Weight improvement with the use of protein and energy enriched nutritional formula in infants with a prolonged PICU stay


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Introduction
Critically ill children are at risk of developing malnutrition during a stay in a paediatric intensive care unit (PICU). Studies in Dutch populations have shown that 14% to 32% of critically ill infants already suffer from acute or chronic malnourishment upon admission to the PICU. Development of malnutrition during PICU stay is associated with increased mortality, length of mechanical ventilation and length of stay. Infants are...
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particularly vulnerable to malnutrition because of their limited body reserves and their higher nutrient requirements for growth and development (4–6). Also, a prolonged PICU stay is associated with lower weight-for-age (WFA) Z-scores during and after admission in critically ill infants (2). Therefore, providing optimal nutritional support is especially important in critically ill infants admitted for a prolonged time to the PICU (6,7).

This optimal nutritional support should account for the different phases (acute, stable and recovery) of critical illness (8). During the acute phase, there is a considerable risk of overfeeding and nutrient restriction might be beneficial in the early acute catabolic phase (9). During the stable and recovery phase, there will be a shift from catabolism to anabolism and nutritional support should focus on increasing protein and energy intake to enable recovery, growth and catch-up growth (8).

The preferred route to meet energy and nutrient requirements is via enteral nutrition (EN). This is challenged by multiple barriers such as delayed initiation, fluid restriction, interruptions as a result of perceived feeding intolerance and prolonged fasting around procedures (6). The use of standard infant formulas may result in nutritional deficits as a result of the lower energy and protein content of these formulas. Previously, it has been shown in a small group of infants that protein balances were positive in the first days after admission with the use of protein and energy-enriched (PE)-formula compared to standard formula (10). However, no data are available on the prolonged use of PE-formula on recovery and growth. The present study aimed to describe the feasibility of PE-formula in infants with a prolonged PICU admission by means of assessing gastrointestinal tolerance parameters and weight achievement.

Materials and methods

Patients and setting
This retrospective database study was conducted at a multidisciplinary tertiary PICU. All medical records of infants admitted from January 2007 until June 2017 using a PE-formula (Infatrini®; Nutricia, Zoetemeer, The Netherlands) were reviewed concerning demographic variables, daily nutritional intake and duration of PE-formula and gastrointestinal symptoms.

Inclusion criteria were: (i) age between 37 post-menstrual weeks and 12 months; (ii) a prolonged PICU stay defined as a PICU stay of ≥14 days; (iii) a minimum of 14 days enteral feeding with PE-formula; and (iv) at least 80% of energy intake from PE-formula on days with PE-formula use (energy intake provided by PE-formula divided by the total energy intake; enteral and parenteral). Exclusion criteria were: (i) oral intake other than human milk or formula; (ii) interruptions from PE-formula of more than 5 days or of more than 20% of the total duration of PE-formula use; and (iii) less than two weight measurements reported or weight measurements less than 14 days apart during the period of PE-formula. The study protocol was approved by the institutional review board of the Erasmus Medical Center, Rotterdam, The Netherlands (MEC-2017-316). The committee waived informed consent as a result of the retrospective design.

Nutritional intake

The type of enteral feeding was mainly chosen on discretion of the clinician using a nutritional protocol in which fluid restriction was taken into account. Human milk was the first choice and preferred in all critically ill infants. In general, a PE-formula (100 kcal per 100 mL; 2.6 g protein per 100 mL) was started if human milk was not available in mechanically ventilated children ≥3.5 kg and below the age of 12 months and in nonventilated children on the discretion of the clinician. The preferred route was via a post-pyloric tube. EN was started as soon as possible after admission, preferably the day after admission. PE-formula was generally switched to standard formula after weaning from ventilation or when the weight goal was achieved. If EN was tolerated, feeding was increased until an energy target of twice the individual calculated resting energy expenditure (using the Schofield equation for weight) was achieved in all critically ill infants (11).

Anthropometric measurements

Weight measurements were performed according to local protocol at the start and end of PE-formula use. Z-scores for WFA were calculated using Dutch reference standards (GROWTH ANALYSER RCT, version 4.0; https://growthanalyser.org) (12). Changes in nutritional status were determined as the difference between WFA Z-scores at start and end of PE-formula use. The age of the infants was corrected for prematurity for all measurements. A WFA Z-score < −2 was used to indicate acute malnutrition (13). Birth weight Z-scores were compared with WFA Z-scores at start and end of PE-formula use. Birth weight Z-scores were converted using the Fenton growth charts for preterm infants (14). As a result of the different standard values for expected growth, growth velocity in g kg⁻¹ day⁻¹ was calculated separately for infants between the ages of 0–3 months, 3–6 months and 6–12 months (15).

