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TITLE: Priorities for nutrition research in pediatric critical care

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Conflict of interest statement and financial disclosure statement: Frederic Valla is a consultant for Baxter and Nutricia; this has not influenced this paper. Praveen Goday is consultant to Nutricia and serves on a Data and Safety Monitoring Board for Shire Pharmaceuticals, neither have influenced this paper. On behalf of the rest of the authors, there are no conflicts of interest to declare, nor any financial disclosure to declare.

ABSTRACT

Background: Widespread variation exists in pediatric critical care nutrition practices, largely because of the scarcity of evidence to guide best practice recommendations. **Objective:** The objective of this paper was to develop a list of topics to be prioritized for nutrition research in pediatric critical care in the next 10 years. **Methods:** A modified three-round Delphi process was undertaken by a newly established multidisciplinary group comprising of 11 international researchers in the field of pediatric critical care nutrition. Items were ranked on a 5 point Likert scale. **Results:** Forty-five research topics (with a mean priority score>3.0/5) were identified within the following 10 domains: the pathophysiology and impact of malnutrition in critical illness; nutritional assessment: nutritional risk assessment and biomarkers; accurate assessment of energy requirements in all phases of critical illness; the role of protein intake; the role of pharmaco-nutrition; effective and safe delivery of enteral nutrition; enteral feeding intolerance: assessment and management; the role of parenteral nutrition; the impact of nutritional status and nutritional therapies on long term patient outcomes and nutritional therapies for specific populations. Ten top research topics (that received a mean score >4.0/5) were identified as the highest priority for research. **Conclusions** This paper has identified important consensus-derived priorities for clinical research in pediatric critical care nutrition. Future studies should determine topics that are a priority for patients and parents. Research funding should target these priority areas and promote an international collaborative approach to research in this field, with a focus on improving relevant patient outcomes.

Clinical Relevancy Statement Efforts to identify and prioritize research in clinically important topics allow meaningful resource allocation. In 2017, adult critical care nutrition experts described priority areas for research, and we believe our current effort to identify priority topics for pediatric critical care nutrition research is timely.

Introduction

Bedside nutrition practice in the pediatric intensive care unit (PICU) continues to be driven largely by expert opinion or consensus, with very few practices supported by high-level evidence.[1] This has resulted in widespread variations in practice and an inability to examine their impact on patient outcomes. Large randomized controlled trials in this field are difficult to conduct, may have limited external validity and often do not answer clinically important research questions. Adult and preterm neonatal data cannot be extrapolated to the PICU population, which represents a heterogeneous group with varied ages, physiological states and pathophysiological processes. Hence, there is an urgent need for more pediatric research studies with robust designs, addressing important research uncertainties around nutritional practices associated with improved patient outcomes. The burden of conducting large well-designed studies in an era of resource limitations requires that important research questions are prioritized. Similar prioritization efforts have been undertaken in adult intensive care nutrition and nutrition in general. [2, 3] We present the results of a consensus process to highlight key areas in pediatric critical care nutrition where research resources need to be prioritized.

Aims

The objective of this paper was to develop a list of priority topics that would guide nutrition research in pediatric critical care in the next 10 years.

Methods

Eleven researchers in the field of pediatric critical care nutrition, representing multiple regions (Canada, United States of America, Brazil, Singapore, United Kingdom, France, Switzerland and the Netherlands), disciplines (nursing, medicine and dietetics), and research experience, formed a new international collaborative research group to undertake this project. A modified three-round Delphi process was utilized to generate a list of research topics for prioritization.[4] First, each member of the expert panel was asked to submit up to three top research priority topics in nutrition for each of the four phases of illness trajectory (acute phase, stable phase, recovery phase and post-intensive care phase). These were defined as: *i) acute phase*: resuscitation phase when the patient requires actively titrated or escalating vital organ support (sedation, mechanical ventilation, vasopressors, fluid resuscitation); *ii) stable phase*: the patient is stable on, or can be weaned, from this vital support; *iii) recovery phase*: patient who is actively mobilizing and *iv) post-intensive care phase*: after discharge from the PICU both the time within hospital and after hospital discharge. Members were asked to specify the topic in a PICO question format and consider the priority of this topic for the next decade. No other guidance was

