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A.S.P.E.N. Clinical Guidelines: Nutrition Support of the Critically Ill Child

Nilesh M. Mehta, MD, DCH1; Charlene Compher, PhD, RD, CNSD2; and A.S.P.E.N. Board of Directors

Background

The prevalence of malnutrition among critically ill patients, especially those with a protracted clinical course, has remained largely unchanged over the last 2 decades. The profound and stereotypic metabolic response to critical illness and failure to provide optimal nutrition support therapy during the intensive care unit (ICU) stay are the principal factors contributing to malnutrition in this cohort. The metabolic response to stress, injury, surgery, or inflammation cannot be accurately predicted and the metabolic alterations may change during the course of illness. Although nutrition support therapy cannot reverse or prevent this response, failure to provide optimal nutrients during this stage will result in exaggeration of existing nutrient deficiencies and in malnutrition, which may affect clinical outcomes. Both underfeeding and overfeeding are prevalent in the pediatric intensive care unit (PICU) and may result in large energy imbalances. Malnutrition in hospitalized children is associated with increased physiological instability and increased resource utilization, with the potential to influence outcome from critical illness. The goal of nutrition support therapy in this setting is to augment the short-term benefits of the pediatric stress response while minimizing the long-term harmful consequences. Accurate assessment of energy requirements and provision of optimal nutrition support therapy through the appropriate route is an important goal of pediatric critical care. Ultimately, an individualized determination of nutrient requirements must be made to provide appropriate amounts of both macro- and micronutrients for each patient at various times during the illness course. The delivery of these nutrients requires careful selection of the appropriate mode of feeding and monitoring the success of the feeding strategy. The use of specific nutrients, which possess a drug-like effect on the immune or inflammatory state during critical illness, continues to be an exciting area of investigation. The lack of systematic research and clinical trials on various aspects of nutrition support in the PICU is striking and makes it challenging to compile evidence based practice guidelines. There is an urgent need to conduct well-designed, multicenter trials in this area of clinical practice. The extrapolation of data from adult critical care literature is not desirable and many of the interventions proposed in adults will have to undergo systematic examination and careful study in critically ill children prior to their application in this population.

In the following sections, we will discuss some of the key aspects of nutrition support therapy in the PICU; examine the literature and provide best practice guidelines based on evidence from PICU patients, where available. While some PICU populations include neonates, A.S.P.E.N. Clinical Guidelines for neonates will be published as a separate series.

Methodology

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization comprised of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of nutrition support therapy. A.S.P.E.N. vigorously works to support quality patient care, education, and research in the fields of nutrition and metabolic support in all healthcare settings. These clinical guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing clinical guidelines since 1986. Starting in 2007, A.S.P.E.N. has been revising these clinical guidelines on
An ongoing basis, reviewing about 20% of the chapters each year in order to keep them as current as possible.

These clinical guidelines were created in accordance with Institute of Medicine recommendations as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.” These clinical guidelines are for use by healthcare professionals who provide nutrition support services and offer clinical advice for managing adult and pediatric (including adolescent) patients in inpatient and outpatient (ambulatory, home, and specialized care) settings. The utility of the clinical guidelines is attested to by the frequent citation of this document in peer-reviewed publications, and their frequent use by A.S.P.E.N. members and other healthcare professionals in clinical practice, academia, research, and industry. They guide professional clinical activities, they are helpful as educational tools, and they influence institutional practices and resource allocation.

These clinical guidelines are formatted to promote the ability of the end user of the document to understand the strength of the literature used to grade each recommendation. Each guideline recommendation is presented as a clinically applicable definitive statement of care and should help the reader make the best patient care decision. The best available literature was obtained and carefully reviewed. Chapter author(s) completed a thorough literature review using Medline, the Cochrane Central Registry of Controlled Trials, the Cochrane Database of Systematic Reviews and other appropriate reference sources. These results of the literature search and review formed the basis of an evidence-based approach to the clinical guidelines. Chapter editors work with the authors to ensure compliance with the author’s directives regarding content and format. The initial draft is then reviewed internally to ensure consistency with the other A.S.P.E.N. Guidelines and Standards and externally reviewed (by experts in the field within our organization and/or outside of our organization) for appropriateness of content. Then the final draft is reviewed and approved by the A.S.P.E.N. Board of Directors.

The system used to categorize the level of evidence for each study or article used in the rationale of the guideline statement and to grade the guideline recommendation is outlined in Table 1.

The grade of a guideline is based on the levels of evidence of the studies used to support the guideline. A randomized controlled trial (RCT), especially one that is double blind in design, is considered to be the strongest level of evidence to support decisions regarding a therapeutic intervention in clinical medicine. A level of I, the highest level, will be given to large RCTs where results are clear and the risk of alpha and beta error is low (well-powered). A level of II will be given to RCTs that include a relatively low number of patients or are at moderate-to-high risk for alpha and beta error (under-powered).

### Table 1

<table>
<thead>
<tr>
<th>Grading of Guidelines</th>
<th>Levels of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Supported by at least two level I investigations</td>
</tr>
<tr>
<td>B</td>
<td>Supported by one level I investigation</td>
</tr>
<tr>
<td>C</td>
<td>Supported by level II investigations</td>
</tr>
<tr>
<td>D</td>
<td>Supported by level III investigations</td>
</tr>
<tr>
<td>E</td>
<td>Supported by level IV or V evidence</td>
</tr>
</tbody>
</table>

Table 2 provides the entire set of guidelines recommendations for nutrition support in the critically ill child.

#### 1. Nutrition Assessment

1A) Children admitted with critical illnesses should undergo nutrition screening to identify those with existing malnutrition or those who are nutritionally at-risk. Grade D

1B) Formal nutrition assessment with the development of a nutrition care plan should be required, especially in those children with pre-morbid malnutrition. Grade E

##### Rationale

The prevalence of malnutrition in hospitalized children has remained unchanged over several years and has implications on hospital length of stay (LOS), illness course
and morbidity.4,5 Children admitted to the PICU are further at risk of longstanding altered nutrition status and anthropometric changes that may be associated with morbidity.13 Hulst et al. observed a correlation between energy expenditure using available standard equations are often unreliable. 2B) In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using indirect calorimetry (IC) is desirable. If IC is not feasible or available, initial energy provision may be based on published formulas or nomograms. Attention to imbalance between energy intake and expenditure will help to prevent overfeeding and underfeeding in this population.