Gastrointestinal symptoms and tolerance

There is no validated definition for feeding intolerance; therefore, gastrointestinal symptoms that are frequently
used to describe feeding intolerance were used to determine tolerance to PE-formula. Parameters of enteral feeding tolerance were recorded each day during PE-formula use and consisted of gastric residual volume (GRV) (mL kg\(^{-1}\) day\(^{-1}\)); yes/no), vomiting (frequency) and defecation (frequency), as well as treatment for vomiting, diarrhea and constipation. Constipation was defined as 4 or more days without stools. According to protocol, GRV was checked every 4 h via a nasogastric tube. Gastric retention was defined as GRV exceeding more than 50% of the volume received in the previous 4 h when infants were continuously fed or of the previous bolus feeding volume when intermittently fed. When PE-formula was interrupted by the clinician because of signs of gastrointestinal symptoms, these were also recorded.

Statistical analysis

Data are reported as the number (%), mean (SD or SEM) if normally distributed or as the median (range (IQR)) if not normally distributed. A paired-sample t-test was used to evaluate the mean difference in WFA Z-scores between start and stop of PE-formula. These measurements were also compared with the WFA Z-scores at birth. Stepwise multivariate linear regression analysis was used to identify which baseline and admission variables were associated with alterations in WFA Z-score during PE-formula use. Investigated variables were gender, birth weight Z-score, prematurely born infants, age and weight Z-score at start of PE-formula, diagnosis, reason to start PE-formula, post-pyloric feeding and caloric intake compared to the target. Variables were included in the model if the association with the outcome had a significance of \(P \leq 0.1\). Multicollinearity was assessed by the variance inflation factor (VIF) calculated through a linear regression between all included predictor variables. VIF was calculated by \(1/(1 - r^2)\), using the total \(r^2\) from the regression. Multicollinearity assumption is met if VIF is below 2.5. The constant, unstandardised beta values with their corresponding standard errors, 95% confidence intervals (CIs) and \(P\)-values were reported for multivariate linear regression model. All statistical analyses were performed using SPSS, version 24 (IBM Corp., Armonk, NY, USA). \(P < 0.05\) (two-tailed) was considered statistically significant.

Results

Patients

In total, 470 infants received PE-formula during PICU admission within the inclusion period of whom 70 infants were eligible for inclusion in the analysis. Reasons for exclusion were receiving PE-formula <14 days or <14 days between weight measurements \((n = 335)\); <37 post-menstrual weeks or >1 year at start \((n = 28)\); caloric intake received via PE-formula less than 80% of total caloric intake \((n = 33)\); and an interruption of more than 20% of feeding duration \((n = 8)\).

Of infants eligible for analyses, the median (IQR) PICU length of stay was 49.7 (34.9–83.1) days in which they received PE-formula for 29.2 (20.9–54.3) days. Predominant diagnostic groups were post-cardiac surgery (34%), respiratory diseases (19%), cardiac diseases (11%) and neurological conditions (6%) (Table 1).

Nutritional intake

The median (IQR) time between admission to the PICU and start of PE-formula was 8 (1–24) days. Reasons to start PE-formula were 30 (43%) infants in accordance with the protocol for ventilated infants; 30 (43%) infants because of insufficient growth; three (4%) infants because of fluid restriction; five (7%) infants who had already started before admission; and four (6%) infants where the reason to start was not documented in the medical files. The reasons to stop PE-formula were discharge from PICU \((n = 32)\); reaching weight goal \((n = 12)\); signs of enteral feeding intolerance \((n = 8)\); and switching to standard formula after weaning from ventilation \((n = 3)\). In two (3%) infants, PE-formula was stopped because the infant died during admission and the remaining 13 (19%) infants had no documented or other reason to stop (Fig. 1).

The mean (SD) energy intake from PE-formula was 104.6 (19.4) kcal kg\(^{-1}\) day\(^{-1}\), which was 100.9% (21.5%) of the energy target. Forty (57%) infants received the amount of energy which was set as target. The mean (SD) protein intake from PE-formula was 2.72 (0.50) g kg\(^{-1}\) day\(^{-1}\).

