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Feasibility of Enteral Protein Supplementation in Critically Ill Children

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Abstract

Background: We describe the protein type and concentration in standard enteral nutrition (EN) formulas and the effect of protein supplementation on the osmolality of standard formulas. We also aimed to examine factors associated with optimal protein delivery in critically ill children. *Methods:* Protein content and other characteristics of pediatric EN formulas used worldwide were recorded. Factors associated with achievement of recommended protein delivery and tolerance of protein-supplemented formulas were recorded prospectively in a cohort of critically ill children. A range of protein supplement doses was added to 2 standard formulas and water, and the osmolality was recorded by cryoscopy in a bench experiment. *Results:* We reviewed 125 formulas used in a multicenter study including sites from >13 countries. A majority of the EN formulas (73.6%) were polymeric, with a nonprotein calorie/nitrogen ratio of 182 ± 66 and protein content of 3.53 ± 2.00 g/100 mL. In the cohort of critically ill children, 28.5% achieved protein intake goal within 4 days, with no intolerance. In addition to optimal protein prescription ($P < 0.001$), protein supplementation ($P = 0.018$) and early EN initiation ($P = 0.006$) were associated with significantly higher odds of achieving goal protein intake. Formulas supplemented with up to 8 g/100 mL polymeric protein had osmolality <450 mOsm/kg. *Conclusions:* The protein content of current pediatric formulas may be inadequate to meet the needs of critically ill children. Protein supplementation of formulas allows early achievement of goal and is likely to be safe.) (*JPEN J Parenter Enteral Nutr.* 2018;42:61–70)

Keywords

protein; supplement; enteral nutrition; critical illness; intensive care; parenteral nutrition; osmolality; trial

Clinical Relevancy Statement

A randomized controlled trial examining the impact of protein dose on outcomes in critically ill children is necessary and will provide evidence for protein delivery in this population. Our findings provide critical information that will guide the design of a feasible protein supplementation trial in this group of patients. In particular, we have shown the inadequacy of protein content in currently available enteral formulas and the feasibility and tolerance of the protein supplementation necessary to achieve higher protein delivery in the interventional arm.

Background

Protein catabolism is a characteristic response to stress from a variety of injuries in critically ill children.[1] In the setting of prolonged or excessive protein breakdown, loss of muscle mass and strength may occur, potentially leading to poor outcome that includes delayed weaning of mechanical ventilation and higher risk of mortality.[2] Optimizing protein intake during acute illness might enhance protein synthesis, facilitate wound healing and the inflammatory response, and minimize muscle mass depletion. Protein supplementation was associated with increased anabolism in infants with viral bronchiolitis.[3] Enteral protein intake was associated

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with improved 60-day mortality in a multicenter prospective cohort of 1245 mechanically ventilated children.[4] An association between positive protein balance and protein intake ≥1.5 g/kg/d has been reported in randomized controlled trials.[5-7] However, the optimal amount of protein intake associated with improved clinical outcomes is not known, and current recommendations are based on a small number of studies and expert opinion.[8,9] Hence protein supplementation trials examining the impact on clinical outcomes in critically ill children are desirable.

However, protein supplementation in an interventional trial may need to overcome barriers to protein delivery during acute illness.[10-12] Furthermore, most enteral nutrition (EN) formulas were not designed for critically ill children, and standard formulas with their limited protein/energy ratio may restrict the amount of protein intake delivered in the interventional arm of a study.[13] The addition of modular protein supplements to standard formula may alter its osmolality, with the risk for diarrhea and abdominal distention.[14] A detailed analysis of existing enteral formulas and their protein content, the effect of protein supplementation on the osmolality of standard formulas, tolerance of formula supplemented with protein, and factors associated with achieving recommended protein delivery would guide the design of a protein dosing trial.

Aims

Our current study had the following aims: (1) to determine the characteristics, particularly the protein type and concentration, of EN formulas used globally in critically ill children enrolled in a multicenter study of nutrition therapy; (2) to determine factors associated with adequate enteral protein delivery in the first 4 days after pediatric intensive care unit (PICU) admission, and to determine the tolerability and feasibility of protein-supplemented standard formulas in a single-center prospective study; and (3) to determine the protein content and osmolality of formulas supplemented with a wide range of protein doses in a bench experiment.