provided. The process coordinator (LT) managed the data and communications using blinded electronic surveys (Qualtrics ™) to reduce the risk of bias from individual opinions. Two members of the group (LT and FV) then independently analyzed these data and categorized these topics into broad domain areas for ranking by the group. Duplicate topics in the list were reconciled; topics were clarified or combined where necessary and differences were resolved through discussion into a final list. Specific research topics were categorized under broad thematic domain areas, and the topics were distributed to the group members for ranking by providing a relative priority score for each topic. Members utilized a 5-point Likert scale (from very low priority (1) to very high priority (5)), and a mean score was calculated for each topic. Topics with mean scores <3.0 were removed from the list. The next version of the survey round summarized the mean score for each topic, and members were asked to re-rank the questions (using the same Likert scale). Items with a mean score <3.0 were removed and a final list of high priority research questions was generated with items ranking >3.0.

Results

A total of 115 topics were submitted by the experts in the first round (Figure 1). After duplicate topics were removed and similar topics were combined, a list of 92 unique topics was generated. These 92 topics were categorized under 10 broad domains. In round two, eight topics with mean score <3.0 were removed, and the remaining 84 topics were reduced to 71 by combining similar topics, which were then categorized under the 10 broad domain topics (Table 1). In the final round nine topics scored <3.0 and were removed. Ten topics scored >4.0 (Table 2), and further rationalization of similar topics was undertaken, leaving 48 research topics within the broad 10 domains. For each domain, two experts were assigned to summarize the rationale for this domain and describe the specific uncertainties and research questions that are a priority. This is presented across all phases of critical illness.

1. Pathophysiology and impact of malnutrition during critical illness

Critical illness affects the gut both structurally and functionally. Delayed enteral feeding, multi-organ failure and the use of broad spectrum antibiotics result in an unfavourable environment for commensal bacteria in the intestinal lumen. The intestinal microbiome exhibits changes to composition and diversity in critical illness, but this is still inadequately understood.[5] The resultant loss of species crucial to the functional capacity of the gut impacts fermentation, appetite regulation, immune regulation and maintenance of the intestinal luminal barrier. These effects need to be examined in the context of malnutrition, as well as identifying what constitutes the best definition of malnutrition in the critically ill child. We need to be able to identify the

different phases of metabolic response in pediatric critical illness and their impact on gut function, with the aim of providing individualized nutritional therapy. Muscle wasting occurs in critically ill patients.[6] However, this phenomenon is not adequately understood. The immunological alterations associated in children and their interplay with critical illness and malnutrition require further study. We also need a better understanding of the mechanisms that lead to poorer outcomes in non-optimally nourished children, and in those who receive under and over feeding. The metabolic and inflammatory response to pediatric critical illness can be varied and unpredictable; therefore it is important to describe the relationship between pre-existing undernutrition, the metabolic response, and systemic inflammation during critical illness.

