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Controversies in nutritional support for critically ill children

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ABSTRACT

Nutritional support for critically ill infants and children is of paramount importance and can greatly affect the outcome of these patients. The energy requirement of children is unique to their size, gestational age, and physiologic stress, and the treatment algorithms developed in adult intensive care units cannot easily be applied to pediatric patients. This article reviews some of the ongoing controversial topics of fluid, electrolyte, and nutritional support for critically ill pediatric patients focusing on glycemic control and dysnatremia. The use of enteral and parenteral nutrition as well as parenteral nutritional-associated cholestasis will also be discussed.

Introduction

Nutritional support for critically ill infants and children is an important element of their care. Children have specific requirements for proper growth and neurodevelopment in addition to their maintenance fluid and energy needs. The stress of trauma and surgery can increase these nutritional needs, while adding to their complexity, especially when deciding on the optimal route of administration. Balancing the needs of the patient, with their physiologic and clinical status, is the basis for much controversy, as we attempt to discover the optimal nutritional and fluid administration in these challenging patients.

Energy requirements and physiologic stresses

Malnutrition has been associated with increased morbidity and mortality in critically ill children since 1985[1] and has more recently been associated with an increase in risk-adjusted mortality as well as PICU length of stay.[2] The percentage of patients admitted to the PICU with acute malnutrition, defined as 2 SD below the average weight-for-age, has been reported from 19–32%.[3,4] Malnutrition has also been associated with increased morbidity and mortality in critically ill children.[1] Critical illness also places variable energy demands on patients and attempts have been made to predict those energy needs with standard equations; however, rather inconsistently.[5,6] Providing the proper amount of nutritional support to critically ill children is of paramount importance to their survival and outcomes.

Calculating the correct caloric and energy needs in children can be challenging, and the dangers of inappropriate nutrition can be devastating (i.e., bone demineralization, rickets, cholestatic jaundice, poor wound healing, impaired lung function, and slow growth). Open wounds, such as the open abdomen and burn patients, have additional protein losses. Caloric needs are also altered by several factors such as surgical procedures, stress, hypothermia, infection, and trauma.[7,8] Similarly, intensive care interventions can also decrease energy needs, such as mechanical ventilation, paralysis, or sedation, and a temperature-controlled environment.[6] The Harris–Benedict equation has often been used to calculate the energy needs of children; however, these formulas were based on adult populations and are not easily or correctly applied to the pediatric population. Indirect calorimetry was first performed in children in the beginning of the 20th century by Fritz Talbot and still serves as an appropriate standard for calculating basal metabolic rates.[6] Several studies of critically ill children have shown a significant difference in measured vs. predicted values of energy needs and expenditures when standard equations were utilized.[9–11]

Mehta et al.,[7,12,13] as well as the ASPEN guidelines, recommend indirect calorimetry to estimate the energy needs of the patient, as well as obtaining their baseline nutritional status upon admission to the PICU. This may also help identify patients that may be at risk for refeeding syndrome. Despite these recommendations, few critical care units routinely perform these measurements and its impact on clinical outcomes still needs to be demonstrated.[7] Consequently, it remains an area of controversy regarding initiation and maintenance of nutrition in the ICU.

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Fluid management in critically ill pediatric patients—Hypotonic vs. isotonic fluids

Critically ill children are often in need of intravenous fluid resuscitation and vasopressor support. Pediatricians and critically ill trained physicians often differ from surgeons in their fluid administration tactics. Hyponatremia, defined as a sodium level less than 135 mEq/L, is relatively common, especially in critically ill patients, with an incidence reported from 19–50% of hospitalized patients.[14–17] Recent case reports of catastrophic results of hyponatremia causing neurologic morbidity as well as death[18–23] have increased awareness of this problem, and debate continues between the type of fluid to administer to patients, both in the critical care units as well as on the wards.

There are several factors thought to contribute to hyponatremia in the post-operative setting. Volume depletion, pain, nausea, and stress are thought to increase the non-osmotic stimulus for ADH release.[24] Isotonic fluids can assist in mitigating some of these factors, while helping to maintain normonatremia. Opponents argue that istotonic fluids may cause hypernatremia, as well as fluid overload and hypertension. While these side effects are seen in older adult patients whose cardiac and renal function may be impaired, they are rare in the pediatric population.