Weight achievement

The mean (SD) WFA Z-score at start of PE-formula was –1.93 (1.68); 33 (47%) infants had a WFA Z-score < –2. The changes in WFA Z-scores from birth to start of PE-formula and from start to stop of PE-formula are shown in Fig. 2. A significant \((P < 0.001)\) increase in mean (SD) WFA Z-score of 0.48 (1.10) was noted during PE-formula use and, at the end of PE-formula, the number of infants with a WFA < –2 had decreased to 23 infants (33%). Overall, the median (IQR) increase in body weight during PE-formula use was 5.80 (3.28–9.04) g kg\(^{-1}\) day\(^{-1}\) and 7.54 (4.70–10.47), 4.49 (1.48–5.82) and 3.88 (2.92–6.18) g kg\(^{-1}\) day\(^{-1}\) in infants between the age 0–3 months \((n = 40)\), 3–6 months \((n = 13)\) and 6–12 months \((n = 17)\) respectively.
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Table 1 Patient and admission characteristics

<table>
<thead>
<tr>
<th>Total group (n = 70)*</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Gender male, n (%)</td>
<td>36 (51)</td>
</tr>
<tr>
<td>Birth weight (g), mean (SD)</td>
<td>2448 (±855)</td>
</tr>
<tr>
<td>Birth weight Z-score, median (SD)</td>
<td>−0.64 (±1.21)</td>
</tr>
<tr>
<td>Gestational age (days), median (IQR)</td>
<td>260 (242–270)</td>
</tr>
<tr>
<td>Age at start (days), median (IQR)</td>
<td>76.2 [30.0–181.8]</td>
</tr>
<tr>
<td>Weight at start (g), median (IQR)</td>
<td>3943 [3289–5803]</td>
</tr>
<tr>
<td>WFA Z-score at start, median (SD)</td>
<td>−1.93 (±1.68)</td>
</tr>
<tr>
<td>HFA Z-score at start (n = 14), median (IQR)</td>
<td>−1.44 (−2.44 to −0.75)</td>
</tr>
<tr>
<td>Admission duration (days), median (IQR)</td>
<td>49.7 [34.9–83.1]</td>
</tr>
<tr>
<td><strong>Nutritional intake</strong></td>
<td></td>
</tr>
<tr>
<td>Post-pyloric feeding, n (%)</td>
<td>45 (64)</td>
</tr>
<tr>
<td>Continuous</td>
<td>27 (39)</td>
</tr>
<tr>
<td>Portion</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Both*</td>
<td>33 (47)</td>
</tr>
<tr>
<td>Duration admission to start PE-formula (days), median (IQR)</td>
<td>8 [1–24]</td>
</tr>
<tr>
<td>Duration PE-formula (days), median (IQR)</td>
<td>29.2 [20.9–54.3]</td>
</tr>
<tr>
<td>Percentage of PE-formula, median (IQR)</td>
<td>98.9 [93.8–100]</td>
</tr>
<tr>
<td><strong>Diagnostic groups</strong></td>
<td></td>
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<tr>
<td>Reason for admission, n (%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>30 (43)</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td>10 (14)</td>
</tr>
<tr>
<td>GI surgery</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Surgery other</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Sepsis/infection</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neurology</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Primary diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>24 (34)</td>
</tr>
<tr>
<td>Respiratory*</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Neurology**</td>
<td>4 (6)</td>
</tr>
<tr>
<td>GI surgery</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Surgery other</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infection/sepsis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (23)</td>
</tr>
</tbody>
</table>

EN, enteral nutrition; GI, gastrointestinal; PE-formula, protein and energy-enriched formula; PN, parenteral nutrition.

*Data are presented either as the number of subjects (%), median (IQR) or mean (± SD).

1Age at start was corrected for prematurity in case gestational age was below 37 weeks.

2Patient received continuous drip and portion feeding during the period of PE-formula.

3Percentage of energy intake from PE-formula divided by total energy intake (PE-formula, EN and PN).

4Includes pneumonia, respiratory syncytial virus bronchiolitis and bronchopulmonary dysplasia.

5Includes neurosurgery, neurotrauma and epilepsy.

