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Original article

Association between enteral macronutrient delivery and inflammatory response in critically ill children

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ABSTRACT

Background and aims: An important goal of nutrition support in paediatric critical illness is minimising catabolism. While focussing on providing full energy requirements, macronutrient balance is often neglected. Studies suggest that there is interplay between nutrition and inflammation. We aimed to assess the amount of enteral macronutrients delivered compared to estimated requirements, and the association between delivered macronutrients and systemic inflammation in critically ill children.

Method: We prospectively evaluated energy and macronutrient intake in critically ill children who required at least 72 h of mechanical ventilation. Data on enteral energy and macronutrient intake was collected and expressed as a percentage of the estimated requirements. Circulating levels of inflammatory cytokines were measured by ELISA and association assessed with delivery of macronutrients from the previous 24 h.

Results: A total of 87 children (0–16 years) were included in this study. By day 3 the median (IQR) intake of energy, fat, carbohydrate (CHO) and protein were 75% (50–103), 85% (43–120), 63% (42–102) and 45% (23–65) respectively. We have also shown that delivery of enteral fat and protein was associated with elevation in the levels of tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6).

Conclusion: The inflammatory response in critically ill children is influenced by the amount of enteral fat and protein delivered. Our data suggests that within the feed delivered, fat is often higher than protein and CHO. It is crucial to take into account the proportion of macronutrients required and not only aim to achieve the energy goal.

1. Introduction

An important goal of nutrition support in paediatric critical illness is minimising catabolism and supporting basal physiological function [1]. There is often a clinical focus on delivering the energy and protein requirements of a patient, but the balance of macronutrients is often neglected. Ready-to-feed energy-dense (ED) formulae (1 kcal/ml below 1 year of age and 1.5 kcal/ml > 1 year of age) are often used to achieve energy requirements in critically ill children for a number of reasons. A higher prevalence of chronic illness and co-morbidity means that critically ill children are more likely to be malnourished on admission to the Paediatric Intensive Care Unit (PICU) than healthy children [2,3]. It is important to prevent further deterioration of their nutritional status. Furthermore, these feeds are used to compensate for restrictions in fluid intake and the often frequent interruptions to enteral feeding (EN) [4,5]. However, it is also important to point out the potential risk of overfeeding among this population particularly the malnourished children, who exhibit a hypo-metabolic pattern [6].

The effect of under and over-feeding has been previously investigated, and both have been shown to be detrimental in critically ill children [7–9,37,38]. Although more is known about energy balance and protein requirements [10], the ideal balance of macronutrients, carbohydrates, protein and fats has not yet been

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established. Current recommendations for macronutrients requirements in this population are based on the understanding of their metabolism and handling during the course of their illness [7,10]. Critical illness is characterized by impaired glucose metabolism and increased protein catabolism [10–13]. Likewise the rate of lipid turnover is generally accelerated, suggesting that critically ill children utilise fat preferentially as a substrate for their energy metabolism [7,14,15].

There is a growing body of evidence suggesting that there is interplay between nutrition and inflammation. Increased levels of inflammatory cytokines have been reported before in undernourished children with cirrhosis [16]. Studies also suggested that a diet high in fat might induce systemic low-level inflammation in adult population [17–19]. In this study, we aimed to assess the amount of macronutrient delivered compared to estimated requirements and investigate the association between delivered macronutrients and systemic inflammation in a cohort of critically ill children.

2. Material and methods

We prospectively evaluated energy and macronutrients intake in ventilated children admitted to PICU at Addenbrooke's Hospital in Cambridge, between November 2014 and May 2017, as a part of study looking at gut microbiome in critically ill children. Ethical approval was authorized by City and Hampstead LREC (Reference: 13/LO/0974).

Inclusion criteria:

- Age 1 week to 16 years.
- Mechanically ventilated for >72 h.
- Enterally fed.

Exclusion criteria:

- Preterm gestation (birth < 37 weeks).
- Known pre-existing immune paresis, oncological diagnosis and HIV.
- Children who were on full/supplemental parenteral nutrition (PN) or ketogenic diet.

The actual nutritional intake was recorded daily using patient clinical records until discharge from PICU. The type of enteral feed, total volume delivered, energy and macronutrient delivered was calculated for each patient from the nutrition data card of each formulae (in the Supplementary Appendix). Calculation of breast milk composition was based on data from previous published study on breast milk composition [20].

Enteral formulae were classified into 3 types, energy dense formula (1 kcal/ml for infant <1 year and 1.5 kcal/ml feed for older children), standard formulae (0.67 kcal/ml for infant < 1 year and 1 kcal/ml feed for older children) and breast milk. Energy requirements were estimated using the Schofield-equation [21] as suggested by The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines in absence of indirect calorimetry [10,22,23]. Protein requirements were calculated according to ASPEN guidelines for critically ill children (0–2 years, 2–3 g/kg/day; 2–13 years, 1.5–2 g/kg/day; and >13 years, 1.5 g/kg/day) [7,10]. Due to lack of published guidelines regarding enteral CHO and fat requirements for critically ill children, the age appropriate UK reference nutrient intake (RNI) for healthy children was used as a guide for establishing CHO requirements as 50% of the total energy requirements [24]. Fat requirements of 40% for children <1 year and 35% for those >1 year were used, corresponding to European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommendations (25, 26). Energy and macronutrient intake were transformed from crude values (kcal or grams/day) into percentage of the reference requirements based on age and weight.

