Strategies to optimize enteral feeding and nutrition in the critically ill child: a narrative review

Sharon Y. Irving[1,2]^, **Ben D. Albert**[3,4], **Nilesh M. Mehta**[3,4], **Vijay Srinivasan**[2,5]

[1]University of Pennsylvania School of Nursing, Philadelphia, PA, USA; [2]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [3]Boston Children's Hospital, Boston, MA, USA; [4]Harvard Medical School, Boston, MA, USA; [5]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

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

Correspondence to: Sharon Y. Irving. University of Pennsylvania School of Nursing; Children's Hospital of Philadelphia, Philadelphia, PA, USA. Email: ysha@nursing.upenn.edu.

Background and Objective: The provision of nutrition therapy is an integral component of care for the critically ill child. Essential factors to consider include the child's evolving metabolic needs, age, underlying disease, co-morbidities and severity of illness. The stress response has a significant impact on energy requirements and protein utilization during critical illness. To ameliorate the impact of the stress response, nutrition therapy is a crucial aspect of care. Scientific support for early enteral nutrition is strong, yet application in clinical practice remains challenging. The aim of this narrative review is to discuss the physiology of metabolic derangements that occur during critical illness, outline optimal nutrition prescription, and discuss benefits of early enteral nutrition. Considerations of special populations, such as the surgical patient, and the patient requiring vasoactive medications will also be discussed.

Methods: The authors reviewed literature pertinent to the topic area, with incorporation of their collective expert opinion on topics related to nutrition in critically ill children. A structured appraisal of the literature was not conducted.

Key Content and Findings: Enteral feeds should be initiated as soon as safely possible with advancement in a careful stepwise manner. The post-operative surgical patient presents unique challenges to nutrition therapy. Enteral nutrition for children requiring vasoactive medications can be safe, well-tolerated and beneficial.

Conclusions: Despite the heterogeneity of age, diagnosis, overall presentation at time of illness onset and interventions in the PICU setting, evidence suggests that enteral nutrition is associated with improved clinical outcomes, decreased length of hospitalization and decreased mortality in critically ill children. Strategies to optimize enteral feeding in critically ill children must consider the severity of illness, the child's nutritional status, include determination of energy and protein needs and have clear criteria for monitoring feeding tolerance with the child's changing clinical status. Future inquiry must explore the impact of enteral nutrition in various phases of pediatric critical illness and determine optimal approaches to assessment, prescription, delivery and evaluation of feeding tolerance in this population.

Keywords: Pediatric nutrition; pediatric critical care; enteral nutrition; critical illness; perioperative nutrition; Enhanced Recovery after Surgery (ERAS)

^ ORCID: 0000-0003-2967-0721.

Introduction

Enteral nutrition (EN) is the preferred method of providing nutrition therapy in critically ill children with a functional gastrointestinal (GI) tract. EN has been shown to be safe, well-tolerated and associated with improved outcomes. Literature has associated decreased hospital acquired infections, increased ventilator-free days, decreased length of stay, and decreased mortality with EN during critical illness (1-4). Despite this evidence, challenges related to optimal provision of nutrition therapy in this population remain. Current guidelines recommend early enteral nutrition (EEN) as a core component of best practices for care delivery (1,5-8). While these recommendations emphasize the benefit(s) of EN in critically ill children, questions persist regarding timing, route, and rate of enteral feeding as well as determining acceptable targets for feed volume, energy and protein intake.

The goal of nutrition therapy during critical illness is to meet the patient's basal metabolic needs, support the body in response to stress and illness, and prevent the ongoing loss of lean body mass (4,9,10). The aim of this review is to discuss the metabolic derangements that occur during critical illness, the benefits of EEN and the practical strategies to optimize nutrition in critically ill children.

Methods

Collaboratively, the authors reviewed literature pertinent to the topic of interest and combined this with their collective expert opinion on nutrition therapy in pediatric critical illness to develop this summation in a narrative review format. A structured appraisal using scoping, systematic, or meta-analysis review methodology was not employed to construct this review.

Determining nutritional needs in critically ill children

Nutrition therapy during critical illness is expected to offset the burden of the metabolic stress response and prevent loss of lean mass to improve clinical outcomes. This includes prudent prescription of nutrients individualized to the patient and the phase of illness, and provide nutrients in an efficient and safe manner (*Figure 1*). There have been several key advances to improve understanding of energy and protein requirements. However, the amount that is most associated with improved clinical outcomes is not yet determined. Hence, there remains significant uncertainty
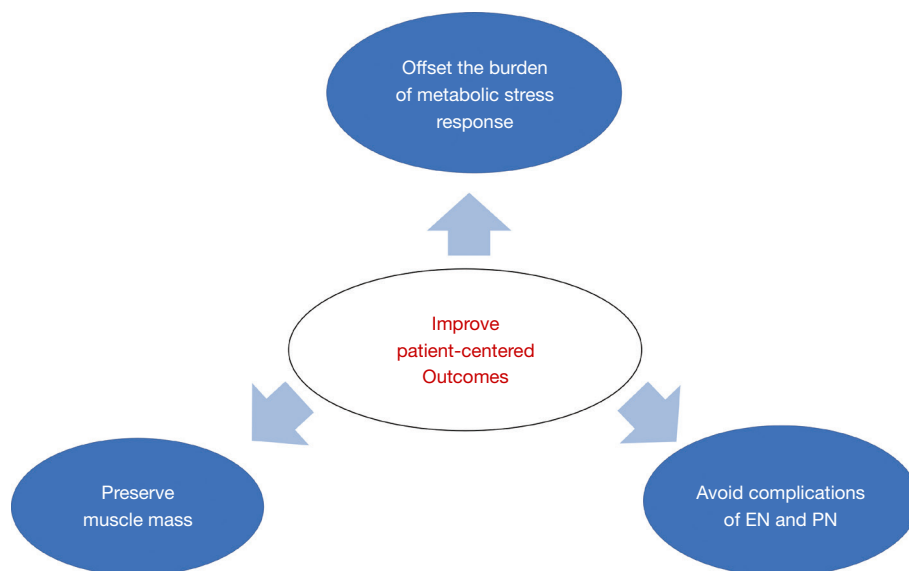
Figure 1 Goals of nutrition therapy. Meeting metabolic needs, will offset the stress response and avert loss of lean mass and fat, improving outcomes from critical illness. Legend: EN, enteral nutrition; PN, parenteral nutrition.

in the best approach to prescribing energy and protein, especially during the early phase of pediatric critical illness.

