(Chapter 20.Nutrition in Critical Illness, Including Immunonutrition)

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Introduction

Adequate nutrition is essential to the critically ill patient. It helps support anabolism, ameliorate uncontrolled catabolism, maintain a competent immune system, and ultimately improve patient outcome. Critically ill patients usually present with multiple medical problems that are associated with significant metabolic and nutritional alterations. Severe trauma, burns, sepsis, and head injury are associated with marked hypermetabolism and hypercatabolism, which lead to dramatic metabolic alterations, including increased glycogenolysis, gluconeogenesis, and lipolysis. Balancing nutritional needs while avoiding metabolic and iatrogenic complications is a challenge. Evidence suggests that enteral feedings should begin early to preserve gut integrity. The use of parenteral nutrition (PN) should be kept as low as possible, although concomitant use of PN may be necessary while enteral feeding tolerance is established. The pediatric intensive care patient population, with patients from birth to adolescence, encompasses a wide variety of critically ill patients, including postoperative patients and patients with trauma, congenital heart disease, severe respiratory disorders, sepsis, liver or renal failure, or multiorgan dysfunction. The prevalence of malnutrition in patients admitted to the pediatric intensive care unit (PICU) ranges between 15% and 20%, with a higher prevalence in patients with congenital heart disease. This chapter discusses the metabolic and nutritional changes that occur in adult and pediatric critically ill patients and provides guidelines for providing safe and effective nutrition support, including immunonutrition, to these patients.

I. Metabolic Response to Stress

Critically ill patients exhibit a characteristic metabolic response to severe illness or traumatic injury independent of cause. Both types of inciting events activate the immune system and induce a coordinated systemic inflammatory response syndrome aimed at limiting the extent of injury and restoring normal physiologic processes. The specific nature and extent of this response can vary widely based on the causative insult. See Table 20-1.

Table 20-1. Metabolic Response During Starvation and Injury

Characteristic Finding	Starvation (Marasmus)	Injury (Protein-Energy Malnutrition)
Energy needs	Decreased	Increased
Primary fuel (RQ)	Lipids (0.75)	Mixed (0.85)
Insulin	Decreased	Increased (resistance)
Ketones	Present	Absent
Counterregulatory hormones	Basal	Increased
Total body water	Decreased	Increased
Proteolysis	Decreased	Accelerated
Glycogenolysis	Increased	Accelerated
Lipolysis	Increased	Increased
Body stores		
Skeletal muscle	Reduced	Reduced
Fat	Reduced	Reduced

Visceral proteins	Preserved	Increased liver/immune
Refeeding response	Net anabolism	None (unless reversed)
Weight (lean tissue loss)	Gradual	Accelerated
Typical setting	Patient with chronic diseases	Patient in hospital/ICU (cardiac, COPD, etc)

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; RQ, respiratory quotient

Adapted from Daley BJ, Bistrian BR. Nutritional assessment. In: Zaloga GP, ed. *Nutrition in Critical Care*. St Louis, MO: Mosby-Year Book; 1994:9–33 with permission from Elsevier.

In critical illness, there is increased release of inflammatory mediators or cytokines (eg, interleukins 1 and 6, tumor necrosis factor) and simultaneous increased production of counterregulatory hormones (eg, catecholamines, cortisol, glucagon, growth hormone). The release of cytokines and counterregulatory hormones leads to a cascade of events that affect various body systems and have a profound impact on the patient's metabolic and nutritional status. (1) When physiologically controlled, this response can facilitate recovery. When uncontrolled, it can impair host responses to critical illness.

When severe infection is the etiology of the critical illness, the metabolic and physiologic responses to systemic infection are referred to collectively as "sepsis" or "sepsis syndrome." The most severe form, septic shock, is associated with the development of multiorgan dysfunction and may ultimately cause death. Sepsis leads to significant metabolic changes that result in increased energy expenditure. In nonsurgical, mechanically ventilated septic patients, energy requirements have been estimated by the Harris-Benedict (HB) equation at 20% above the basal energy expenditure (BEE). (2) Since sepsis may occur in the setting of other concomitant organ dysfunction, energy expenditure varies with the severity of illness.

The metabolic response to severe head injury is even more dramatic, exceeding the HB prediction of BEE by 40% to 50%. Urinary nitrogen losses exceeding 25 g/day have been reported (3).[3] It may take several weeks following injury to restore a neutral to positive nitrogen balance in these patients.

Nutritional Alterations in Critically Ill Patients.

The cascade of events following injury may affect multiple organ systems, can last from hours to days, and may be accompanied by impaired immune function and delayed wound healing. The magnitude of the response depends mainly on the severity of illness, with individual variability resulting from patient-specific illness(s) and genetic variations.