Several studies have demonstrated the relationship between the administration of hypotonic fluids and hyponatremia in a variety of patient populations.[14,25–27] Choong et al.[25] randomized 258 children after elective surgery to receive either hypotonic or isotonic maintenance IV fluids and reported a significant risk of hyponatremia in the hypotonic group (40.8% vs. 22.7%, RR = 1.82, $p = 0.004$). Similarly, Rey et al.[26] randomly assigned children admitted to 3 PICUs to receive hypotonic vs. isotonic maintenance IV fluids and reported a 5.8-fold increased risk of hyponatremia in the hypotonic group. Caradang et al. retrospectively examined a cohort of normonatremic hospitalized children who had received either hypotonic or isotonic fluids. They found that hyponatremia was more likely to occur with administration of hypotonic fluids, but also found that hyponatremia developed in nearly 28% of patients who received isotonic fluids.[28] Surgical admissions and certain admitting diagnoses also appear to have a strong impact on developing hyponatremia. A recent meta-analysis of 10 randomized controlled trials demonstrated a significantly higher risk of both hyponatremia ($Na < 136$) and severe hyponatremia ($Na < 130$), when hypotonic fluids were administered.[29] While fluid volume and clinical volume status at admission may contribute to dysnatremia, there is increasing evidence supporting the use of isotonic fluids for post-surgical and trauma patients.

Stress hyperglycemia and the use of insulin

Stress hyperglycemia is a relatively common occurrence in critically ill children. Through multiple mechanisms at the cellular level, the overall effect is increased blood glucose concentrations to provide an easily available fuel source for vital organs. While especially useful in the acute phase of illness when metabolic demand is higher, persistence of stress hyperglycemia may eventually become harmful.[30]

Several studies have demonstrated an association with hyperglycemia and mortality in critically ill children.[31–42] This association has been demonstrated in several different patient populations within the PICU, namely patients with severe burns, trauma including traumatic brain injury, septic shock, and post-cardiac surgery. While these studies have demonstrated strong associations between hyperglycemia and critical care outcomes, no direct causal relationship has been elucidated. Rather, hyperglycemia induced by physiologic stress appears to be a marker of severe illness, which can ultimately lead to increased infectious complications and even mortality.

In 2001, the first randomized controlled trial in critically ill adult surgical patients demonstrated a significant decrease in mortality in patients receiving insulin therapy to achieve a glucose levels between 80 and 110 mg/dL.[43] Despite some controversy in duplicating these results in different population groups, as well as the significant risk of iatrogenic hypoglycemia, there was intense interest in expanding these findings into the care of critically ill children.

Vlasselaers et al. attempted to examine this relationship in a largely post-cardiac surgical cohort in a randomized study evaluating intensive insulin therapy vs. conventional therapy. They demonstrated decreased mortality and infections with tight glycemic control, but the rate of hypoglycemia was 25% in the intensive insulin group compared to 1% in the conventional group.[44] Attempts to replicate these findings have been less successful.

Macrae et al.[45] recently published results of a multicenter randomized controlled trial examining tight glycemic control with insulin therapy in pediatric patients admitted to the PICU. Thirteen sites participated, with 1369 children randomized to receive either tight glycemic control or conventional management. No difference was found in the primary outcome between the 2 groups: ventilator-free days alive within 30 days of trial entry. The groups were also similar in their risk of infection, length of stay, and mortality. However, a lower proportion of renal replacement therapy was noted in the tight glycemic control arm, as well as a higher proportion of hypoglycemia. In non-cardiac surgical patients, there was a decrease in average costs at 12 months in the tight glycemic control arm. While there was no apparent clinical outcome benefit attributable to the tight glycemic control arm, there still remained a significant risk of iatrogenic hypoglycemia.

The balance between preventing the harmful effects of hyperglycemia to the physiologically stressed infant or child with the potential risk of iatrogenic hypoglycemia has decreased enthusiasm for tight glycemic control with intensive insulin therapy. Currently, there are no consensus recommendations, and the practitioner is left to determine the best course of action with regard to insulin therapy in response to stress hyperglycemia. Additional study is needed to identify an improved method to monitor and reduce the harm of hyperglycemia while decreasing the risk of inducing potentially devastating hypoglycemia.