Methods

This study consisted of 3 phases. The first phase was the description of the main characteristics of 125 pediatric EN formulas that were used in an international study of EN delivery in 59 PICUs.[15] The second phase was a prospective cohort study of critically ill children who were receiving EN at a single center. Nutrition therapy details associated with the achievement of recommended protein intake within 4 days of PICU admission were analyzed. In addition, we assessed tolerability of protein supplementation in this cohort. The third phase was a bench study to evaluate the impact of supplementing standard formulas or water with varying doses of protein powder supplement on total protein content and osmolality.

Phase 1: Characteristics of Available EN Formulas

The nutrition composition of 125 EN formulas used in a cohort study in an international multicenter study[15] was evaluated. Details including protein source and structure, nonprotein calories/nitrogen ratio, carbohydrate and fat, energy density, and type of formula (complete vs infant formula) were recorded. The nonprotein calories/nitrogen ratio was calculated, using the factor of 6.25,[1] which is the average amount of nitrogen content in protein. The results were expressed as mean and standard deviation or absolute values and frequency.

We simulated the addition of 1, 2, and 4 g of protein supplement (97% Fresubin Protein Powder; Fresenius Kabi, Bad Homburg, Germany) in 100 mL of the 125 EN formulas described in Table 1. The impact of this supplementation on total protein amount, the percentage of energy from protein, and the nonprotein calories/nitrogen ratio was assessed. The results were expressed in mean and standard deviations.

Phase 2: Cohort Study—Factors Associated With Optimal Protein Delivery and Its Tolerance in a Single Center

In a prospective observational cohort study conducted between July 2013 and February 2016, critically ill children aged 1 month to 15 years of age, admitted to the PICU of a tertiary hospital in South of Brazil, were eligible for enrolment. We enrolled patients who were receiving any EN (EN only or EN + parenteral nutrition [PN]) for ≥ 72 hours. The study was approved by the local ethics committee (protocol no. 402.469). Informed consent was obtained from the parents or legal guardians.

Demographic characteristics and clinical variables were collected from patient medical records. The Pediatric Index of Mortality 2 (PIM 2) illness severity score was assessed on admission.[16] Anthropometric parameters of weight and height were measured within 72 hours of admission.[17] Weight was measured on a pediatric scale (Filizola BP Baby, São Paulo, Brazil). Length/height was measured with a pediatric anthropometer (Caumaq, Cachoeira do Sul, Brazil) or, when not feasible, for children ≥6 years old, it was predicted based on knee height.[18]

Nutrition therapy variables, including time to initiate EN, the prescribed and actual energy and protein intake, the number of interruptions to EN therapy, and signs of EN intolerance (abdominal distension and stool frequency), were recorded in the first 4 days of admission. Early nutrition therapy (EN and/or PN) was defined as

Table 1. Characteristics of the Enteral Nutrition Formulas Used Globally for Critically Ill Children, Stratified by Protein Structure (N = 125).

Variables	Polymeric (n = 92)	Semi-Elemental (n = 24)	Elemental (n = 9)
Product details, mean (±SD)			
Energy (kcal/100 mL)	99.57 ± 32.45	100.92 ± 37.48	81.55 ± 17.72
Carbohydrate (g/100 mL)[a]	12.22 ± 5.55	12.76 ± 3.96	12.56 ± 5.57
Fats (g/100 mL)[a]	4.54 ± 2.03	3.96 ± 1.71	3.00 ± 1.91
Protein (g/100 mL)	3.53 ± 2.00	3.61 ± 2.23	2.53 ± 1.16
Nonprotein calories/nitrogen ratio	182 ± 66	183 ± 65	199 ± 65
Osmolality (mOsm/kg water)[b]	334 ± 153	355 ± 106	447 ± 124
Formula classification, n (%)			
Infant formula	38 (41.30)	11 (45.83)	4 (50.00)
Complete enteral formula	54 (58.69)	13 (54.16)	4 (50.00)
Protein source, n (%)			
Casein + whey	43 (46.74)	0 (0)	0 (0)
0%–40% of casein[c]	11 (31.43)	–	–
40%–60% of casein[c]	12 (34.29)	–	–
60%–80% of casein[c]	12 (34.29)	–	–
Mixed source[d]	21 (22.83)	0 (0)	0 (0)
100% Casein	14 (15.22)	4 (16.67)	0 (0)
100% Whey protein	7 (7.61)	19 (79.17)	0 (0)
100% Soy	7 (7.61)	1 (4.17)	0 (0)
Free amino acids	0 (0)	0 (0)	9 (100)