All anthropometry measurements were performed by PICU nurses on admission, the information required for this study including gender, age, weight, height and diagnosis were collected for each patient from the hospital electronic system. Weight/height for age z-scores were calculated based on WHO growth charts using the WHO Anthro and Anthro Plus software (version 3.2.2, January 2011) [27]. Moderate under-nutrition was considered if weight/height z-score was between −2 and -3 standard deviation (SD), and severe under-nutrition if below −3 SD [28].In addition to patient demographics, the Paediatrics Index of Mortality 2 (PIM2) scores [29] and inotrope scores [30] were calculated. Clinical outcomes such as hours free of mechanical ventilation (ventilator free hours, VFH) at 30 days and days free of intensive care at 30 days were also recorded.

Measurements of circulating levels of key inflammatory mediators including pro-inflammatory TNF-α, IL-6, interleukin-1 beta (IL-1β) and anti-inflammatory response pathways interleukin-10 (IL-10) were undertaken between Day 2 and 8. Serum levels of these cytokines were measured by ELISA (MSD, Rockville, Maryland, USA). Cytokine levels were measured at an early (acute) phase, during nutrition deprivation (day 2–3) and a later sample taken between 4 and 8 days after admission. The lower limit of detection for TNF-α was 0.01–0.13 pg/ml, IL-10 0.01–0.15 pg/ml, IL-6 0.01–0.11 pg/ml and for IL-1β was 0.01–0.27 pg/ml. Values for the amount of energy and macronutrients delivered were calculated to the 24-h period prior to each sample collection.

Statistical analysis

The statistical analysis was conducted using IBM SPSS v25 USA. The Shapiro–Wilk Test was used to assess the normality of the data distribution. Quantitative variables with non-normal distribution were expressed as a median with interquartile ranges (IQR). Wilcoxon signed rank test, was used to compare the difference in energy and macronutrient delivery between day 1 and day 3 of admission. Whilst the Mann- Witney U was applied to assess differences in disease severity variables between children. The Spearman correlation coefficient was used to establish the correlation between variables, which was followed by stepwise linear regression analysis to assess factors that impact on cumulative energy intake, inflammatory cytokines (TNF-α, IL-10, IL-6 and IL-1β) and clinical outcomes. A p-value of $\leq$0.05 was considered statistically significant and log transformation was performed on cytokines prior to regression analysis.

3. Results

A total of 87 critically ill children [51 (58%) males] were enrolled to the study. The summary of the recruitment and consenting procedure is shown in (Fig. 1). Anthropometric and clinical characteristics of the children are shown in Table 1. The admission diagnosis for all study participants is presented (Fig. 2). Inpatient mortality was 2/87 patients (2.3%).

3.1. Feeding in PICU

EN started at a median time of 8 h (IQR 5–14) following PICU admission. Fifty-four children (62%) started their enteral feeding within the first 12 h of admission. EN was suspended for a median duration of 19 (IQR 11–28) hours within the first 3 days of admission. The most common reason for holding EN among our cohort was the presence of perceived large gastric aspirates.

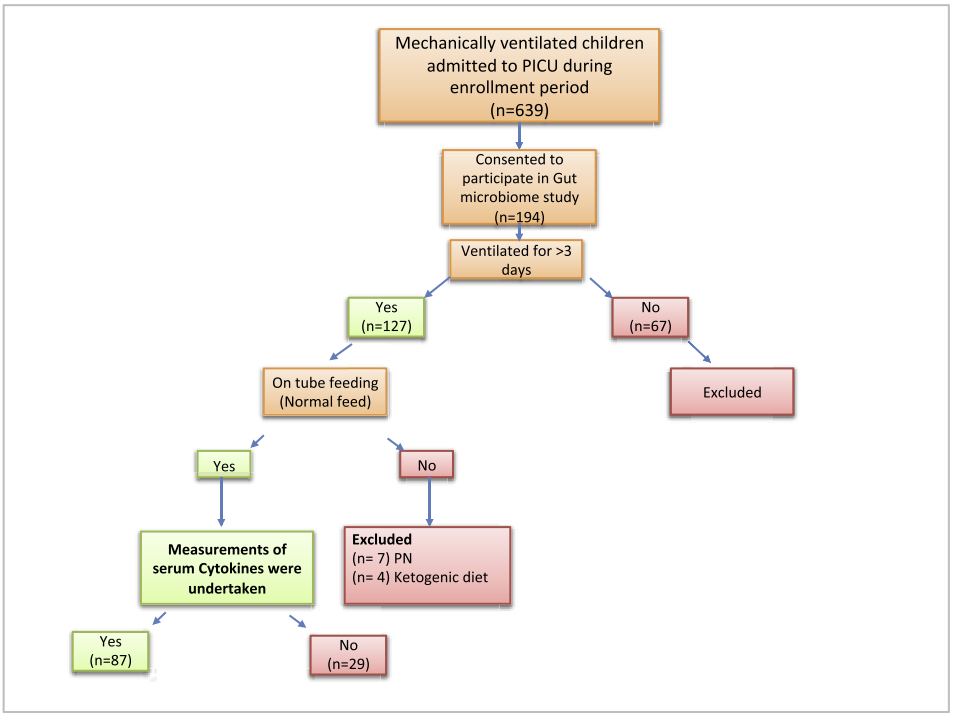


Fig. 1. Summary of recruitment procedure. The above figure shows the stages of patient recruitment and consent.

Table 1
Anthropometric and clinical characteristics of children enrolled to the study.

