The impact of nutrition on clinical outcomes in the critically ill child

Luise V. Marino[1], **Clémence Moullet**[2], **Corinne Jotterand Chaparro**[2]

[1]Department of Dietetics/Speech & Language Therapy, NIHR Biomedical Research Centre Southampton, University Hospital Southampton NHS Foundation Trust and School of Health Sciences, University of Southampton, Southampton, Nutrition and Dietetics, Faculty of Health and Wellbeing, Winchester University, Winchester, UK; [2]Nutrition and Dietetics Department, Geneva School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland, Geneva, Switzerland

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Corinne Jotterand Chaparro, PhD. Rue des Caroubiers 25, 1227 Carouge, Geneva, Switzerland. Email: corinne.jotterand@hesge.ch.

Abstract: In critically ill children, appropriate nutritional support can improve short- and long term outcomes. When prescribing nutritional support, clinicians in Pediatric Intensive Care Unit (PICU) have to answer numerous questions. These include how much macro- and micronutrients to provide, when to begin nutrition and, which type of feeding should be preferred i.e. enteral or parenteral nutrition (PN). In case of enteral feeding, the PICU team has to choose between continuous vs. intermittent feeding, polymeric vs. semi-elemental formula. The different phases of critical illness and patient age, nutritional and clinical status at admission must also be considered. The impact of these different nutritional strategies on clinical outcomes must be assessed in well-performed randomized controlled trials. Due to the heterogeneity of the population, small sample size, ethical considerations and multiples confounding factors, interventional studies are rare in this population group, and nutritional guidelines often rely on observational studies, results of which describing worse clinical outcomes associated with overfeeding, poor nutritional status or vitamin D deficiency at PICU admission. In contrast randomized controlled trials have shown that withholding PN for one week in critically ill children may be of benefit. However, many questions still remain including the optimal macro- and micronutrients during the various phases of critical illness all of which require future studies. The aim of this review is to give an overview of the current available studies assessing the effect of different nutritional strategies on clinical and functional outcomes in critically ill children.

Keywords: Paediatric intensive care; critically ill children; clinical outcomes; nutrition

Received: 24 July 2020; Accepted: 24 September 2020; Published: 30 November 2020.
doi: 10.21037/pm-20-73
View this article at: http://dx.doi.org/10.21037/pm-20-73

Introduction

Children requiring admission to Paediatric Intensive Care Unit (PICU) is reported to be 0.15% to 1.5% (1,2), with the majority of children (41.4%) being below 1 year of age (2). Mortality rate amongst critically ill children in the North America and Europe is reported to be 3–5% (3), which increases in the children with septic shock up to 10% (4), and more so in middle-income countries such as South Africa where mortality rates can be up to 27% (5). In more recent times the focus on critical illness has moved towards improving clinical outcomes and survivorship (6), and there is increasing efforts to design interventions which improve post-PICU survivorship of which nutrition is an important component.

Malnutrition and clinical outcomes

Undernutrition has been associated with increased length of hospital stay (7-9). The reported prevalence of undernutrition at PICU admission varies largely, depending on the definition of undernutrition used. Multicentre studies observed prevalence around 18–25% (10-12), but it may be more than 50% in single centre studies (13,14). During PICU stay, nutritional status of children may also be altered. Valla *et al.* (15) has reported that 24% of children are malnourished on admission or developed faltering growth as a result of PICU admission. Further to this, children with long term conditions such as congenital heart disease may have a higher incidence of persistent malnutrition with height for age <−2 z scores (16). Sub-optimal nutritional status has been shown to have a significant effect on muscle strength (17), reduced wound healing due to altered immunity with increased rates of sepsis (18), mechanical ventilation days (19), with poorer post-operative resilience (18), longer PICU stay (20), particularly amongst children post-surgery (15,16,19,21,22) and poorer clinical outcomes (23). A recent study has shown that undernutrition at PICU admission was predictor of 60-day mortality and longer time to discharge alive from the PICU (23). A study showed that at six months post discharge from PICU, all children demonstrated nutritional recovery with regards to weight and height (24).

Regarding overweight and obesity, data in critically ill children is still missing. A multicenter study including 90 PICUs from 16 countries (60% of children from PICUs in USA and Canada) showed that 15% of children admitted in PICUs suffered from overweight and 13% from obesity (11). Recently, a systematic review has investigated the association between obesity and clinical outcomes in critically ill children. The findings show that critically ill children with obesity have higher risk of mortality and increased length of hospital stay compared to the group without obesity. The role of obesity and underlying mechanisms in predicting clinical outcomes of this population remains unclear (25).