[a]Data from 122 formulas.
[b]Data from 80 formulas.
[c]Data from 35 formulas.
[d]Casein and/or whey protein and/or soy and/or pea and/or chicken.

initiation within 24 hours after PICU admission. Energy and protein prescriptions were defined by the PICU staff. Energy goal was defined using Schofield equations, based on weight and length,[19] without addition of a stress factor. To test the feasibility of designing a protein dosing trial, we intended to explore factors that would allow achieving lower protein goals without high amounts of protein supplementation. We have previously observed alarmingly low protein delivery in the critically ill population when using standard formulas. Hence we used the minimum value in the age-based range per American Society for Parenteral and Enteral Nutrition (ASPEN) recommendations to define the protein goal and determine the feasibility of achieving protein delivery via enteral route in a future trial.[8]

The main outcome was achieving protein goal within the first 4 days of admission. Statistical data analysis was performed by STATA 11.0 (Stata Corporation, College Station, TX, USA). Categorical variables were described in absolute values and frequency. Quantitative variables were reported as median and interquartile range (IQR). Mann-Whitney, χ^2, or Fisher χ^2 tests were used to evaluate differences in clinical and nutrition characteristics of the group of critically ill children who received enteral protein supplement within the first 4 days. Univariate logistic regression analysis was performed to explore the variables associated with achievement of protein recommendation. Results were expressed in odds ratio (OR). A P value <0.05 was considered significant.

Phase 3: Impact of Varying Levels of Protein Supplement on the Total Protein Content and the Osmolality of Standard Formulas

In a bench study, we measured the osmolality of water and 2 polymeric enteral formulas at baseline and after the addition of protein supplements in the following dilutions: 0.5 g of supplement/100 mL, 1 g of supplement/100 mL, 2 g of supplement/100 mL, 4 g of supplement/100 mL, 6 g of supplement/100 mL, and 8 g of supplement/100 mL. Two powdered protein supplements, composed of whey protein, were used: a polymeric supplement, with 97% protein (Fresubin Protein Powder); and an oligomeric supplement, with 82% protein (Nutri Protein HWP; Nutrimed, Fortaleza, Brazil). For the dilution of the supplements, 2 pediatric enteral formulas were used: polymeric nutritionally complete EN formula (Trophic Basic; Prodiet, Curitiba, Brazil) and an infant starter formula (Nan 1; Nestlé, Araçatuba, Brazil). The osmolality of each solution was determined by cryoscopy (MK 540 Flex electronic Cryoscope; ITR – Instrumentos para Laboratório, Esteio, Brazil), which provides the freezing point of the solutions. Subsequently,

the value obtained was converted to osmolality (mOsm/kg water).

Results

Characteristics of EN Formulas

A majority of the EN formulas analyzed (58.69%) were complete (balanced and contained nutrients necessary for normal growth and development),[20] and 73.6% contained polymeric protein. The median amount of protein in the polymeric formulas was 3.53 ± 2 g/100 mL, and the nonprotein calories/nitrogen ratio was 182 ± 66. The osmolality ranged from 160 to 960 mOsm/kg water, and it was higher in elemental formulas. The main protein sources were casein and whey, in varying ratios (Table 1).

Using the average values of the EN formula characteristics described in Table 1, in an analysis of all of the formulas combined, the addition of 2g/100 mL of a polymeric protein supplement increased the total amount of protein to 5.42 ± 2.01 g/100 mL. The percentage of energy from protein in the simulation was 20.36 ± 4.07, and the nonprotein calories/nitrogen ratio was 102.02 ± 22.52. The separation by characteristics is shown in Table 2.

Cohort Study—Factors Associated With Optimal Protein Delivery and Its Tolerance in a Single Center

A total of 151 critically ill children were enrolled, with a median age of 15.6 months (IQR: 3.7; 87.5), 62.9% were male, the median PIM 2 score was 4.6% (IQR: 1.4; 16.0), and PICU length of stay was 8 days (IQR: 5; 13) (Table S1). Overall, of the 151 children, 28.5% achieved protein recommendation defined by the minimum ASPEN recommendation within the first 4 days of admission.

Critically ill children who received protein supplement in addition to EN formula were 3.88 times more likely to achieve protein recommendation within 4 days (OR: 3.88; 95% CI: 1.26; 11.98; $P = 0.018$). In addition, increments of 1 kcal/100 mL in energy density, increasing 1 g/100 mL in total amount of protein, and initiation of EN within the first 24 hours were associated with achievement of recommended protein delivery within the first 4 days of admission (Table 3).

