Enteral Nutrition in the Critically Ill Patient

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INTRODUCTION

Clinical factors, such as premorbid nutritional status and severity of illness, determine the overall efficacy of nutritional support. Malnutrition may be defined as "a disorder of body composition in which macronutrient and/or micronutrient deficiencies occur when nutrient intake is less than required." Malnutrition leads to reduced organ function, abnormal laboratory chemistry values, and poorer clinical outcome. For all hospitalized patients, the reported prevalence of malnutrition is as high as 50%. Although difficult to quantify, the incidence in intensive care unit (ICU) patients is closer to 5%. A malnourished patient is more likely to have infectious morbidity, a prolonged hospital stay, and increased mortality. However, not all patients in the ICU need nutritional support, and disease and nutrition exhibit complex interactions. In critical illness, malnutrition results from abnormal nutrient processing and not starvation. Each individual patient should receive a nutritional formula specific to their disease process. Keeping this in mind, it is important to provide early nutritional support during critical illness. Approaches to nutritional support in the critically ill patient are detailed later in this article.

KEYWORDS

- Nutrition
- Critical illness
- Enteral nutrition
- ICU

KEY POINTS

- Early enteral nutrition is the preferred route of nutrition for the critically ill patient.
- Enteral nutrition maintains the intestinal barrier to prevent bacterial translocation.
- Parenteral nutrition is beneficial in the small group of patients who are malnourished on arrival to the ICU or in patients in whom the intestinal tract is unable to be used for greater than a week.
- Attention to calories and blood sugar control may reduce complications in patients receiving parenteral nutrition.

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METABOLIC RESPONSE TO INJURY

Injury and stress produce a constellation of signs and symptoms known as the “systemic inflammatory response syndrome” (SIRS), defined in 1992 by the American College of Chest Physicians and the Society of Critical Care Medicine. Three or more of the following are required to diagnose SIRS:

- Body temperature of greater than 38°C or less than 36°C
- Heart rate greater than 90 beats per minute
- Respiratory rate greater than 20 breaths per minute or a PaCO2 level of less than 32 mm Hg
- Abnormal white blood cell count (>12,000/μL or <4000/μL or >10% bands)

Another important component of SIRS is a hypermetabolic response lasting up to 1 month after injury. Besides trauma, other etiologies associated with SIRS include ischemia, inflammation, infection, or a combination of these. SIRS is nonspecific and its pathophysiologic properties are independent of the inciting mechanism. The body’s response to insult is inflammation and SIRS is considered a self-defense mechanism. The complex interactions between the various components of the inflammatory cascade and SIRS were summarized by Bone and coworkers as a three-stage process:

- Stage I: For example, intestinal ischemia leads to local cytokine production, initiating an inflammatory response to promote wound healing and activation of the reticular endothelial system.
- Stage II: The local response is augmented by the release of small quantities of local cytokines, stimulating release of growth factor and recruitment of macrophages and platelets. This acute response is balanced by a reduction in proinflammatory mediators and release of endogenous antagonists.
- Stage III: The goal of stage II is homeostasis, and a significant systemic reaction occurs if this is not achieved. Dysregulated cytokine release leads to an overall destructive rather than protective environment, eventually resulting in end-organ dysfunction.

The progression from SIRS to organ dysfunction and multisystem organ failure (MSOF) is thought to result from a series of insults, with each additional insult provoking an exaggerated response. The key to preventing the multiple effects is timely identification of the cause of SIRS and appropriate resuscitation and therapy, including provision of adequate nutrition.

Hypermetabolism in critical illness is characterized by accelerated protein catabolism to supply energy and substrates for increased protein synthesis in visceral organs. Excessive protein breakdown in skeletal muscle leads to amino nitrogen production and an increase in urinary nitrogen excretion (with approximately 85% as urea) roughly proportional to the severity of injury. Nitrogen balance is determined by the net loss or gain of body protein and is a measure of the catabolic state of the patient. It is imperative to recognize that the accelerated proteolysis occurs even in noninjured extremities.