3 There are insufficient data to make evidence-based recommendations for macronutrient intake in critically ill children. After determination of energy needs for the critically ill child, the rational partitioning of the major substrates should be based upon understanding of protein metabolism and carbohydrate- and lipid-handling during critical illness.

4 4A) In critically ill children with a functioning gastrointestinal tract, enteral nutrition (EN) should be the preferred mode of nutrient provision, if tolerated. 4B) A variety of barriers to EN exist in the pediatric intensive care unit (PICU) Clinicians must identify and prevent avoidable interruptions to EN in critically ill children. 4C) There are insufficient data to recommend the appropriate site (gastric vs post-pyloric/transpyloric) for enteral feeding in critically ill children. Post-pyloric or transpyloric feeding may improve caloric intake when compared to gastric feeds. Post-pyloric feeding may be considered in children at high risk of aspiration or those who have failed a trial of gastric feeding.

5 Based on the available pediatric data, the routine use of immunonutrition or immune-enhancing diets/nutrients in critically ill children is not recommended.

6 A specialized nutrition support team in the PICU and aggressive feeding protocols may enhance the overall delivery of nutrition, with shorter time to goal nutrition, increased delivery of EN, and decreased use of parenteral nutrition. The affect of these strategies on patient outcomes has not been demonstrated.

Table 2

<table>
<thead>
<tr>
<th>#</th>
<th>Guideline Recommendations</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1A) Children admitted with critical illnesses should undergo nutrition screening to identify those with existing malnutrition and those who are nutritionally-at-risk. 1B) A formal nutrition assessment with the development of a nutrition care plan should be required, especially in those children with premorbid malnutrition.</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>2A) Energy expenditure should be assessed throughout the course of illness to determine the energy needs of critically ill children. Estimates of energy expenditure using available standard equations are often unreliable. 2B) In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using indirect calorimetry (IC) is desirable. If IC is not feasible or available, initial energy provision may be based on published formulas or nomograms. Attention to imbalance between energy intake and expenditure will help to prevent overfeeding and underfeeding in this population.</td>
<td>E</td>
</tr>
<tr>
<td>3</td>
<td>There are insufficient data to make evidence-based recommendations for macronutrient intake in critically ill children. After determination of energy needs for the critically ill child, the rational partitioning of the major substrates should be based upon understanding of protein metabolism and carbohydrate- and lipid-handling during critical illness.</td>
<td>E</td>
</tr>
<tr>
<td>4</td>
<td>4A) In critically ill children with a functioning gastrointestinal tract, enteral nutrition (EN) should be the preferred mode of nutrient provision, if tolerated. 4B) A variety of barriers to EN exist in the pediatric intensive care unit (PICU) Clinicians must identify and prevent avoidable interruptions to EN in critically ill children. 4C) There are insufficient data to recommend the appropriate site (gastric vs post-pyloric/transpyloric) for enteral feeding in critically ill children. Post-pyloric or transpyloric feeding may improve caloric intake when compared to gastric feeds. Post-pyloric feeding may be considered in children at high risk of aspiration or those who have failed a trial of gastric feeding.</td>
<td>C</td>
</tr>
<tr>
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<td>D</td>
</tr>
<tr>
<td>6</td>
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<td>E</td>
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</table>
Energy Requirement in the Critically Ill Child

2. Energy Requirement in the Critically Ill Child

2A) Energy expenditure should be assessed throughout the course of illness to determine the energy needs of critically ill children. Estimates of energy expenditure using available standard equations are often unreliable. 

Grade D

2B) In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using indirect calorimetry (IC) is desirable. If IC is not feasible or available, initial energy provision may be based on published formulas or nomograms. Attention to imbalance between energy intake and expenditure will help to prevent overfeeding and underfeeding in this population. Grade E

Rationale

Acute injury markedly alters energy needs. Acute injury induces a catabolic response that is proportional to the magnitude, nature, and duration of the injury. Increased serum counter-regulatory hormone concentrations induce insulin and growth hormone resistance, resulting in the catabolism of endogenous stores of protein, carbohydrate, and fat to provide essential substrate intermediates and energy necessary to support the ongoing metabolic stress response. In mechanically ventilated children in the PICU, a wide range of metabolic states has been reported with an average early tendency towards hypermetabolism. Children with severe burn injury demonstrate extreme hypermetabolism in the early stages of injury whereby standard equations have been shown to underestimate the measured REE. Failure to provide adequate energy during this phase may result in loss of critical lean body mass and may worsen existing malnutrition. Stress or activity correction factors have been traditionally factored into basal energy requirement estimates to adjust for the nature of illness, its severity and the activity level of hospitalized subjects. On the other hand, critically ill children who are sedated and mechanically ventilated may have significant reduction in true energy expenditure, due to multiple factors including decreased activity, decreased sensible fluid losses and transient absence of growth during the acute illness. These patients may be at a risk of overfeeding when estimates of energy requirements are based on age-appropriate equations developed for healthy children and especially if stress factors are incorporated. The application of a uniform stress correction factor for broad groups of patients in the ICU is simplistic, likely to be inaccurate and may increase the risk of overfeeding. IC testing may be considered before incorporating stress factor correction to energy estimates in critically ill children. Therefore, the application of correction factors for activity, insensible fluid loss and the energy or caloric allotment for growth, which is substantial in infancy, must be reviewed.