Fourteen patients (9.2%) in the cohort received enteral protein supplement, and the median amount of protein supplement received was 4.4 g/d (IQR: 2.8; 6.52). This group was characterized by younger age ($P = 0.029$) and early initiation of EN ($P = 0.042$) (Table 4). In comparison with children who did not receive protein-supplemented formula, the group with protein supplementation did not have significant differences in EN interruption, abdominal distension, or stool frequency.

Protein Content and Osmolality of Formulas With Varying Levels of Supplementation

The osmolality, measured in 2 EN formulas and in water, increased on average by 11.11 mOsm/kg after adding 2 g/100 mL of a polymeric protein supplement, by 22.6 mOsm/kg at 4 g/100 mL, and by 39.0 mOsm/kg at 6 g/100 mL. The addition of 8 g/100 mL of an oligomeric protein module to a standard EN formula increased the osmolality by 175.81 mOsm/kg, with a final value of 548.39 mOsm/kg (Table 5).

Discussion

Optimal protein delivery during critical illness has been associated with improved outcomes.[8,21,22] However, there is no high level of evidence favoring this strategy, and the optimal protein dose remains controversial.[23] Current recommendations for protein intake in the PICU population are based on minimal evidence.[24] A dosing study of protein delivery in critically ill children is therefore necessary. However, the feasibility of achieving higher protein delivery in the intensive care environment needs to be considered when designing such a study. In this study, we have shown that the protein content of currently available pediatric EN formulas may not be adequate to achieve higher protein intakes in critically ill children. The use of protein supplements and early EN initiation were associated with achieving protein delivery goals within 4 days in our PICU cohort. The use of protein supplementation, observed in 9.2% (n = 14) of the cohort, was well tolerated. Furthermore, our simulation describes the amount of supplement needed to achieve higher protein delivery via the enteral route. The osmolality of formulas that are supplemented with up to 8 g/100mL protein was <450 mOsm/kg. These observations will provide critical guidance for the design of a feasible protein supplementation trial for this group of patients. Intervention trials comparing higher vs lower protein dosage will require EN with protein supplementation. In some cases, PN supplementation may be necessary to achieve higher levels of intake, especially in patients who are receiving low-volume EN.

Standard polymeric formulas usually contain approximately 85% water; have a caloric density of 1 kcal/mL, and the protein content accounts for 12%–15% of the total calories. For critically ill children, a higher protein delivery is recommended, with a nonprotein calories/nitrogen ratio ranging from 80:1 to 150:1.[25,26] However, the standard pediatric EN formulas used globally have a nonprotein calories/nitrogen ratio of 182 (±66):1. Hence a majority of the pediatric EN formulas are not designed for critically ill children. To optimize protein synthesis and limit the use of protein as an energy source, protein intake should be administered with a certain amount of nonprotein energy.[27] However, the energy provision in excess of requirements can lead to overfeeding and is associated with higher

Table 2. Impact on Enteral Nutrition Characteristics After Addition of Protein Supplement[a] in Formulas Commonly Used for Critically Ill Children (N = 125).