Energy requirement in critical illness

Significant improvements in surgical, anesthetic and intensive care therapies may be responsible for a more subdued metabolic state in critically ill patients (11,12). This includes enhanced sedation and analgesic therapies, improved patient respiratory ventilator synchrony, and advancements in bedside care. Studies that examine resting energy expenditure (REE) demonstrate an unpredictable energy requirement in the heterogeneous pediatric intensive care unit (PICU) population (13). Energy requirements evolve and may vary widely over the course of critical illness.

Recommended as a precise measure of REE in critically ill children, indirect calorimetry (IC) should be used whenever possible to guide energy prescription (14). However, IC is not available at all centers, it requires significant resources and expertise, and may not be feasible in some patients during the acute phase of critical illness (14,15). In the absence of measured REE by IC, standard prediction equations such as the Schofield (16) and World Health Organization (WHO) (17) are recommended to estimate REE (1,6). Developed from measurements in healthy children these equations should be used with caution owing to the unpredictable nature of critical illness and the metabolic alterations that occur.

Driven by a complex neuroendocrine cascade, the stress response incited during critical illness imposes a varied energy burden characterized by alterations in carbohydrate, lipid, and protein metabolism (11). Predictive equations cannot account for the dynamic nature of these alterations and therefore risk under or overpredicting energy requirements in critically ill children (12,18). Attempts to develop a predictive equation specifically for use with mechanically ventilated children have met with inaccuracies and are not recommended (18). Additionally, the practice of adding disease, condition or activity-based stress factors to REE (estimated or measured) is also not recommended when estimating energy needs in critically ill children (1,6). Overall, it is prudent to be mindful of the risk of unintended over or underestimation of energy requirements due to reliance on inaccurate equations to estimate REE in the PICU population.

The optimal amount of energy necessary to improve clinical outcomes is unknown (15,16). No current trials demonstrate the benefits of matching energy intake to REE measured by IC. Importantly, a study of 500 critically ill, mechanically ventilated children, demonstrated that a higher percentage of goal energy intake was delivered via the enteral route and was significantly associated with lower 60-day mortality [odds ratio (OR) for increasing energy intake from 33.3% to 66.6%, 0.27 (0.11, 0.67), P=0.002] (2). Comparatively, the same study demonstrated higher mortality in patients who received parenteral nutrition (PN) [OR 2.61 (1.3, 5.3), P=0.008] (2). Based on such observational data showing associations between energy intake and outcomes when using predictive equations, current guidelines for nutrition delivery in critically ill children recommend targeting two-thirds (2/3rds) of the estimated REE during the first week of illness (1,2).

Protein requirement in critical illness

Children with burns have similar clinical outcomes as critically ill children who experience a depletion of lean muscle mass. Thermal or burn injury is illustrative of the burden and significance of protein catabolism, a key characteristic of the metabolic stress response during critical illness (19). Postoperative measurement of protein turnover using the ^{15}N-glycine based urinary end-product enrichment technique in children following thoracic surgery, demonstrates elevation of both protein synthesis and breakdown (19,20). However synthetic rates of protein intake are unable to offset the degree of breakdown resulting in a net negative protein balance, and loss of muscle mass (20). The critical depletion in lean mass from a prolonged stress response may be further exacerbated by lack of intake of protein/amino acid substrate to support protein synthesis (21,22). Using measurements of isokinetic dynamometry (measures force and torque), the impact of this loss of lean mass in pediatric burn patients resulted in a decrease in functional muscle assessments (19).

Practical aspects of protein intake during critical illness

Protein delivery remains low in the acute phase of critical illness (22-24). Findings from a study of more than 1,200 children mechanically ventilated for greater than 48 hours, with median protein prescription of 1.9 g/kg/day, and delivery of 0.66 g/kg/day (38% of prescribed) showed protein intake (as a percentage of the prescribed goal) was indirectly associated with increased 60-day mortality (22,25).

Optimal protein delivery and intake is elusive and

the ideal dose that results in improved clinical outcomes unknown. Several small randomized trials compare high versus low protein dose and its impact on protein balance in pediatric critical illness (1). These trials are inconclusive due to being conducted in heterogeneous populations, protein dose variation, route of delivery and inability to provide significant, consistent outcomes relationships. Despite this, based on large observational studies and small trials, a minimum protein intake of 1.5 g/kg/day is recommended to maintain positive nitrogen balance and prevent loss of lean mass in critically ill children (1,6). A dose outcome relationship has only been established with enteral protein intake. While it is currently more feasible to consistently deliver increased doses of protein parenterally, the benefit of increased parenteral protein delivery has not been adequately demonstrated and recent data suggests harm with PN protein delivery during the initial 24 hours of PICU admission (24,26).

Strategies for energy and protein delivery

Once energy and protein needs are determined, enteral feeds should be initiated as soon as possible with feed advancement in a stepwise manner using feeding algorithms to attain target energy and protein intake (25-28). In vulnerable patients where the oral or enteral route EN is insufficient or not feasible, PN must be considered by the end of the first PICU week (29). However, such a pragmatic approach, where it is initiated neither too early nor too late, has not been tested in a well-designed trial. A strategy of using an approach of EEN combined with pragmatic PN aimed at delivering individualized macronutrient targets may be the most reasonable approach in certain patient populations.