The findings of these different studies demonstrate the importance of nutritional status assessment at PICU admission and the need of a validated nutrition screening tool to identify patients at risk of worse clinical outcomes. In addition, ensuring optimal nutritional support during critical illness to prevent a further decline in nutritional status has been seen as essential to improving short and longer term outcomes in this vulnerable patient cohort.

Nutrition intake and clinical outcomes

Although, nutrition support during a PICU admission is important, requirements in terms of the type and amount of macro- and micronutrients remains poorly defined. The PEPaNIC study, a large prospective (short and long term) outcome study considering the use of early compared to late parenteral nutrition (PN) support during the first week of admission (26), at 2- and 4-year follow reported that withholding PN for 1 week was not associated with increased mortality, and did not negatively impact on anthropometry, overall health status or cognitive and emotional development (27-29). Interestingly, withholding of PN was associated with improved inhibitory control. Those most at risk of developmental harm, associated with the use of early PN, were infants, aged 26 days to 11 months of age at the time of exposure. As such withholding early PN in this age group may be of benefit with regards to improved developmental outcomes in the longer term (30). The mechanisms associated with these findings may be leukocyte telomere shortening, which was independently found in children receiving early PN (31), and may occur as a result of changes to DNA methylation associated with early administration of amino acids and not glucose (32). These findings require further investigation, particularly relating to causality and the influence early compared to late nutrition support may have on longer term clinical outcomes.

Energy intake and clinical outcomes

Some observational studies have investigated the association between energy intake and clinical outcomes. A multicentre observational study, including 31 PICUs, has shown that energy intake of at least 67% of prescribed (mean prescription of 64 kcal/kg per day) was associated with significant decrease in 60-day mortality (21). However, energy expenditure was not measured by indirect calorimetry, but estimated by various methods. More recently, Larsen *et al.* (33) completed a five year retrospective study of critically ill children who had resting energy expenditure measured using indirect calorimetry and the association of over- and underfeeding with clinical outcomes. The analysis has shown that only 12% of critically ill children were appropriately fed (as defined by energy intake ±10% of measured resting energy expenditure), 53% were overfed and 35% were underfed. Children who were overfed had significantly longer duration of hospital stay and PICU length of stay compared to those who were appropriately fed, and those who were underfed had the shortest duration of hospital and PICU length of stay. The authors stress the relationship described does not infer causality, however, when considered along with the results described in the PEPaNIC study may suggest that overfeeding early during the acute phase of critical illness may be detrimental. However, prolonged underfeeding with inadequate nutritional intakes may be harmful to children in the longer term. They concluded that research is still relatively new in this area and that prospective studies are needed to further investigate these relationships.

Protein intake and clinical outcomes

In the PEPaNIC study, amino acid intake exceeding the reference nutrient intake for age was associated with significant increased risk of mortality. With increasing amounts of amino acid, the risk of harm for acquiring a new infection increased with every 10% increase, and the likelihood of discharge from PICU alive reduced. In comparison, more glucose during the first 72 hours was independently associated with few infections and lipids were independently associated with earlier discharge from (34). The PEPaNIC study has raised important considerations regarding the mechanisms associated with improved neurocognitive outcomes in children randomised to the late PN group; and it has been postulated the suppression of autophagy as a result of nutrition support in excess of requirements (particularly parenteral amino acids) (26,27,32,35) during the acute phase of critical illness may be detrimental (35). It is not known if enteral nutrition (EN) provided in excess of reference nutrient intake for age has the same effect.

In contrast to these findings, a systematic review published in 2017 examined the literature for studies describing the effect of total protein intake on protein balance and clinical outcomes in critically ill children. This review that included 18 studies [eight randomised controlled trials (RCTs)] found that a total daily protein intake >1.1 g/kg per day, especially above 1.5 g/kg per day, was associated with improved clinical outcomes, including reduced mortality and positive protein balance (36). Most included studies used the enteral route for protein delivery, which may explain the differences with the findings of the PEPaNIC study (26). However, although 18 studies were included in the systematic review, only five were considered to have a strong study design. The main limitations of the studies reviewed were patient selection, sample size, lack of blinding in the RCTS and in the observational studies, loss to follow up, unrepresentative samples sizes and loss to follow up (36).

