Nutrition in Trauma and Critically Ill Patients

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Abstract
Despite significant improvements in the practice of metabolic support of critically ill patients in recent years, malnutrition continues to be common among surgical patients, adding significantly to complications, infections, length of stay, costs, and increased mortality. Furthermore, hypercatabolism is the major metabolic response after major trauma and emergency surgery, making this patient population a unique subgroup of critically ill patients vulnerable to further decline in nutritional status. Many questions have already been answered, such as whether critically ill patients should be fed, when they should be fed, and how nutrients should be delivered. What is not entirely clear is what we should feed critically ill patients at different phases of specific diseases and disorders, as well as whether or not we should enhance and/or modulate patients' immunity.

Key Words
Emergency surgery · Nutrition support · Total parenteral nutrition · Enteral nutrition · Trauma · Critically ill patients

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Biochemical and Physiologic Consequences of Key Nutrients

Protein and Nitrogen Metabolism

Severely injured and critically ill patients characteristically demonstrate significant muscle losses and, consequently, are in negative nitrogen balance [1, 2]. The metabolic response to injury involves a striking increase in protein catabolism, along with a marked increase in urinary losses of nitrogen, phosphorus, sulfur, potassium, magnesium, and creatinine. The process of increased nitrogen losses is complex; it correlates with an increased metabolic rate, which peaks several days after an injury and gradually returns to normal over several weeks. This process occurs consistently after major fractures, blunt injuries, burns, sepsis, and various other insults. The metabolic response to severe surgical illness is associated with mobilization and the use of nutrient substrates, such as fatty acids, amino acids, and glucose.

In human patients, the rates of tissue protein synthesis vary after different traumatic injuries, but correlate with clinical status and with overall metabolic indices; the rates, clearly exacerbated during critical illness, are directly influenced by the illness, by the disease process, and by how the metabolic status of patients correlates with clinical indices of the severity of their illness [3]. The mobilization of amino acids from muscle protein leads to an irretrievable loss of nitrogen from the body in the form of urea, ammonia, uric acid, creatinine, and other excreted compounds [4]. If left uncorrected, the adverse consequences for critically ill patients include a rapid loss of muscle mass and subsequent marked debility.

Glutamine

Glutamine, a nonessential amino acid, serves as an important respiratory substrate for enterocytes and other rapidly dividing cells, including bone marrow, endothelial cells, and proliferating cells in wounds and areas of inflammation [5]. In patients with sepsis, glutamine depletion is even more severe and lasts longer, as compared with the hypercatabolism after an injury not complicated by infection. In addition, after surgery, glutamine consumption by the gastrointestinal tract is greatly increased and has been identified as a primary fuel for enterocytes and for other rapidly dividing masses of cells. Glutamine supplementation has been shown to exert trophic effects on intestinal mucosa.

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A recent prospective, double-blind, randomized trial of patients with major burns (>50% body surface) demonstrated that supplemental intravenous glutamine infused continuously over 24 h provided significantly better support than isonitrogenous enteral or parenteral amino acid solutions without glutamine. In that trial, 26 severely burned patients (i.e., with full-thickness burns covering 25–90% of their total body surface) were randomized. The group receiving glutamine had a lower incidence of gram-negative bacteremia as well as significant improvements in serum transferrin and prealbumin values at 14 days after the injury. Furthermore, in the group receiving glutamine, a trend was noted toward a lower mortality rate, a decreased incidence of bacteremia, and less antibiotic use [6].

Arginine

Arginine is considered to be a nonessential amino acid in the diet of healthy adults, but has been identified as a very important conditionally essential amino acid in critically ill and injured patients [7]. Arginine stimulates the release of growth hormone and prolactin, induces a marked release of insulin, improves weight gain, increases nitrogen retention, accelerates wound healing, and has trophic effects on the immune system in humans. In both animals and humans, plasma arginine levels decrease significantly after a burn injury. The potential mechanisms for the beneficial effects of exogenous arginine in patients with sepsis include enhanced (protein) metabolism, improved microcirculation and organ function, augmented immune function, increased antibacterial effects, improved gut function, and its possible antioxidant role [8].