1. **The rate of protein catabolism** exceeds the rate of protein synthesis, resulting in negative nitrogen balance. There is loss of muscle mass and protein degradation in vital organs. The accelerated skeletal muscle proteolysis causes movement of amino acids (especially alanine and glutamine) from the periphery to the viscera for gluconeogenesis. Alanine is the major amino acid used for hepatic gluconeogenesis. Glutamine is the preferred energy source for enterocytes, cells of the immune system, and cells involved in tissue repair. It serves as a substrate for renal gluconeogenesis and for hepatic synthesis of the intracellular antioxidant glutathione. Branched-chain amino acids such as leucine, isoleucine, and valine also become important oxidative substrates during critical illness. Cytokines released from monocytes and macrophages cause the liver to reprioritize its protein synthesis, reflected by increased production of the "positive" acute-phase proteins (eg, C-reactive protein, a1-antitrypsin) and decreased synthesis of the constitutive "negative" acute-phase proteins (albumin, prealbumin,

retinol-binding protein, transferrin). There are decreased blood levels of visceral proteins regardless of the patient's nutritional status.

2. **Glucose metabolism**
    a. During stress, increased endogenous glucose production is the result of increased counterregulatory hormones and cytokines that stimulate glycogenolysis and gluconeogenesis. Major substrates for gluconeogenesis are glycerol (from adipose tissues), alanine (from skeletal muscles), and lactate (from peripheral tissues and skeletal muscles). This response is believed to satisfy the glucose needs of the brain, leukocytes, and the cells involved in tissue repair.
    b. Hyperglycemia may exist even with normal or increased blood insulin level, as insulin resistance is characteristic of generalized stress. Septic patients have a significant increase in glucagon, the primary hormonal mediator of gluconeogenesis. Changes in whole-body glucose uptake and glucose oxidation in sepsis are complex. Whole-body glucose uptake and oxidation may be increased in the early stages of sepsis and endotoxemia. This is possibly the result of a cytokine-induced increase in non-insulin-mediated glucose uptake by tissues rich in mononuclear phagocytes (eg, liver, spleen, ileum, lung).
3. Lipolysis is accelerated with mobilization of glycerol and free fatty acids, and there is increased fatty acid oxidation. Overall, the patient's energy stores are reduced.
4. Critical illness is also characterized by activation of the hypothalamic-pituitary-adrenal axis with the release of cortisol from the adrenal gland. This essential response to illness and stress contributes to maintenance of cellular and organ homeostasis.
5. Significant fluid and electrolyte disturbances may occur in the critically ill patient, depending on the patient's underlying medical problems, nutritional status, and drug or resuscitative therapy. A detailed review of fluid and electrolytes disturbances can be found elsewhere.[4]
6. The physiologic response to stress and injury and its effects on the metabolic and nutritional status of pediatric critically ill patients are similar to those for adults. Due to their limited tissue reserves, pediatric patients may develop malnutrition faster than adults.

Nutrition Support in Critically Ill Patients

Assessment of nutritional status in adults

The assessment of nutritional status includes a medical, surgical, and dietary history obtained from the patient or caregiver. In contrast to isolated trauma or burn patients, septic patients often have some degree of underlying malnutrition before the septic episode. This may be a predisposing factor to immune dysfunction that compromises the patient's ability to fight infection. Since no single measure can provide an accurate assessment of nutritional status, combined subjective and objective data should be used (see Chapter 1). A multitude of factors may limit the accuracy of nutritional assessment.

a) A history of acute or chronic weight loss or gain before hospital admission is an essential indicator of the patient's nutritional status. Because body weight fluctuates with large-volume fluid resuscitation, preinjury weight in critically ill patients provides useful information on nutritional status.
b) Anthropometric parameters including skinfold thickness and arm circumference measurements may be unreliable and are seldom used in critically ill patients because the patient's positioning and fluid status affect their accuracy.
c) Visceral protein (eg, albumin, prealbumin) levels are affected by stress, fluid shifts, and other factors that limit their specificity and sensitivity.
d) Delayed hypersensitivity skin testing that measures cell-mediated immunity also has limitations in the critically ill patient. Many nonnutritional factors such as tissue

disruption, acute hemorrhage, hypovolemic shock, anesthesia, surgery, and the use of steroids and immunosuppressants depress immune function, independent of nutritional status.