In addition to the spleen and heart, the liver uses the protein redistributed from skeletal muscle to synthesize structural, plasma, and acute-phase proteins. The amino acids arginine and glutamine comprise 50% to 75% of the amino acid nitrogen released from skeletal muscle. Both amino acids are important as glucose precursors and are central to the immune response. Glutamine is also important in acid-base homeostasis and is a precursor for glutathione.
GUT DISUSE

The gastrointestinal (GI) tract normally provides a barrier to invasion by pathologic microorganisms. The functional and structural integrity of the intestinal epithelium is affected by the intake and processing of nutrients and the route of delivery of these nutrients, such as enteral feeding. The GI tract is also home to one of the largest immune organs in the body, known as the gut-associated lymphoid tissue (GALT). This tissue contains 70% to 80% of all immunoglobulin-secreting cells. The gut is responsible for 50% of the body’s total immunoglobulin production, with the primary component for mucosal immunity and barrier integrity being IgA. Decreased gut use results in reduced mucosal mass (about 10%–15% in humans) and disruption of the intestinal mucosa. When nutrients are not provided to the gut, there is shortening of the microvilli, the fingerlike projections in the intestinal wall that serve to increase the surface area for nutrient absorption, and the surface architecture of the small bowel mucosa is disrupted. Animal studies have revealed reductions in villus height after only a few days of complete bowel rest. This effect is not prevented by the use of parenteral (intravenous) nutrition, but rather villus atrophy is commensurate with the duration of parenteral feeding.

The structural and functional changes occurring in the small intestine increase permeability. In addition, distinct metabolic changes occur during stress versus starvation, including increased caloric expenditure and metabolic rate, mobilization of carbohydrate and fat stores, protein breakdown, and loss of lean body mass. The afferent limb of the stress response is the central nervous system, specifically activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. The effector response is mediated by the immune system (inflammatory cytokines, such as tumor necrosis factor [TNF]; interleukins [IL]-1 and -6; and the humoral response in the form of catecholamines, glucagon, insulin, cortisol, and growth hormone). Intestinal permeability is not increased as drastically in starvation alone as when the starvation is preceded by an injury. Ammori and coworkers reported that the increased gut permeability may be directly correlated to the severity of illness in patients with pancreatitis. In burn patients, the degree of gut permeability is inversely correlated to the percentage of goal calories provided by enteral nutrition (EN).

BACTERIAL OVERGROWTH

During critical illness, the gut barrier hypothesis suggests that certain substances can cross the gut mucosal lining and initiate and amplify the SIRS response. Decreased gut use leads to bacterial overgrowth and an increase in bacterial translocation. It has been demonstrated in animal models that intestinal IgA levels are inversely correlated with changes in intestinal permeability, degree of bacterial overgrowth, and translocation. Bacterial overgrowth leads to a predominance of aerobic bacteria. Reduced peristalsis (ileus) can also contribute to bacterial overgrowth. Bile salt secretions and secretory IgA (sIgA) levels are reduced, promoting bacterial adherence to the mucosa. The phenomenon of bacterial translocation and increased gut permeability explains the approximately 30% of patients who are found clinically or at autopsy to suffer from severe sepsis and MSOF without an identifiable focus of infection.

It is not known whether the process of translocation involves live bacteria or such products as endotoxins. After these products translocate across the bowel lumen, they enter the portal vein. An inflammatory cascade is initiated, including stimulation of Kupffer cells in the liver parenchyma. Moore and coworkers failed to find bacteria or endotoxin in the portal blood of severely injured patients, including a subgroup...
developing MSOF. Although clinical trials of selective decontamination of the digestive tract resulted in reduced incidence of pneumonias, primary bacteremias, and other infectious complications by approximately 50%, they did not improve survival rates. Another hypothesis is that gut-derived factors actually enter the mesenteric lymph rather than the portal bloodstream. Support for this latter theory is obtained from indirect evidence in which hemorrhagic-shock-induced lung injury was prevented after division of mesenteric lymphatic ducts. The lung is the first organ exposed to mesenteric lymph and clinically is one of the first organs to fail in severely injured patients. In vitro studies of mesenteric lymph compared with portal vein plasma have revealed increased endothelial cell monolayer permeability, increased activation of neutrophils, and endothelial cell death. Proof of clinical translation is difficult to conclusively show and change in outcome is even harder but some translocation of bacteria or their products occurs in humans and provision of enteral nutrients may prevent this.