Early initiation of EN in critically ill children

Unlike adults, nutrition therapy in critically ill children must also account for differences in maintenance of nutritional status, safeguarding growth, and variances in metabolism as a function of age, size and state of illness (1,6). Adult and pediatric guidelines for nutrition therapy in critical illness recommend early initiation of enteral feeds to improve clinical outcomes (1,6,30,31). Enteral feeds promote and maintain GI mucosal integrity and function (31,32). Studies suggest benefits include fewer infections and better healing, with overall improved short-term and long-term clinical outcomes (33-36).

Pediatric data for the efficacy of EEN are largely derived from observational and retrospective studies, and do not have the same evidence from randomized controlled trials (RCTs) as adult studies (37-42). Globally, surveys of clinical practice demonstrate wide variation in approach to nutrition therapy in critically ill children (8,43-45). Smaller studies in this population have demonstrated beneficial changes in nutritional biomarkers, nitrogen balance, inflammatory cytokines and immune mechanisms from provision of EEN (38-42,46,47).

Defining EEN varies widely, from as early as six hours to as late as 72 hours following onset of critical illness and PICU admission (48-51). Studies of EEN in critically ill children vary and include the general PICU population as well as children with disease specific states (48-56). *Table 1* summarizes key studies of EEN in critically ill children.

EEN in general PICU population

In general studies of EEN in PICU populations have reported a trend of fewer infections, a reduction in measures of ICU dependency, less organ dysfunction and decreased mortality (28,48,49). In addition, there may be an association between an increased proportion of EEN relative to goal energy prescription and decreased mortality, supporting a dose-response relationship (2,28,31,56,57).

EEN in children with critical illness specific disease states

In specific disease states as with a general PICU population, studies suggest EEN to be safe and beneficial even with heterogeneity of diagnosis, presentation at time of illness and interventions in the PICU setting. Retrospectives studies where EEN was initiated in critically ill children with acute respiratory failure from acute lung injury and/or acute respiratory distress demonstrated decreased length of stay, lower severity of respiratory failure, reduced use of vasoactive agents and decreased mortality (3,50,58).

Evidence for EEN is lacking in children with septic shock or other sepsis-associated illness and organ dysfunction. In the absence of such evidence and without contraindications to provision of EN, there is a clinical preference to commence EEN within 48 hours of admission in children with septic shock or sepsis-associated organ dysfunction. Recent pediatric sepsis guidelines, support initiation of EEN when appropriate, based on the child's clinical status (7).

Initiation of EEN in children with traumatic brain injury (TBI) is associated with better clinical and functional outcomes (51,52). Recent studies favored EEN initiated in within 72 hours and demonstrated that delayed initiation of EN (greater than 48 hours) in children with TBI was an independent risk factor for worse functional status at PICU

Table 1 Key studies for enteral nutrition in critically ill children

Author, year	Population	Number of sites, sample size n	Study design	Definition of early EN and late EN	Outcome	Secondary outcomes/comments
Mikhailov, 2014, (28)	General PICU	12 sites, n=5,105	Retrospective	<48 h, >48 h	Mortality: aOR 0.51 (95% CI: 0.34–0.76)	Increasing proportion of EN relative to goal calories at 48 h associated with lower mortality (P<0.001)
Prakash, 2016, (48)	General PICU	1 site, n=120	RCT	<6–24 h, >24 h	Median duration of PICU stay: 168 h (early EN) vs. 143 h (late EN), P=0.41	Mortality: 30% (early EN) vs. 48% (late EN), P=0.07
Wong, 2017, (3)	Acute respiratory distress syndrome	1 site, n=107	Retrospective	<24 h, >24 h	Mortality: 26.2% (early EN) vs. 73.8% (late EN)	Adequate energy and protein delivery associated with better outcomes
Haney, 2018, (50)	Acute respiratory failure	1 site, n=106	Retrospective	<72 h, >72 h	Median PICU LOS: 10.7 days (early EN) vs. 12.9 days (late EN), P=0.001	Median hospital LOS: 22 days (early EN) vs. 28.7 days (late EN), P<0.001
Meinert, 2018, (51)	Traumatic brain injury	15 sites, n=90	Secondary analysis of RCT	<72 h, No EN/>72 h	Improved survival with early EN (P=0.01)	Improved GOS-E Peds scores at 6 months (P=0.03) and 12 months (P=0.04) with early EN
Ong, 2018, (53)	Extracorporeal membrane oxygenation	1 site, n=51	Retrospective	Not defined	Timing of EN initiation: 37 h (survivors) vs. 50 h (non-survivors), P=0.03	Greater EN energy adequacy was associated with better clinical outcomes
Greathouse, 2018, (54)	Extracorporeal membrane oxygenation	1 site, n=49	Retrospective	Not defined	Any EN by day 5 of ECMO and mortality: OR 0.37 (95% CI: 0.15–0.96)	Adequacy of EN intake by day 5 of ECMO was associated with survival
Kalra, 2018, (56)	Cyanotic heart disease undergoing surgery	1 site, n=30	RCT	4–6 h, >48 h	Duration of MV: 58 h (early EN) vs. 89 h (late EN), P<0.05	ICU LOS: 179 h (early EN) vs. 229 h (late EN), P<0.05
Balakrishnan, 2019, (52)	Traumatic brain injury	5 sites, n=416	Retrospective	<48 h, >48 h	Functional outcomes: change in POPC at ICU discharge 0 (early EN) vs. 2 (late EN), P<0.0001	ICU LOS: 1.2 days (early EN) vs. 4.9 days (late EN), P<0.0001; Hospital LOS: 3 days (early EN) vs. 11 days (late EN), P<0.0001; Mortality: 1% (early EN) vs. 12% (late EN), P<0.0001
Srinivasan, 2020, (49)	General PICU	35 sites, n=608	Secondary analysis of RCT	<48 h, >48 h	90-day mortality: aOR 0.43 (95% CI: 0.24–0.80)	ICU-free days: HR 1.26 (95% CI: 1.03–1.55); Hospital-free days: HR 1.62 (95% CI: 1.18–2.23); Ventilator-free days: HR 1.29 (95% CI: 1.07–1.57)