	All children (n = 87)	0–10 kg (n = 33)	10–20 kg (n = 31)	>20 kg (n = 23)
Anthropometrics				
Age (years)	2 (0.6–4.9)	0.4 (0.1–1)	2.6 (1.8–3.5)	11 (8–13.4)
Weight (kg)	14 (8–21)	7.3 (3.6–8.6)	14.6 (12.3–16.0)	35 (25–45)
Height (cm)	95 (74–112)	68.5 (52–75)	97 (86–101)	132 (114–149)
Weight for age Z-score	−0.1 (−1.4–0.72)	−1.0 (−2.2–−0.05)	0.47 (−0.11–1.4)	0.35 (−0.87–1.1)
% of children below <-2 z scores	15%	30%	3%	9%
Height for age Z-score	−0.15 (−1.9–1.2)	−0.5 (−7–0.8)	0.45 (−0.21–2.04)	−0.54 (−2.2–1.04)
% of children below <-2 z scores	17%	21%	9%	21%
Weight height Z-score	0.05 (−1.1–0.81)	−0.8 (−1.8–−0.02)	0.36 (−1.1–1.07)	0.69 (0.01–2.1)
% of children below <-2 z scores	8%	12%	9%	0%
Disease severity				
PIM2 score	3.2 (0.9–6.2)	4 (1.1–7.3)	2.4 (0.93–5.7)	2.9 (0.88–4.4)
Inotrope score	0 (0–22)	2 (0.0–20)	0.0 (0.0–22)	0.0 (0.0–28)
Maximum lactate	1.9 (1.3–3.3)	2.3 (1.5–3.9)	1.7 (1.2–2.5)	2.5 (1.3–3.3)
Maximum CRP	85 (29–193)	55 (18–142)	105 (25–223)	139 (34–285)
VFH at 30 days	622 (542–651)	601 (601–651)	636 (559–654)	609 (487–645)
PICU free days at 30 days	23 (19–24)	23 (18–24)	23 (20–24)	22 (18–24)

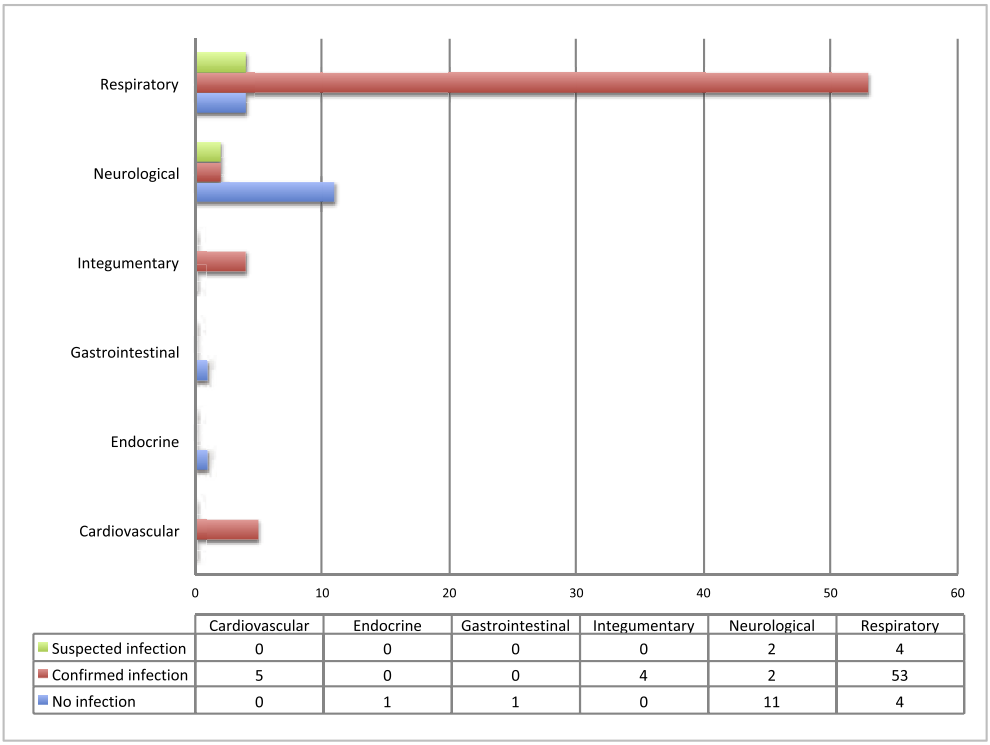
Data presented as median (IQR).
VFH at 30 days: ventilation free hours at 30 days.
PICU free days at 30 days: days free of Paediatric intensive care at 30 days.

No statistical difference in PIM2 score and inotrope score was recorded between children based on the time of commencing EN. Seventy patients (80%) of the cohort received energy dense formulae, 6 (7%) expressed breast milk and 11 (13%) were on standard formulae (Table 2).

We calculated the daily energy and macronutrient intake for the first 3 days of PICU admission (Fig. 3). The enteral intake of energy and each macronutrient on day 1 and day 2 were lower than the calculated requirements. By day 3 the median (IQR) intake of energy, fat, CHO and protein were 75% (50–103), 85% (43–120), 63% (42–102) and 45% (23–65) respectively. Fat intake on day 3 exceeded 100% of the requirements in 35 (40%) children. The delivery of energy and macronutrient was significantly improved by day 3 compared to day 1.

We went on to examine how the daily intake varied among different weight groups. Our results showed that the children with lower weight (0–10 kg) received higher doses of energy and macronutrient. The average intake of energy and macronutrient from admission up to day 3 are presented in Table 3.

Linear regression analysis was performed using the cumulative energy intake at 3 days as outcome to determine the factors affecting the delivery of energy. The regression model suggested that age and weight for age z-score statistically impacted the cumulative amount of energy delivered, this regression model



	Cardiovascular	Endocrine	Gastrointestinal	Integumentary	Neurological	Respiratory
Suspected infection	0	0	0	0	2	4
Confirmed infection	5	0	0	4	2	53
No infection	0	1	1	0	11	4

Fig. 2. Distribution of patients based on their admission diagnostic categories. Each cluster of bars represent specific diagnostic category, individual bars represent the number of patients admitted with infection, suspected infection and no infection.