Enteral nutrition in critically ill children

Optimal nutritional support is a fundamental goal in the care of critically ill children; however, the optimal timing and best way to achieve this goal remains relatively controversial. Parenteral nutrition has obvious benefits in critically ill children, as it does not need to be interrupted for procedures or rely on gut motility. However, it has significant risks related to central venous access, infection rates, as well as interference with electrolyte and glucose homeostasis. In adult critically ill patients, enteral nutrition has been associated with decreased infectious complications and length of stay when compared with parenteral nutrition.[46–48] There may also be physiologic benefits with decreased expression of cytokines, such as IL-6, in patients that receive enteral nutrition.[49] Consequently, enteral nutrition has been promoted by consensus-based guidelines in both adult and pediatric intensive care units.[50] But when should enteral nutrition be initiated and is there a preferred method of delivery in critically ill children?

When possible, the enteral route has become the preferred route for administration of nutrition in critically ill children. There

are several benefits that may be gained from enteral nutrition. Animal studies have demonstrated the maintenance of antioxidant levels as a result of enteral feeds after injury.[51,52] Early enteral nutrition has also been shown to improve protein synthesis necessary for wound healing.[53–55] Maintenance of gut villi and prevention of gut atrophy to help maintain the intestinal barrier function has also been attributed to enteral feeding.[56,57] There may also be some protection to the liver and kidneys after hemorrhage or rhabdomyolysis that may result from enteral feedings.[58,59] In addition to the above, enteral nutrition is more physiologic than parenteral nutrition and is also much more cost effective.[50] There may also be the added benefit of fewer infectious or other complications related to central lines that are necessary for parenteral nutrition.

Adult studies have demonstrated that the early initiation of enteral nutrition within 24–48 h of ICU admission can improve outcomes and decrease mortality.[60,61] This was extrapolated to the pediatric burn patients and demonstrated improved caloric and protein intake, as well as decreased mortality.[62,63] When early enteral nutrition was given to a more expanded pediatric critical care population, again decreased mortality was observed.[2,64] Mehta et al.[64] reported a decreased 60-day mortality rate when at least two-thirds of the estimated calorie and energy needs were administered via an enteral route within day 8 of PICU admission. In a recent study, Mikhailov et al.[2] described a decreased mortality in patients given early enteral nutrition, but only one-quarter of the entire cohort of patients achieved that goal during the study period. Kyle et al.[65] recently reported that only 75% of estimated energy and 40% of protein requirements were being provided within the first 8 days of PICU stays in a major tertiary multidisciplinary PICU. Similarly, Martinez et al.[66] examined an international cohort of 31 PICUs and determined that 33% of patients received optimal enteral nutrition (defined as $\geq$66.6% of full caloric needs) by day 7 in the PICU, and only 13% by day 3. While the benefit of enteral nutrition has been demonstrated, there still remain significant obstacles to its implementation.

Some argue that the type of feeding tube influences the implementation of enteral feedings. When compared to gastric feeding tubes, post-pyloric feeding tubes have been associated with deliverance of a higher proportion of the overall daily nutrient goal, but have not prevented feeding intolerance or aspiration events.[67] In addition, the use of post-pyloric feeding tubes has not been shown to influence the adequacy of enteral nutrition intake.[64] Of note, gastroesophageal reflux is still present with post-pyloric feedings, and increases in response to feeding despite the post-pyloric nutritional stimulus.[68] Unlike fluoroscopically guided nasojejunal feeding tube placement, orogastric or nasogastric feeding tubes typically do not require advanced training or specialty equipment. Consequently, gastric feeding should be implemented, unless there is a contraindication to its use (i.e., gastric surgery or gastric outlet obstruction) or evidence of intolerance. Post-pyloric feedings can be initiated for patients with signs of feeding intolerance. Regardless of position (gastric or post-pyloric), tube placement needs to be frequently monitored radiographically to help prevent complications that may arise from tube dislodgement.

Feeding intolerance is frequently cited as a reason for stopping enteral feeds and is largely a clinical diagnosis based on abdominal distension, diarrhea, or constipation and gastric residual volumes. Despite the lack of evidence for gastric residual volumes as a marker for feeding intolerance, this clinical measurement continues to be widely used as a proxy for enteral nutrition tolerance.[50] Other common factors that may impede achievement of optimal enteral nutrition include pre-procedural fasting (which often occurs for periods of time longer than recommended) and feeding tube issues, especially clogging.[50]

Some patients do not qualify for enteral nutrition, including immediate post-operative patients or patients with post-operative ileus, active upper GI bleeding, patients at risk of intestinal ischemia, or patients with intestinal obstructions. Patients with increasing vasopressor support with ongoing hemodynamic instability and oncology patients who have undergone bone marrow or stem cell transplants may also be poor candidates or ineligible for enteral nutrition.[50] These patients should receive parenteral nutrition, especially if the anticipated period of fasting is longer than 5 days, or if the patient has pre-existing malnutrition.