2. Nutritional assessment at admission and during critical illness: nutritional risk assessment tools and biomarkers

The application of an individualized approach to nutrition therapy is predicated on accurate assessment of vulnerable patients, such as those with existing malnutrition. Malnutrition includes children who are overweight and obese, and these children have been poorly studied and their specific requirements in PICU remain unknown. However, a uniform strategy for assessment of nutrition status and accurate markers of nutritional state during critical illness are not available. Variables, such as history, anthropometry and disease state have been used to develop screening tools that predict risk of nutritional and clinical deterioration.[7] Single anthropometric measurements do not capture important elements of nutrition status, such as growth velocity, chronicity, and functional status, and there are no reliable screening tools for risk detection validated in pediatric critical illness. Anthropometric and other variables and new biomarkers that together predict nutritional deterioration and poor clinical outcomes need to be identified, developed and incorporated into a screening tool.[1] These then must be used to determine if they improve both nutritional delivery and other outcomes, and future studies must examine the role of individualized nutrition targeted to risk categories on improving patient outcomes. Monitoring the impact of nutrition therapies on nutritional status throughout the PICU admission is desirable. Tracking patient weight can be technically challenging and confounded by volume status during acute illness. Focus has therefore shifted to other non-invasive assessments, including arm circumference and muscle mass/volume. Despite its promise in adults, the quantification of muscle thickness by ultrasound in critically ill children is still not fully understood, and we need further evidence to determine its role as a surrogate for muscle atrophy.[8, 9] We need to better assess the relative impact of nutritional status deterioration during PICU stay on the metabolic shift towards catabolism, underfeeding, immobilization-related atrophy and cachexia. Biomarkers including albumin, pre-albumin, and retinol-binding protein have also been found to be ineffective as nutrition

markers given their decrease in acute illness, and the confounding effects of inflammation and vascular permeability. [10] Identifying novel biomarkers to track nutritional status during critical illness and in response to interventions is a research priority.

3. Accurate assessment of energy requirements in all phases of critical illness

There is a need for more accurate estimation of energy requirements of critically ill children and to determine the optimal timing of this estimation, in addition to re-assessment of these requirements throughout the child's critical illness. Unintended underfeeding and overfeeding, from inaccurate estimations of energy requirement, are associated with poor outcomes [11] Indirect calorimetry (IC) is considered the gold standard for assessing energy expenditure (EE).[1] However, IC is not widely available and may not be feasible in most patients.[12] In the absence of IC, the common practice is to estimate the EE using predictive equations without the addition of stress factors. However, these equations, developed in healthy infants and children, are inaccurate for critically ill children, risking unintended underfeeding or overfeeding, especially in the youngest children.[13, 14] Future studies must explore the optimal patients, timing and indications for IC testing. Alternative methods of accurate EE estimation or measurement must be developed. We need to determine which variables affect energy expenditure to enable us to develop more accurate predictive equations. The development of an EE predictive equation based on physiologic variables might be an alternative approach when IC is not feasible. Delivery of at least two-thirds of the prescribed energy goal by the end of the first week in the PICU is associated with a reduced risk of 60-day mortality.[15] However, we do not know if energy delivery that is matched to measured energy expenditure improves outcomes. Indeed we also need to understand how to interpret and act on any changes in energy requirements throughout the PICU stay.

4. The role of protein intake

Current recommendations for the provision of protein in pediatric critical illness are based on limited evidence.[16] The optimal protein "dose" that is associated with improved clinical outcomes in this population is not known. Studies have demonstrated an association between increased protein delivery and improved clinical outcomes. [17,18] In a post-hoc analysis of a large randomized trial designed to compare early versus late parenteral nutrition, provision of amino acids was associated with a higher risk of nosocomial infections, higher risk of longer mechanical ventilation and longer time to live PICU discharge.[19] Future studies must investigate the effect of low versus high protein intake on clinical outcomes during critical illness. These studies must determine the optimal timing and dosing of protein provision during the first week of PICU admission;

particularly its role in preserving muscle mass, reducing muscle wasting and improving functional outcomes. Studies of protein supplementation must account for the impact of route used for protein (enteral protein vs. parenteral amino acids) supplementation and the total energy delivered. Functional recovery is dependent on preservation of muscle mass, which in turn is modulated by a variety of factors such as physical rehabilitation, sedative drug choices, neuromuscular blockade and nutritional support, in particular protein supplementation[20]. The theoretical benefit of higher protein delivery in the recovery phase, is to offset the effects of protein catabolism by increasing synthesis and reducing net muscle wasting. Future research must explore the relationship between protein delivery, muscle mass, muscle biology, and muscle function. The utility of skeletal muscle mass assessment using ultrasonography and bioelectrical impedance analysis in the PICU are some of the potential modalities to track lean mass during critical illness which need to be further explored.[8,21]