Table 2
Number of patients receiving standard and ED formulae.

	All children (n = 87)	0–10 kg (n = 33)	10–20 kg (n = 31)	>20 kg (n = 23)
Breast milk	6	6	0	0
Standard infant formula	4	4	0	0
Standard paediatric formula	7	0	2	5
Energy dense infant formula	20	17	3	0
Energy dense paediatric formula	50	6	26	18

Table 2 indicates the number of children received, standard and ED formulae among each weight group.

accounted for 16% of the variation in the cumulative energy intake (Table 4).

3.2. Feeding and inflammatory response

Serum inflammatory markers were measured in a total of 125 samples collected from the 87 children enrolled to the study. The number of samples collected from each age group are presented in Table 5. All patients included in the study had an early sample, and those for whom vascular access was available had a second ('late') sample. Prior to performing regression analysis, correlation analysis was used to explore the association between macronutrient intake and the inflammatory mediators.

3.2.1. Early cytokines (samples obtained on day 2–3)

There was no correlation between macronutrient intake and early cytokine levels except for IL-6, which showed a weak negative correlation with energy ($r = -0.22$, $p = 0.04$) and protein ($r = -0.26$, $p = 0.01$).

Stepwise linear regression analysis was performed, with IL-6 as an outcome variable to determine whether feeding contributed to a change in IL-6 independently from the severity of disease and age. The results indicated that both PIM2 score and % of delivered protein were statistically related to IL6 ($p < 0.01$). This regression model accounted for 20% of the variation in IL-6 levels (Table 6).

In children <1 year of age low protein intake was associated with increase in IL-6 levels, $r = -0.554$, $p = 0.024$. Whilst in older children, no evidence of statistical association was recorded between the percentage of protein received and IL-6, $r = -0.221$, $p = 0.077$ (Table 6).

3.2.2. Late cytokines (samples obtained between day 4–8)

With the later samples, both TNF-α and IL-10 were positively correlated with the delivery of energy, fat and CHO whilst no evidence of statistically significant correlation was observed with protein intake.

Stepwise linear regression analysis was performed, with TNF-α as the outcome to determine whether energy and macronutrients intake contributed to increase in TNF-α independently from the age and severity of disease. Our results indicated that higher delivery of fat and less delivery of protein statistically contributed to increase in TNF-α, $p < 0.01$, this regression model accounted for 31% of the variation in TNF-α levels (Table 7).

We further investigated the effect of feeding on TNF-α, between different age groups. Our regression models suggested that the percentage of enteral fat delivered was the only variable