	Amount of Protein Supplement											
	Formula Only			1 g/100 mL			2 g/100 mL			4 g/100 mL		
Variables	Protein g/100 mL	% Energy From Protein	Nonprotein Calories/ Nitrogen Ratio	Protein g/100 mL	% Energy From Protein	Nonprotein Calories/ Nitrogen Ratio	Protein g/100 mL	% Energy From Protein	Nonprotein Calories/ Nitrogen Ratio	Protein g/100 mL	% Energy From Protein	Nonprotein Calories/ Nitrogen Ratio
Formula classification												
Infant formula (n = 54)	1.83 ± 0.49	10.19 ± 1.78	227.4 ± 43.1	2.80 ± 0.49	14.9 ± 1.63	144.7 ± 18.1	3.77 ± 0.49	19.13 ± 1.63	106.6 ± 11.2	5.71 ± 0.49	26.44 ± 1.85	70.0 ± 7.0
Complete enteral formula (n = 71)	4.73 ± 1.81	15.91 ± 5.29	149.7 ± 60.3	5.70 ± 1.81	18.69 ± 5.12	118.2 ± 37.9	6.67 ± 1.81	21.28 ± 5.03	98.5 ± 27.8	8.61 ± 1.81	25.99 ± 4.99	74.5 ± 18.5
Age												
Prematurity (n = 7)	2.23 ± 0.41	11.84 ± 1.97	191.3 ± 37.4	3.2 ± 0.41	16.21 ± 2.19	131.5 ± 19.6	4.17 ± 0.41	20.15 ± 2.47	100.5 ± 14.0	6.11 ± 0.41	27.01 ± 2.98	68.4 ± 9.7
0–1 y (n = 47)	1.81 ± 0.59	10.09 ± 1.93	230.8 ± 44.2	2.78 ± 0.59	14.83 ± 1.66	145.5 ± 18.2	3.74 ± 0.59	19.10 ± 1.54	106.8 ± 29.6	5.69 ± 0.59	26.45 ± 1.59	69.9 ± 6.2
1–10 y (n = 33)	4.06 ± 1.94	14.13 ± 5.94	173.4 ± 58.3	5.03 ± 1.94	17.07 ± 5.73	133.3 ± 39.3	6.00 ± 1.94	19.80 ± 5.59	108.8 ± 29.6	7.94 ± 1.94	24.74 ± 5.44	80.0 ± 19.8
>10 y (n = 38)	5.26 ± 1.53	17.28 ± 5.94	131.6 ± 56.9	6.23 ± 1.53	19.94 ± 4.22	106.6 ± 32.9	7.20 ± 1.53	22.43 ± 4.23	90.5 ± 23.7	9.14 ± 1.53	26.95 ± 4.39	70.2 ± 16.2
Energy density												
<1 kcal/mL (n = 90)	2.71 ± 1.53	12.68 ± 5.11	195.0 ± 63.1	3.68 ± 1.53	16.79 ± 4.52	131.6 ± 30.7	4.65 ± 1.53	20.52 ± 3.99	100.4 ± 19.3	6.59 ± 1.53	27.04 ± 3.60	68.8 ± 10.9
1–1.5 kcal/mL (n = 27)	5.04 ± 1.51	15.23 ± 4.21	156.0 ± 68.5	6.01 ± 1.51	17.69 ± 4.09	125.2 ± 41.6	6.99 ± 1.51	20.00 ± 3.99	105.5 ± 29.5	8.92 ± 1.51	24.26 ± 3.89	80.8 ± 18.4
>1.5 kcal/mL (n = 8)	6.79 ± 1.88	15.96 ± 4.64	143.4 ± 48.8	7.76 ± 1.88	17.84 ± 4.58	123.0 ± 37.0	8.73 ± 1.88	19.64 ± 4.53	107.9 ± 29.3	10.67 ±1.88	23.02 ± 4.45	86.9 ± 53.4

[a] Polymeric protein supplement contains 97% of protein: Fresubin Protein Powder (Fresiunus Kabi, Bad Homburg, Germany).

Table 3. Variables Associated With Achievement of Protein Recommendation Within 4 Days in Critically Ill Children (n = 151).

Variables	Odds Ratio (95% CI)	*P*
Patient characteristics		
Female sex	1.33 (0.64; 2.73)	.444
Age (mo)	1.00 (0.99; 1.01)	.599
Undernutrition (body mass index <-2 *z* score)	1.17 (0.46; 2.95)	.737
Pediatric Index of Mortality 2	0.97 (0.94; 1.00)	.051
Enteral nutrient delivery		
Estimated energy recommendation (kcal/kg/d)	1.01 (0.98; 1.04)	.510
Prescribed energy (kcal/kg/d)	**1.06 (1.03; 1.08)**	**<.001**
Actual energy intake (kcal/kg/d)	**1.06 (1.04; 1.08)**	**<.001**
Protein recommendation (g/kg/d)	0.60 (0.14; 2.49)	.486
Prescribed protein (g/kg/d)	**31.77 (10.45; 96.53)**	**<.001**
Actual protein intake (g/kg/d)	**62.33 (16.30; 238.29)**	**<.001**
Volume recommendation (mL/kg/d)	0.99 (0.98; 1.01)	.770
Actual volume intake (mL/kg/d)	**1.03 (1.01; 1.05)**	**<.001**
Fluid balance (mL/kg/d)	0.99 (0.99; 1.00)	.373
EN formulas characteristics		
Structure of the first EN formula used		
Polymeric	1.00	
Semi-elemental or elemental	0.46 (0.17; 1.21)	.118
Amount of energy (kcal/100mL)	**1.04 (1.02; 1.07)**	**.001**
Amount of protein (g/100mL)	**1.51 (1.07; 2.14)**	**.019**
Nonprotein calories/nitrogen ratio	1.00 (0.99; 1.01)	.197
Use of protein supplement	**3.88 (1.26; 11.98)**	**.018**
Early EN (within 24 h of admission)	**3.77 (1.46; 9.72)**	**.006**
EN interruption	0.89 (0.43; 1.80)	.739