Assessment of nutritional status in pediatric patients

Surgical and medical problems that may affect the patient's nutritional status should be identified. Examples in the pediatric patient include congenital defects, gastrointestinal surgeries, impaired neurological status, chronic lung disease, history of premature birth, and the presence of gastrointestinal symptoms that impair food intake or absorption, such as nausea, vomiting, constipation, or diarrhea. Among patients admitted to the PICU with a diagnosis of congenital heart disease, 15% to 20% are malnourished. (5,6)

Anthropometric measurements such as length or height, weight, and head circumference should be obtained upon admission to the PICU and compared with existing standards (see Chapter 1). The measurements are compared against weight-for-age, length-for-age, and weight-for-length or BMI standard tables to determine whether the patient is adequately nourished or is experiencing moderate or severe malnutrition. Weight or length status and growth patterns are the primary parameters for nutritional assessment. Body weight should be obtained daily in the PICU patient using the same scale. Fluid shifts and imbalances are common in critically ill patients and may make weight changes an inaccurate indicator of nutritional status.

Energy requirements

1. Because either overfeeding or severely restricting energy can be detrimental to the outcome of critically ill patients, sound estimates of energy requirements are necessary. Many equations have been derived to estimate energy requirements; the HB equation is the most widely used. Stress factors for various disease states have been empirically determined by the use of indirect calorimetry and are added to the estimated energy expenditure calculated using the HB equation. The stress and activity factors used to adjust for the severity of illness may be excessive and can lead to overfeeding critically ill patients. In fact, experimental studies suggest that matching nutritional intake to metabolic expenditure may exacerbate inflammation and increase mortality. (7) [7] Although energy requirements at approximately 25 to 30 kcal/kg/day have been recommended for the critically ill patient, (8) [8] there is increasing evidence that lower caloric intake (not exceeding 25 kcal/kg/day) may be safer in these patients. In obese patients, nutrition should be provided based on adjusted body weight (see Chapter 28).
2. The gold standard for measuring energy expenditure in the clinical setting is indirect calorimetry (see Chapter 22). This is problematic in pediatric patients because of low gas flow rates and the use of noncuffed endotracheal tubes, which create an air leak, making gas collections incomplete.
3. Energy requirements of the critically ill pediatric patient change with the patient's clinical status. Aside from the severity of illness and stress level, other factors that affect energy expenditure include crying, blood draws, physical therapy, and endotracheal tube suctioning.
4. The recommended daily allowance (RDA) for age includes a 30% to 40% factor for growth in young infants and for activity in children and thus typically overestimates energy requirements for PICU patients. (9,10) [9,10] Energy requirements can be estimated at 1 to 1.2 times the resting energy expenditure, depending on the nutritional status, stress level, and nutrient tolerance.

Protein requirements

1. Protein requirements for critically ill adult patients are approximately 1.5 g/kg/day. Proteins are administered based on the patient's premorbid body weight or the adjusted ideal body weight in obese patients. The magnitude of nitrogen loss varies with the clinical condition

(Figure 20-1) and parallels the energy expenditure and stress level. Requirements may be up to 2 g/kg/day in patients with trauma, severe burns, and head injury and as high as 2.5 g/kg/day in adult patients treated with continuous renal replacement therapy (CRRT). (11) [11]