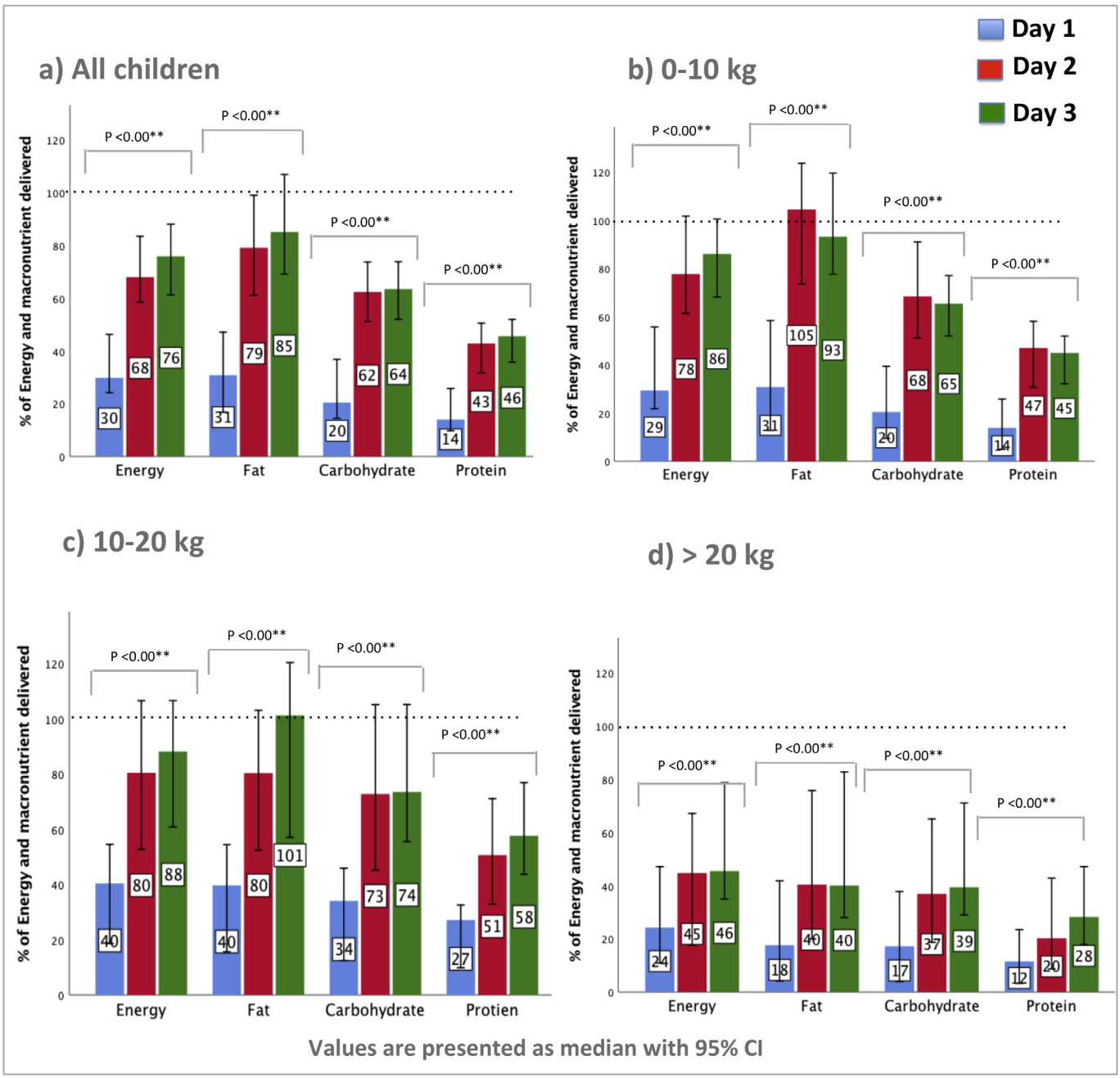


Fig. 3. Percentage of enteral energy and macronutrient delivered expressed as percentage of the calculated requirements. a) Shows the daily enteral intake (day 1–3) of energy and macronutrient in 87 critically ill children. b), c) and d) Shows the daily enteral intake (day 1–3) of energy and macronutrient in different weight groups. The above figure clearly indicated that smaller children (0–10 kg) received higher doses of energy and macronutrient. The enteral intake of both energy and macronutrient has statistically improved on day 3 compared to day 1 ($p < 0.001^{**}$).

Table 3
Average enteral intake of energy and macronutrient from admission up to day 3.

Average intake up to day 3	0–10 kg (n = 33)		10–20 kg (n = 31)		>20 kg (n = 23)	
	Crude value kcal or g/kg/day	%of reference intake	Crude value kcal or g/kg/day	%of reference intake	Crude value kcal or g/kg/day	%of reference intake
Energy	35 (27–48)	64 (52–86)	37 (25–44)	75 (48–83)	13 (6.3–25.9)	41 (21–68)
Fat	1.8 (1.2–2.3)	81 (58–100)	1.6 (0.8–1.9)	76 (42–94)	0.48 (0.18–1.07)	33 (17–72)
Carbohydrate	4.3 (3.7–5.6)	53 (39–71)	4.9 (3.5–5.6)	67 (40–81)	1.8 (1.2–3.3)	33 (15–65)
Protein	0.9 (0.6–1.1)	36 (22–45)	0.99 (0.56–1.1)	43 (31–64)	0.3 (0.17–0.69)	21 (9–43)

Data presented as median (IQR).
The above table shows the average doses of enteral energy and macronutrient presented as crude values and as a percentage of reference requirements.

Table 4
Regression model to determine the factors affecting the cumulative energy intake.

Model	R	R^2	Adjusted R^2	R	P value
Cumulative Energy Intake[a]	0.421	0.177	0.157		
Age [b]				−0.351	0.00*
Weight for age z −score [b]				−0.326	0.001*
PIM2 score [c]				−0.160	0.07

* A p-value of <0.05.
[a] Dependent variable.
[b] Predictors: (constant).
[c] Excluded variables.

statistically related to the increase in TNF-α (r = 0.440, p = 0.032) in children > 1 year of age. This was not replicated in the younger age group (r = 0.387, p = 0.077) (Table 7).

We also investigated the effect of energy and macronutrient intake in a stepwise linear regression analysis where IL-10 was the outcome variable. This model suggested that both energy intake and PIM2 score had a statistically significant effect on IL-10. This regression model accounted for 46% of the variation in IL-10 (Table 8). In children <1 year both the percentage of energy intake and PIM2 score were statistically related to IL-10, whilst in older children PIM2 score was the only variable statistically related to increase in IL-10 (Table 8).

3.3. Effect of enteral feeding on clinical outcomes

We investigated the independent association of clinical outcomes and the average intake of energy and macronutrient. Two stepwise regression models were performed; in these regression models PICU free days and VFH were the outcome variables. There was no evidence of statistical association between energy or macronutrient intake and clinical outcomes in this cohort (Table 9).

Table 6
Factors affecting IL-6 during early admission period.

Model	R	R^2	Adjusted R^2	R	P value
IL-6[a] (all children)	**0.457**	**0.209**	**0.189**		
PIM2 score[b]				0.346	0.001*
%of enteral protein received[b]				−0.295	0.007*
% of enteral Energy received[c]				−0.053	0.638
% of enteral CHO received[c]				0.104	0.351
% of enteral Fat received[c]				0.077	0.490
Age[c]				0.213	0.055
IL-6[a] (children < 1 year)	**0.544**	**0.296**	**0.249**		
%of enteral protein received[b]				−0.544	0.024*
% of enteral Energy received[c]				−0.203	0.450
% of enteral CHO received[c]				0.459	0.074
% of enteral Fat received[c]				0.229	0.394
PIM2 score [c]				−0.074	0.0784
Age [c]				0.034	0.90
IL-6[a] (children > 1 year)	**0.505**	**0.255**	**0.232**		
PIM2 score[b]				0.429	0.00*
Age[b]				0.300	0.014*
%of enteral protein received[c]				−0.221	0.077
% of enteral Energy received[c]				−0.203	0.105
% of enteral CHO received[c]				−0.156	0.216
% of enteral Fat received[c]				−0.124	0.326

* A p-value of <0.05.
[a] Dependent variable.
[b] Predictors: (constant).
[c] Excluded variables.

4. Discussion

Protein energy malnutrition and abnormalities in glucose metabolism have been strongly linked to prolonged ventilation and hospital stay, multiple organ dysfunction and mortality [11,31,32]. Therefore it is crucial to take into account the proportion of macronutrients required and not only aim to achieve the energy goal. **In this study,** there was no association between energy and macronutrient intake and clinical outcomes. However, we recorded weak association between the amount of energy and macronutrient delivered with the inflammatory markers.