The text in boldface refers to variables with statistically significant difference between the groups. $p<0.05$
EN, enteral nutrition.

risk for infection and hyperglycemia, and an increase in volume of carbon dioxide produced.[28] Lower nonprotein energy/nitrogen ratios are recommended to achieve protein recommendations, while maintaining optimal caloric intake, to prevent overfeeding.[29] The provision of higher protein intake in a trial will therefore necessitate the addition of protein supplement to standard formula.[13,30,31]

Besides attention to the composition of EN, earlier initiation of EN is necessary to achieve protein delivery goals in the first week of illness. Early EN is usually feasible and improves the nutrition therapy delivery and clinical outcomes in critically ill patients.[32,33] In a large, prospective, multicenter cohort study of critically ill children undergoing surgery, delays in initiating EN (>2 days) and EN interruptions were associated with failure to achieve adequate protein delivery.[34] Furthermore, suboptimal protein prescriptions and barriers may also result in inadequate protein delivery, especially because of restriction of fluid intake.[35] For these reasons, the implementation of nutrition support guidelines, with focus on time of EN delivery and nutrition prescription, have a positive effect on improving protein delivery in critically ill children.[36] Patients with the highest risk for protein deficit are those with relatively low energy requirements because of small body size, fed using a standard formula with higher energy/protein ratio.

The addition of a protein module may be necessary to supplement the protein content of standard formulas to achieve higher protein intakes in a trial, especially in cases where full EN volumes are not possible or tolerated.[29,37] Although the group who received protein supplement had higher volume intake (66 vs 26 mL/kg/d), the actual protein intake was due to the protein supplement. The group who received protein supplement was younger (5.03 vs 18.65 months) and, although not significant, the amount of protein from the EN formulas used was lower. In our cohort, the infants received infant formulas, which present lower protein content (1.83 vs 4.73 g/100 mL) and higher nonprotein calories/nitrogen ratio in comparison with complete enteral formula designed for older children (Table 4). Although the actual number of patients receiving protein supplementation in this cohort was small, it was well tolerated. In a randomized clinical trial of protein supplementation in infants, adding a protein module to EN resulted in significantly higher protein delivery in the intervention group.[6] All patients tolerated the nutrition therapy well; no patient experienced hyperproteinemia, elevated urea, or required withdrawal of the protein supplement. When modifying the EN formula by adding protein supplementation, some characteristics of EN formulas have to be considered, such as the renal solute load, nutrient composition and distribution,

Table 4. Clinical and Nutrition Therapy Characteristics of Critically Ill Children Who Received Enteral Protein Supplement Within the First 4 Days (N = 151).

Variables	Use of Protein Supplement (n = 14), n (%)/Median (IQR)	No Use of Protein Supplement (n = 137), n (%)/Median (IQR)	*P*
Female sex, n (%)	**1 (7.14)**	**55 (40.15)**	**0.011**[a]
Age (mo), median (IQR)	**5.03 (2.03; 17.8)**	**18.65 (4.55; 89.15)**	**0.029**[b]
Pediatric Index of Mortality 2 (%), median (IQR)	2.6 (1.6; 9.9)	4.62 (1.4; 17.7)	0.460[b]
Diagnostic category, n (%)			0.467[a]
Medical	13 (92.86)	113 (82.48)	
Surgical	1 (7.14)	24 (17.52)	
Mortality, n (%)	1 (7.69)	20 (14.93)	0.693[a]
Pediatric intensive care unit length of stay, median (IQR)	7.5 (5;13)	9 (5; 14)	0.509[b]
Undernutrition (body mass index <-2 *z* score), n (%)	2 (14.29)	24 (18.18)	1.000[a]
Structure of the first EN formula used, n (%)			0.519[a]
Polymeric	10 (71.43)	107 (78.10)	
Oligomeric or elemental	4 (28.57)	30 (21.90)	
Actual volume intake (mL/kg/d), median (IQR)	**66.04 (47.08; 78.56)**	**26.03 (13.65; 50.76)**	**<0.001**[b]
Energy (kcal/100 mL), median (IQR)	74.0 70.4; 100.4)	100.0 (70.0; 100.0)	0.529[b]
Protein (g/100 mL), median (IQR)	1.77 (1.51; 2.61)	2.5(1.82; 3.00)	0.248[b]
Early EN, n (%)			**0.042**[c]
≤24 h	**13 (92.86)**	**91 (66.42)**	
>24 h	1 (7.14)	46 (33.58)	
EN interruption, n (%)			0.523[c]
Yes	6 (42.86)	71 (51.82)	
No	8 (57.14)	66 (48.18)	
Abdominal distention, n (%)			Not applicable
Yes	0 (0.00)	23 (16.79)	
No	23 (100.00)	114 (83.21)	
≥3 Defecations/d, n (%)	1 (7.14)	11 (8.03)	1.000[a]