EN, enteral nutrition; PICU, pediatric intensive care unit; RCT, randomized controlled trial; aOR, adjusted odds ratio; 95% CI, 95% confidence intervals; HR, hazard ratio; LOS, length of stay; GOS-E Peds, Glasgow Outcome Scale score Extended for Pediatrics; POPC, pediatric overall performance category; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation.

discharge (51,52,59).

In studies of critically ill children supported with extracorporeal membrane oxygenation (ECMO) findings suggest improved survival with use of EEN (53,54). Despite its suggested benefit and evidence in other PICU populations, use of EEN in children who require ECMO is variable and without clear guidelines (53-55).

Evidence to support EEN initiation in children with congenital heart disease undergoing cardiac surgery with cardiopulmonary bypass is limited but growing. This group constitutes an important cohort of critically ill children (56,57). Studies suggest use of EN is associated with decreased duration of mechanical ventilation, PICU length of stay and overall improved nutritional outcomes (56,57,60).

Strategies for nutrition delivery in PICU populations

Strategies related to initiation of enteral feeding in critically ill children must consider the severity of illness, the child's nutritional status, and presence of clear criteria for monitoring feeding tolerance.

Use of a feeding protocol is a strategy that has demonstrated positive utility in EN provision for critically ill children (25-27), and current feeding guidelines recommended their use (1,6). Additionally, feeding protocol use is aligned with early feed initiation, minimization of avoidable interruptions and achievement of targeted fluid, energy and protein goals (25-27). Common avoidable interruptions for delivery of EN in critically ill children include real or perceived feeding intolerance, emesis, diarrhea, feeding device occlusion or malfunction, and unplanned procedures (23,58,59,61). Collaboration with a critical care trained registered dietitian and a focus on accurate assessment, determination of energy requirements and clear, timely and accurate prescription are additional strategies to successful EN initiation and advancement in critically ill children (1,6,29,30,32,62-66).

Nutrition considerations in pediatric surgical critical care

Preparation for surgery begins months in advance with a detailed history, nutrition assessment, and review of growth parameters to identify and correct derangements and optimize the child's health prior to surgical intervention (60,67,68). Malnutrition is an associated independent variable in surgical outcomes, putting these children at increased risk for adverse postsurgical reactions

(63,64,69). The risk increases for children who require PICU admission, up to 30% present with malnutrition (2,43,65,70). Multidisciplinary coordination with a systematic plan of care is necessary to ensure nutrition therapy continues throughout the perioperative period with close follow-up after discharge.

Integral to the success of the surgical encounter are the Enhanced Recovery after Surgery (ERAS) guidelines (63). First introduced in adults, these guidelines have gained momentum in pediatric surgery. ERAS is a multidisciplinary, multimodal approach to longitudinal pediatric surgical care, with overarching principles designed to limit the amount of time without nutritional intake, reduce perioperative stress and adjust treatment and therapies that will potentially contribute to long term caloric and protein deficits (63,66). ERAS guidelines are to limit variability across the numerous services who care for pediatric surgical patients during the hospitalization.

At the core of the ERAS guidelines are a focus on nutrition and metabolism, while limiting surgical stress and minimizing barriers to restoring normal digestion, absorption and utilization of energy (63). Studies evaluating use of ERAS are limited, yet findings report a reduction in hospital length of stay, decreased time to resume oral or enteral intake and reduced time to return of bowel function (66,71,72). Children are more sensitive to operative stress, to alterations in thermoregulation and glucose control. They have unique considerations that differ from adults, therefore use of the ERAS bundle guidelines may be a useful strategy to enhance postoperative care and improve surgical outcomes (73).

Preoperative considerations

A major aspect to consider in the immediate preoperative period are fasting times. Limited glycogen stores make children and infants more sensitive to fasting than adults (74,75). The purpose of enteral fasting is to achieve gastric emptying prior to induction of anesthesia to minimize the risk of aspiration and subsequent complications (76). Current perioperative guidelines no longer instruct families to fast children for prolonged periods prior to surgery (77). Instead, preoperative guidelines now recommend an allowance for clear liquids up to two hours prior to surgery, with breast milk and solids permissible until four and six hours, respectively (74,78). Despite this, fasting times remain widely variable with reported preoperative median times ranging from four to 10.5 hours (74,78-80). In the critically ill patient, pre-operative fasting guidelines require

individualized modification due to gastric dysmotility induced by the illness.

Aligned with the updated preoperative fasting guidelines, administration of a carbohydrate drink has been used in pediatric ERAS protocols. In adults, this approach has been found to maintain glycogen reserves, decrease insulin resistance and minimize protein breakdown (75,81). Data suggests carbohydrate drinks may improve comfort and reduce anxiety and further implies that these drinks do not increase the risk of aspiration, and may facilitate gastric emptying (81). There is growing evidence suggesting that hyperosmotic preoperative bowel prep is not necessary, it can potentially increase the risk of surgical site infection, wound dehiscence and cause bowel edema leading to gastric dysmotility and enteral feeding intolerance (75). Planned preoperative nutritional strategies may help maintain metabolic homeostasis and achieve a euvolemic state. Studies to better understand the impact of these interventions and their effect on surgical recovery in children are needed.