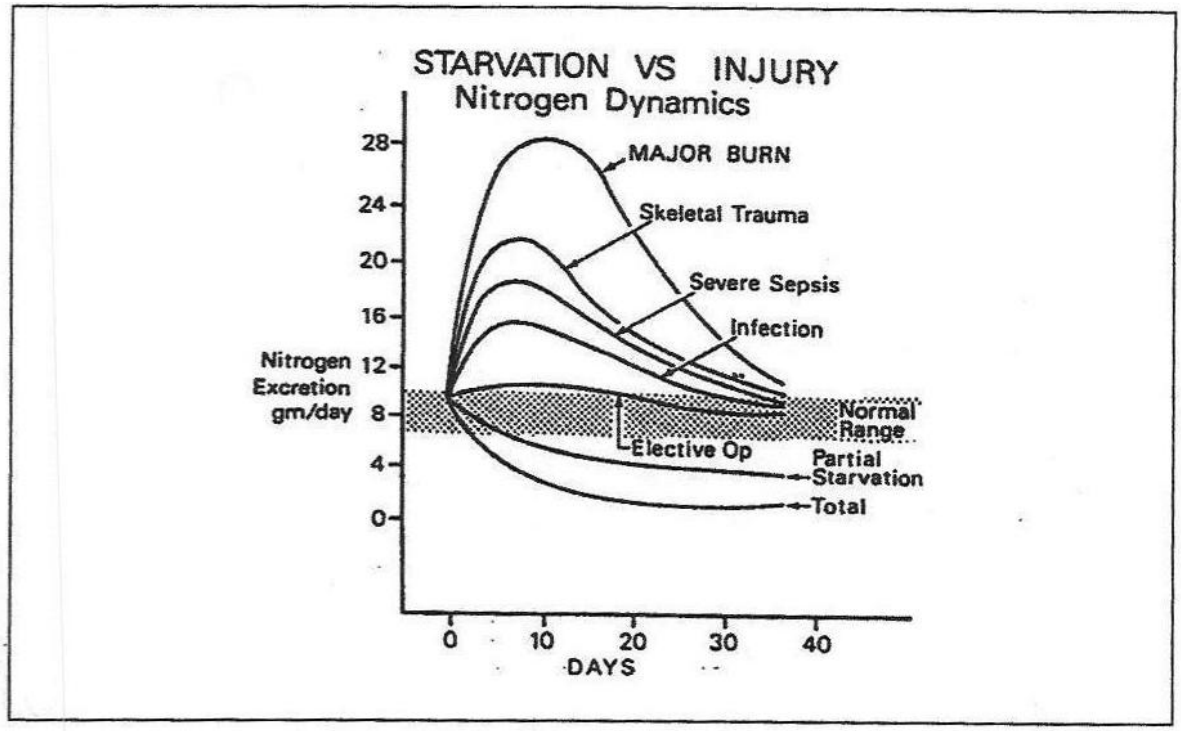

Figure 20-1 Change in nitrogen excretion in various disease states. Reprinted from Long CL, et al. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. J Parenter Enteral Nutr 1979;3:452-56 with permission from A.S.P.E.N.

2. It is the underlying paradigm that nutrition intervention is designed to sustain the body's nutritional stores until the increased energy and protein requirements subside. Since the catabolic rate exceeds the anabolic rate in critical illness, nutritional support can only limit the loss of the body's protein and calorie stores. The goal is to administer sufficient nitrogen to provide a positive or neutral nitrogen balance. This is best assessed by nitrogen balance studies, which are discussed in Section V.
3. Protein requirements for the PICU patient vary with age and clinical status. Protein/amino acids requirements in PN support for term infants are 2.5 to 3 g/kg/day. In older children, amino acid requirements are 2 to 2.5 g/kg/day, and critically ill adolescent patients require 1.5 to 2 g/kg/day. Higher protein/amino acid amounts are required for trauma patients and those treated with CRRT to make up for the amino acid losses via the hemodiafilter.

Benefits of enteral feeding

1. Enteral nutrition (EN) should be considered within the first 48 hours of injury once the patient is resuscitated and stabilized. Early initiation of EN is crucial to minimize the effects of hypercatabolism and hypermetabolism.
2. Oral nutrition is the preferred route of nutrient intake. If the patient cannot or should not be fed orally, then EN is the preferred feeding route. EN is more physiologic, cheaper, and safer than PN.
3. The gastrointestinal tract has a highly metabolically active mucosa. Lack of enteral feeding results in gastrointestinal mucosal atrophy, bacterial overgrowth, increased intestinal permeability, depletion of the liver's antioxidant enzymes, and possible translocation of

bacteria and/or bacterial products. EN increases mucosal blood flow, provides a direct source of nutrients, and maintains the metabolic activity and hormonal and enzymatic balance between the gastrointestinal tract and the liver. Even low rates of enteral feeding (eg, 10 mL/hr in adults) will have protective effects on the gut mucosa and liver. Enteral feeding maintains gut integrity, prevents gut mucosal atrophy, may prevent bacterial translocation, and preserves gut-associated lymphoid tissue (GALT), which is the major source of gut mucosal immunity. EN has been shown to replete the GALT that may become depleted with PN use. While PN bypasses first-pass liver metabolism, EN allows most nutrients to go through the portal circulation. This may have a protective effect on the liver. (12) [12]

4. Enteral feeding is also associated with lower rates of infectious complications than PN. Kudsk et al demonstrated significantly fewer cases of pneumonia, intra-abdominal abscesses, and episodes of catheter sepsis with lower septic morbidity in trauma patients who were enterally fed than in those who received PN. The most significant differences were seen in the more severely injured patients. (13) [13]
5. EN is associated with improved wound healing, greater wound strength, and more wound hydroxyproline and collagen accumulation, which may explain the lower risk of anatomic leaks and fistulas in bowel surgery patients who receive EN instead of PN. (12) [12]
6. Although EN has many safety and metabolic advantages over PN and is associated with fewer complications, it does not seem to affect patient mortality or the incidence of multiple organ failure. (14) [14]