To account for dynamic alterations in energy metabolism during the critical illness course, REE values remain the only true guide for energy intake. It is likely that resource constraints and lack of available expertise restricts the regular use of IC in the PICU. Estimating energy expenditure needs based on standard equations has been shown to be inaccurate and can significantly underestimate or overestimate the REE in critically ill children (see Table 4). This exposes the critically ill child to potential underfeeding or overfeeding during the ICU stay, with significant morbidity associated with each scenario. While the problems with underfeeding have been well documented, overfeeding too has deleterious consequences. It increases ventilatory work by increasing carbon dioxide production and can potentially prolong the need for mechanical ventilation.
Overfeeding may also impair liver function by inducing steatosis and cholestasis, and increase the risk of infection secondary to hyperglycemia. Hyperglycemia associated with caloric overfeeding has been associated with prolonged mechanical ventilator requirement and PICU LOS.\textsuperscript{27} The use of the respiratory quotient (RQ) as a measure of substrate use in individual children cannot be recommended. However, a combination of acute phase proteins (CRP) and RQ may reflect transition from the catabolic hypermetabolic to the anabolic state. There are no data in general pediatric populations for the role of hypocaloric feeding. The application of hypocaloric feeding in a select group of chronically ill children at high risk of obesity is currently sporadic. In general, the energy goals should be assessed and reviewed regularly in critically ill children.

Table 3 summarizes studies examining the performance of estimated energy needs in relation to measured REE in critically ill children requiring mechanical ventilator support. In general, these small sized, prospective or retrospective cohort studies demonstrate the variability of the metabolic state and the uniform failure of estimated energy needs in accurately predicting the measured REE in critically ill children. In the absence of REE, some
### Table 4
Estimated Energy Expenditure vs Measured Resting Energy Expenditure (REE)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Sample Size</th>
<th>Clinical Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Klerk et al&lt;sup&gt;28&lt;/sup&gt; 2002</td>
<td>Children needing &gt; 24 hours of mechanical ventilator support in a PICU</td>
<td>Serial measured REE Respiratory Quotient (RQ) Energy balance = actual energy intake – total energy expenditure</td>
<td>N = 18</td>
<td>Variability in total daily energy expenditure (40-64 kcal/kg/d) CV was &lt; 10% Positive energy balance in many children (n=8) [Average RQ in this group was 0.89] Negative balance (n=10) [Average RQ in this group was 0.84]</td>
<td>Single measurement appears to accurately reflect total daily energy requirement. Results of this study do not suggest the need for serial REE. RQ was marginally affected by energy balance.</td>
<td></td>
</tr>
<tr>
<td>White et al&lt;sup&gt;29&lt;/sup&gt; 1999</td>
<td>Mechanically ventilated children in the PICU</td>
<td>24 h indirect calorimetry measurement 30 minute steady state REE compared to 24-h total energy expenditure Daily CV in measured REE was calculated</td>
<td>N = 11</td>
<td>30-minute REE CV was 7.2% ± 4.5% 30-min vs 24 h: no difference (P &lt; 0.69) No diurnal variation Between-day CV = 21% ± 16%</td>
<td>Small numbers. No correlation examined with clinical state. 30-minute REE accurately represented the 24-h values. The authors recommend serial REE measurements based on significant between-day CV.</td>
<td></td>
</tr>
<tr>
<td>White et al&lt;sup&gt;30&lt;/sup&gt; 2000</td>
<td>Mechanically ventilated children in a PICU</td>
<td>Clinical variables REE by indirect calorimetry</td>
<td>N = 100 (derivation) N = 25 (validation)</td>
<td>A new equation for estimated REE was derived, incorporating age, weight, temperature, days in the PICU, and disease.</td>
<td>The authors concluded that there is no substitute for measured REE. Their derived equation performed better than existing standard equations.</td>
<td></td>
</tr>
<tr>
<td>Derumeaux-Burel et al&lt;sup&gt;31&lt;/sup&gt; 2004</td>
<td>Obese children BMI z score ≥ 2 Measured REE</td>
<td>Fat free mass—obtained by bioelectric impedance assessment Predicted equations</td>
<td>N = 471 (derivation) N = 211 (validation)</td>
<td>REE equation using fat-free mass was more accurate than weight-based equations</td>
<td>Special equations may be necessary for obese children. Body composition is an important factor in REE. Measured REE is ideal.</td>
<td></td>
</tr>
<tr>
<td>Mlcak et al&lt;sup&gt;32&lt;/sup&gt; 2006</td>
<td>Children &lt; 18 years with total body surface area burn &gt; 40%, and consent to return at 6, 9, and 12 months for post-burn follow up</td>
<td>Measured REE vs Harris-Benedict equation and corrected by BMI REE measurements were repeated at 6, 9, and 12 months post-burn when the patients returned for outpatient surgery.</td>
<td>N = 100 (40 female)</td>
<td>REE was expressed in 3 different ways: actual REE in kcal per day, percent of predicted REE, and actual REE divided by the BMI. Hypermetabolism persisted 12 months after burn injury. Female children exerted a decreased hypermetabolic response compared with male children.</td>
<td>Increased REE persisted for over 12 months after burn injury.</td>
<td></td>
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</table>

(continued)
investigators recommend that basal energy requirements should be provided without correction factors to avoid the provision of calories and/or nutrition substrates in excess of the energy required to maintain the metabolic homeostasis of the injury response. Criteria for targeting a select group of children in the PICU for IC measurement of REE may be useful for centers with limited resources for metabolic testing. Some children in the PICU are likely to be at risk of altered metabolism or malnutrition, where estimates of energy expenditure using standard equations are likely to be inaccurate. If resources are limited, this subset of the population may benefit from targeted IC for accurate measurement of REE to guide energy administration.