Multivariate regression showed that a lower WFA Z-score at start was associated with a higher increase in WFA Z-score during PE-formula use (r² = 0.26; β = 0.35; 95% CI = −0.50 to −0.19; P < 0.001). Other predictive baseline variables (e.g. WFA Z-score at birth, respiratory diagnosis, corrected age at start and reason to start) were not associated with changes in WFA Z-score during PE-formula use.

Gastrointestinal symptoms and tolerance

Overall, five (7%) infants had constipation, whereas another 19 (27%) infants were treated for constipation at least once during PICU stay without fulfilling the criteria for constipation. In total, 47 (67%) infants vomited at least once during the period on PE-formula. Three infants (4%) were treated for vomiting with oral rehydration solution during the use of PE-formula. GRV was measured in 43 (61%) infants receiving EN via gastric or combined (gastric and post-pyloric) route and in 22 (31%) infants receiving EN via a post-pyloric route. The median (IQR) daily GRV of infants receiving EN via gastric or combined route was 0.81 (0.13–2.08) mL kg⁻¹ per 24 h. The feeding was provided via boluses (n = 10), continuous (n = 5) or both continuous and boluses (n = 28) in these 43 infants. Gastric retention occurred in two (5%) of the 43 infants via gastric of combined route, as well as in one (5%) infant receiving EN via a post-pyloric route. Parameters of gastrointestinal tolerance are summarised in Table 2.

PE-formula was stopped in eight (11%) infants as a result of signs of enteral feeding intolerance, which comprised vomiting (n = 4), gastric retention (n = 2) and signs of discomfort (n = 2) (Fig. 1). Infants received PE-formula for a median (IQR) of 24.5 (15.9–55.0) days before PE-formula was stopped and switched to standard infant formula or an extensively hydrolysed (whey-based) protein and energy-enriched formula.

Discussion

The present retrospective study describes weight gain and parameters of enteral feeding tolerance in critically ill infants with a prolonged PICU stay and beyond the acute phase when using PE-formula. In the majority of the infants, an improvement of WFA Z-score was achieved and, overall, PE-formula was well tolerated. Before starting PE-formula, 47% of the critically ill infants were identified as acutely malnourished, emphasising the importance of adequate nutritional support in this patient group. Previous studies have reported difficulties with respect to achieving energy targets, with enteral intakes ranging from 12% to 38% of the prescribed targets (1,16–18). In the present study, using PE-formula, 57% of the infants were able
to reach the energy target based on twice the individual calculated resting energy expenditure (11).

Previous studies focusing on the effects of PE-formula compared to standard formula were performed in infants with viral bronchiolitis, infants after cardiac surgery and mechanically ventilated children aged 1 month to 16 years (10,19,20). In these studies, PE-formulas were well tolerated and a higher energy and protein intake and a positive nitrogen balance were achieved compared to standard formula. In all of these studies, no data were reported about the follow-up of these children and specifically not about growth.

So far, only a limited number of studies have investigated weight achievement when using PE-formulas in non-critically ill children (21,22). In a study investigating infants with faltering growth receiving either a nutrient dense formula or an energy supplemented formula, the nutrient dense formula showed a trend toward better improvement in length compared to the energy supplemented formula after 6 weeks (21). Also, infants with complex medical conditions receiving extensively hydrolysed PE-formula for 28 days showed a significant increase in WFA Z-scores (22). To our knowledge, the present study is the first to examine the course of weight in critically ill infants using PE-formula for a longer period of time. In our study, weight gain was achieved in 93% of the infants, whereas, in 71% of the infants, an increase in WFA Z-score was observed. Moreover, it appeared that infants who had a lower WFA Z-score at start of the PE-formula benefited the most.
However, catch-up growth during the recovery phase of critical illness and the implications for short- and long-term outcome have never been reported. Previously, our research group showed a decrease in WFA Z-score during PICU stay in critically ill infants and children that was related to cumulative negative energy and protein balances (2). In this previous study, no PE-formula were used. Overall, median weight velocity was 5.80 g kg⁻¹ day⁻¹. Also, and as might be expected, weight velocity in infants aged 0–6 months was higher than in infants aged 6–12 months. Compared with the normal weight velocity data for healthy infants, weight achievement in the present study was similar for the three age groups: 0–3 months, 3–6 months and 6–12 months (13). Weight gain was achieved by following the nutritional protocol with energy target set at twice the resting energy expenditure (calculated with the Schofield equation for weight) (11). Although indirect calorimetry is currently the golden standard for determining the individual energy requirement during critical illness in the acute phase and to detect over- or underfeeding (23,24) in the stable and recovery phase of (critical) illness, an increase in the amount of energy to enable weight gain is recommended in those infants who have a prolonged stay in the PICU (8). Moreover, it is suggested to increase the protein-energy ratio to enable adequate (catch-up) growth, especially in (critically) children with acute malnutrition (25–27).