Enteral feeding in pediatric patients

1. Pediatric patients on an oral diet who stay longer than 5 days in the intensive care unit should have ongoing calorie count monitoring.
2. The patient's fluid requirements should be the primary consideration when the enteral formula is being selected. Then the energy and protein requirements should be considered. A 20 kcal/oz formula is equivalent to 0.67 kcal/mL, and a 24 kcal/oz formula is equivalent to 0.8 kcal/mL.
3. In infants with congenital heart disease, fluid restriction often dictates concentrating enteral formulas beyond 24 kcal/oz to meet energy and protein requirements in small volumes.
4. Enteral feeding is usually initiated at full strength since all infant and pediatric formulas are hypotonic or isotonic and there is minimal risk for hyperosmolar diarrhea with these formulas.
5. Continuous gastric or small-bowel feeding should be attempted first. Enteral feeding in infants is usually initiated at 1 mL/kg/hr and advanced to energy goal at a rate of 1 to 2 mL/kg/hr every 8 to 12 hours as tolerated. The initial volume should not exceed 50 mL/hr regardless of the patient's age or weight.

Immunonutrition

1. A number of specific nutritional supplements are now recognized to modulate the biologic response to injury, inflammation, and infection. Collectively referred to as immunomodulating agents, they include glutamine, omega-3 fatty acids, arginine, and antioxidants. These agents are included in various combinations in selected enteral feeding formulas.
2. Immunomodulating agents have specific favorable biological and clinical effects. Randomized clinical trials have evaluated the role of different immunomodulating enteral formulas in critically ill adult patients but not the individual components, and the results of these studies have been widely debated. A meta-analysis by Heyland et al demonstrated reductions in infectious complications, particularly in elective surgery patients, and reductions in length of stay in the intensive care unit. (15) [15] However, the effect of these

formulas on organ failure and mortality is less clear. These formulas have not yet been studied in the pediatric population.

3. Glutamine, the most abundant amino acid in skeletal muscles, is a precursor of the antioxidant glutathione and a primary nutrient for enterocytes and the GALT. Lack of glutamine may have profound effects on gut integrity and lymphoid tissue. Prophylactic administration of glutamine to critically ill patients has been attempted to improve patient outcome, but data remain inconclusive.
4. The long chain omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) found in fish oil are commonly added to immunomodulating enteral formulas. Increased intake of omega-3 fatty acids instead of omega-6 fatty acids has numerous potentially positive biological effects. Eicosanoids derived from linoleic and arachidonic acids are proinflammatory. Those derived from omega-3 fatty acids are less inflammatory and less immunosuppressive than eicosanoids derived from omega-6 fatty acids.
5. Arginine, a nonessential amino acid, may become conditionally essential in the critically ill patient. Biological actions include stimulation of growth hormone, prolactin, and insulin-like growth factor. Arginine is required for the synthesis of hydroxyproline, is essential for lymphocyte function, and is the precursor of nitric oxide. Arginine levels may fall in septic patients due to deceased intake, increased metabolism to nitric oxide, and catabolism of arginine in the urea cycle as a consequence of increased arginase expression. If sepsis is potentially an arginine-deficient state, then arginine supplementation should be beneficial in septic patients. In a meta-analysis, immunomodulating enteral formulas with high arginine content resulted in a significant reduction of infectious complications (15) [15] but had no effect on mortality. At this point, the role and safety of arginine supplementation for critically ill patients are not fully elucidated and require further studies. (16,17) [16,17]

Parenteral nutrition

1. PN is used in patients for whom oral nutrition or EN is not feasible or is contraindicated and who are malnourished or at high risk for malnutrition (eg, critically ill patients). In adult patients who are not malnourished or at high risk for malnutrition, PN can be safely withheld for up to 5 to 7 days while the enteral route is pursued. PN should be used for the shortest duration possible.
2. PN should not be used to correct acute fluid and electrolyte deficiencies; instead, a separate intravenous solution with electrolyte supplements should be used as needed. The assessment and management of electrolyte disturbances should take into consideration electrolyte sources and losses, acid-base status, clinical conditions, and medications that affect electrolyte balance.
3. Dextrose tolerance is dependent on its rate of infusion and underlying patient conditions. Dextrose use is reduced in stressed patients, patients with diabetes, patients with acute pancreatitis, and patients treated with medications that alter glucose metabolism (eg, corticosteroids, tacrolimus, catecholamine vasopressors). Critically ill patients have a lower tolerance to dextrose infusion compared to nonstressed subjects. In hypermetabolic burn patients, glucose oxidation reaches a plateau at a dextrose infusion rate of 5 mg/kg/min. (18) However, lower dextrose infusion rates are even better tolerated, and rates should be kept at =4 mg/kg/min in adult critically ill patients and should not exceed 60% of total daily energy. (19) In critically ill diabetic patients and those requiring insulin, the dextrose infusion rate should be started at no more than 2 mg/kg/min and advanced slowly over a few days to energy goal while glucose control is maintained with intensive insulin therapy. Uncontrolled hyperglycemia may cause fluid and electrolyte abnormalities, hyperglycemic hyperosmolar nonketotic syndrome, and increased susceptibility to infections. Hyperglycemia is also an early sign of sepsis, so sepsis should be ruled out in patients who are stable on PN and suddenly develop hyperglycemia or increased insulin requirements.