Initiation of enteral feeds should be administered via a consensus algorithm for ease of administration, uniformity of practice within a group, as well as for educational purposes of the residents and nurses that are part of the treatment team. Mehta[50] has developed an algorithm that outlines feeding regimen; type of feeding; and recommendations for challenges associated with constipation, diarrhea, or feeding intolerance. While each institution may elect to utilize different criteria for advancement of feeds or feeding intolerance, implementing a nutrition bundle can assist in the measurement of adherence as well as patient tolerance of enteral feeds to assist in better tracking patient outcomes in response to this therapy.

Parenteral nutrition-associated cholestasis

Parenteral nutrition is a lifesaving modality for many patients with the inability to tolerate enteral feeds. However, the risks associated with parenteral nutrition can be quite severe. The complications that can occur related to obtaining and maintaining central venous access can be life threatening, and are beyond the scope of this current discussion. Hyperglycemia as well as other electrolyte disturbances can be induced by parenteral nutrition, and close monitoring of these parameters is essential after initiating as well as during maintenance periods. Parenteral nutrition-associated cholestasis (PNAC) is one of the most challenging problems associated with prolonged parenteral nutrition, especially when it progresses to liver disease. This complication is multifactorial, and there are both modifiable and non-modifiable risk factors. Prematurity, birth weight, and underlying surgical conditions that prevent achieving adequate caloric intake via the enteral route are generally considered non-modifiable risk factors for the development of PNAC; however, there is some disagreement whether prematurity is truly an independent risk factor.[69–74] Necrotizing enterocolitis (NEC), sepsis, and duration of parenteral nutrition have all been associated with PNAC.[75] Of these modifiable risk factors, the prevention of NEC and sepsis continues to be an ongoing problem. Research efforts have also been concentrated on the potential use of alternative sources for lipids within parenteral nutrition. Recent studies have shown that PNAC may be prevented or treated with restriction of soy-based lipid formulations or replacement by the fish oil lipid emulsion, Omegavan, which is currently only available by research study authorization in the United States.

Lipids are an important part of parenteral nutrition and provide both caloric content as well as essential fatty acids. Phytosterols are naturally occurring steroid alcohols that are derived from the cell membranes of plants and are used as part of intravenous lipid components of parenteral nutrition.[75] Soybean-based lipid emulsions, the most common source, are rich in omega-6 fatty acids and have been implicated in hepatocyte damage through a pro-inflammatory mechanism.[76] Omega-6 fatty acids also promote thromboxanes, which are mediators of platelet aggregation and are associated with immunosuppression.[75] Omegaven® 10% is a fish oil emulsion that contains no phytosterols and has an omega-6-to-omega-3 ratio of 1:7. This product has been used to treat

parenteral nutrition-associated liver disease[77]; although currently not available commercially in the United States, it can be utilized as part of some research protocols. There is some evidence that limiting the amount of soybean-based lipid emulsions to 1 g/kg 2–3 times per week may reduce total bilirubin and subsequently reduce PNAC without producing essential fatty acid deficiency.[78] Some clinicians employ a restrictive strategy for patients receiving parenteral nutrition with elevated direct bilirubin, giving only 1 g/kg/d of soybean-based lipid emulsion. However, long term neurodevelopmental outcomes are still unclear and remain an area of ongoing research.

Conclusion

Malnutrition is a pervasive problem in critically ill children and requires a team approach to adequately monitor and treat with proper nutritional support. Hyponatremia and hyperglycemia are clinical signs of severity of illness and require recognition in order to adequately diagnose and prevent complications that may be associated with these disturbances. Both enteral and parenteral nutrition have intricate roles in the care of critically ill children. Despite controversy in the management of intravenous fluids, stress hyperglycemia, early enteral nutrition and surrounding the type and frequency of lipid emulsions utilized in parenteral nutrition, there are still many areas of ongoing research that will help improve the care of these patients.

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