**Table 4 (continued)**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Grade</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Sample Size</th>
<th>Clinical Outcome Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framson et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>2007</td>
<td>Children admitted to a PICU. Both spontaneously breathing and mechanically ventilated patients were included. No children with chronic disease.</td>
<td>REE measurement within 24 hours of admission, then 48 hours after the first measurement, and finally within 24 hours before discharge from the PICU. Measured REE was compared to estimates from Schofield and White equations.</td>
<td>N = 44 (29 males)</td>
<td>In general, equations performed well. Mean REE for all measurements was 821 ± 653 kcal/24 hours. The Schofield equation estimate was 798 ± 595 kcal/24 h and the White equation estimate was 815 ± 564 kcal/24 h (P not significant). Only 45% of REE were within 90%–110% of that predicted by the Schofield equation. The White equation was inaccurate (not within 10% of REE) in 66 of 94 measurements (70%). The discrepancy was greatest (100%) in children with REE &lt;450 kcal/24 h.</td>
<td>The hypermetabolic response apparent in adults was not evident in these critically ill children. Authors do not recommend the use of REE estimates from equations as a guide for caloric intake in critically ill children.</td>
<td></td>
</tr>
<tr>
<td>Vazquez Martinez et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>2004</td>
<td>Mechanically ventilated children in a PICU</td>
<td>Measured REE was compared to estimates from various equations/formulas such as Harris-Benedict, Caldwell-Kennedy, Schofield, FAO/WHO, Maffeis, Fleisch, Kleiber, Dreyer, and Hunter equations.</td>
<td>N = 43 (18 female); 35 surgical and 8 medical</td>
<td>Measured REE = 674 ± 384 kcal/day. Patients noted to be hypometabolic in the first 6 h after admission to PICU. Most equations overestimated measured REE in ventilated, critically ill children during the early post-injury period. Measured and predicted energy expenditure differed significantly (P &lt; .05) except when the Caldwell-Kennedy and the Fleisch equations were used.</td>
<td>Children may be hypometabolic in the first 6 h after PICU admission. Equations overestimate energy expenditure. Authors do not recommend equations for predicting energy expenditure in critically ill children.</td>
<td></td>
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</table>

BMI, body mass index; CV, coefficient of variation; FAO/WHO, Food and Agriculture Organization/World Health Organization; PICU, pediatric intensive care unit.

**Future Research**

IC remains sporadically applied in critically ill children in the setting of mounting evidence of the inaccuracy of estimated basal metabolic rate using standard equations. This could potentially subject a subgroup of children in the PICU to the risk of underfeeding or overfeeding. In the era of resource constraints, IC may be applied or targeted for certain high-risk groups in the PICU. Selective application of IC may allow many units to balance the need for accurate REE measurement and limited resources (Appendix 1). Studies examining the role of simplified IC technique, its role in optimizing nutrient intake, its ability to prevent overfeeding or
underfeeding in selected subjects, and the cost-benefit analyses of its application in the PICU are desirable. The effect of energy intake on outcomes needs to be examined in pediatric populations especially in those on the extremes of body mass index (BMI).

Appendix 1

Children at high risk for metabolic alterations who are suggested candidates for targeted measurement of REE in the PICU include the following:

- Underweight (BMI < 5th percentile for age), at risk of overweight (BMI > 85th percentile for age) or overweight (BMI > 95th percentile for age)
- Children with >10% weight gain or loss during ICU stay
- Failure to consistently meet prescribed caloric goals
- Failure to wean, or need to escalate respiratory support
- Need for muscle relaxants for >7 days
- Neurologic trauma (traumatic, hypoxic and/or ischemic) with evidence of dysautonomia
- Oncologic diagnoses (including children with stem cell or bone marrow transplant)
- Children with thermal injury
- Children requiring mechanical ventilator support for >7 days
- Children suspected to be severely hypermetabolic (status epilepticus, hyperthermia, systemic inflammatory response syndrome, dysautonomic storms, etc) or hypometabolic (hypothermia, hypothyroidism, pentobarbital or midazolam coma, etc.)
- Any patient with ICU LOS >4 weeks may benefit from IC to assess adequacy of nutrient intake.

3. Macronutrient Intake During Critical Illness

There are insufficient data to make evidence-based recommendations for macronutrient intake in critically ill children. After determination of energy needs for the critically ill child, the rational partitioning of the major substrates should be based upon basic understanding of protein metabolism and carbohydrate- and lipid-handling during critical illness. Grade E

Rationale

Critical illness and recovery from trauma or surgery are characterized by increased protein catabolism and turnover. An advantage of high protein turnover is that a continuous flow of amino acids is available for synthesis of new proteins. Specifically, this process involves a redistribution of amino acids from skeletal muscle to the liver, wound, and other tissues involved in the inflammatory response. This allows for maximal physiologic adaptability at times of injury or illness. Although children with critical illness have increases in both whole-body protein degradation and whole-body protein synthesis, it is the former that predominates during the stress response. Thus, these patients manifest net negative protein and nitrogen balance characterized by skeletal muscle wasting, weight loss, and immune dysfunction. The catabolism of muscle protein to generate glucose and inflammatory response proteins is an excellent short-term adaptation, but it is ultimately limited because of the reduced protein reserves available in children and neonates. Unlike during starvation, the provision of dietary carbohydrate alone is ineffective in reducing the endogenous glucose production via gluconeogenesis in the metabolically stressed state. Therefore, without elimination of the inciting stress for catabolism (ie, the critical illness or injury), the progressive breakdown of muscle mass from critical organs results in loss of diaphragmatic and intercostal muscle (leading to respiratory compromise), and to the loss of cardiac muscle. The amount of protein required to optimally enhance protein accretion is higher in critically ill than in healthy children. Infants demonstrate 25% higher protein degradation after surgery and a 100% increase in urinary nitrogen excretion with bacterial sepsis. The provision of dietary protein sufficient to optimize protein synthesis, facilitate wound healing and the inflammatory response, and preserve skeletal muscle protein mass is the most important nutrition intervention in critically ill children. The quantities of protein recommended for critically ill neonates and children are based on limited data. Certain severely stressed states, such as significant burn injury, may require additional protein supplementation to meet metabolic demands. Excessive protein administration should be avoided as toxicity has been documented, particularly in children with marginal renal and hepatic function. Studies using high protein allotments of 4–6 g/kg/day have been associated with adverse effects such as azotemia, metabolic acidosis, and neurodevelopmental abnormalities. A similar evaluation of the effects of high protein administration using newer formulas is desirable. Although the precise amino acid composition to best increase whole-body protein balance has yet to be fully determined, stable isotope techniques now exist to study this issue. Estimated protein requirements for injured children of various age groups are as follows: 0–2 years, 2–3 g/kg/day; 2–13 years, 1.5–2 g/kg/day; and 13–18 years, 1.5 g/kg/day.