4. Lipid requirements

a) Lipid clearance is reduced in stressed patients due to decreased activity of lipoprotein lipase (LPL), the main enzyme released in the bloodstream that hydrolyzes lipid particles into fatty acids. Since critically ill patients have reduced tolerance to lipid emulsion infusion, the lipid infusion rate should not exceed 0.12 g/kg/hr to avoid the development of elevated triglyceride levels. (20)

b) A dose of intravenous lipid emulsion at 0.5 to 1 g/kg/day prevents essential fatty acid deficiency. Lipid emulsions may need to be withheld in pediatric patients when serum triglyceride concentrations exceed 275 mg/dL.

c) Although it has been suggested that lipid emulsions may have immunosuppressive effects by helping to reduce phagocytosis and cytokine secretion, these effects have not been clinically proven. (21)

d) There is a difference in the clearance of various lipid emulsion concentrations due to the differences in the phospholipid-to-triglyceride (PL/TG) ratio of each emulsion. The PL/TG ratios of the 10%, 20%, and 30% lipid emulsions are 0.12, 0.06, and 0.04, respectively. In critically ill patients, lower plasma triglycerides, phospholipids, and cholesterol concentrations have been seen with the use of 30% lipid emulsions compared to 10% and 20% lipid emulsions. (22-24)

e) Structured lipids made of medium-chain triglycerides (MCT) are currently available only in Europe. These mixtures contain MCT and long-chain triglycerides (LCT) in 75/25 or 50/50 MCT/LCT ratios. The inclusion of LCT in the MCT/LCT mix provides the essential fatty acids that are not provided in MCT. MCT are oxidized faster than LCT, a possible advantage in patients with reduced lipid clearance, such as critically ill patients.(25) Although some research data showed that the MCT/LCT lipid emulsion may result in a better blood lipid profile and improved nitrogen balance, these results were not replicated in other studies.(26)

f) In patients with acute renal failure, the clearance of both LCT and MCT was found to be equally reduced in comparison to healthy volunteers, with similar increases in serum triglyceride levels between the 2 groups.

g) In patients with respiratory failure, variable effects have been seen in measures of respiratory function and pulmonary and arterial hemodynamics.(27-29) Hyperlipidemia during lipid emulsion infusion has been reported to affect pulmonary gas diffusion and pulmonary vascular resistance in patients with preexisting pulmonary disease.(30,31) More research is needed before routine use of the mixed MCT/LCT lipid emulsions can be recommended.

5. Multivitamin and trace element requirements

1. Typical standard adult multivitamins and trace element formulations are added to the daily PN. However, no specific guidelines for multivitamin and trace element supplementation are available for critically ill patients. Modification of specific micronutrients is rather based on the patient's underlying diseases (eg, liver failure, wounds, burns, fistulas).(32)

2. Blood trace element concentrations may not necessarily reflect their total body stores due to changes in tissue distribution, metabolism, or elimination. For example, during stress, blood zinc concentrations may fall due to sequestration in the liver, increased use in metabolic pathways, and increased renal elimination.

3. Supplementation of specific micronutrients is based on the patient's underlying diseases (eg, liver failure, wounds, burns, short gut syndrome) when alterations in micronutrient metabolism and requirements are needed.

The role of antioxidant supplementation (eg, supplementation of vitamins C, E, and A and selenium) in critically ill patients remains unknown. (33)[33]

4. Iron metabolism is also altered under stress, leading to decreased plasma iron concentrations. However, this may not necessarily indicate iron deficiency. Intravenous iron administration in the septic patient is discouraged since iron is essential for bacterial growth and may theoretically worsen sepsis.