The text in boldface refers to variables with statistically significant difference between the groups. $p<0.05$
EN, enteral nutrition; IQR, interquartile range.
[a]Fisher test.
[b]Mann-Whitney test.
[c]χ^2 test.

product availability, cost, and osmolality.[38] Osmolality is influenced by the amount of nutrients in the diet.[14,39] The American Academy of Pediatrics, in 1976, recommended that the osmolality of infant formula should not exceed 450 mOsm/L (approximately an osmolarity of 400 mOsm/kg).[40] Due to the residual volume in the stomach, osmolarity for gastric administration <700 mOsm is desired. However, in the case of jejunal administration, the osmolarity should be <300 mOsm.[41] Hyperosmolar formula can trigger the gut to secrete additional fluid to dilute it to a comfortable osmolality, potentially causing diarrhea. In clinical practice, this effect is not often seen, because foods and medications can have much higher osmolality than tube feeds (fruit juice: 800 mOsm/kg, medications: >1000 mOsm/kg).[39,41] Breast milk has an osmolality of approximately 300 mOsm/L.[42] Adding human milk fortifier increased osmolarity from 297 to 436 mOsm/L.[43] In our bench simulation, additional protein supplementation of whey protein with 82% of protein increased osmolality by 23.5 mOsm/L per 0.5-g increment, up to a maximum of 605 mOsm/L. As noted in our current results (Table 5), osmolality of the protein-supplemented formulas is unlikely to be a barrier to tolerance of feedings. The osmolality of solutions with 6–7 g protein/100 mL is estimated at 380–450 mOsm/kg water, which is within the usual range for commonly prescribed formulas for critically ill children. These solutions would provide 25%–28% calories from protein, an important but reasonable increase from standard formula proportions.

As seen in our single-center cohort study, the volume intake of EN provided is an important limitation to achieving adequate nutrient provision in the PICU population.[35] We conducted a simulation, using arbitrary but physiologically plausible age-based groups, to examine the amount of enteral protein supplementation that might be required to achieve goals in the high-protein arm in patients who receive appropriate vs low-volume feeds (Table 6). Patients with only 25% of goal volume intake via enteral route were unable to meet higher protein delivery despite maximal protein supplementation. A majority of patients in the PICU will be unable to achieve full-volume feedings within the first days

Table 5. Osmolality of Pediatric Enteral Formulas Before and After Addition of Polymeric or Oligomeric Protein Supplement.