**EFFECT OF NUTRITION DELIVERY METHOD ON GUT IMMUNE FUNCTION**

Mucosal immunity is dependent on slgA production. Although levels of slgA diminish within 5 days of gut disuse whether or not parenteral nutrition (PN) is used, lymphocyte populations are altered by an absence of EN. Normally, there is a balance between the proinflammatory arm and the anti-inflammatory arm of the immune system. The proinflammatory arm consists of differentiated T helper (Th) 1 lymphocytes and proinflammatory cytokines, such as IL-2, interferon gamma (IFN-γ), and TNF. Stimulation of naive cell differentiation into Th1 cells occurs by IL-12. The response of the proinflammatory arm of the immune system results in increased inflammation and is essential for host defense. This is counterbalanced by the anti-inflammatory response, consisting of IL-4-differentiated Th2 lymphocytes and secretion of additional IL-4, IL-6, and IL-10. The latter moderates Th1 response and is essential to prevent self-injury. In addition, IL-4 stimulates IgA-positive B cells in Peyer patches; further differentiation of IgA-positive B cells produces slgA-secreting plasma cells in the lamina propria.

Reduced gut use decreases IL-4 and IL-10 secretion and subsequent differentiation of naive lymphocytes into Th2 lymphocytes, eventually reducing slgA levels. In contrast, Th1 lymphocyte differentiation and production of IFN-β, TNF, and IL-2 are not affected by lack of EN. This leads to an unbalanced ratio of Th1 to Th2 lymphocytes and upregulation of the proinflammatory arm of the immune system, possibly contributing to host injury.

EN not only affects differentiation of lymphocyte populations, but also expression of adhesion molecules important in homing of naive B cells to the intestinal lamina propria and GALT. Proper homing of B cells is mediated by the ligand MADCAM-1, whose expression is decreased with gut disuse. Without an influx of B cells from the vascular space into the lamina propria, the intestinal Peyer patches atrophy. The decrease in IL-4 and IL-10 levels caused by intestinal disuse results in increased expression of the adhesion molecules ICAM-1 and E-selectin in the intestine and pulmonary microvasculature. The latter plays a role in sequestration of polymorphonuclear neutrophils into the microvasculature, exacerbating organ injury.

**GUT USE**

The functional and structural integrity of the GI tract is positively affected by normal enteral feeding. The benefits of EN include maintenance of mucosal mass, cellular proliferation, production of brush border enzymes, and maintenance of villus height. There is decreased intestinal epithelial cell permeability and small bowel blood flow is
stimulated with provision of enteral nutrients. A variety of endogenous agents, such as cholecystokinin, gastrin, bombesin, and bile salts, are produced. These agents have trophic effects on gut mucosa and can reverse the detrimental effects of PN on histologic and functional aspects of the intestinal tract. Cholecystokinin can partially restore the GALT system after use of PN.

Enteral feeding encourages the proliferation of Th2 CD4+ helper T lymphocytes, which in turn stimulates the production and release of IgA-stimulating cytokines, such as IL-4, IL-5, IL-6, and IL-10. Through a series of steps, IL-4 converts IgA-positive B cells in Peyer patches, whereas IL-10, IL-5, and IL-6 eventually promote differentiation of IgA-positive B cells into slgA-secreting plasma cells in the lamina propria.

Colonization resistance was first reported by van der Waaij and describes a process in which the predominant anaerobic flora of the GI tract limits the overgrowth of potentially pathogenic (mostly aerobic) organisms. The normal gut environment contains more than 400 obligate species in a total concentration of 10^{11} to 10^{12} CFU/g of feces. The concentration of aerobic flora is much lower, with aerobes accounting for less than 0.1% of the normal composition. Among the gram-negative bacilli in the bowel, Escherichia coli species are dominant. Secondary gram-negative bacilli other than E coli are ingested daily with food, but these secondary gram-negative bacilli fail to colonize the bowel in the presence of successful E coli populations in healthy volunteers. Among the aerobic gram-positive cocci, the enterococci are dominant, whereas staphylococci or streptococci also populated the bowels of healthy volunteers at low concentrations (<10^5 CFU/g of feces).

Most endogenous infections are caused by aerobic flora, and provision of EN maintains the normal, predominant, anaerobic flora of the gut.

Another important process is known as "oral tolerance." A small fraction of the food passing through the human adult intestinal tract consists of intact immunologic antigens. Oral tolerance refers to hyporesponsiveness to these food antigens. The immune system is downregulated in its response to common antigens in food and in the commensal bacterial flora of the GI tract. An alternative pathway for CD4+ helper T-cell differentiation occurs to support this process. Special regulatory T cells (Th3 and Tr1) stimulated by enteral feeding help promote a balanced Th2-Th1 profile. Normal intestinal immunity is maintained by the large dietary and indigenous microbial antigenic loads. The intestinal B-cell system is also stimulated by the antigenic constituents of food. Thus, continued EN supports a high concentration of IgA-secreting immunocytes and preserves the indigenous microbial flora in the gut, balancing the proinflammatory and anti-inflammatory arms and preventing an exaggerated inflammatory response.