Complications of Parenteral Nutrition

1. In a meta-analysis of studies that evaluated PN use in critically ill adult patients, the benefits of PN were most noticed in malnourished patients, who also had fewer complications with PN than nonmalnourished patients given PN. Critically ill patients who received PN had almost twice the risk of mortality (relative risk 1.78; 95% confidence interval 1.11–2.85). (34) Similarly, the Veterans Affairs cooperative study showed that perioperative PN improved the outcome only of high-risk severely malnourished patients. (35)
2. The deleterious effects of PN may be most evident in critically ill patients who are at a particularly high risk for nosocomial infections. A number of studies reported an increased risk of infectious complicationslonger hospital stay, and an increased risk of mortality in patients receiving PN. The Veterans Affairs study evaluated the role of perioperative PN (7–10 days before and 3 days after surgery) in patients who required noncardiac surgery. There were significantly more infectious complications in the PN group than in the control group that did not receive PN (14.1% vs 6.4%). Also, a trend toward higher 90-day mortality was observed in the PN group compared to the control group (13.4% vs 10.5%). Only those with severe malnutrition appeared to benefit from PN as administered in that study. (35)
3. PN may also be associated with a more pronounced proinflammatory response than EN. Clinical and experimental data have shown higher levels of local and systemic proinflammatory mediators with PN than EN. Higher levels of interleukins (IL-6, IL-8) were found after colorectal and major abdominal surgeries in patients receiving PN compared to patients who were fed enterally. (36,37) PN may be particularly harmful in patients with severe inflammation such as acute pancreatitis; such patients were shown to have higher infective and noninfective complications if they received PN compared to jejunal feeding.
4. A recent meta-analysis of six randomized controlled trials compared the safety and clinical outcomes of PN versus EN in patients with acute pancreatitis. Results of the meta-analysis showed that EN was associated with a significantly lower incidence of infections, shorter length of stay, and reduced surgical interventions compared to control pancreatitis patients. However, no statistically significant difference was found for mortality and noninfectious complications between the PN and EN groups.(38)
5. Complications of excess dextrose infusion include hyperglycemia, hypertriglyceridemia, hepatic steatosis, respiratory decompensation, and depression of immune function. Hyperglycemia is now thought to be a major driver of parenteral nutrition complications, which are reduced when insulin is used to maintain euglycemia. (39) (See Chapter 27.)
    a. Dextrose overfeeding resulting in hyperglycemia can depress the immune system and increase infection risk. Hyperglycemia may impair cellular and humoral host defenses by reducing phagocytosis, impairing neutrophil chemotaxis and adhesion, and inhibiting complement fixation. In vitro and animal data showed a reduction in phagocytic activity of polymorphonuclear granulocytes and inhibition of immunoglobulin function with hyperglycemia. In humans, postsurgical diabetic and nondiabetic hyperglycemic patients have increased

nosocomial and wound infections. Controlling hyperglycemia has resulted in improved phagocytic function as well as improved patient outcome.

b. Hyperglycemia has traditionally been defined as a random serum glucose concentration >200 mg/dL. Serum glucose concentrations of 150 to 200 mg/dL have long been considered acceptable in stressed patients because it is believed that modest hyperglycemia may promote cellular glucose uptake by glucose-dependent tissues (brain, red blood cells, wounds). However, recent data show that maintaining euglycemia between 80 and 110 mg/dL reduces complications and improves patient outcome. Van den Berghe et al, in a prospective randomized controlled study, evaluated the effects of intensive and conventional insulin therapies in 1548 adult surgical intensive care unit patients. Surgical patients were randomized to receive intensive insulin therapy to maintain serum glucose concentrations between 80 and 110 mg/dL or to receive a conventional insulin regimen to maintain serum glucose concentrations between 180 and 200 mg/dL. Study results showed that intensive insulin therapy was associated with a 34% reduction in overall in-hospital mortality and a 46% reduction in septicemia. Intensive insulin therapy significantly reduced mortality in the intensive care unit (from 8% to 4.6%) and in patients who remained more than 5 days in the intensive care unit (from 20.2% to 10.6%) compared to conventional insulin therapy. Intensive insulin therapy was also associated with reduced morbidity factors such as acute renal failure, ventilator dependency, and polyneuropathy.(39) A follow-up multivariate logistic regression analysis of the data by the same investigators showed that the benefits of intensive insulin therapy were the result of normalizing serum glucose rather than the result of the insulin dose. (40) The Van den Berghe study data are applicable to adult surgical intensive care patients; studies are under way to determine the role of tight glucose control in other intensive care and hospitalized patients.

c. In the absence of dextrose overfeeding, insulin therapy may be necessary to control hyperglycemia while meeting the patient's caloric needs, as insulin resistance is characteristic of generalized stress. Insulin stimulates glucose uptake and reduces hepatic glucose production. However, insulin does not increase glucose oxidation, and excess dextrose is largely converted to fat instead of being oxidized to carbon dioxide (CO_2). In adults, the use of a sliding scale subcutaneously administered insulin is not recommended due to variability of tissue perfusion that may lead to inadequate glycemic control between intermittent insulin dosing. The most effective way to maintain serum glucose concentrations between 80 and 110 mg/dL in hyperglycemic critically ill patients is the use of continuous insulin infusion that allows flexible titration of the insulin dose based on frequent serum glucose monitoring. A serum glucose threshold that is associated with increased morbidity and mortality has not been determined.