An earlier systematic review has also found that a minimum protein intake of 1.5 g/kg per day and 57 kcal/kg per day was associated with positive nitrogen balance in critically ill children, but did not determine the optimal dose in regard to clinical outcomes (37). Wong *et al.* (38) also reported recently in an observational study that a protein intake of >1.5 g/kg per day was significantly associated with decreased mortality in critically ill children with ARDS.

Type of feeding and clinical outcomes

Early EN and clinical outcomes

EN support of critically ill children is often challenging due to fluid restriction, perceived feed intolerance and interruptions as a result of procedures (21,39,40). A large multi-centred observational cohort study considering nutritional practices and the relationship to clinical outcomes in critically children across 31 PICUs in eight countries, reported a positive relationship between higher enteral feeding intake and improved 60-day mortality, whereas the converse was true of PN which was associated with higher mortality (21). A similar relationship was described by Mikhailov *et al.* (41), who retrospectively review medical records of 5,105 patients, and found that (I) children who received early EN <48 hours were less likely to die compared to those who did not, even when adjusted for age, risk stratification score and propensity score, and (II) early EN was significantly associated with a lower mortality in children with a PICU length of stay of >96 hours. Similarly, the recent secondary analysis of the Heart and Lung Failure-Pediatric Insulin Titration RCT has shown that early EN (within 48 hours after PICU admission) was independently associated with better clinical outcomes in critically ill children with hyperglycemia. Early EN was associated with lower 90-day hospital mortality, more PICU-free days, more ventilator-free days, and less organ dysfunction. Daily energy intake over the first eight study days in PICU was similar in both studied groups (median, 36 kcal/kg/day) (42).

Continuous or intermittent EN and clinical outcomes

The types of EN delivery methods, either continuous or intermittent, have been little studied and the results of these studies are contradictory. Therefore, there is no evidence to support the use of either of these methods to improve clinical outcomes (43). Three randomized studies, two with the same authors, compared the impact of continuous EN and intermittent EN on clinical outcomes (44-46). The first one showed that the group with continuous EN reached the caloric target significantly faster and received more calories over 7 days than the group with intermittent EN. However, the results showed no significant difference in the incidence of gastrointestinal complications and length of stay (44). Furthermore, the results of the two other studies showed no significant difference between the two groups in terms of caloric intake, length of stay and gastrointestinal complications (45) and volume of gastric residues, volume of nutrition administered and duration of the study (46). In contrast, the intermittent group started EN more quickly (46).

Type of nutrition solution

EN polymeric or semi-elemental and clinical outcomes

To date, no studies have compared polymeric to semi-elemental formulas in relation to clinical outcomes. European guidelines recommend using the polymeric solution as the first choice for EN, unless there are proven contraindications (43).

Protein and energy enriched or standard enteral formulas and clinical outcomes

The ESPNIC guidelines recommend considering protein and energy-dense formulas for critically ill children with fluid restrictions to achieve their nutritional needs (43). The studies are few and do not study the same type of enriched solutions, so it is not possible to recommend one over the other with regard to their potential benefits and side effects. A randomized study of children post-operatively after cardiac surgery compared a group receiving high-energy EN solution to a group receiving standard EN. The results showed that the intervention group lost significantly less weight and received more energy intake. In contrast, children in the intervention group had more gastrointestinal intolerance. However, the authors concluded that these disorders could be related to medication or to causes other than nutrition (47). A retrospective study, to document weight gain and gastrointestinal symptoms in children with prolonged PICU hospitalization who were fed with protein and energy-enriched formulas, showed weight improvement when using enriched formulas and were well tolerated (48,49). A randomized study investigated the impact of a protein-enriched solution compared to a standard solution. The protein-enriched diet group had a higher blood protein level, caloric and protein intakes and protein balance were higher but not significantly. No side effects or hyperproteinemia were demonstrated (50).

Pharmaconutrition and clinical outcomes

Pharmaconutrition is defined as the use of specific nutrients in amounts higher than the recommended dietary intakes to impact on immune and clinical outcomes. There is an increasing interest for this field, but data in critically ill children remains scare. Nutritional guidelines concluded there are insufficient evidence to recommend the use of pharmaconutrition (glutamine, lipids and/or micronutrients) in this population (43,51).

