Editorial

The current state of knowledge and research required around nutrition in pediatric critical illness

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The papers in this themed edition all demonstrate there is still much we do not know about how nutrition can potentially modify critical illness or the gut in children. More is known about adult critical illness and nutritional therapies (1). However, children and not little adults, and the broad age range in pediatrics from term neonates to young adults, along with vastly different pathologies leading to pediatric intensive care unit (PICU) admission represents a challenge to PICU nutrition researchers. This concluding editorial will outline the current state of knowledge in the field and identify what we need to research in the future, based on a recent expert Delphi study (2).

What do we currently know about nutrition in pediatric critical illness?

Several professional societies have recently published their updated guidelines around nutrition in pediatric critical care (3,4) and despite suggesting multiple recommendations, most of these recommendations are based on evidence graded as low. Despite this paucity of well-designed clinical trials in this field, and the drawbacks of circumstantial evidence as we expressed in our editorial introduction, there is observational evidence to show the association between worsened clinical outcomes and nutritional inadequacy. This is both at ICU admission, in malnourished children, and during PICU stay (5), with prolonged mechanical ventilation, more healthcare associated infections (HCAIs), impaired wound healing and delayed sternal closure and increased mortality on children receiving inadequate enteral nutrition (6-10). Randomized trial evidence also showed the potential harm of overfeeding by early parenteral nutrition (PN) in critically ill children (11,12). It appears that throughout the different (and not yet clearly identified) phases of a child's critical illness, different nutritional targets may be required putting the critically ill child at risk for both under—as well as overfeeding depending on the course of illness. What is apparent is that a 'one size fits all' approach will not work, and different subgroups of patients may have different requirements, and these are likely to evolve throughout the course of their critical illness, similar to a pharmacological approach, as discussed in the first editorial.

We also are becoming increasingly aware that predictive energy equations are inadequate for critically ill children (2,13), and although indirect calorimetry (IC) is accurate in some of the PICU population after the acute phase, limitations still exist for the youngest children and those with air leaks (14). Furthermore, energy expenditure is dynamic and determined by multiple intrinsic patient factors and by the PICU therapies applied to the child, yet IC only measures EE at a point in time, and very few (14%) PICUs worldwide have access to a device (15). What we also increasingly know is that many barriers exist to delivering adequate enteral nutrition in the PICU (16), but that many of these are perceived rather than substantiated, lack robust

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evidence and are applied by risk-averse clinicians (17). Thus, the effective implementation of recommendations and guidance is paramount, with many PICU practices still based on little or no evidence. The routine monitoring of gastric residual volume (GRV) to guide feeding is one such example. This historical practice, lacking any evidence, but used extensively (18,19), almost certainly contributes significantly to time spent without enteral feeds in the PICU and a small study has showed not measuring this did not lead to increased harms (20). This is the challenge for clinicians and researchers now, to implement recent best evidence around nutrition (3,4) into clinical PICU practice and evaluate the effects of this.

What future research is required around nutrition in pediatric critical illness?

In addition to identifying parameters and biomarkers that would allow us to 'know' that a child has moved from one phase of critical illness to another, we also do not know the evidence for many of our usual nutritional therapies, different formulas or methods of delivering nutrition. Importantly, unlike adult critical illness (21), we have no valid nutritional risk score for critically ill children, to enable us to predict those at greater risk at the outset and in whom specific nutritional needs and support should be directed to. Uncertainty also persists around the optimal method to determine energy expenditure in many patients such as those on non-invasive respiratory support. Furthermore, we need to know whether a child's energy expenditure, corresponds directly to their energy requirements. This is the same for protein requirements. The protein balance can be measured, but the optimal target is unknown, and the requirements are almost certain to evolve throughout the course of critical illness. What micronutrient requirements and whether supplementation of specific micronutrient deficits improves outcomes, as does whether pharmaconutrition is beneficial in specific patients and phases of their critical illness.

In addition to understanding the child's nutritional requirements, then different methods to delivering and achieving nutritional targets need to be better understood. Identification of the optimal methods (gastric versus post-pyloric and continuous versus bolus feeds) and timing for enteral nutrition to in the pediatric critical population is also unknown, and whether certain patients do better with a specific delivery method. Whether one type of enteral nutrition formula (semi-elemental or polymeric) results in better clinical outcomes or improves feed tolerance remains unknown. Indeed, this implies that we have a consistent and reliable definition of feed intolerance and evidence of effective strategies for its management, none of which currently exist. We need to urgently gain international consensus on the definition of 'feed intolerance' (22,23). This nebulous concept has been defined differently, thus makes studies difficult to compare and adds to clinician uncertainty (24).

Targeting the improvement of healthcare professionals' knowledge around nutrition is important, as is the implementation of written protocols and auditing compliance. This 'implementation science' must be a fundamental part of future nutrition research, as well as basic and applied science.

We also need to know whether the severe and often rapid muscle breakdown seen in critical illness (25) can be ameliorated by nutrition or additional protein intake or by a combination of nutrition and early rehabilitation interventions. Given the emerging data on the harm of overfeeding in the acute phase of critical illness, we need to know whether targeted permissive underfeeding is beneficial, and if so what level of underfeeding. Finally, a 'one size fits all' approach to nutrition in the PICU will not work. Not only does the PICU admit children from term (and sometime preterm) neonates up to young adults, but with vastly different pathologies from sepsis, trauma, congenital heart disease, chronic illness, burns and infectious illnesses. Making assumptions that all these pathological conditions result in the same nutritional demands is misleading and almost certainly incorrect. Yet only a few of these conditions have been studied in some depth: major burns, congenital heart disease, head trauma and bronchiolitis.

In conclusion, although research in this field is rapidly increasing, much of this research is low level evidence and with the biases of being conducted in a single center. Future well conducted clinical trials are urgently needed in many aspects of nutritional care for the critically ill children.

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