Operative considerations

In response to surgical stress the body releases catecholamines, cortisol, glucagon and cytokines (82). The surgical and anesthesia teams each have a role in limiting this stress. An anesthetic plan with limited use of opiates will reduce the incidence of postoperative intestinal ileus and promote early reintroduction of oral or enteral feeds. Regional anesthesia is used to decrease the amount and frequency of postoperative sedatives and anxiolytics and has been shown to reduce the inflammatory and metabolic responses while increasing gut motility (83). Intraoperatively, the goal of fluid administration is euvolemia. Fluid overload potentially has several adverse effects including increase in mechanical ventilation days, bowel edema leading to an ileus with intolerance of nutrients into the GI tract, and prolonged time to mobilization and rehabilitation. Lastly, avoidance of prolonged use of unnecessary enteral tubes and drains (nasogastric tube, or gastric decompression catheters) and promotes early mobilization and return of gastric motility.

Postoperative considerations

Following surgery, the major nutritional goal is the restoration of normal GI function allowing nutrient intake. If mechanically ventilated, clear metrics of criteria for extubation should be set. Once extubated, a postoperative nausea and vomiting regimen may be needed to support the re-introduction of oral or EN (84). Some pediatric postoperative feeding protocols recommend starting clear fluids within two hours following surgery in low-risk patients with the goal of starting EN within 24 hours. Progressing the patient to full oral or enteral intake will facilitate the provision of nutrient delivery to mitigate the catabolism that occurs with surgical stress and enhance wound healing.

Suboptimal nutritional intake during the postoperative period, put children at risk for nutritional deterioration causing slow restoration of endogenous protein and delaying recovery (85). Potential postoperative complications such as infection, inflammation, protein loss and prolonged catabolism may extend surgical stress if appropriate interventions such as nutrition therapy are not implemented (77). Feeding interruption with prolonged duration is a known causative factor of decreased EN intake in the postoperative patient (85,86). Real or perceived feeding intolerance, feeding device mechanical issues, and preprocedural fasting are commonly identified reasons for feeding cessation (85).

The multidisciplinary focus on nutrition and metabolism throughout the entire perioperative period may positively impact surgical outcomes.

EN for critically ill children on vasoactive medications

Provision of EN to critically ill children who require use of vasoactive medication infusions is variable (86,87). In addition to overall clinical status, factors to consider are vasoactive medication infusion dose, known or suspected GI dysfunction, and evidence of tissue hypoxia with subsequent multiple organ dysfunction syndrome. Gut dysfunction with disruption of the intestinal barrier can occur due to an alteration in splanchnic circulation owing to the severity of illness, the resuscitation efforts, and the current treatments and therapies the child requires (87-90). Data in both adult and pediatric critically ill patients demonstrate safe, well-tolerated administration of EN while receiving vasoactive medications (4,88,91,92). Recent guidelines for nutrition therapy in critically ill adults acknowledge that patients may benefit from EN while receiving vasoactive medications (30,31).

The use of vasoactive medications for hemodynamic support is often thought to be a contraindication to EN due to hypoperfusion to the gut that can result in mesenteric ischemia. Uncertainty in adequacy of splanchnic circulation

and GI perfusion often causes reluctance to feed a gut that may be compromised (86,93). Alterations in splanchnic perfusion can decrease normal function of the GI tract, causing an increase in oxygen demand, reduced absorption, and a decrease in peristalsis. This can increase the risk for bowel obstruction or perforation which is associated with increased mortality (87,91). In fact, EN may have a protective role in preserving gut integrity, by stimulating blood flow to the GI tract, enhancing gastric emptying and lowering the risk of bacterial translocation (94). Studies suggest use of the functioning GI tract in patients who require vasoactive medications is well tolerated and the benefits may outweigh the risks.

The American and European Guidelines for nutrition therapy in critically ill children recommend EN when safe and appropriate, including those children who require vasoactive medication support (1,6). Retrospective studies in children on vasoactive medication infusions of dobutamine, dopamine, epinephrine, milrinone, norepinephrine, phenylephrine and vasopressin who were enterally fed suggest the provision of EN is safe and use of vasoactive medications is not exclusively contraindicated and may overall be beneficial (84,92).

A systematic approach including use of a feeding protocol, close monitoring with clear definitions of feeding intolerance is a strategy to employ in critically ill children requiring vasoactive medications to optimize nutrient delivery, support GI function and decrease risks that may ensue due to the patient's changing clinical status. The lack of RCTs and limited evidence in this area of pediatric critical care should not be an absolute contraindication to enterally feeding patients who require vasoactive medication infusions, instead an understanding of the risks and benefits of EN in these patients is warranted.

Conclusions

Optimizing EN in the pediatric critically ill patient can be extremely challenging. The heterogeneity of children by disease entity and the response to stress, age, nutrition status and differences in body size require special attention to nutrition therapy. All children admitted to the PICU are at increased risk for suboptimal nutrition therapy owing to competing priorities of care. However, there is ever-increasing data favoring EN therapy. This combined with demonstrated improved clinical outcomes, heightened understanding of the benefits of nutrition therapy, particularly EN, and the availability of evidence-based guidelines to support provision of nutrition for critically ill children, enable pediatric critical care providers collectively to appropriately modify care based on each patient's demonstrated need. Further research is necessary to better understand how to improve nutrition therapy in various populations of critically ill children.

Acknowledgments

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 has undergone external peer review.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups. com/article/view/10.21037/pm-21-6/coif). The series "Nutrition in the Critically Ill Child" was commissioned by the editorial office without any funding or sponsorship. Dr. Srinivasan serves as an unpaid editorial board member of *Pediatric Medicine* from Jan 2021 to Dec 2022. 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.