Once protein needs have been met, safe caloric provisions using carbohydrate and lipid energy sources have similar beneficial effects on net protein synthesis and overall protein balance in critically ill patients. Glucose is the primary energy used by the brain, erythrocyte, and renal medulla and is useful in the repair of injured tissue.
Glycogen stores are limited and quickly depleted in illness or injury, resulting in the need for gluconeogenesis. In injured and septic adults, a 3-fold increase in glucose turnover and oxidation has been demonstrated as well as an elevation in gluconeogenesis. A significant feature of the metabolic stress response is that the provision of dietary glucose does not halt gluconeogenesis. Consequently, the catabolism of muscle protein to produce glucose continues unabated, and attempts to provide large carbohydrate intake in critically ill patients have been abandoned.

The Surviving Sepsis Campaign has recommended tight glucose control in critically ill adults based on results of a single trial that showed decreased mortality in critically ill adults randomized to this strategy. Subsequent studies examining the role of strict glycemic control in adults have yielded conflicting results and the incidence of hypoglycemia in these studies is concerning. Hyperglycemia is prevalent in critically ill children and has been associated with poor outcomes in retrospective studies. The etiology of hyperglycemia during the stress response is multifactorial. Despite the prevalence of hyperglycemia in the pediatric intensive care population, no data exist currently evaluating the effects of tight glycemic control in the pediatric age group. Both hypoglycemia and glucose variability also are associated with increased LOS and mortality, and hence are undesirable in the critically ill child. In the absence of definitive data, aggressive glycemic control cannot be recommended as yet in the critically ill child.

Lipid turnover is generally accelerated by critical illness, surgery, and trauma. Recently, it has been shown that critically ill children do, indeed, have a higher rate of fat oxidation. Thus, this suggests that fatty acids are, in fact, the prime source of energy in metabolically stressed children. Because of the increased demand for lipid use in critical illness coupled with the limited fat stores in the pediatric patient, critically ill children are susceptible to the evolution of biochemically detected essential fatty acid deficiency if administered a fat-free diet. Clinically, this syndrome presents as dermatitis, alopecia, thrombocytopenia, and increased susceptibility to bacterial infection. To avoid essential fatty acid deficiency in critically ill or injured infants, the allotment of linoleic and linolenic acid is recommended at concentrations of 4.5% and 0.5% of total calories, respectively. The provision of commercially available intravenous fat emulsions (IVFE) to parenterally fed critically ill children reduces the risk of essential fatty acid deficiency, results in improved protein use, and does not significantly increase CO₂ production or metabolic rate. Most centers, therefore, start IVFE supplementation in critically ill children at 1 g/kg/day and advance over a period of days to 2-4 g/kg/day, with monitoring of triglyceride levels. IVFE administration is generally restricted to a maximum of 30%–40% of total calories, although this practice has not been validated by clinical trials.

4. Route of Nutrient Intake (Enteral Nutrition)

4A) In critically ill children with a functioning gastrointestinal tract, enteral nutrition (EN) should be the preferred mode of nutrient provision, if tolerated. Grade C

4B) A variety of barriers to EN exist in the PICU. Clinicians must identify and prevent avoidable interruptions to EN in critically ill children. Grade D

4C) There are insufficient data to recommend the appropriate site (gastric vs post-pyloric/transpyloric) for enteral feeding in critically ill children. Post-pyloric or transpyloric feeds may improve caloric intake when compared to gastric feeds. Post-pyloric feeding may be considered in children at high risk of aspiration or those who have failed a trial of gastric feeding. Grade C

Rationale

Following the determination of energy expenditure and requirement in the critically ill child, the next challenge is to select the appropriate route for delivery of nutrients. In the critically ill child with a functioning gastrointestinal tract, the enteral route is preferable to parenteral nutrition (PN). EN has been shown to be more cost-effective without the added risk of nosocomial infection inherent with PN. However, the optimal route of nutrient delivery has not been systematically studied in children and there is no RCT comparing the effects of EN vs PN. Current practice in many centers includes the initiation of gastric or post-pyloric enteral feeding within 48-72 hours after admission. PN is being used to supplement or replace EN in those patients where EN alone is unable to meet the nutrition goal.

In children fed with EN, there are insufficient data to make recommendations regarding the site of enteral feeding (gastric vs post-pyloric). Meert et al examined the role of small bowel feeding in 74 critically ill children, randomized to receive either gastric or post-pyloric nutrition. The study was not powered to detect differences in mortality. EN was interrupted in a large number of subjects in this study and caloric goals were met in a small percentage of the population studied. This unblinded RCT did not show difference in microaspiration, enteral access device displacement, and feed intolerance between the gastric or post-pyloric fed groups. A higher percentage of subjects in the small bowel group achieved their daily caloric goal compared to the gastric fed group. Sanchez et al report better tolerance in critically ill
children receiving early (< 24 hours after PICU admission) vs late (started after 24 hrs) post-pyloric nutrition. Of the 526 children in their cohort who were deemed to have intolerance to EN, 202 received early post-pyloric nutrition and had decreased incidence of abdominal distension. Despite evidence to suggest that it is reasonably tolerated, the routine use of postpyloric feeding in the critically ill child cannot be recommended. It may be prudent to consider this option in patients who do not tolerate gastric feeding or those who are at a high risk of aspiration. Postpyloric or transpyloric feeding may be limited by the ability to obtain small bowel access, and the expertise and resources in individual PICUs are likely to be variable. A standardized approach to optimizing benefits and minimizing risks with EN delivery will help clinicians identify patients who would benefit from small bowel feeding.