Vitamin D deficiency is frequently low in critically ill children (52,53). Recently, three meta-analyses have shown that vitamin D deficiency at PICU admission was associated with greater mortality (52-54), while two others did not observe this association, but still an increased risk of sepsis (55,56). In this setting, vitamin D supplementation is an interesting option. A recent RCT conducted in 109 critically ill children with vitamin D deficiency has found that a single dose of vitamin D improved their 25OHD levels and decreased the incidence of septic shock and sepsis (55). The available evidence shows that vitamin D concentration should be verified in critically ill children, especially those at risk of deficiency and suggests that vitamin D supplementation could be beneficial in critically ill children. However, most RCTs are needed to confirm that optimization of vitamin D status improves clinical outcomes.

The impact of glutamine has been assessed in a few studies in critically ill children, leading to conflicting results. In three studies, glutamine supplementation was provided by the enteral route (57-59). Two of these studies showed a positive impact on the mediation of inflammation, but did not affect clinical outcomes (58,59), and the effect of glutamine could not be delineated from the effect of other nutrients as a cocktail was used. In two trials, glutamine supplementation was provided by the parenteral route (60,61). A meta-analysis including the findings of these trials showed no significant effect on the occurrence of new infections and on mortality (43).

Enteral feeds containing pharmaconutrients may module the immune response, however no impact on clinical outcomes has been observed in critically ill children. A

RCT assessed the impact of zinc supplementation in critically ill infants and found no difference in lung injury score, length of hospital stay, and duration of mechanical ventilation (62). A small RCT compared an enteral formula containing arginine, glutamine, omega 3 fatty acids and antioxidants (vitamin C, selenium and zinc) with a standard enteral formula (58). No difference was observed in inflammatory mediators, secondary infections, duration of mechanical ventilation, and length of stay or mortality rates. There is a paucity of data on micronutrient supplement in critically ill children and well-designed RCTs are needed to determine micronutrients requirements and the role of supplementation in critically ill children during the different phases of disease (63).

There is insufficient data are available in the literature on the optimal energy and protein intake and increase during the PICU stay. Although there are guidelines and recommendations relating to nutritional intake during critical illness, many provide expert consensus due to the paucity of high quality evidence available (43,51). Further research is urgently required to better understand the short and longer term outcomes and the mode of nutrition support e.g., macro- and micronutrient requirements, EN versus PN, type of macronutrients e.g., whole protein versus peptide, prebiotic fibres and the source of fatty acids and impact on functional outcomes such as body composition and neuro-cognitive (43). Micronutrient status may also be an important consideration during critical illness and future studies need to consider the effect of short term supplementation on longer term outcomes, particularly with regards to rehabilitation (63).

Functional outcome at PICU discharge

There are very few studies considering the impact of critical illness in children on body composition and acquired function impairments. Lee *et al.* (6) aimed to describe associations between body habitus at baseline and functional recovery in children; as in adult studies a higher body mass index on admission is associated within improved recovery possibly due to greater skeletal muscle mass at baseline. Functional impairment post PICU discharge is increasingly recognised, although the mechanisms and pathophysiology remain poorly described. Ong *et al.* (64) reported that 37-51% of children experienced a new functional temporary impairment at PICU discharge, with a further 7–12% of patients experiencing persistent functional impairment. In contrast to adults' reports, children with a high body mass index at baseline (e.g., admission) were significantly more likely to have persistent acquired impairment at hospital discharge. Body composition analysis using computed tomography scans described two phenotypes (I) high skeletal muscle mass and (II) high visceral fat mass. High visceral fat was associated with increased risk of persistent acquired impairment even after adjusting for confounders. Of interest, children with a greater baseline skeletal muscle mass were also independently associated with acquired impairment, although the relationship of these findings requires further investigation particularly as the sample size was small. There is also considerable variability in the tools and how these are applied, but as skeletal muscle mass is closely related to the ability to complete physical activity (6,64), understanding the relationship between critically illness, nutrition support and recovery is imperative especially if there may be negative sequela between macronutrient intake, nitrogen balance and muscle function e.g., less may be better.