Clinical investigations comparing EN with PN have shown that patients treated with EN demonstrate no apparent difference in mortality rate but that EN is associated with a significant reduction in infectious complications (relative risk [RR], 0.61; 95% confidence interval [CI], 0.44–0.84). Early EN compared with delayed forms of nutrition also resulted in reduced mortality (RR, 0.52; 95% CI, 0.25–1.08) and fewer infectious complications (RR, 0.66; 95% CI, 0.36–1.22). Both of these findings approached but did not reach statistical significance.

The site of EN delivery (gastric vs postpyloric) has also been studied. Postpyloric nutrition is associated with a decreased frequency of regurgitation and aspiration and the incidence of ventilator-associated pneumonia was significantly reduced with this method. Finally, EN is preferred to PN to avoid serious risk of catheter-induced sepsis in acute lung injury–acute respiratory distress syndrome. In my ICU, a postpyloric nasojejunal feeding tube is placed within 72 hours of admission, preferably within 48 hours, and EN is initiated.
IMMUNONUTRITION

Immunonutrition refers to therapy in which a particular nutrient is administered to induce a specific metabolic function not usually associated with nutrition support. These “immune-enhancing diets” are thought to modulate the immune system, facilitate wound healing, and reduce oxidative stress. When research first began in this area, nutrition was added as a therapeutic modality after control of the underlying disease process and restoration and stabilization of oxygen transport in patients who manifested severe malnutrition associated with organ dysfunction, nosocomial infections, and wound failure. Investigators believed that the postresuscitation phase consisted of a hypermetabolic pathologic state of persistent inflammation and suppression of immune function, eventually leading to MSOF and death. Enteral formulas containing supraphysiologic amounts of L-arginine, omega-3 fatty acids, L-glutamine, and antioxidants and vitamins have been developed and are discussed individually next. There is little direct evidence of the overall clinical efficacy of each of these immune compounds or their effects on hypermetabolism.

L-ARGININE

The amino acid L-arginine becomes an essential nutrient under stress conditions because the normal quantities endogenously produced to maintain muscle mass are insufficient because of increased protein turnover after injury. Arginine is required for stimulation and release of growth hormone, prolactin, insulin, and glucagon; plays a fundamental role in polyamine and nucleic acid synthesis; and is essential for growth but not viability of cells in vitro. It is also a critical substrate for nitric oxide (NO) production, which is mediated by a family of enzymes known as “nitric oxide synthases” (NOSs) that exist in constitutive and inducible isoforms. NO is an important mediator of vascular dilation, protein synthesis in hepatocytes, and electron transport in hepatocyte mitochondria.

Under normal circumstances and in some disease states, small quantities of NO are produced by the constitutive form of NOS (cNOS). This exerts a beneficial effect on tissue oxygenation and immune function. Supplemental administration of arginine (which is then metabolized to NO by cNOS) is associated with increased lymphocyte and monocyte proliferation, enhanced T-cell production, activation of macrophages and natural killer cells, and increased phagocytosis. Manufacturers have noted the benefits of arginine and have added supraphysiologic concentrations to their immune-enhancing formulas. Unfortunately, this had led to excessive NO production mediated through the inducible isoform of NOS (iNOS) that exist in constitutive and inducible isoforms. NO is an important mediator of vascular dilation, protein synthesis in hepatocytes, and electron transport in hepatocyte mitochondria.

Evidence concerning the effects of arginine administration on mortality is lacking. In critically ill patients with sepsis, arginine supplementation led to excessive mortality compared with an isonitrogenous control diet (23% vs 9.6%; \( P = .03 \)). In patients undergoing major cancer surgery, arginine supplementation has been associated with reduced length of stay. The mechanism behind this is thought to be increased thymic and peripheral blood lymphocyte blastogenic responses to mitogens from arginine supplementation.