Table 5
The number of samples collected from each age group.

All children				
Early samples (Day 2–3)	**Number of samples**	**Median number of samples per patient**		
	87	1 (1–1)		
	TNFα (pg/ml)	**1L-6 (pg/ml)**	**IL-10 (pg/ml)**	**IL1-β (pg/ml)**
	3.8 (2.3–7.5)	6.5 (1.8–19)	2.5 (0.9–7.8)	0.2 (0.2–0.3)
Late samples (Day 4–8)	**Number of samples**	**Median number of samples per patient**		
	39	1 (1–2)		
	TNFα (pg/ml)	**1L-6(pg/ml)**	**IL-10 (pg/ml)**	**IL1-β (pg/ml)**
	3.7 (2.5–6.8)	3.5 (1.5–8.6)	1.6 (0.9–2.4)	0.2 (0.1–0.2)
<1 year				
Early samples (Day 2–3)	**Number of samples**	**Median number of samples per patient**		
	20	1 (1–1)		
	TNFα (pg/ml)	**1L-6 (pg/ml)**	**IL-10 (pg/ml)**	**IL1-β (pg/ml)**
	5.8 (4.5–9.6)	88 (2.8–14)	4.3 (1.1–28)	0.25 (0.2–0.5)
Late samples (Day 4–8)	**Number of samples**	**Median number of samples per patient**		
	15	1 (1–2)		
	TNFα (pg/ml)	**1L-6 (pg/ml)**	**IL-10 (pg/ml)**	**IL1-β (pg/ml)**
	6.8 (4–7)	3. (1.5–5.9)	1.8 (0.9–3.1)	0.2 (0.1–0.4)
>1year				
Early samples (Day 2–3)	**Number of samples**	**Median number of samples per patient**		
	67	1 (1–1)		
	TNFα (pg/ml)	**1L-6 (pg/ml)**	**IL-10 (pg/ml)**	**IL1-β (pg/ml)**
	3.2 (1.8–6.1)	5.9 (1.7–20.2)	2.2 (0.9–7)	0.2 (0.2 0.21)
Late samples (Day 4–8)	**Number of samples**	**Median number of samples per patient**		
	24	1 (1–2)		
	TNFα (pg/ml)	**1L-6 (pg/ml)**	**IL-10 (pg/ml)**	**IL1-β (pg/ml)**
	3.1 (2.2–4.3)	3.6 (0.8–10.9)	1.1 (0.7–2.3)	0.2 (0.1–0.2)

Data presented as median (IQR).

Table 7
Factors affecting TNF-α.

Model	R	R^2	Adjusted R^2	R	P value
TNF-α[a] (all children)	**0.561**	**0.315**	**0.277**		
% of enteral Fat received [b]				0.534	0.001*
% of enteral protein received [b]				−0.347	0.033*
% of enteral Energy received [c]				−0.004	0.983
% of enteral CHO received [c]				0.008	0.963
PIM2 score [c]				0.187	0.269
Age [c]				−0.191	0.257
TNF-α[a] (children < 1 year)					
% of enteral Fat received [c]				0.387	0.077
% of enteral protein received [c]				0.0.119	0.377
% of enteral Energy received [c]				0.212	0.224
% of enteral CHO received [c]				0.229	0.206
PIM2 score [c]				0.037	0.448
Age [c]				−0.202	0.337
TNF-α[a] (children > 1 year)	**0.440**	**0.193**	**0.157**		
% of enteral Fat received [b]				0.440	0.032*
% of enteral protein received [c]				0.094	0.669
% of enteral Energy received [c]				−0.094	0.669
% of enteral CHO received [c]				−0.009	0.969
PIM2 score [c]				0.322	0.134
Age [c]				−0.010	0.963

* A p-value of <0.05.
[a] Dependent variable.
[b] Predictors: (constant).
[c] Excluded variables.

The recent ASPEN guidelines targets delivery of at least two thirds of the prescribed daily energy requirement by the end of the first week in the PICU to avoid undesired clinical outcomes associated with cumulative nutrition deprivation [10]. The majority of our children achieved this energy goal by day 3, which was likely to occur as EN was generally commenced within a few hours of admission (median of 8 h) in accordance with our unit enteral feeding protocol. However, over the first 3 days protein intake on average achieved only 35% of requirements and reached 46% by day 3. In addition, our results showed that children >20 kg were at the most risk of not achieving their requirements, with only achieving an average of 21% of the requirements over 3 days. Insufficient delivery of protein is common, particularly in the early stages of admission. Our findings are similar to previously published data where under-delivery of protein was also reported [31,33–35]. On the contrary, on day 3 the median fat intake was 85% and exceeded the calculated requirements in almost 40% of children among two weight groups (0–10 kg) and (10–20 kg). This discrepancy of achieving energy requirements, under delivery of protein and exceeding fat requirements is related to two aspects: the use of standardised, ready to feed energy dense formulae, in our unit and the aim requirements for macronutrients in critically ill children. The only guidelines available for enteral nutritional support in this population is for energy and protein [7,10]. However, none have been set for fat and CHO. The ESPGHAN guidelines for healthy children were used as a guide to estimate fat requirements in our critically ill population, as we believe that younger children particularly breast-fed infants might have higher fat requirements. RNI for healthy children was used as a guide for establishing CHO requirements. In our study almost 80% of patients were fed energy dense formulae to help meet their energy needs. These formulae have a higher energy density and provide on average 50% of energy from CHO, 10% from protein and 40% from fat. The macronutrient composition of all medical formulae in European is guided by the European Commission of Food for Special Medical Purposes (FSMP) guidelines [36]. Many factors need to be taken into account with the development of these enteral feeds, including macronutrient composition, osmolality, volume of feed for nutritional adequacy, safety ranges for macro and micro nutrients for children with a wide range of diagnoses. As energy requirements are lower and protein requirements are higher in critically ill children [7,10,22,23], the distribution of macronutrients in standardised feeds do not match the specific requirements of critically ill children.