5. The role of pharmaco-nutrition

Pharmaco-nutrition is defined as supraphysiologic doses of nutrients that may modulate inflammation, host immunity and clinical outcomes beyond the nutritional value such as energy provision and growth compared to a standard nutrient dose [22]. The benefits of immune-enhanced nutrition for malnourished critically ill children are unclear, and adult work has shown potential for harm.[23] In the PICU setting, limited data are available on a limited number of pharmaco-nutrients, the most studied being omega-3 fatty acids, selenium, zinc, and glutamine. Plasma levels of several micronutrients have been shown to be significantly decreased at PICU admission, and associated with suboptimal outcomes.[24] However, these low levels may be an expression of adaption to critical illness, and so far supplementation studies do not support the routine use of pharmaconutrition in this population.[25,26] Furthermore, these studies were based on generic dosing in heterogeneous populations in differing phases of critical illness. Therefore, pressing research questions remain about the possible benefit of pharmaco-nutrient supplementation (and indications for) in targeted populations, on both functional outcomes and other outcomes such as wound healing. The route of supplementation (enteral versus parenteral) for such therapies must be accounted for in future research on this subject.

6. Effective and safe delivery of enteral nutrition (EN)

The effective delivery of adequate nutrients via the enteral route is an important facet of nutritional strategy for the critically. However, EN remains challenging during the vulnerable period of acute critical illness. Despite timely energy goal prescription, delivery is often suboptimal due to interruptions or perceived feed intolerance (FI) during acute illness. Yet evidence to support optimal EN delivery methods is scant. Two

small trials did not find clinical outcome benefit, but suggested that small bowel feeding may allow higher energy goals to be delivered, compared to the gastric route.[27,28] Although there are theoretical benefits of feeding these patients intermittently, this has not been investigated sufficiently.[29] One trial examined continuous versus intermittent gastric feeding, finding no difference in FI.[30] The routine measurement of gastric residual volume (GRV) to guide EN delivery and advancement is another practice that has come under scrutiny, in terms of impairing the delivery of enteral feeding. A small observational study found no difference in ventilator associated pneumonia incidence between the groups, but could not demonstrate better achievement of energy goals.[31] The use of feeding protocols to improve energy goal achievement is one of the most studied aspect of nutrition delivery, mostly in high-risk groups, with the majority using before and after designs. A systematic review found weak evidence that protocols do improve delivery, but this was limited by these study designs.[10] Future research needs to investigate the impact of protocols on other patient outcomes such as length of ventilation, healthcare acquired infections, and longer term outcomes such as the preservation of muscle mass and function. Other key uncertainties, in need of urgent research, include the definition of permissive underfeeding and the impact of trophic (or non-nutritive) feeding on clinical outcomes and gut function and integrity. We do not know whether early EN (both nutritive and non-nutritive) changes the gut microbiome with the ability to affect outcomes such as nosocomial infections. Nor do we know if there is an optimal EN formula/solution to reduce FI and improve clinical outcomes in critically ill children. These are all key areas for nutrition research if we want to improve the delivery of EN.

7. Enteral feeding intolerance (FI): assessment and management

Enteral nutrition benefits the intestinal microbiome, which further supports host metabolism and immunity. In pediatric critical illness, concerns related to the integrity of the intestinal mucosa and gastrointestinal motility may prevent clinicians from starting or advancing enteral feeds. The enteral route is the desired method for delivery of nutrients during critical illness, but FI is one of the most widely reported reasons for withholding enteral feeding [32,33] Yet, because there is no consistent and agreed definition of FI in critically ill children, the true prevalence of FI is unknown. The diagnosis is often subjective, and a survey of PICU clinicians, showed the definitions of FI and the plan of action for managing intolerance were highly variable.[34] Markers commonly used to indicate FI include increased gastric residual volume, upper gastro-intestinal (GI) signs and symptoms (such as vomiting and gastro-esophageal reflux), abdominal pain and/or distention, in addition to the frequency and consistency of bowel movements, and the presence or absence of bowel sounds.[35,36] A systematic review in adult critical care noted 49 different definitions of FI used. [36] The most