OMEGA-3 FATTY ACIDS

Polyunsaturated fatty acids (PUFAs) are a major component of cell membranes and consequently influence the structure and function of cellular membranes. Experimentally, dietary PUFAs reduce platelet aggregation, slow blood clotting, participate in
cell surface enzyme activity, and limit the production of proinflammatory cytokines. Synthesis of all PUFAs occurs in humans, except those in the omega-3 and omega-6 families. Fish oil contains high concentrations of eicosapentaenoic acid, docosahexaenoic acid, and alpha-linolenic acid, which are naturally occurring omega-3 acids. The omega-3 PUFAs alter the physiologic characteristics of cell membranes and compete with arachidonic acid for cyclooxygenase metabolism. In response to lipopolysaccharide stimulation, arachidonic acid metabolism results in formation of type 2 prostaglandins and type 4 leukotrienes. These substances promote immunosuppression and inflammation. In contrast, omega-3 PUFA are metabolized to type 3 prostaglandins and type 5 leukotrienes, which are less inflammatory and do not suppress immune function. The North American diet contains very low levels of omega-3 PUFAs and n-3 PUFA can preferentially replace the n-6 PUFA, thus changing the physiologic characteristics of the cell membrane to stimuli, such as lipopolysaccharide.

Gadek and colleagues randomly assigned patients with acute lung injury–acute respiratory distress syndrome to either an experimental diet containing fish oils (eicosapentaenoic acid and docosahexaenoic acid) and antioxidants or a high-fat, low-carbohydrate control diet. Those receiving the experimental diet had higher plasma phospholipid fatty acid levels and fewer total cells and neutrophils recovered from bronchoalveolar lavage fluid. The experimental group also had fewer ventilator days, shorter ICU lengths of stay, fewer new organ failures, and a trend toward decreased mortality. Unfortunately, it is difficult to attribute beneficial clinical outcomes solely to PUFAs when other nutrients, such as antioxidants, are also likely to exert a significant influence. In addition, the high-fat diet used for the control group may have been harmful. This study and limited other studies do not clearly demonstrate the benefits of PUFAs.

**L-GLUTAMINE**

L-glutamine plays a central role in nucleotide synthesis and serves as an important fuel for rapidly dividing cells, such as lymphocytes and gut epithelial cells. It is also important in endogenous synthesis of the antioxidant glutathione. Glutamine is considered a conditionally essential amino acid during stress and critical illness. Consumption may overcome endogenous production during these periods, and low circulating levels of glutamine have been associated with immune dysfunction and increased mortality.

There is some debate whether the route of administration (parenteral vs enteral) affects the efficacy of glutamine. The gut and liver metabolize most enterally administered glutamine; therefore, it may not have a systemic effect. However, clinical studies have demonstrated that parenteral and enteral glutamine supplementation is beneficial in patients after bone marrow transplantation, multiple trauma, critical illness, or surgery.

As a single agent, glutamine supplementation has a broad spectrum of beneficial effects in humans. These include reducing infectious complications, acting as a trophic agent for the GI tract, and upregulating the immune system. published the first major clinical study demonstrating a reduction in infectious complications and hospital length of stay in patients with bone marrow transplant supplemented with glutamine. Houdijk and coworkers reported a nonsignificant reduction in the number of infections in trauma patients receiving a glutamine-supplemented enteral formula compared with those receiving a control formula (20 [57%] of 35 vs 26 [70%] of 37).

Other human studies have described the benefits of glutamine as a trophic substance for the GI tract, repairing damaged intestinal epithelial cell layers, and maintaining the
barrier function of the GI tract. In burn patients, improved immune cell function and a reduction in mortality with enteral glutamine have been demonstrated.

**ANTIOXIDANTS, VITAMINS, AND TRACE MINERALS**

Increased levels of reactive oxygen species (ROS) are present during critical illness because of an imbalance between protective endogenous antioxidant mechanisms and ROS production. Examples of ROS include superoxide anion, hydroxyl radical, hydrogen peroxide, and hypochlorous acid. Oxidative stress plays a central role in the pathophysiology of SIRS and MSOF. ROS cause cellular injury through numerous mechanisms, including destruction of cell and organelle membranes through peroxidation of fatty acids; hyaluronic acid and collagen degradation; damage to DNA and RNA; and damage to key enzymes, such as Na⁺/K⁺-ATPase.

The endogenous antioxidant defense system consists of enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. All of these enzymes contain heavy metals, such as manganese, selenium, copper, or zinc, at their active sites. When this system is overwhelmed, ROS react with target molecules and cause cellular damage. The endogenous system is the first line of defense against ROS, but cells can also use water-soluble nonenzymatic antioxidants, such as selenium, zinc, or vitamin C, or lipid-soluble antioxidants, such as vitamin E and betacarotene.