We assessed factors that had an impact on cumulative energy intake and found that age and weight for age z-score were the strongest predictor of the cumulative energy intake among our children. Our findings regarding the age are similar to Mehta et al. (2011) but contradictory to the work done by Hulst et al. (2004), where they found that younger children accumulated the highest energy deficits. This controversy could be explained by the fact that younger children had the highest percentage of malnutrition (30%) as assessed by weight for age Z-score. Due to the well-documented impact of early malnutrition [39,40], it is likely that the nutrition support team focussed more on providing full nutritional requirements particularly for smaller (lower weight for age Z scores) children to avoid further deterioration of their nutritional status during PICU stay.

Table 8
Factors affecting IL-10.

Model	R	R^2	Adjusted R^2	R	P value
IL-10[a] (all children)	**0.679**	**0.461**	**0.415**		
% of enteral Energy received [b]				0.575	0.00*
PIM2 score [b]				0.437	0.004*
%of enteral protein received [b]				0.163	0.018*
% of enteral CHO received [c]				0.082	0.636
% of enteral Fat received [c]				−0.082	0.636
Age [c]				−0.188	0.271
IL-10[a] (children < 1 year)	**0.758**	**0.575**	**0.504**		
% of enteral Energy received [b]				0.698	0.006*
PIM2 score [b]				0.540	0.046*
% of enteral protein received [c]				−0.357	0.231
% of enteral CHO received [c]				0.257	0.397
% of enteral Fat received [c]				−0.185	0.546
Age [c]				−0.143	0.642
IL-10[a] (children > 1 year)	**0.510**	**0.260**	**0.227**		
PIM2 score [b]				0.510	0.011*
% of enteral Fat received [c]				0.183	0.403
% of enteral energy received [c]				0.207	0.344
%of enteral protein received [c]				0.146	0.507
% of enteral CHO received [c]				0.177	0.420
Age [c]				−0.198	0.365

* A p-value of <0.05.
[a] Dependent variable.
[b] Predictors: (constant).
[c] Excluded variables.

Table 9
Regression model to determine the effect of feeding on clinical outcomes.

Model	R	R^2	Adjusted R^2	R	P value
VFH[a]					
PIM2 score[b]				0.132	0.114
Age[b]				−0.091	0.319
Average energy received (3 days)[b]				−0.160	0.072
Average CHO received (3 days)[b]				−0.186	0.044
Average protein received (3 days)[b]				−0.089	0.208
Average fat received (3 days)[b]				−0.184	0.046
PICU free hours at 30 days					
PIM2 score[b]				−0.198	0.034
Age[b]				0.45	0.203
Average energy received (3 days)[b]				0.028	0.397
Average CHO received (3 days)[b]				−0.002	0.493
Average protein received (3 days)[b]				−0.090	0.206
Average fat received (3 days)[b]				−0.009	0.466

VFH at 30 days: ventilation free hours at 30 days.
PICU free days at 30 days: days free of Paediatric intensive care at 30 days.
[a] Dependent variable.
[b] Excluded variables.

In this study we also assessed the association between macronutrient intake and inflammatory mediators. We found that both protein deficit and higher delivery of fat were associated with elevation in the levels of inflammatory cytokines; in particular under-delivery of protein was associated with an increase in serum IL-6 and TNF-α. The association between dietary protein and inflammatory markers has not previously investigated in critically ill population. However, increased levels of inflammatory markers have been recorded in malnutrition studies where presumably energy and protein intake is compromised [40,41]. Low protein intake has been shown to be associated with increased serum IL-6 in a murine model, in addition, IL-6 and TNF-α have been proposed as a possible biomarker of nutritional deficits [16,42].

Despite the current knowledge about the contribution of dietary fatty acids in modulating the production of lipid mediators and signalling molecules in cells that are involve in immune regulation and inflammation [42], to our knowledge no previous data has been published linking fat intake with elevated levels of circulatory cytokines in critical illness. The current study recorded an association between enteral fat delivery and elevation in TNF-α, particularly in children >1 year of age. Although the younger group received higher doses of enteral fat and their median TNF-α was higher, but surprisingly we did not record such a statistical association. This could be attributed to variation in fat requirements, particularly in young children who have a higher fat requirement [25,26]. There are limited data describing the changes in lipid metabolism in relation to inflammation during critical illness. In septic patients the changes in plasma fatty acids profiles appear to be related to the intensity of the inflammatory response, besides interleukins have shown to be inversely related to low-LDL/low-HDL [43,44]. In septic children increased expression of Neutrophil CD64 was associated with low HDL and LDL levels [45]. None of the above mentioned studies recorded the EN intake or investigated the dietary factors. Studies linking inflammation to dietary factors do exist in other populations including obesity, heart disease and inflammatory bowel disease. In patients with heart failure TNF-α levels were elevated with higher intake of saturated fat [46]. In an obese rat model, use of a high fat diet induced expression of TNF-α, IL1β and IL-6 in skeletal muscle, visceral fat and blood [47–50]. Studies also suggest that the high fat western diet might induce systemic low-level inflammation as a result of changes in gut microbiota [17,18]. In a study conducted on 15 overweight men, a low-fat diet resulted in statistically significant reduction in TNF-α [19]. However, it is important to point out that the type of fat delivered might also impact the inflammatory response. In an experimental induced colitis rat model, medium-chain triglycerides (MCT) rich diet reduced IL-6, IL-8 levels, indicating that MCT rich formulae exert an anti-inflammatory effect in colitis [51].