Despite the absence of sound evidence to support the superiority of one route of feeding over the other, the enteral route has been successfully used for nutrition support of the critically ill child. In another unblinded RCT, Horn et al randomized 45 children admitted to the PICU to receive gastric tube feeding either continuously or intermittently every 2 hours. The main outcome measure examined in this study was tolerance of enteral feedings. The small sample size and the short observation period of < 66 hours makes any meaningful interpretation difficult. However, the number of daily stools, diarrheal episodes, or vomiting episodes was similar between the 2 groups. Intolerance to enteral feedings may limit intake and supplementation with PN may be required. Prospective cohort studies and retrospective chart reviews have reported the inability to achieve daily caloric goal in critically ill children. The most common reasons for suboptimal enteral nutrient delivery in these studies are fluid restriction, interruptions to EN for procedures, and EN intolerance due to hemodynamic instability. The percent of estimated energy expenditure actually administered to these subjects was remarkably low. In a study examining the endocrine and metabolic response of children with meningococcal sepsis, goal nutrition was achieved in only 25% of the cases. Similar observations have been made in a group of 95 children in a PICU where patients received a median of 58.8% (range 0%-277%) of their estimated energy requirements. In this review, EN was interrupted on 264 occasions for clinical procedures. In another review of nutrition intake in 42 patients in a tertiary-level PICU over 458 ICU days, actual energy intake was compared with estimated energy requirement. Only 50% of patients were reported to have received full estimated energy requirements after a median of 7 days in the ICU. Protocols for feeding use of transpyloric feeding tubes and changing from bolus to continuous EN during brief periods of intolerance are strategies to achieve estimated energy goals in this population. Consistently underachieved EN goals are thought to be one of the reasons for the absence of beneficial effect in multiple studies and meta-analysis of the efficacy of immunonutrition in preventing infection. Awareness of these factors hindering the achievement of EN goals is essential in order to address preventable interruptions in enteral feeding in critically ill children. There is not enough evidence to recommend the use of prokinetic medications or motility agents (for EN intolerance or to facilitate enteral access device placement), prebiotics, probiotics, or synbiotics in critically ill children.

Future Research

Future studies may be directed at examining methods to ensure optimal prescription and delivery of nutrient intake at the bedside, identifying and preventing common reasons for avoidable interruptions in nutrient intake, selection of children at risk of aspiration in the PICU, and the role of EN (gastric vs postpyloric feeds) in this subgroup. The advantages of EN in terms of its role in gut immunity, prevention of PN related complications and the cost benefit analysis when compared to PN require further evaluation.

5. Immunonutrition in the PICU

Based on the available pediatric data, the routine use of immunonutrition or immune-enhancing diets/nutrients in critically ill children is not recommended. Grade D

Rationale

The use of specific nutrients aimed at modulating the inflammatory or immune response has been reported for several years. Despite several RCTs employing immunonutrition in critically ill patients, a positive treatment effect of immunonutrition or the use of immune-enhancing diets (IED) has not been demonstrated. These studies are flawed by their poor methodology and small sample size. The studies were conducted using a variety of nutrients in combination that were administered to heterogeneous patient populations. The studies do not allow meaningful interpretation of the safety or efficacy of individual nutrients and fail to detect significant differences in relevant clinical outcomes. Arginine, glutamine, aminopeptides, ω-3 fatty acids and antioxidants are some of the nutrients studied for their immune modulation effects. Systematic reviews of immunonutrition studies in adults have cautioned against the use of arginine and other nutrients due to potential for harm in septic and critically ill patients. Fish oils, borage oils, and antioxidants may have a role in patients with acute respiratory distress.
Table 5
Clinical Outcomes Associated With Enteral Feeding

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Population</th>
<th>Intervention</th>
<th>Sample Size</th>
<th>Clinical Outcome Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meert et al 2004</td>
<td>Critically ill children (&lt;18yrs) in a PICU</td>
<td>RCT comparing gastric vs small bowel continuous tube feeds</td>
<td>N = 74</td>
<td>Daily caloric goal achieved was significantly lower ($p &lt; 0.01$) in gastric group (30 ± 23%) vs small bowel group (47 ± 22%). Proportion of patients with microaspiration, tube displacement, and EN intolerance were similar between the 2 groups.</td>
<td>Small number of patients studied. Difficult to blind such a study at the bedside (due to need for radiographic confirmation of placement of tip of enteral access device). Fairly high number of subjects in the study experienced EN interruptions and percent of caloric goals met was low in both groups.</td>
</tr>
<tr>
<td>Horn et al 2003</td>
<td>Children &lt; 18y in a PICU with EN</td>
<td>RCT comparing gastric EN administered either continuously or every 2 h</td>
<td>N = 45</td>
<td>Tolerance—number and type of stools, diarrhea and vomiting were similar between the continuous and intermittent gastric fed group.</td>
<td>Small number of patients studied. The duration of study was too small to detect meaningful differences—median 64.5 and 66 hours for the 2 groups. Energy requirements were estimates and not measured. Barriers to EN remain a significant challenge to ensuring the delivery of prescribed calories to patients in the PICU.</td>
</tr>
<tr>
<td>De Oliveira Iglesias et al 2007</td>
<td>Children in a PICU with EN ≥ 2 d</td>
<td>Required (estimates) vs prescribed vs. delivered calories were recorded.</td>
<td>N = 55</td>
<td>EN started on day 3 ± 1 and maintained for 6 ± 3 d. 71% received the required calories (38% of which reached caloric goal by day 5 of PICU admission). Daily average caloric intake was 60% of required and 85% of prescribed.</td>
<td>Barriers to EN were procedures, clinical instability, use of inotropic agents, enteral access device displacement, postoperative fasting, and feeding intolerance (abdominal distension, vomiting, and diarrhea).</td>
</tr>
<tr>
<td>Sanchez et al 2007</td>
<td>Children over 10 years of age admitted to a PICU were eligible for transpyloric tube placement if they were deemed to not tolerate enteral feedings within 24-48 hrs after admission. Tolerance of feeds was compared between patients started on transpyloric feeds early (&lt; 24 hours after admission) vs those started late (&gt; 24 hrs)</td>
<td>Calories delivered, duration of nutrition, abdominal distension and diarrhea were recorded.</td>
<td>N = 526 (202 were fed early)</td>
<td>Clinical characteristics, nutrients delivered and incidence of diarrhea were similar in both groups. Abdominal distension was less frequent in early EN group (3.5%) vs late (7.8%); $P &lt; .05$.</td>
<td>Retrospective cohort Children tolerate early postpyloric feeds.</td>
</tr>
</tbody>
</table>
syndrome (ARDS). Glutamine may have beneficial effects in adults with burn injury and trauma.