frequently reported as markers to determine feed tolerance included: measurement of gastric residual volume (GRV), assessing abdominal girth, vomiting and diarrhea. Despite the lack of evidence to support GRV as a valid marker of FI, 88% of adult critical care studies defined FI by GRV alone or GRV in combination with other signs. Assessing 'readiness to enterally feed' also remains a clinical challenge, in the absence of reliable biomarkers, methods or screening tools to identify FI. A uniform definition of FI in critically ill children is urgently needed in the first instance, so we can determine a true prevalence of the condition. Once a consistent and valid definition of FI is agreed upon, the effect of probiotics, prokinetic drugs, different enteral formulae (with fiber or without or the use of partially or fully hydrolyzed formulae) and different feeding strategies (gastric vs. post-pyloric, continuous vs. intermittent) on FI need to be investigated.

8. The role of parenteral nutrition (PN)

Despite EN being the preferred route for nutrient delivery, some patients in the PICU may require PN either because EN is contraindicated or not tolerated. Parenteral nutrition may be needed on its own or as a supplement to insufficient EN. However, PN may be associated with higher costs and morbidity.[37] The prudent use of PN requires attention to timing and dose of nutrients delivered, as recent work in pediatric critical care has demonstrated harm from early PN initiation.[38] In the PEPaNIC randomized trial [38] children were randomized to early PN (within 24 hours) or late PN (on day 8), to achieve caloric goal. Multivitamins and micronutrients were administered intravenously and EN advancement was attempted using institutional guidelines in both arms. The study reported withholding PN for one week resulted in fewer new infections, earlier live discharge from the PICU, shorter duration of mechanical ventilation, and lower odds of renal replacement therapy. These benefits were reported also in those perceived to be most vulnerable to macronutrient deficits during critical illness; term neonates and undernourished children. Despite questions around the design of this trial, the results challenge the rationale for an early aggressive approach to PN.[39,40] Future investigations must determine the impact of supplemental PN initiated between day 2 and day 7, and beyond day 7 on relevant clinical outcomes. Other pressing research questions are: At what threshold of nutrient delivery by EN should PN be initiated? Is there a vulnerable group that might benefit from PN initiated earlier than day 8? Is the composition of the PN important? And how much PN supplementation is needed? These investigations must account for the confounding effects of nutrient dose, both underfeeding and overfeeding, when examining the impact of nutrient delivery via PN on clinical outcomes. It is unlikely that a universal PN strategy will be appropriate for the heterogeneous patients in the PICU.

9. The impact of nutritional therapy on long-term patient outcomes

With pediatric survival from critical illness the highest ever (around 97%) future investigations must also describe the impact of nutritional interventions on long-term outcomes.[41] Muscle protein catabolism, a major metabolic derangement during critical illness, and its resulting muscle weakness impairs short and long-term outcomes. Physical exercise and nutrition are prerequisites for muscle anabolism during health, and thus seem obvious strategies to preserve functional muscle mass in the ICU setting. Early rehabilitation and mobilization to counter muscle weakness in the PICU have been shown to be safe and feasible in a recent systematic review, but efficacy trials combining rehabilitation with targeted nutritional strategies on long-term functional outcomes are lacking.[42] Although there is some evidence that outcomes may be modifiable by nutritional and metabolic interventions [43,44], randomized controlled trials with large enough sample size to detect clinically relevant long-term outcome differences are lacking. Most nutritional studies focus on intermediate or surrogate endpoints such as nitrogen balance and inflammatory markers [19, 45]. In critically ill adults, early high amino acid intake via the parenteral route was associated with impaired muscle function and architecture in one RCT [45]. These observations contrast with previous observational studies suggest that early nutritional support with high amino acids intakes lead to improved outcome [15, 17]. Furthermore, we do not know whether there is a role for catch-up feeding regimens to improve nutritional and functional long term outcomes. Finally, evidence for the impact of nutritional therapies on long-term outcomes is lacking, and future research should focus on the use of new and existing validated tools, such as Peds-QOL and the functional status scale to assess nutritional outcomes.