Although the exact mechanism that links dietary fat to inflammation is not fully understood, but several mechanisms have been proposed. It is generally accepted that pro-inflammatory fatty acids may act directly and activate receptors that signals inflammatory response [52]. It has also been suggested infiltration of macrophages associated with adiposity accounts for the increased adipose expression of TNF-α [47]. However, one of the recently proposed mechanisms that links dietary fat to inflammation, is related to it's effect on promoting the translocation of microbial products from the gut into the bloodstream [53]. Given the well-documented evidence of intestinal dysbiosis during critical illness makes this explanation plausible and of clinical justification.

In the current study association between energy intake and IL-10 could be related to stimulation of insulin secretion. IL-10 signalling has been proposed as a potential mechanism to increase energy expenditure and improve insulin sensitivity [54,55].

This study suggests that the energy and macronutrient delivery in the later phase are associated with alterations in the inflammatory response when data was analysed in a single cohort. However, we recorded in consistency in the findings with further stratification to different age groups, which could be related to reduction in the sample size. This could also be attributed to variation in macronutrient requirements between infants and older children. It is worth mentioning that the changes in clinical condition could be contributory or indeed driving this association to a large extent and this needs to be explored in further studies.

In the absence of guidelines regarding enteral macronutrient requirements, it is not surprising that there have been no trials of enteral macronutrient targets in critically ill children. In a landmark study of parenteral nutrition in this patient group (the Paediatric Early versus Late Parenteral Nutrition In Critical Illness (PEPaNIC) trial [56], the dose of amino acids delivered was associated with an increased rate of infection and a longer ventilation time. The authors postulate this to be due to repression of autophagy by amino acids in critical illness. Another potential mechanism is the early induction of Resistin leading to repression innate immunity and changes in amino acids kinetics, including increase levels of phenylalanine and serine and reduce glutamine concentrations [57–59]. The PEPaNIC trial indicated that parenteral delivery of glucose and lipids were associated with fewer infections and earlier PICU discharge respectively. We did not observe such an association between enteral nutritional intake and the duration of ventilation or the length of PICU stay. It is important to note that the route of delivering nutrition was different from our study; also a distinctive statistical plan was carried out. Unlike the PEPaNIC study, we monitored the intake for 3 days which may be insufficient to detect a statistical effect of nutritional intake on clinical outcomes. Importantly, our cohort had significantly lower protein intake compared to requirements than patients enrolled into the PEPaNIC trial (36% vs 80%) [56]. although we only measured intake to 3 days compared to 7 in the PEPANIC trial, making a comparison between data from the two studies challenging.

There is a lack of published guidelines regarding enteral fat and CHO requirements for critically ill children. Although the PePANIC study contributes significantly to our knowledge for PN nutrient delivery in critically ill children, the requirements used for PN are not applicable for enteral nutrition. There are key differences in the metabolisms of enteral versus parenteral carbohydrates, lipids and protein are related to intestinal absorption of nutritional substrates, insulin and inflammatory stimulation and visceral protein synthesis [59]. We therefore used guidelines from ESPGHAN for fat and RNI for CHO for healthy children, whilst utilising published guidance for recommended protein and energy intake in paediatric critical illness [7,10,22,23].

Our study has several limitations including the relatively small sample size and heterogeneity of the patient cohort. Ideally we would divide the children into more than two age groups and investigate the relationship between macronutrient and cytokines more deeply. As this study suggests that fat intake may drive a pro-inflammatory response, it seems prudent to investigate the relationship between omega3:omega6 in this study. In our smaller patient cohort, where formula delivery was protocolised and most children received a similar type of formula, this type of analysis was not feasible. Within the linear regression model, there were some variables that had a relatively low r-value that limit how well the changes in inflammatory cytokines can be attributed to them. However the results of our analysis appear to be in agreement with reported associations between macronutrient intake and inflammation in other disease state [19,41,42,44,50–53].It is clear that further work is needed to establish appropriate enteral CHO and fat requirements in critically ill children, and also to examine the effect

of specific fat sources such MCT and omega-3 on inflammatory response and other clinical outcomes. Imminent studies must also include data from children discharged after a PICU admission in order to consider long-term effects of enteral macronutrient delivery compared to requirements.

Conclusion

The inflammatory response in critically ill children is complex and mediated by many factors. Our study suggests that the enteral fat and protein intake is associated with changes in the inflammatory response. This wider significance of our findings need to be examined in a larger study based on clinical endpoints. Our data suggests that within the feed delivered, fat intake is often above requirements compared to protein and CHO delivery. This imbalance of nutrient provision may result from using the standard paediatric feeds that may not necessarily match the macronutrient requirements of critically ill children. Therefore it is crucial to take into account the proportion of macronutrients required and not only aim to achieve the energy goal. These findings are based on generalised guidelines for macronutrient requirements in healthy children and future work should examine whether critically ill children have specific macronutrient needs.

Statement of authorship

SZ conceived the study, participated in its design, collected, analysed and interpreted the data, collected and processed serum samples, performed the statistical analysis, obtained funding and draughted the manuscript. DW and JR recruited patients, acquired clinical data, collected serum samples and revised the manuscript. RB supervised statistical analysis and interpretation and revised the manuscript. FV participated in data interpretation and revised the manuscript. RM participated in conception and design the study, supervised statistical analysis and interpretation revised the manuscript. NP conceived the study, participated in its design and coordination, obtained funding, supervised statistical analysis, draughted and revised the manuscript.

Ethics approval and consent to participate

Ethical approval was authorized by City and Hampstead LREC (Reference: 13/LO/0974). Informed consent for participation and publication was obtained from parents of the children.

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Conflicts of interest

No conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.10.001.

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