6. **Enteral feeding** is associated with fewer complications than PN and allows carbohydrate to pass through the liver with resultant hormonal/metabolic responses before reaching the systemic circulation. This reduces the hyperglycemic effect of glucose. In the Van den Berghe study, (39) patients who received exclusive PN required 26% more insulin to maintain euglycemia than those who received partial enteral feeding. (40)

7. **Hypertriglyceridemia in patients receiving PN** denotes excess triglyceride synthesis or reduced fat clearance. Hypertriglyceridemia during PN infusion is primarily due to dextrose overfeeding or excess lipid infusion. Stressed patients are at higher risk for hypertriglyceridemia due to increased lipolysis and hepatic fatty acid re-esterification, increased hepatic triglyceride synthesis from dextrose infusion, and decreased LPL

enzyme activity that results in reduced clearance of intravenously administered lipids. Also, certain medications used in critically ill patients, such as corticosteroids and immunosuppressants (sirolimus, cyclosporine), alter fat metabolism and increase serum triglyceride levels. Patients who are especially at risk for hypertriglyceridemia include those with sepsis, multiorgan failure, diabetes, liver disease, renal failure, or pancreatitis.

8. **Total energy and dextrose overfeeding may result in hypercapnia**, especially in patients with borderline respiratory function and limited pulmonary reserve. Excess carbon dioxide is produced relative to oxygen (O_2) consumption during excess carbohydrate administration, resulting in an increased respiratory quotient (RQ = VCO_2/VO_2). The RQs for carbohydrate, protein, and fat oxidation are 1, 0.8, and 0.7, respectively. Energy-mixed substrates from fat, protein, and carbohydrates normally yield an RQ of 0.85. The RQ exceeds 1 during carbohydrate overfeeding. As a result, increased carbon dioxide generation causes increased respiratory workload and minute ventilation. Mechanically ventilated patients may have prolonged ventilator dependence. In critically ill patients, overfeeding should be ruled out when the RQ exceeds 1. When total energy intake is appropriate, reducing the carbohydrate load and substituting fat calories lowers the RQ. However, the RQ may be an insensitive indicator of overfeeding in hypermetabolic patients. Only minor changes to the RQ may occur despite major increases in minute ventilation and oxygen consumption.
9. **Liver complications associated with PN** include steatosis (fatty liver), cholestasis, biliary sludge, and cholelithiasis. In the critically ill intensive care unit patient, these complications are unlikely to occur, due to the short duration of PN, assuming overfeeding is avoided. Although PN-associated steatosis is more common in adults and cholestasis is more common in children, both conditions may coexist in either patient population.
    a. Steatosis occurs when fat accumulation exceeds its transport from the liver. In patients receiving PN, high dextrose load is the primary cause of steatosis. However, lipid overfeeding and deficiencies of certain nutrients such choline, carnitine, and essential fatty acids may also lead to steatosis. Patients with hepatic steatosis are usually asymptomatic, and liver enzymes are poorly sensitive to the degree of fatty infiltration. Hepatic steatosis in patients receiving PN is usually reversible. The key to preventing hepatic steatosis is to avoid overfeeding and provide balanced PN with no more than 60% of total calories from dextrose, about 20% to 30% of total calories from fat, and the remaining calories from protein.
    b. PN-associated cholestasis is more common in long-term PN patients. Factors that predispose such patients to cholestasis include PN dependence, bowel rest, overfeeding, short gut syndrome, sepsis, and premature birth in newborn babies. Elevated serum bilirubin concentrations, especially conjugated bilirubin, are the earliest clinical signs of cholestasis. Patients supported with the extracorporeal membrane oxygenation (ECMO) system may show hyperbilirubinemia because of hemolysis from the mechanical stress on red blood cells as they pass through the ECMO circuit. (41) Jaundice may or may not be present depending on the severity of cholestasis. Measures to prevent PN-associated cholestasis include initiating enteral or oral feeding, weaning off PN, avoiding overfeeding, using balanced sources of calories, and cycling PN.

Monitoring

1. Standard laboratory parameters are monitored in critically ill patients receiving EN and PN (see Chapters 5 and 8).

2. Nitrogen balance is a generally accepted method for evaluating the adequacy of protein intake and retention. Its validity can be limited by many factors, such as adequacy of urine collection, unrecorded nitrogen losses from large open wounds, severe burns, diarrhea, or renal failure or liver failure with nitrogen accumulating in the blood. Ideally, nitrogen balance should be measured in a "steady state," but this may be impossible in critically ill patients. Values should be interpreted in the context of the patient's clinical status. Difficulty with urine collection makes determining nitrogen balance very difficult in young pediatric patients.

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Suggested Readings

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