10. Nutritional therapies for specific populations

Most published guidelines on PICU nutrition are limited by their use of heterogeneous PICU cohorts with a range of medical or surgical conditions, at different stages of their critical illness and with varying illness severity. The contribution of chronic illness and co-morbidities is another confounder. Therefore, some subgroups of critical care may have unique nutritional requirements. The long-term nutritional consequences of critical illness on functional recovery remain poorly defined in each of these subgroups. Children admitted to the cardiac intensive care unit and those with severe burn injury are two PICU subgroups who have been most studied. Energy and protein requirements as well as general management of nutritional needs in these groups are unique and well described.[46,47] However, 'enteral feeding readiness', and 'the safe dosing of' and 'number of' vasoactive medication infusions to safely deliver enteral nutrition remains unknown.In this setting, plasma lactate level is frequently used as surrogate for shocked state, with limited evidence to support this. Identifying relevant indicators of 'readiness to feed' for these high-risk groups in the PICU would be incredibly useful.

We know very little about the energy needs and optimal modes of nutrient delivery in children on non-invasive ventilation, despite its increasing use in the last decade.[48] Indirect calorimetry is technically impossible, resulting in difficulties in assessing nutritional requirements; feeding intolerance is also debated in this setting, with various recent reports of EN success in the literature. Similarly, the specific needs of children undergoing renal replacement therapy have been highlighted in terms of amino acid and micronutrient losses, but nutrient supplementation needs have not yet been studied.[49] Similarly, in children with severe respiratory failure (pARDS) questions remain around whether a targeted nutrition strategy would improve clinical outcomes. Finally, little is known about nutritional requirements, EN timing or delivery methods of children with traumatic brain injury, who may have specific metabolic shifts.[50]

Study design and outcome measures for nutritional research in pediatric critical care

Pediatric intensive care research is affected by fewer patients and better outcomes than adult intensive care, consequently is beset by many small and inadequately powered trials; often involving very heterogeneous patient populations both in age and pathology, making results difficult to interpret. Furthermore, due to a heterogeneous group of outcome measures used in studies, many which are ambiguous and inconsistently defined (such as the all-encompassing 'feed intolerance'), it is rarely possible to pool data in meta-analyses. Therefore, an urgent need is to develop a core outcome set for studies of nutritional interventions in pediatric critical care that could be used in trials. Furthermore, other efficient study designs may be important to consider in the future, to account for reduced patient numbers and to test multiple therapies in the same study. Not all research questions can be tested in randomized trials, but the research design chosen should be appropriate to the question and the strongest design possible, with an adequate sample size to be able to draw genuine conclusions.

Limitations

We acknowledge this is not a comprehensive list of all the research questions that need answering in the field. Our goal was to generate a list of priorities as perceived by our multidisciplinary group. The results may reflect the individual biases of the authors. We did not undertake a systematic review of the literature, as this has previously been done, nor have we recommended particular research methods for each of the topics. The next important step is to understand patients and parents priorities for research in this area, so that research conducted is meaningful and relevant for our patients and their families.

Conclusions

Using a Delphi method to achieve consensus, a multidisciplinary group of researchers generated 10 broad domains, and 10 top ranking topics, that we believe are high priority research areas for the next decade in the field of pediatric critical care nutrition. Answers to these questions will help to guide best practices in bedside nutrition delivery in the PICU, with the aim of optimizing patient outcomes. We hope this work will guide research resource allocation and promote a collaborative international research agenda in the field of pediatric critical care. The next step is to develop a core set of clinical and nutritional outcomes that must be reported in future nutritional studies.