References

1. Mehta NM, Skillman HE, Irving SY, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of critical care

medicine and american society for parenteral and enteral nutrition. Pediatr Crit Care Med 2017;18:675-715.

2. Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children--an international multicenter cohort study*. Crit Care Med 2012;40:2204-11.

3. Wong JJ, Han WM, Sultana R, et al. Nutrition delivery affects outcomes in pediatric acute respiratory distress syndrome. JPEN J Parenter Enteral Nutr 2017;41:1007-13.

4. Nutrition of Children Who Are Critically Ill. In: Kleinman RE, Greer FR, editors. Pediatric Nutrition. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2014:907-16.

5. Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the management of pediatric severe traumatic brain injury, Third Edition: Update of the brain trauma foundation guidelines. Pediatr Crit Care Med 2019;20:S1-82.

6. Tume LN, Valla FV, Joosten K, et al. Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) metabolism, endocrine and nutrition section position statement and clinical recommendations. Intensive Care Med 2020;46:411-25.

7. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med 2020;21:e52-106.

8. Campos-Miño S, López-Herce Cid J, Figueiredo Delgado A, et al. Nutrition Committee, Latin American Society of Pediatric Intensive Care (SLACIP). The Latin American and Spanish Survey on Nutrition in Pediatric Intensive Care (ELAN-CIP2). Pediatr Crit Care Med 2019;20:e23-9.

9. Valla FV, Baudin F, Gaillard Le Roux B, et al. Nutritional status deterioration occurs frequently during children's ICU stay. Pediatr Crit Care Med 2019;20:714-21.

10. Wilson B, Typpo K. Nutrition: A primary therapy in pediatric acute respiratory distress syndrome. Front Pediatr 2016;4:108.

11. Jones MO, Pierro A, Hammond P, et al. The metabolic response to operative stress in infants. J Pediatr Surg 1993;28:1258-62; discussion 1262-3.

12. Mehta NM, Bechard LJ, Leavitt K, et al. Cumulative energy imbalance in the pediatric intensive care unit: role of targeted indirect calorimetry. JPEN J Parenter Enteral Nutr 2009;33:336-44.

13. Mehta NM, Costello JM, Bechard LJ, et al. Resting energy expenditure after Fontan surgery in children with single-ventricle heart defects. JPEN J Parenter Enteral Nutr 2012;36:685-92.

14. Mehta NM, Smallwood CD, Graham RJ. Current applications of metabolic monitoring in the pediatric intensive care unit. Nutr Clin Pract 2014;29:338-47.

15. Kyle UG, Arriaza A, Esposito M, et al. Is indirect calorimetry a necessity or a luxury in the pediatric intensive care unit? JPEN J Parenter Enteral Nutr 2012;36:177-82.

16. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39:5-41.

17. Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation. World Health Organ Tech Rep Ser 1985;724:1-206.

18. Jotterand Chaparro C, Taffé P, Moullet C, et al. Performance of Predictive Equations Specifically Developed to Estimate Resting Energy Expenditure in Ventilated Critically Ill Children. J Pediatr 2017;184:220-226.e5.

19. Elwyn DH, Kinney JM, Askanazi J. Energy expenditure in surgical patients. Surg Clin North Am 1981;61:545-56.

20. Fullerton BS, Sparks EA, Khan FA, et al. Whole body protein turnover and net protein balance after pediatric thoracic surgery: A noninvasive single-dose. JPEN J Parenter Enteral Nutr 2018;42:361-70.

21. Sundström Rehal M, Liebau F, Tjäder I, et al. A supplemental intravenous amino acid infusion sustains a positive protein balance for 24 hours in critically ill patients. Crit Care 2017;21:298.

22. Mehta NM, Bechard LJ, Zurakowski D, et al. Adequate enteral protein intake is inversely associated with 60-d mortality in critically ill children: A multicenter, prospective, cohort study. Am J Clin Nutr 2015;102:199-206.

23. Moreno YM, Hauschild DB, Barbosa E, et al. Problems with optimal energy and protein delivery in the pediatric intensive care unit. Nutr Clin Pract 2016;31:673-80.

24. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506-17.

25. Hamilton S, McAleer DM, Ariagno K, et al. A stepwise enteral nutrition algorithm for critically ill children helps achieve nutrient delivery goals*. Pediatr Crit Care Med 2014;15:583-9.

26. Brown AM, Forbes ML, Vitale VS, et al. Effects of a Gastric Feeding Protocol on Efficiency of Enteral Nutrition in Critically Ill Infants and Children. ICAN: Infant, Child, & Adolescent Nutrition 2012;4:175-80.

27. Petrillo-Albarano T, Pettignano R, Asfaw M, et al. Use of a feeding protocol to improve nutritional support through early, aggressive, enteral nutrition in the pediatric intensive

care unit. Pediatr Crit Care Med 2006;7:340-4.

28. Mikhailov TA, Kuhn EM, Manzi J, et al. Early enteral nutrition Is associated with lower mortality in critically ill children. JPEN J Parenter Enteral Nutr 2014;38:459-66.

29. Jimenez L, Mehta NM, Duggan CP. Timing of the initiation of parenteral nutrition in critically ill children. Curr Opin Clin Nutr Metab Care 2017;20:227-31.

30. Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). Crit Care Med 2016;44:390-438.

31. Dhaliwal R, Cahill N, Lemieux M, et al. The canadian critical care nutrition guidelines in 2013: An update on current recommendations and implementation strategies. Nutr Clin Pract 2014;29:29-43.

32. Nguyen NQ, Besanko LK, Burgstad C, et al. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. Crit Care Med 2012;40:50-4.

33. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009;37:666-88. Erratum in: Crit Care Med. 2009 Apr;37(4):1536.