Branched-Chain Amino Acids (BCAAs)

After trauma and during sepsis, branched-chain amino acid (BCAA) oxidation is increased; evidence indicates that skeletal muscle is the major site of BCAA degradation [9]. Because the concentration of BCAAs is low in patients with sepsis, supplementation with these important nutrient substrates may be beneficial. Despite some controversy over the use of BCAAs, a recent study demonstrated significantly lower morbidity and mortality rates in critically ill patients who received total parenteral nutrition (TPN) fortified with BCAAs (at a concentration of either 23 or 45%), as compared with the standard TPN that provided 1.5 g/kg/day of protein. The decrease in the mortality rate correlated with higher doses of BCAAs (up to > 0.5 g/kg/day) [10].

Evidence-Based Nutritional Support

Nutritional support is indicated either when return to a full diet is expected to be delayed or when postoperative complications further impair nutritional status. Little controversy remains about the need for early enteral nutrition in critically ill patients, if at all possible and if there are no contraindications to using the gastrointestinal tract. Many reports in the early 1980s defined the importance of early nutritional support. Two major prospective, randomized, controlled trials (PRCTs) done by Moore and Jones [11] in trauma patients and Alexander et al. [12] in patients with major burns found significant benefit for patients with early nutrition. Moore and Jones showed that the early nutritional support group had significantly fewer major septic complications and significant changes in nutrition parameters, as compared with the control group [11]. In the burn patient trial, which studied low vs. high protein caloric intake, Alexander et al. showed that the high-protein group spent significantly fewer days on antibiotics and had a significantly lower mortality rate.

Early nutritional support has the potential to reduce disease severity, diminish complications, and decrease the length of stay in the intensive care unit (ICU) and to favorably affect patient outcome; it should be started in the first 24–48 h after ICU admission, then advanced toward the target regimen over the next 48–72 h [13, 14].

Nutrient Substrate Delivery

The nutrient contents of enteral and parenteral formulations clearly differ in major ways. The delivery of nutrients such as proteins, sugars, and amino acids varies. Both types of formulations can maintain people during both health and disease [14]. The first major PRCT in the trauma population to compare total enteral nutrition (TEN) and TPN was done by Moore et al. [15]. The incidence of major infections in the TPN group was significantly greater than in the TEN group; in addition, multiple logistic regression analysis of potential risk factors for infections identified TPN as the only independent predictor. But the Moore et al. study was criticized because the TPN group had abnormally elevated blood sugar levels, which could explain its high infection rate [16].

Another PRCT done by Kudsk et al. [17] also found that the TEN group had significantly fewer major infections than the TPN group. In addition, the TPN group had a significantly higher incidence of catheter-related sepsis.

Despite current beliefs that TEN has fewer complications, TPN remains an important and vital technique for providing nutritional substrates, especially in patients who do not have a functioning gastrointestinal tract or gut access [3, 14]. TPN should be provided early in the clinical course and during the transition from nil per os (NPO, i.e., nothing by mouth) status, until patients are able to obtain all calories and nutrients by mouth or by the enteral route. When administered by specialized nutritional support teams and under the supervision of nutrition experts, TPN is superior to TEN in providing all nutrients to critically ill patients [16].

Lipids or No Lipids?

Although there is evidence that critically ill patients should not be given lipid emulsions, ICUs across the country continue to do so on a daily basis. A study by Gould et al. [18] proved that the fear of essential fatty acid deficiency, if fatty emulsions are not given to critically ill patients, is unfounded. In this study, designed to arrest and eliminate atherosclerotic plaque formation in patients with severe heart disease, TPN was administered, with no lipids, for 3 months. None of the patients on TPN without lipids developed a fatty acid deficiency, as measured by the triene:tetraene ratio and by clinical examinations. A subsequent study found that trauma patients on TPN with no lipids had better clinical outcomes than patients on TPN with lipids [19].

The latest guidelines of the American Society for Parenteral and Enteral Nutrition (ASPEN) call for no fat in the first week in the ICU [13]. Until intravenous omega-3 fatty acids become available everywhere, we should be very cautious when using fat emulsions in critically ill patients, because the effect may actually be detrimental.

Immune-Enhancing Enteral Nutrition

Immune-enhancing diets are becoming more and more a part of our nutritional support armamentarium. In addition to glutamine, arginine, and omega-3 fatty acids, such diets contain nucleotides, nucleosides, and other nutrients. In critically ill patients, the rationales for the use of omega-3 fatty acids in dietary formulas include their ability to incorporate into a cell membrane, their increased use during the inflammatory process, and their ability to modify the inflammatory response [20]. Omega-3 fatty acids affect cytokine production, decrease both tumor necrosis factor (TNFα) and interleukin-1 (IL-1) synthesis, and significantly modulate the inflammatory response in patients with acute respiratory distress syndrome (ARDS). Immune-enhancing formulas have reduced major infection rates, decreased the use of antibiotics, and shortened hospital stays in severely injured trauma patients. Enteral formulas fortified with immune-enhancing substrates are associated with a significant reduction in the risk of infectious complications and with a shorter overall hospital stay. However, providing adequate standard enteral or parenteral nutrition support does not necessarily protect critically ill patients from developing nosocomial infections. Nonetheless, since most critically ill patients are immunocompromised, modulating or enhancing their immune status with nutrient substrates has great potential value [21–26].