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Figure Legends

Figure 1 Diagram of the Delphi consensus process with results

Table 1 Top 10 broad domains with research topics for nutrition research in pediatric critical care

Table 2 Top 10 highest ranked research topics

Figure 1 The Delphi process and results

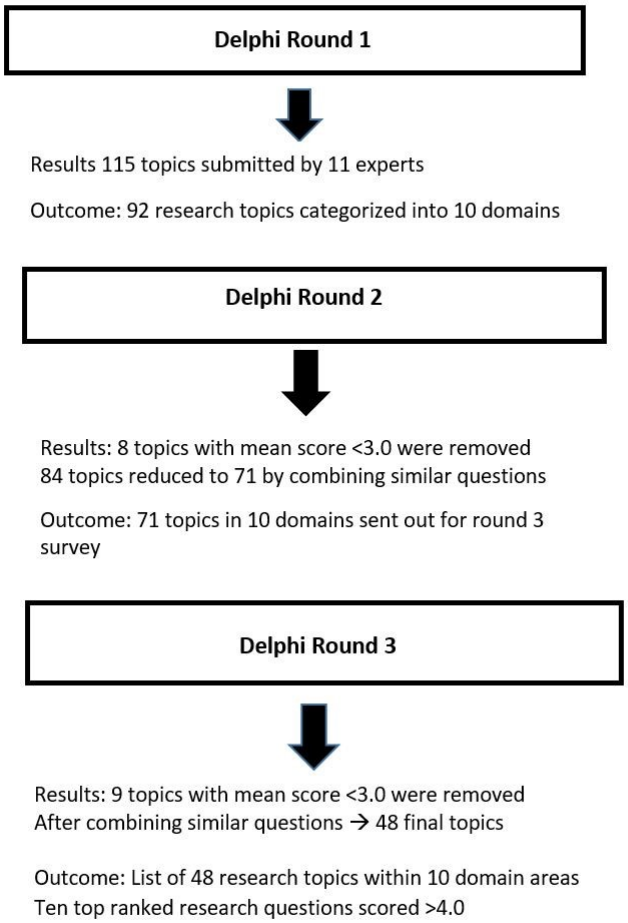

Table 1 Top 10 broad domains with research priorities for nutrition research in pediatric critical care

Domain topic	Research topic
1. Pathophysiology and impact of malnutrition during critical illness	• To determine the optimal definition of malnutrition in critically ill children • To define the phases of critical illness (e.g., acute, stable, recovery) in terms of gut function and nutritional needs • To identify the factors (clinical and nutritional) that impact on gut health/function (motility, absorption, microbiome) • To describe and understand the relationship between malnutrition and inflammatory response • To determine how critical illness induces lean muscle wasting
2. Nutritional assessment in pediatric critical illness: nutritional risk assessment tools and biomarkers	• ***To develop a valid nutritional risk assessment score that identifies children at risk of nutritional deterioration, who might benefit from targeted interventions.*** • To determine the impact of nutritional status at PICU admission on clinical outcomes • To identify the best indicators of changing nutritional status over time • To determine whether nutritional risk assessment improves time to initiation of EN and other clinical outcomes • ***To identify biomarkers of anabolism during critical illness*** • To identify the optimal measures for assessing muscle wasting.
3. Accurate assessment of energy requirements in all phases of critical illness	• To determine the optimal timing and accurate method for assessment of energy goals • To identify variables (e.g. disease state, severity of illness, inflammation etc) that predict energy expenditure • To determine whether a physiology-derived equation can provide accurate estimation of resting energy expenditure • To examine whether energy delivery matched to measured energy expenditure improves clinical outcomes
4. The role of protein intake	• To examine the impact of critical illness and inadequate protein intake on lean muscle wasting • ***To determine whether early protein provision in the first 48 hours preserves muscle mass*** • To determine the optimal timing and accurate method for assessment of protein goals during critical illness • ***To determine the impact of low versus high protein intake on clinical outcomes*** • ***To understand the role of early combined mobilisation and protein supplementation on preserving muscle mass and function*** • To determine the optimal strategy for enhancing protein delivery (enteral protein supplementation or parenteral amino acids)
5. The role of pharmaco-nutrition	• To examine the impact of pharmaco-nutrition on clinical outcomes • To understand the role of micronutrient supplementation on functional and clinical outcomes
6. Effective and safe delivery of EN	• To determine the optimal site for EN delivery: gastric or small bowel? • To understand the impact of early EN (non-nutritive) on the gut microbiome, gut motility and gut integrity • To examine the impact of nurse-driven feeding protocols on volume of EN delivered and clinical outcomes • ***To examine the impact of continuous versus intermittent bolus enteral feeding on clinical outcomes*** • To agree on a definition of permissive underfeeding and to determine its impact on outcomes • To determine whether the advancement of EN without measuring GRV improves nutrient target achievement without additional risks