34. Xi F, Li N, Geng Y, et al. Effects of delayed enteral nutrition on inflammatory responses and immune function competence in critically ill patients with prolonged fasting. Hepatogastroenterology 2014;61:606-12.

35. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. Nutr Clin Pract 2009;24:305-15.

36. Briassoulis G, Zavras N, Hatzis T. Malnutrition, nutritional indices, and early enteral feeding in critically ill children. Nutrition 2001;17:548-57.

37. Joffe A, Anton N, Lequier L, et al. Nutritional support for critically ill children. Cochrane Database Syst Rev 2016;27:CD005144.

38. Silva FM, Bermudes AC, Maneschy IR, et al. Impact of early enteral nutrition therapy on morbimortality reduction in a pediatric intensive care unit: a systematic review. Rev Assoc Med Bras (1992) 2013;59:563-70.

39. Zamberlan P, Delgado AF, Leone C, et al. Nutrition therapy in a pediatric intensive care unit: Indications, monitoring, and complications. JPEN J Parenter Enteral Nutr 2011;35:523-9.

40. Gottschlich MM, Jenkins ME, Mayes T, et al. The 2002

Clinical Research Award. An evaluation of the safety of early vs delayed enteral support and effects on clinical, nutritional, and endocrine outcomes after severe burns. J Burn Care Rehabil 2002;23:401-15.

41. Khorasani EN, Mansouri F. Effect of early enteral nutrition on morbidity and mortality in children with burns. Burns 2010;36:1067-71.

42. Briassoulis G, Filippou O, Hatzi E, et al. Early enteral administration of immunonutrition in critically ill children: Results of a blinded randomized controlled clinical trial. Nutrition 2005;21:799-807.

43. Kerklaan D, Fivez T, Mehta NM, et al. Worldwide survey of nutritional practices in PICUs. Pediatr Crit Care Med 2016;17:10-8.

44. Wong JJ, Ong C, Han WM, et al. Survey of contemporary feeding practices in critically ill children in the Asia-Pacific and the Middle East. Asia Pac J Clin Nutr 2016;25:118-25.

45. Tume LN, Balmaks R, da Cruz E, et al. Enteral feeding practices in infants with congenital heart disease across European PICUs: A European Society of Pediatric and Neonatal Intensive Care Survey. Pediatr Crit Care Med 2018;19:137-44.

46. van Waardenburg DA, de Betue CT, Goudoever JB, et al. Critically ill infants benefit from early administration of protein and energy-enriched formula: A randomized controlled trial. Clin Nutr 2009;28:249-55.

47. Mehta NM, McAleer D, Hamilton S, et al. Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. JPEN J Parenter Enteral Nutr 2010;34:38-45.

48. Prakash V, Parameswaran N, Biswal N. Early versus late enteral feeding in critically ill children: A randomized controlled trial. Intensive Care Med 2016;42:481-2.

49. Srinivasan V, Hasbani NR, Mehta NM, et al. Early enteraln Is associated with improved clinical outcomes in critically ill children: A secondary analysis of nutrition support in the Heart and Lung Failure-Pediatric Insulin Titration trial. Pediatr Crit Care Med 2020;21:213-21.

50. Haney A, Burritt E, Babbitt CJ. The impact of early enteral nutrition on pediatric acute respiratory failure. Clin Nutr ESPEN 2018;26:42-6.

51. Meinert E, Bell MJ, Buttram S, et al. Initiating nutritional support before 72 hours is associated with favorable outcome after severe traumatic brain injury in children: A secondary analysis of a randomized, controlled trial of therapeutic hypothermia. Pediatr Crit Care Med 2018;19:345-52.

52. Balakrishnan B, Flynn-O'Brien KT, Simpson PM, et

al. Enteral nutrition initiation in children admitted to pediatric intensive care units after traumatic brain injury. Neurocrit Care 2019;30:193-200.

53. Ong C, Mok YH, Tan ZH, et al. Nutritional practices and adequacy in children supported on extracorporeal membrane oxygenation. Clin Nutr ESPEN 2018;26:21-6.

54. Greathouse KC, Sakellaris KT, Tumin D, et al. Impact of early initiation of enteral nutrition on survival during pediatric extracorporeal membrane oxygenation. JPEN J Parenter Enteral Nutr 2018;42:205-11.

55. Farr BJ, Rice-Townsend SE, Mehta NM. Nutrition support during pediatric extracorporeal membrane oxygenation. Nutr Clin Pract 2018;33:747-53.

56. Kalra R, Vohra R, Negi M, et al. Feasibility of initiating early enteral nutrition after congenital heart surgery in neonates and infants. Clin Nutr ESPEN 2018;25:100-2.

57. Zhang J, Cui YQ, Luo Y, et al. Assessment of Energy and Protein Requirements in Relation to Nitrogen Kinetics, Nutrition, and Clinical Outcomes in Infants Receiving Early Enteral Nutrition Following Cardiopulmonary Bypass. JPEN J Parenter Enteral Nutr 2021;45:553-66.

58. Wong JJ-M, Ong C, Han WM, et al. Protocol driven enteral nutrition in critically ill children: A systematic review. JPEN J Parenter Enteral Nutr 2014;38:29-39.

59. Lee H, Koh SO, Kim H, et al. Avoidable causes of delayed enteral nutrition in critically ill children. J Korean Med Sci 2013;28:1055-59.

60. Canada NL, Mullins L, Pearo B, et al. Optimizing perioperative nutrition in pediatric populations. Nutr Clin Pract 2016;31:49-58.

61. Weckwerth JA. Monitoring enteral nutrition support tolerance in infants and children. Nutr Clin Pract 2004;19:496-503.

62. Wakeham M, Christensen M, Manzi J, et al. Registered dietitians making a difference: Early medical record documentation of estimated energy requirement in critically ill children is associated with higher daily energy intake and with use of the enteral route. J Acad Nutr Diet 2013;113:1311-6.