Intolerance to EN is frequently reported in critical illness but, surprisingly, no uniform definition exists. To report tolerance to PE-formula, we decided to describe gastrointestinal symptoms that are frequently used in relation to EN intolerance in critically ill children, such as large GRV, vomiting, diarrhoea or constipation (28–30). In the present study, PE-formula was well tolerated because signs of intolerance only occurred in few of the infants. This is in accordance with previous findings in which early administration of PE-formula in critically ill infants with viral bronchiolitis was also well-tolerated (10). GRV is one of the most routinely used parameters in the PICU despite a lack of evidence to support this parameter and current guidelines challenge the use of GRV as a marker for feeding intolerance (6,31). There is also no consensus for a standardised threshold for large GRV; however, the threshold of more than 50% of the feeding volume of the previous 4 h has been used in some studies and is the standard of care in our PICU (32,33). In the present study, gastric retention occurred in two infants receiving their feeding via a gastric route or a combined route and in one infant receiving EN via a post-pyloric route. We reported GRV separately for the two feeding routes because there is some evidence advising against the routine advancement of postpyloric tubes. In these infants, large GRV might not indicate feeding intolerance or correlate with delayed gastric emptying. However, gastric aspiration might be useful for detecting tube dislocation when gastric retention does not solely consist of gastric secretion (34,35). The prevalence of constipation was 7%, which is much lower than previously reported in a study of critically ill children (prevalence of 46.7%) (36). Of note, we did find a large number of infants (62%) who vomited at least once when on PE-formula. In this age group, some regurgitation could be physiological as a result of immaturity. We were not able to differentiate between physiological and nonphysiological vomiting. In 11% of infants, the PE-formula was stopped because of signs of enteral feeding intolerance, with vomiting being the most reported reason. This percentage is relatively low compared to the prevalence of enteral nutrition discontinuation as a result of the feeding intolerance reported in literature (prevalence ranging from 7% to 29%) (37–40).

The lack of a comparison group receiving (fortified) human milk or standard infant formula and the retrospective design are major limitations of the present study. It is therefore not known whether the same growth would have been achieved with human milk or standard formula. However, in clinical practice, it is known that achieving adequate nutritional goals is very difficult because these children frequently have fluid restriction, in addition to any consideration of the lower protein-energy ratios of these types of feeding. Other factors, such as i.v. fluid administration and the presence of oedema, might influence body weight and therefore the measured weight may not accurately display the alterations in lean body mass. Unfortunately, we were unable to account for these influencing factors, such as the presence of oedema, because no information was reported in the records. However, by using a long interval between measurements, in conjunction with our experience with respect to children often being oedematous at the start of admission to the PICU, we consider that the influence of possible fluid imbalances on our results was limited. Additional anthropometric measurements to assess the nutritional status, such as length and mid-upper arm circumference, could not be evaluated in this retrospective study. Infants with chromosomal or syndromic disorders were not excluded and specific growth charts were not taken into account. The final limitation is a possible selection bias in the description of enteral gastrointestinal parameters. Only infants with a prolonged PE-formula use were considered to be eligible in our analysis of the weight course. Consequently, infants in the present study already tolerated PE-formula for at least 2 weeks.

Conclusions

The majority of critically ill infants receiving protein and energy-enriched formula for a prolonged period gained...
weight and had an increase in WFA Z-score during PICU admission. Furthermore, signs of gastrointestinal intolerance were sparse during PE-formula use.

Acknowledgments

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Ethical approval

The study protocol was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam, The Netherlands (MEC-2017-316). The committee waived informed consent as a result of the retrospective chart review. Ethical approval has been explained. Any discrepancies from the study as planned have been reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

This study was financially supported by a grant from Nutricia Research BV (Utrecht, The Netherlands). All authors contributed to the design of the study. RE and DD acquired and analysed the data. All authors interpreted the data, drafted and revised the manuscript. All authors approved the final version of the manuscript submitted for publication.

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