Feeding difficulties in PICU survivors

Picky eating and food refusal is common in young children (65,66), with 17% of three year olds reported to have a low appetite and 12% described as fussy eaters (67). Children with long-term conditions are known to have feeding difficulties including those with cystic fibrosis (68), gastrointestinal disorders (69), food allergy (70), and congenital heart disease (71) with up to 22% of infants affected following surgery (72), causing parental anxiety and distress (73,74). There is a paucity of information relating to feeding difficulties in children who were otherwise healthy prior to admission (75), although risk factors for feeding issues post adult intensive care unit (ICU) discharge include the use of an endotracheal tube intubation for longer than 48 hours, ICU associated malnutrition and muscle weakness (76-79). In addition to this, adult survivors report alterations in the perception of food and functional changes regarding appetite, taste changes and food preference lasting up to three months post-ICU discharge (80). More work needs to be done in this area to understand whether bedside intervention to reduce painful oral stimuli along with parental resources and support would reduce the incidence of feeding issues amongst children following discharge (75).

Future research

The current review shows that strong evidence on the impact

Table 1 Nutritional variables that were related to clinical outcomes in published studies

Outcomes	Type of study design	References
Worsen clinical outcomes		
Undernutrition status at PICU admission	Observational studies	(15,16,18,19,21-23)
Overweight and obesity at PICU admission	Systematic reviews and meta-analyses of observational studies	(11,25)
Overfeeding during PICU stay (>10% measured resting energy expenditure)	Observational study	(32)
Vitamin D deficiency at PICU admission	Systematic reviews and meta-analyses of observational studies	(50-52)
Improved clinical outcomes		
Withholding parenteral nutrition for 1 week	Randomized controlled trial	(26)
Early enteral nutrition <48 hours	Observational studies and secondary analysis of a randomized controlled trial	(39,40)
Energy intake at least 67% of prescribed (mean prescription of 64 kcal/kg per day)	Observational study	(31)
Enteral protein intake >1.1 (1.5) g/kg per day	Observational studies and systematic review	(34-36)
Single dose of vitamin D in deficient patients	Randomized controlled trial	(53)

of nutrition on clinical outcomes is missing in important areas in PICU. In 2018, an expert group has investigated which research topics needed to be addressed in this field (81). A total of 45 research topics were identified in ten domains: the pathophysiology and impact of malnutrition in critical illness; nutrition assessment: nutrition risk assessment and biomarkers; accurate assessment of energy requirements in all phases of critical illness; the role of protein intake; the role of pharmaconutrition; effective and safe delivery of EN; enteral feeding intolerance: assessment and management; the role of PN; the impact of nutrition status and nutrition therapies on long-term patient outcomes; and nutrition therapies for specific populations. Among these topics research, five research questions were identified by the expert group as the most urgent to answer (81):

- To determine the impact of low *vs.* high protein intake on clinical outcomes;
- To determine whether early protein provision in the first 48 hours preserves muscle mass;
- To understand the role of early combined mobilization and protein supplementation on preserving muscle mass and function;
- To examine the impact of continuous *vs.* intermittent bolus enteral feeding on clinical outcomes;
- To determine if children on vasoactive medications have a higher risk of complications during enteral feeding and whether there is a "safe dose" for enteral feeding.

The PEPaNIC study has already provided interesting data on the role of high protein intake provided by the parenteral route, an option that should be avoided (26). Today, future trials need to investigate whether providing early provision of protein by the enteral route in order to reach 1.5 g/kg per day may be beneficial (12). The optimal amount of energy intake, determined by using a validated indirect calorimeter, also needs to be addressed (33,82). Besides types of EN and micronutrient supplementation are important issues among others (*Table 1*). Well-controlled RCTs are required to assess the impact nutritional treatment and observational studies are needed to better understand the metabolic pathways during the different phases of illness. Sample size must be sufficient and the population not too heterogenous although these represent major difficulties in PICU (81).

Conclusions

As mortality rates amongst critically ill children continue to decline there is increasing focus on survivorship.

Future studies need to characterise the effect of different nutritional strategies on clinical and functional outcomes in critically ill children.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Lyvonne Tume, Frederic Valla and Sascha Verbruggen) for the series "Nutrition in the Critically Ill Child" published in *Pediatric Medicine*. The article was sent for external peer review organized by the Guest Editors and the editorial office.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/pm-20-73). The series "Nutrition in the Critically Ill Child" was commissioned by the editorial office without any funding or sponsorship. Dr. CM reports non-financial support from Baxter, non-financial support from Nutricia, outside the submitted work. Dr. CJC reports non-financial support from Baxter, non-financial support from Nutricia, outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pm-20-73
Cite this article as: Marino LV, Moullet C, Jotterand Chaparro C. The impact of nutrition on clinical outcomes in the critically ill child. Pediatr Med 2020;3:21.