### Selenium

Selenium is the most-studied single nutrient. It is an important cofactor for the enzyme glutathione and exerts beneficial effects on immune function. Selenium deficiency has been associated with encephalopathy, progressive muscle weakness, myopathy, and cardiomyopathy. A study of selenium supplements in patients with necrotizing pancreatitis suggested that they reduced mortality, whereas in SIRS patients three separate selenium studies produced three different outcomes: one reported reduced mortality, one described a nonsignificant trend toward reduced mortality, and the final study reported no effect. Considered together, these four studies displayed a trend of reduced mortality with selenium supplementation.

### Zinc

Zinc is an essential element for cell growth, immune function, and disease resistance. A component of the enzyme superoxide dismutase, zinc regulates the expression of metalloproteins and plays a role in cell replication, protein synthesis, gene expression, and immune cell function. Zinc deficiency can inhibit immunologic development; modify the barrier functions of the skin, lungs, and GI tract; and alter the number and function of immune cells, such as neutrophils, monocytes, macrophages, T cells, and B cells, resulting in decreased resistance to infection. In critically ill head-injury patients on ventilators, zinc supplementation was associated with a nonsignificant reduction in mortality.

### Vitamin C

Linus Pauling demonstrated the link between vitamin C and immune function in the 1970s. White blood cells normally contain high concentrations of vitamin C. In patients with cancer who have undergone surgical trauma or are being treated for major infections, dietary requirements for vitamin C are increased.

Two randomized trials were conducted with patients suffering from pressure ulcers. The first study reported a significant reduction in wound area in those receiving high
doses of vitamin C, whereas the second revealed no benefit. Vitamin C improved chemotaxis, exhibited bactericidal activity, and resulted in shorter illness in patients with diseases involving dysfunctional phagocytic cells.

**Vitamin E**

Vitamin E is a lipid-soluble antioxidant shown in animal studies to enhance natural killer cell function, antibody production, macrophage phagocytosis, and resistance to pathogens. There is evidence to support the role of vitamin E in reducing the risk of prostate cancer. Newer conflicting data suggest no risk reduction. Based on these findings, studies examining the incidence of prostate cancer with vitamin E supplementation alone or in combination with selenium are underway.

**Betacarotene**

Carotenoids are naturally occurring pigmented compounds present in a variety of plants in the human diet. Their chemical structure facilitates neutralization of free radicals, making them important antioxidants. Betacarotene has been associated with cancer prevention, the mechanism of which may be related to its antioxidant and immune-enhancing properties. The immune enhancements include an increase in circulating lymphocytes and T-cell mediated immunity. The strongest evidence for the beneficial role of carotenoids is in the incidence of lung cancer, with eight out of eight prospective studies demonstrating a protective effect.

**PARENTERAL NUTRITION**

In patients who cannot tolerate adequate EN, total PN (TPN) is an important source of calories and nutrients. Enteral feeding is always preferable, but there are patients in whom the intestinal tract cannot be used or that must be frequently returned to the operating room. TPN is also appropriate for patients who are malnourished before injury. The main advantage to TPN is that full nutritional requirements may be met within 12 to 24 hours.

**Patient Selection**

In critically ill patients with a wide variety of disease processes (including pancreatitis, trauma, burns, and those on mechanical ventilation with an intact GI tract) TPN should never be selected over EN. The reduction of infections from the use of EN is consistent across almost all critical care patient populations. In comparing standard therapy (no artificial nutritional support provided) with TPN, Braunschweig and colleagues reported a significant reduction in infections with the former (RR, 0.77; 95% CI, 0.65–0.91). An even greater reduction in infectious complications was observed in well-nourished patients receiving standard therapy than with TPN. Trends toward reduced overall complications and hospital length of stay have also been described.

The one patient population in which TPN use reduces infectious morbidity, overall major complications, and mortality in comparison with standard therapy is patients with protein-calorie malnutrition defined by a greater than 10% to 15% weight loss or low body mass index. TPN has greater efficacy in these patients and can favorably affect their outcome compared with standard therapy. The prevalence of this population in ICUs is low, ranging from 8.3% to 12.6%.
**Timing of TPN**

The timing of TPN initiation is based on the underlying nutritional status of the patient. In critically ill patients without premorbid malnutrition (>10%–15% weight loss), it is reasonable to wait 7 to 10 days before starting TPN if oral intake is not possible. An even longer waiting period of 10 to 14 days has been advocated. If TPN is not initiated after 14 days, mortality is increased in patients on standard therapy (dextrose solution) who are not yet eating.

In malnourished patients TPN is superior to standard therapy in the first 7 to 10 days when the enteral route is not available, but should not be started unless it is anticipated that it will be continued for more than 7 to 10 days. Short-term TPN (<7 days) is not effective and does not favorably impact outcome.