	• To understand if there is an optimal type of EN formula (polymeric, semi-elemental, fibre or no fibre, high energy or standard)
7. Enteral feeding intolerance: assessment and management	• ***To develop an agreed working definition of feed intolerance to EN and a screening tool for early detection of intolerance in critically ill children*** • To identify the variables that predict EN intolerance • To determine if probiotics improve feed tolerance • To identify the indications and benefits of small bowel feeding in patients with feed intolerance • To determine the role of prophylactic prokinetics • To understand the effect of feed type and formulae on feed intolerance
8. The role of PN	• ***To examine the role of PN supplementation (to achieve energy/protein goal) on clinical outcomes*** • To understand the optimum timing and EN delivery threshold for supplemental PN
9. The impact of nutritional therapy on long term patient outcomes	• ***To determine the impact of a combined early mobilisation/rehabilitation and targeted nutritional strategy on clinical outcomes*** • To determine whether improving nutritional status before PICU admission (on those we can) improves clinical outcomes • To understand whether catch up feeding regimes (including overnight nutrition) after PICU discharge, improve clinical outcomes • To identify whether nutritional status at discharge is predictive of longer-term clinical outcomes • To understand whether feeding intolerance during PICU admission correlates with failure to thrive after PICU discharge
10. Nutritional therapies for specific populations	• To identify valid indicators of 'readiness to feed' for high-risk groups in the PICU • To understand the nutrition requirements (micronutrients and protein) in children receiving renal replacement therapy • To determine the energy and protein requirements and optimal feeding route for children on non-invasive ventilation • To determine in children with severe respiratory failure (pARDS) whether targeted nutrition therapy (energy and protein supplementation) improves clinical and functional 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***

Abbreviations: EN Enteral Nutrition; GRV Gastric Residual Volume; IV Intravenous; pARDS Pediatric Acute Respiratory Distress Syndrome; PICU Pediatric Intensive care Unit; PN Parenteral Nutrition

Bold italic text indicates highest scoring topics

Table 2: Top 10 ranked PICU nutrition research priorities

Research topic	Group mean score (1-5)
1. To determine the impact of low versus high protein intake on clinical outcomes	4.63
2. To determine whether early protein provision in the first 48 hours preserves muscle mass	4.54
3. To understand the role of combined mobilisation and protein supplementation on preserving muscle mass and function	4.54
4. To determine the impact of an early combined mobilisation/rehabilitation and targeted nutritional strategy on preserving muscle mass and function	4.45
5. To develop a valid nutritional risk assessment score that identifies children at risk of nutritional deterioration, and those who might benefit from timely interventions	4.45
6. To examine the role of PN supplementation (to achieve energy/protein goal) on clinical outcomes	4.27
7. To identify biomarkers of anabolism during critical illness	4.27
8. To develop an agreed working definition of feed intolerance to EN and a screening tool for early detection of intolerance in critically ill children	4.18
9. To examine the impact of continuous versus intermittent bolus enteral feeding on clinical outcomes	4.09
10. 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	4.0

Abbreviations: EN Enteral Nutrition; PN Parenteral Nutrition