	Polymeric Protein Supplement[a]			Oligomeric Protein Supplement[b]		
Enteral Nutrition Formulas	Total Energy (kcal/100 mL)	Total Protein (g/100 mL)	mOsm/kg Water	Total Energy (kcal/100 mL)	Total Protein (g/100 mL)	mOsm/kg Water
Standard formula[c]	100	3.8	372.58	100	3.8	372.58
Protein supplement						
0.5 g/100 mL	101.94	4.29	376.88	101.64	4.21	382.26
1 g/100 mL	103.88	4.77	377.42	103.28	4.62	391.94
2 g/100 mL	107.76	5.74	377.96	106.56	5.44	416.13
4 g/100 mL	115.52	7.68	395.16	113.12	7.08	444.62
6 g/100 mL	123.28	9.62	411.29	119.68	8.72	498.39
8 g/100 mL	131.04	11.56	430.11	126.24	10.36	548.39
Starter infant formula[d]	67	1.20	273.12	67	1.2	273.12
Protein supplement						
0.5 g/100 mL	67	1.69	283.87	67.00	1.61	287.63
1 g/100 mL	68.94	2.17	285.48	68.64	2.02	297.31
2 g/100 mL	70.88	3.14	290.86	70.28	2.84	311.83
4 g/100 mL	74.76	5.08	301.08	73.56	4.48	354.84
6g/100 mL	82.52	7.02	327.42	80.12	6.12	408.6
8 g/100 mL	90.28	8.96	349.46	86.68	7.76	478.49
Water	0	0.00	1.61	0	0.00	1.61
Protein supplement						
0.5 g/100 mL	1.94	0.49	4.3	1.64	0.41	12.37
1 g/100 mL	3.88	0.97	7.53	3.28	0.82	22.04
2 g/100 mL	7.76	1.94	11.83	6.56	1.64	41.04
4 g/100 mL	15.52	3.88	18.82	13.12	3.28	68.28
6 g/100 mL	23.28	5.82	25.71	19.68	4.92	103.76
8 g/100 mL	31.04	7.76	30.02	26.24	6.56	141.94

[a]Polymeric protein supplement contains 97% of protein: Fresubin Protein Powder (Fresenius Kabi, Bad Homburg, Germany).
[b]Oligomeric protein supplement contains 82% of protein: Nutri Protein HWP (Nutrimed, Fortaleza, Brazil).
[c]Trophic Basic (Prodiet, Curitiba, Brazil): polymeric enteral formula.
[d]Nan 1 (Nestlé, Araçatuba, Brazil): polymeric starter infant formula.

Table 6. Feasibility of Achieving Protein Goals With Enteral Nutrition Formula and Protein Supplementation.

	Age Groups			
Variables	1–4 y	4–8 y	8–12 y	12–18 y
Protein goals	4.0 g/kg/d	3.4 g/kg/d	2.8 g/kg/d	2.4 g/kg/d
Required protein concentration of formula[a]	6 g/100 mL	6 g/100 mL	6 g/100 mL	7 g/100 mL
Protein delivery at varying enteral nutrition volumes				
100% Maintenance fluids[b]	4.0 g/kg/d	3.4 g/kg/d	2.8 g/kg/d	2.4 g/kg/d
50% Maintenance fluids	2 g/kg/d	1.7 g/kg/d	1.4 g/kg/d	1.2 g/kg/d
25% Maintenance fluids (trophic feedings)	1 g/kg/d	0.85 g/kg/d	0.7 g/kg/d	0.6 g/kg/d

[a]This could be achieved using standard formulas + protein supplement.
[b]Volume requirement based on Holliday-Segar equation.

of PICU admission, and protein intake is likely to fall short of goals even with EN protein supplementation. Based on our findings, parenteral supplementation of protein may be needed to achieve nutrient intakes in an interventional trial with a high-protein delivery arm.

Our study has limitations that should be recognized. The list of EN formulas reviewed in our study is not exhaustive, and several others were not addressed. However, the list includes formulas used in >14 countries in an international multicenter study. The analysis of EN intolerance was based on a single-center cohort study in which a small sample used protein supplementation. In addition, the osmolality of protein supplementation was measured in 2 standard EN formulas. Our study relied on simulations of volume and protein delivery via the enteral route. It is possible that a stepwise EN algorithm might decrease the number

of patients who remain on low-volume enteral formula and improve protein delivery. Our study did not address the challenges of protein delivery via the parenteral route. Despite these limitations, the observations in this study will be critical when designing clinical trials using protein supplementation.

Conclusions

Pediatric formulas used globally have inadequate protein content to achieve the delivery of recommended doses in critically ill children on low volumes of EN. The use of protein supplement in a small fraction of our cohort and early EN initiation were associated with higher odds of achieving protein recommendation within 4 days, with no signs of EN intolerance. The addition of 6–7 g protein/100 mL may be sufficient to achieve a higher protein intake with estimated osmolality of 380–450 mOsm/kg water. Tolerance of high-protein strategy using EN supplements must be further evaluated in larger cohorts. In patients who are receiving low-volume feeds, PN may be necessary to achieve higher protein intake. The results of our study provide the background for designing a safe and feasible protein supplementation trial in critically ill children.

Statement of Authorship

All authors contributed to the conception/design of the research. All authors contributed to the acquisition and analysis. All authors contributed to the interpretation of the data, drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the supporting information tab for this article.

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