**Lipid Content**

Recent investigations have demonstrated an increase in infectious complications with the use of TPN in surgically stressed patients. This is contrary to findings from earlier studies that reported either a marginal benefit for patients receiving TPN or no difference. One difference between the earlier and later studies is that patients in the more recent studies received a formulation in which 20% to 30% of the nonprotein calories were in the form of an intravenous fat emulsion (IVFE), compared with little or no intravenous lipid in the earlier studies.

IVFE is a widely used source of essential fatty acids. The long-term effects of withholding lipids in TPN are unknown. To prevent essential fatty acid deficiency at least 5% of total calories must be provided as a lipid emulsion. The consequences of not providing sufficient lipid are not observed until after the first 10 days of hospitalization. Lipid infusions have been associated with immune modulation and dysfunction in surgical patients receiving perioperative TPN.

Long-chain fats can cause immune suppression, promote dysfunction of the reticuloendothelial system, promote formation of prostanoids and leukotrienes, generate ROS, and negatively alter cell membrane composition. Battistella and colleagues reported that IVFE in the early postinjury period increased infectious complications (pneumonia and catheter-related sepsis); prolonged pulmonary failure; and increased ICU and hospital length of stay. One criticism of this study is that the no-lipid group did not have the missing calories replaced with additional carbohydrates and was underfed compared with the group receiving the lipid formulation.

Although IVFE is associated with a significant increase in infections in critically ill patients, lipid-free TPN is probably best reserved for short-term use (<10 days). In my ICU, IVFE is administered on Mondays and Thursdays with TPN.

**Hyperglycemia**

Most (50%–75%) of the total calories in the TPN admixture come from glucose (dextrose). In contrast, enteral formulas contain 40% to 55% carbohydrate. Parenteral nutrition leads to more frequent episodes of hyperglycemia. Hyperglycemia has been identified as the cause of increased complications during TPN and the reason for its reduced efficacy. Other studies noted that patients who developed infections had higher serum glucose values than their noninfected cohorts, but these values were still below those expected to increase the risk of infection (serum glucose >220 mg/dL). A wide variety of factors play a role in the dysfunction resulting from hyperglycemia including impaired neutrophil chemotaxis and phagocytosis, less effective wound healing caused by glycosylation of immunoglobulins, complement cascade dysfunction, and promotion of inflammation. Parenteral nutrition has also been
shown to increase the endogenous production of glucose and decrease glucose oxidation.  

Van den Berghe and coworkers demonstrated that compared with conventional treatment (target range for blood glucose concentration 10–11.1 mmol/L), achievement of tight glycemic control (4.4–6.1 mmol glucose/L) was associated with a lower incidence of sepsis \((P=0.003)\), a trend toward reduced ventilator days, and significant reductions in ICU length of stay \((P<0.04)\) and hospital mortality \((P=0.01)\).

More recent studies have compared this intensive regimen with a more conventional treatment goal of keeping target blood sugar levels at 10 mmol or less per liter. A blood glucose target of less than or equal to 10 mmol/L resulted in lower mortality than a target of 4.5 to 6 mmol/L. Further studies are necessary to determine the optimum window for glycemic control with the use of TPN. In my surgical ICU population, blood sugar is maintained between 5 and 7.2 mmol/L (90–130 mg/dL) except in patients with total pancreatectomy.

**PERMISSIVE UNDERFEEDING**

When first considered, the concept of permissive underfeeding in critical illness (total caloric provision set at approximately 20 kcal/kg/d of actual or ideal body weight) may seem counterintuitive. Classical nutritional teaching emphasizes the provision of sufficient nutrients to meet tissue demands. Full nutrient support promotes growth and protein synthesis but may also stimulate pathologic processes, such as bacterial virulence, autoimmune disease, cytokine production, and inflammation, which are also dependent on nutrient supply. Permissive underfeeding is a strategy based on the concept that short-term dietary restriction minimizes pathologic processes while limiting organ dysfunction.

Numerous studies have revealed that unrestricted nutrient intake optimizes growth in animals but shortens longevity. In normal and immunosuppressed animals, increased longevity was achieved when they were given protein-calorie restricted diets. The mechanism of this longevity is a delay in the onset of disease. In humans, several studies have indicated a relationship between excessive calorie intake and increased rates of insulin resistance, infectious morbidity, and mortality.