The role of immune-enhancing EN in children during critical illness has not been extensively studied. Briassoulis et al reported their results of a blinded RCT in children admitted to the PICU with expected LOS and need for mechanical ventilation of ≥5 d. EN was started in these patients within 12 h of admission to PICU. Patients were randomized to receive either a formulation containing glutamine, arginine, ω-3 fatty acids, and antioxidants or standard age-appropriate formulation. Protocolized increase in EN ensured that goal feeds were reached by day 4. The study did not show any outcome differences in the 25 children in each arm, although authors report a trend toward a decrease in nosocomial infection rates and positive gastric aspirate culture rates in the treatment arm. The immunologically active formula used in this study was not specifically tailored for children and transient diarrhea was noted in children receiving this formula, which had a higher osmolarity compared to the control formula.

Another small pilot RCT reported improved outcomes in children fed with a glutamine-enriched formulation, although the numbers are too small for meaningful conclusions. The use of a specialized adult immune modulating enteral formula in pediatric burn victims has been associated with improvement in oxygenation and pulmonary compliance in a retrospective review.

**Future Research**

Future pediatric studies in this field must focus on examining the effects of single (vs combination of) nutrients, in large (multicenter) trials, on homogeneous PICU populations designed to detect differences in important outcome measures. This approach will ensure that results allow meaningful inferences to be made about sound hypotheses on single immune modulating nutrients and will prevent the current absence of strong conclusions despite a large amount of investment in this area of research in adult ICU populations.

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Table 5 (continued)

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Grade</th>
<th>Population Intervention</th>
<th>Sample Size</th>
<th>Clinical Outcome Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers et al 2003 Level III</td>
<td>Children admitted to a PICU with length of stay &gt;3 d and EN intake</td>
<td>N = 42 (18 Cardiac surgical)</td>
<td>Patients received 37.7% (median) of their EER. Cardiac surgical patients had lower caloric intake than others. Only 52% of the pts received full energy intake goal at any time during the PICU stay. Significant weight decrease was noted in cardiac surgical patients. Major barrier to caloric intake—fluid restriction</td>
<td>PICU patients, especially cardiac surgical patients, do not receive their energy goals. Fluid restriction in both groups is the major reason for inability to meet energy goals. Fasting for procedures and EN interruptions due to intolerance were other barriers to nutrition in this study.</td>
<td></td>
</tr>
<tr>
<td>Taylor et al 2003 Level III</td>
<td>Children admitted to PICU with length of stay ≥3 d</td>
<td>N = 95</td>
<td>59% were fed within 24 hours of admission. EN was administered 54% of time. 10% received PN; 9.5% did not receive any nutrition support. PICU pts received 58.8%, median (range 0–277%) of their energy intake goal. Energy intake was greater when supplemented by PN. EN was interrupted 264 times (mainly for procedures).</td>
<td>Poor % energy intake goal achieved with EN. Procedure-related feeding interruptions were significant. The study highlights the need for a proactive approach to bridge the gap between desirable and achieved nutrient intake.</td>
<td></td>
</tr>
</tbody>
</table>

EER, energy efficiency ratio; EN, enteral nutrition; PICU, pediatric intensive care unit; RCT, randomized controlled trial.
A specialized nutrition support team in the PICU and aggressive feeding protocols may enhance the overall delivery of nutrition, with shorter time to goal nutrition, increased delivery of EN, and decreased use of parenteral nutrition. The effect of these strategies on patient outcomes has not been demonstrated. Grade E

### Table 6

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Sample Size</th>
<th>Clinical Outcome Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briassoulis et al22 2005 Level II</td>
<td>Children admitted to the PICU; with an expected LOS and need for mechanical ventilation of ≥ 5 d</td>
<td>No renal disease, no chronic GI disease, or no PN. EN started within 12 h of admission. Intervention group received the study formula providing glutamine/arginine/antioxidants (Zn, vitamin E, β carotene, copper, selenium) and ω-3 fatty acids. Masking of formulations. Protocols for EN delivery: energy intake = 0.5, 1.1.25, 1.5 and 1.5 times predicted estimated energy requirement on days 1, 2, 3, 4, and 5, respectively. Thus, gradual increase in intake with goal feeds to be reached by day 4. Note: energy intake was predicted using FAO equations with Schofield modifications and with stress factors.</td>
<td>N = 50 (25 patients in each group)</td>
<td>Negative nitrogen balance noted on day 1 in both groups. Increased serum osmolality, urea and sodium in intervention group. 64% patients with positive nitrogen balance in intervention vs 40% in control group by day 5. Caloric intake was 120% predicted basal metabolic rate. No changes in mortality. Decreasing trends in nosocomial infection rates and positive gastric aspirate culture rates; <em>P &lt; .05</em>. Transient diarrhea, possibly due to increased osmolarity of study formulation.</td>
<td>Mortality was not affected (but sample size is small). The trends in decreased nosocomial infection and gastric cultures are not statistically significant. Formulation was not adapted to children.</td>
</tr>
<tr>
<td>Barbosa et al60 1999 Level V</td>
<td>Infants (1 m–2 y of age) admitted to PICU and tolerating EN for at least 5 d</td>
<td>Diagnosis of sepsis/respiratory failure. Exclusions: shock, multiple organ failure, AIDS, HIV positivity, immunosuppressant drugs, cancer, chemotherapy, recent surgery, diabetes mellitus, hepatic or renal failure. 2 groups randomized to receive glutamine (commercial EN formulation), casein + semi-elemental formulation.</td>
<td>N = 9 5 Glutamine 4 control</td>
<td>Bacterial infections in 75% of placebo (3/4) vs 20% in treatment group. Deaths: 2/4 in placebo and 0/5 in glutamine group. Duration of mechanical ventilation, LOS in ICU and hospital were similar in both groups.</td>
<td>Very small study</td>
</tr>
</tbody>
</table>

AIDS, Acquired immune deficiency syndrome; FAO, Food and Agriculture Organization; GI, gastrointestinal; HIV, human immunodeficiency virus; ICU, intensive care unit; LOS, length of stay; PICU, pediatric intensive care unit.

