICU-patients showing a median 60% caloric delivery compared to predefined goals during the first 10 d of admission (15). This initial caloric deprivation also has been reported in other studies in critically ill children (22, 23), leading us to believe that this is a common problem in PICU patients.

Malnutrition in the intensive care setting may be determined by different aspects, such as population characteristics, and difficulties in prescription or delivery of nutrition. Our study population represents a cross-section of a general tertiary PICU, with the majority of patients younger than 12 mos (Table 5.1), and is comparable with other populations in Dutch PICUs (24). Neither age nor weight was clinically relevant risk factors for malnutrition (Table 5.3).

Difficulties with prescription of nutrition are another cause of malnutrition. We found only a small and clinically irrelevant, albeit statistically significant, difference between the amounts of prescribed versus delivered nutrition (Figure 5.3). We conclude that malnutrition in the

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**Table 5.3** Multivariate analysis of statistically significant risk factors for caloric undernutrition (energy delivery < 90% of required) and overnutrition (energy delivery > 110% of required)

| Risk factor               | Undernutrition | | | | | Overnutrition | | | |
|---------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                           | OR\(^a\) | 95% CI\(^b\) | p-value | R\(^2\)\(^c\) | OR\(^a\) | 95% CI\(^b\) | p-value | R\(^2\)\(^c\) |
| Catecholamines            | 2.03 | 1.24 to 3.33 | 0.005 | | | | | |
| Weight                    | 1.09 | 1.04 to 1.15 | 0.001 | | 0.98 | 0.95 to 0.99 | 0.041 | |
| Neuromuscular blockade    | 2.18 | 1.21 to 3.92 | 0.010 | | | | | |
| Age                       | 0.98 | 0.97 to 0.99 | 0.008 | | | | | |
| LOS                       | 0.99 | 0.98 to 1.00 | 0.047 | 1.01 | 1.00 to 1.01 | 0.003 | |
| Constant                  | 0.34 | | 13 | 0.48 | | | | |

\(^a\)Odds ratio > 1 increased risk of malnutrition; \(^b\)95% confidence limits; \(^c\)Nagelkerke R square.
first days of PICU admission was the result of inadequate prescription, rather than insufficient delivery. Inadequate prescription was caused by delayed start of nutrition (Figure 5.2), limited use of PN (Figure 5.2), and too little amounts of protein (Figure 5.3D).

Only approximately 40% and 70% of our patients received nutrition on day 1 and 2, respectively. This was also found in a study by Hulst and coworkers who showed that inadequate feeding during the first few days of admission accounted for almost 50% of cumulative caloric and protein deficits (23). However, there is increasing evidence that early (< 12–24 hrs after admission) EN in acutely ill patients can effectively increase cumulative energy intake, and reduce infectious complications and LOS (25, 26). In the first days after admission, early administration of additional PN can increase total energy intake (15). In our study, PN comprised only a relatively small proportion of the feeding. When EN is insufficient in reaching appropriate nutritional goals, addition of PN in an early phase is indicated to achieve adequate and early goal directed nutrition. The uses of catecholamines or neuromuscular blocking agents were risk factors for caloric undernutrition, whereas there were no specific risk factors for overnutrition.

Although we did not reach the preset caloric goal in the first three days of admission, the question is whether we pursued the right goal. Predictive equations have proven to be unreliable in assessing the amount of calories needed by critically ill, ventilated children. Moreover, in surgical PICU patients, the WHO equation overestimates these needs in the early post-operative phase (11). Therefore, in a subset of our population we probably have fed in the range of the actual patients’ caloric needs.

We believe that the main finding of this study is the occurrence of protein undernutrition. Protein energy malnutrition is associated with increased mortality and morbidity, increased number of ventilator days and LOS (27). Since in critical illness breakdown of whole body protein exceeds its synthesis, it is likely that protein needs of critically ill children are equal or higher than those of healthy children in the same age group. In a group of 33 critically ill children (without burns patients), patients with a positive nitrogen balance had a significantly higher protein intake than did patients with a negative nitrogen balance (2.8 ± 0.9 vs. 1.7 ± 0.7 g/kg day, \(p < 0.0001\)), and lower protein oxidation (13 ± 5 mg/min vs. 42 ± 35 mg/min, \(p < 0.01\)) (4). In another study, in critically ill children (including burns) it was demonstrated that the initial negative nitrogen balances on the first day of admission could be converted to positive values at day 5 in 23 of the children by using an aggressive early EN protocol (28). Finally, in a study in ambulatory children with chronic inflammation due to cystic fibrosis, we found that a daily protein intake of 5 g/kg day maximally stimulated whole body protein synthesis (29). Therefore, we believe that in this study the goals for protein intake are to be
considered as a minimum. Standard nutritional solutions are unable to meet these protein demands, if caloric intake is used as a reference for nutritional volume. Whether or not whole body protein synthesis can be enhanced in critically ill children by further increasing their daily protein intake is subject to future research.

Some of the data that are presented in this article show wide scatter. We hypothesize that this reflects the lack of a nutrition algorithm on our PICU, and hence different priorities in nutritional goals and practice by the members of our medical and nursing staff. Implementation of a nutritional support algorithm by a nutritional team has shown to be more effective in reaching nutritional goals (30).

In conclusion, we believe that healthcare workers that are involved in nutrition on PICUs should be focused on starting in an early phase of critical illness, and on reaching nutritional goals as an integral part of early goal directed therapy strategies. Actual caloric needs should be measured bedside by frequent bedside indirect calorimetry as the gold standard, rather than calculated. If nutritional goals cannot be met by EN, PN should be added in an early phase in order to prevent deficits to accumulate. Special attention should be paid to intake of protein, preferably by implementation of nutritional support algorithms by a nutritional support team.
REFERENCES