63. Wischmeyer PE, Carli F, Evans DC, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway. Anesth Analg 2018;126:1883-95.

64. Ladd MR, Garcia AV, Leeds IL, et al. Malnutrition increases the risk of 30-day complications after surgery in pediatric patients with Crohn disease. J Pediatr Surg 2018;53:2336-45.

65. Pawellek I, Dokoupil K, Koletzko B. Prevalence of malnutrition in pediatric hospital patients. Clin Nutr 2008;27:72-6.

66. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: A Review. JAMA Surg 2017;152:292-8.

67. Farooqi N, Carlsson M, Håglin L, et al. Energy expenditure in women and men with COPD. Clin Nutr ESPEN 2018;28:171-8.

68. Alshehri A, Afshar K, Bedford J, et al. The relationship between preoperative nutritional state and adverse outcome following abdominal and thoracic surgery in children: Results from the NSQIP database. J Pediatr Surg 2018;53:1046-51.

69. Williams DGA, Molinger J, Wischmeyer PE. The malnourished surgery patient: a silent epidemic in perioperative outcomes? Curr Opin Anaesthesiol 2019;32:405-11.

70. Hulst J, Joosten K, Zimmermann L, et al. Malnutrition in critically ill children: From admission to 6 months after discharge. Clin Nutr 2004;23:223-32.

71. Pearson KL, Hall NJ. What is the role of enhanced recovery after surgery in children? A scoping review. Pediatr Surg Int 2017;33:43-51.

72. Shinnick JK, Short HL, Heiss KF, et al. Enhancing recovery in pediatric surgery: A review of the literature. J Surg Res 2016;202:165-76.

73. Brindle ME, Heiss K, Scott MJ, et al. Embracing change: the era for pediatric ERAS is here. Pediatr Surg Int 2019;35:631-4.

74. Andersson H, Schmitz A, Frykholm P. Preoperative fasting guidelines in pediatric anesthesia: Are we ready for a change? Curr Opin Anaesthesiol 2018;31:342-8.

75. Rove KO, Edney JC, Brockel MA. Enhanced recovery after surgery in children: Promising, evidence-based multidisciplinary care. Paediatr Anaesth 2018;28:482-92.

76. Fawcett WJ, Thomas M. Pre-operative fasting in adults and children: Clinical practice and guidelines. Anaesthesia 2019;74:83-8.

77. Weimann A, Braga M, Carli F, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr 2017;36:623-50.

78. Dolgun E, Yavuz M, Eroğlu B, et al. Investigation of preoperative fasting times in children. J Perianesth Nurs 2017;32:121-4.

79. Arun BG, Korula G. Preoperative fasting in children: An audit and its implications in a tertiary care hospital. J Anaesthesiol Clin Pharmacol 2013;29:88-91.

80. Schmitz A, Kellenberger CJ, Neuhaus D, et al. Fasting times and gastric contents volume in children undergoing

deep propofol sedation--an assessment using magnetic resonance imaging. Paediatr Anaesth 2011;21:685-90.

81. Tudor-Drobjewski BA, Marhofer P, Kimberger O, et al. Randomised controlled trial comparing preoperative carbohydrate loading with standard fasting in paediatric anaesthesia. Br J Anaesth 2018;121:656-61.

82. Finnerty CC, Mabvuure NT, Ali A, et al. The surgically induced stress response. JPEN J Parenter Enteral Nutr 2013;37:21S-9S.

83. Chalmers DJ, Bielsky A, Wild TT, et al. Continuous local anesthetic infusion for children with spina bifida undergoing major reconstruction of the lower urinary tract. J Pediatr Urol 2015;11:72.e1-5.

84. King W, Petrillo T, Pettignano R. Enteral nutrition and cardiovascular medications in the pediatric intensive care unit. JPEN J Parenter Enteral Nutr 2004;28:334-8.

85. Velazco CS, Zurakowski D, Fullerton BS, et al. Nutrient delivery in mechanically ventilated surgical patients in the pediatric critical care unit. J Pediatr Surg 2017;52:145-8.

86. Hulst JM, Joosten KF, Tibboel D, et al. Causes and consequences of inadequate substrate supply to pediatric ICU patients. Curr Opin Clin Nutr Metab Care 2006;9:297-303.

87. Yang S, Wu X, Yu W, et al. Early enteral nutrition in critically ill patients with hemodynamic instability: An evidence-based review and practical advice. Nutr Clin Pract 2014;29:90-6.

88. Mancl EE, Muzevich KM. Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. JPEN J Parenter Enteral Nutr 2013;37:641-51.

89. Mehta NM, Jaksic T. The Critically Ill Child. In: Duggan CP, Walker W. editors. Nutrition in Pediatrics. 4th ed. Hamilton, Ontario: B.C. Decker, Inc., 2008:663-73.

90. Puleo F, Arvanitakis M, Van Gossum A, et al. Gut failure in the ICU. Semin Respir Crit Care Med 2011;32:626-38.

91. Merchan C, Altshuler D, Aberle C, et al. Tolerability of enteral nutrition in mechanically ventilated patients with septic shock who require vasopressors. J Intensive Care Med 2017;32:540-6.

92. Panchal AK, Manzi J, Connolly S, et al. Safety of enteral feedings in critically ill children receiving vasoactive agents. JPEN J Parenter Enteral Nutr 2016;40:236-41.

93. Wischmeyer PE. Enteral Nutrition Can Be Given to Patients on Vasopressors. Crit Care Med 2020;48:122-5.

94. Chen W, Codreanu I, Yang J, et al. Tube feeding increases the gastric-emptying rate determined by gastroesophageal scintigraphy. Clin Nucl Med 2013;38:962-5.