### 6. Nutrition Support Team and Feeding Protocols

A specialized nutrition support team in the PICU and aggressive feeding protocols may enhance...
### Table 7
Nutrition Support Team and Protocolized Feeding

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Grade</th>
<th>Population</th>
<th>Intervention</th>
<th>Sample Size</th>
<th>Clinical Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurgueira et al(^{62}) 2005</td>
<td>Level IV</td>
<td>Children in a PICU</td>
<td>Retrospective examination of variables during a phased introduction of NST</td>
<td>Sample = 323 (Historical cohorts from 5 time periods studied)</td>
<td>EN administration increased from 25% to 67% by 5 years (medical patients)</td>
<td>Single center experience; Retrospective data analysis.</td>
</tr>
<tr>
<td>Lambe et al(^{63}) 2007</td>
<td>Level IV</td>
<td>PICU</td>
<td>Retrospective review. Time to achieve SOCI, cumulative caloric and protein deficits</td>
<td>N = 82, 41 in each time period</td>
<td>No significant difference in outcomes between the 2 groups</td>
<td>Weekly NST intervention may not be enough to impact outcomes in this study.</td>
</tr>
<tr>
<td>Petrillo-Albarano et al(^{64}) 2006</td>
<td>Level IV</td>
<td>PICU patients who were fed via nasogastric tube</td>
<td>Early EN protocol—start within 6h of admission; physician order; min of twice weekly weighing; prealbumin level every 7 days; goal feeding and fluid requirements according to age; defined feed intolerance (aspiration, abdominal distention, vomiting, and diarrhea 6/d); metoclopramide, docusate + senna for constipation, or prophylactic if on narcotics. Comparison chart review—time to achieving goal nutrition, tolerance and LOS</td>
<td>N = 91 (Pre-protocol) N = 93 (Post-protocol)</td>
<td>Protocol vs Retrospective group: Time to Goal (18.5 h vs 57.8 h); P &lt; .0001 Diarrhea (12% vs 2%); P = .009 Constipation (51% vs 33%); P = .012</td>
<td>This study demonstrates improved time to goal and tolerance to EN after introduction of an aggressive early EN protocol in the PICU.</td>
</tr>
<tr>
<td>Briassoulis et al(^{52}) 2001</td>
<td>Level III</td>
<td>PICU</td>
<td>Prolonged mechanical ventilation requirement</td>
<td>N = 71</td>
<td>Caloric intake equal to the predicted basal metabolic rate and predicted energy expenditure were achieved by day 2 and 4 respectively. Patients tolerated the early aggressive EN well (success rate 94.4%). Successful protocolized feeding was correlated with survival (P &lt; .0001). The PICU mortality rate (5.6%) was different between success (1.5%) and failure (75%) groups (P &lt; .0001) and was lower than that predicted by the admission severity scores (12.1 ± 2%). 54 study patients were discharged on intragastric feedings (76.1%) and 15 on oral feedings (21.1%).</td>
<td>The authors have demonstrated an association between achieving predicted caloric goals (using early EN initiation) and outcome.</td>
</tr>
</tbody>
</table>

CI, confidence interval; EN, enteral nutrition; LOS, length of stay; NST, nutrition support team; OR, odds ratio; PICU, pediatric intensive care unit; PN, parenteral nutrition; SOCI, sustained optimal caloric intake.
Rationale

Despite its widespread application, the practice of providing EN in the PICU is highly variable. A significant portion of children receiving EN does not meet caloric goals due to a multitude of reasons. Some studies have assessed the role of a dedicated nutrition team and the use of protocols and standardized prescriptions for nutrition support therapy to implement optimal nutrition practices in the PICU. A dedicated nutrition support team (NST) has become an integral part of the multidisciplinary critical care group. Recent surveys demonstrate the presence of such a team during rounds and their availability for expert advice and help in many centers around the world. The role of the NST is evolving and the clear benefit on patient outcomes in the PICU is debatable. Gurgueira et al examined historical cohorts of children admitted to their PICU at different intervals during a phased implementation of a specialized NST.52 In their single center retrospective review of 323 patients over 5 years, the authors reported an increase in EN rate from 25% to 67% with a significant decrease in PN rates. The enhanced use of EN correlated with the implementation of the NST. Children in this study who received EN during >50% of their LOS had 83% lower risk of death. A similar historical cohort review by Lambe et al failed to show any significant difference in nutrition outcomes (time to achieve sustained optimal caloric goal, energy, and protein balance) in the PICU population before and after implementation of a specialized NST.65

Feeding protocols may assist in implementing early enteral feedings in critically ill children. Although the benefits of such an approach in affecting important clinical outcomes in the PICU population have not been examined in RCTs, prospective cohort studies have demonstrated reasonable tolerance of feedings and improved time to achieving goal EN.52,64 If indeed early EN is associated with improved patient outcomes, implementation of an early aggressive EN protocol may be desirable and could be assisted by a specialized NST. Such protocols may identify caloric goal, route and time of initiation of EN, type of formulation, rate of increase in infusion rate, and time to reach caloric goal. In addition, protocols may use prokinetic medication therapy to enhance EN tolerance.65 However, despite the sporadic application of feeding protocols and guidelines in the PICU, there is a lack of systematic evidence to support their use.

Future Research

The role of a specialized NST in the PICU in improving the accuracy of prescribed nutrition support, monitoring of nutrition status, identification of metabolic alterations, selection of subjects for IC, and overall cost benefit of such a team needs further examination.

Notice

These A.S.P.E.N. Clinical Guidelines are general. They are based upon general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, practitioners must always exercise professional judgment in their application. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

Acknowledgment

We appreciate the insight of Praveen Goday, MD, for initial comments on the manuscript.

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