When given PN in excess of 35 kcal/kg actual bodyweight, hyperglycemia (blood glucose concentration >200 mg/dL) occurred in greater than 50% of nondiabetic patients. Another study compared a high-dose carbohydrate group (77% of total calories and 42.4 kcal/kg/d, on average) with lower doses of carbohydrates (60.6% of total calories and 34.3 kcal/kg/d, on average) and found more episodes of sepsis and higher mortality in the former group (both \(P<0.05)\). The higher carbohydrate formula in this study contained less protein, but this was not statistically significant. Most hypocaloric feeding is achieved by reducing the amount of carbohydrate or lipid.

Permissive underfeeding has been applied to EN. A recent study by Rice and coworkers hypothesized that trophic feeding would result in shorter duration of mechanical ventilation and better GI tolerance. The study population included patients within 48 hours of acute lung injury and less than 72 hours of mechanical ventilation who were able to receive EN. The study group received 25% of their calculated caloric goal compared with 80% within 6 hours of randomization and demonstrated no improvement in ventilator-free days (14.9 vs 15 days, difference –0.1 [CI, –1.4 to 1.2]) or infectious complications but was associated with less GI intolerance.

Results of these and other studies suggest the detrimental mechanism of excess caloric consumption is a cycle of insulin resistance and subsequent hyperglycemia at lower rates of energy intake. Some degree of malnutrition may be protective and
increase insulin sensitivity. Standard calorie intake in patients with sepsis may increase morbidity and mortality and permissive underfeeding may be beneficial, particularly in patients with sepsis.

SUPPLEMENTAL TPN

Supplemental TPN refers to the addition of TPN for patients receiving insufficient enteral feeding. When comparing EN with TPN-supplemented EN, there was no difference in morbidity or mortality, ICU length of stay, duration of mechanical ventilation, or incidence of respiratory infection. Herndon and coworkers reported a statistically significant increase in mortality in patients receiving supplemental TPN because of a greater depression of T-cell helper-suppressor ratios. In addition, supplemental TPN doubled the cost of nutritional support.

However, low-dose enteral feeding or trophic feeds are beneficial in patients receiving TPN. A small amount of enteral support during TPN might attenuate gut atrophy and improve host defenses, limiting bacterial translocation. This combination feeding may be tapered off when the patient tolerates more than 80% of protein and calorie needs by the intestinal tract. With combination feeding, it is still important not to overfeed the patient.

HOW I DO IT

In my surgical critical care population, I place a small-bore nasojejunal feeding tube into the postpyloric position and start tube feeds within 48 hours of admission to the ICU. The goal tube feed rate is achieved within 12 to 24 hours of placement. There are times when the feeding tube is unable to pass postpylorically and a potential delay in starting nutrition results. This is usually in a multiply injured trauma patient, and I elect to feed into the stomach taking other precautions, such as head of bed elevation. I do not spend the extra resources to send the patient to fluoroscopy for placement. If the patient is undergoing surgery, I ask the operating team to place a postpyloric nasojejunal tube. In the patient with an open abdomen whose bowel is in continuity, I start trophic feeds at 10 to 20 mL/h for the numerous benefits. A recent multi-institutional study by Burlew and coworkers showed for patients without a bowel injury, EN in the open abdomen is associated with increased fascial closure rates (P<.01), decreased complications (P = .02), and decreased mortality (P = .01). It is recommended that EN should be initiated in these patients after resuscitation is completed. In patients with bowel injuries and an open abdomen, EN did not seem to impact outcomes (fascial closure [P = .2], complication rate [P = .19], or mortality [P = .69]). When the intestinal route is unavailable or the patient is not tolerating EN, I begin TPN only if I anticipate using it for more than 7 days. I always reevaluate the feasibility of enteral feeding on a daily basis. For all patients except total pancreatectomy patients, I monitor blood sugars and aim to keep levels lower than 130 mg/dL.

SUMMARY

The stress response to injury involves hypermetabolism, impaired protein synthesis, and a catabolic state. This leads to a metabolic derangement that requires appropriate nutritional support to counteract loss of body protein, improve the metabolic and immunologic responses, and improve overall morbidity and mortality. Optimizing nutritional therapy is based on fully understanding the premorbid nutritional status of the patient and the pathophysiology of the underlying critical illness.
The stress response may be modulated by provision of specific nutrients. It is possible that individual nutritional formulas could be tailored to the patient and disease. The enteral route is preferred in most circumstances, but there are specific situations in which TPN is necessary and may be beneficial, if attention is paid to hyperglycemia and total calorie intake.

REFERENCES