A multicenter study assessed the effect of immune-enhancing formulas on the length of hospital stay and on the complication rate in critically ill patients recovering from trauma, surgery, and/or sepsis [22]. Entry requirements for the study included an Acute Physiology and Chronic Health Evaluation (APACHE) II score higher than 10 and a Therapeutic Intervention Scoring System (TISS) higher than 20; patients were stratified by age (younger than 60 years vs. 60 years of age or older) and by whether they had sepsis or systemic inflammatory response syndrome (SIRS) with fever and leukocytosis. A total of 168 patients were randomized to receive an immune-enhancing formula; 158 were randomized to an isonitrogenous enteral diet using a common formula fortified with arginine, nucleotides, and fish oil (the control group). Both groups tolerated early feeding well, had a low tube-feeding-related complication rate, and achieved similar nitrogen balance. The most beneficial effects of immune-enhancing diets were demonstrated in severely ill patients with sepsis, whose hospital stay was shorter than predicted by 10 days and whose rate of acquired infections was also significantly reduced ($p < 0.01$). In the subgroup of patients with sepsis who achieved early enteral feeding goals, the median length of hospital stay was shortened by 11.5 days. In the SIRS subgroup, no statistically significant differences in benefits were noted.

In another study, an immune-enhancing enteral diet containing glutamine reduced septic complications in patients with severe trauma [23]. That study, unlike the multicenter study described above, included an isonitrogenous control group that did not receive an immune-enhancing diet. A prospective, blinded study, it examined 35 severely injured patients with abdominal

trauma: 18 were on an immune-enhancing diet supplemented with glutamine, arginine, nucleotides, and omega-3 fatty acids and 17 were on an isonitrogenous diet. Another 19 patients without enteral access served as the control group. Significantly fewer major infections complications (6%) developed in patients on the immune-enhancing diet, as compared with those on the isonitrogenous diet (41%, $p = 0.02$) or the control group (58%, $p = 0.002$). The length of hospital stay, antibiotic use, and the incidence of intraabdominal infections were significantly lower in patients on the immune-enhancing diet. Patients who were not fed a special diet (i.e., the control group) had the highest rate of complications.

A prospective, randomized, placebo-controlled, double-blinded, multicenter study of surgical intensive care patients who underwent upper gastrointestinal surgery compared clinical outcomes and cost [24]. Immunonutrition (Impact, Novartis Nutrition, Minneapolis, MN, USA) was given to 77 patients; an isocaloric and isonitrogenous diet was given to 77 patients (the control group). Early enteral feeding (within 12–24 h after surgery, advanced to a target volume of 80 ml/h by postoperative day 5) with arginine, dietary nucleotides, and omega-3 fatty acids (the immunonutrition group) was associated with a significant reduction in the frequency of late postoperative infections and of wound complications. Furthermore, the treatment cost was substantially reduced in the immunonutrition group, as compared with the control group. Early postoperative complications did not differ between the groups; however, the immunonutrition group had significantly fewer late complications.

Another study involving 390 critically ill surgical and medical patients found that achieving nutritional goals early, with an immune-enhancing enteral diet, greatly reduced morbidity and shortened the time on mechanical ventilation [25]. Of the 101 patients who achieved enteral nutrition goals early (within 72 h after surgery), the 50 who were fed with Impact had significantly reduced requirements for mechanical ventilation, as compared with the control group. Those 50 patients also had a shorter hospital stay.

In studies of critically ill patients and patients with gastrointestinal cancer, supplementation with key nutrients (arginine, glutamine, BCAAs, nucleotides, and omega-3 fatty acids) significantly reduced the risk of developing infectious complications and shortened the overall hospital stay [26]. Even though multiple studies have shown the beneficial effects of immune-enhancing diets, their use is not yet widely applied.

Immune-Modulating Nutritional Therapy

In critically ill and trauma patients, ARDS is a common, devastating syndrome of lung injury. It is characterized by acute-onset bilateral infiltrates (as shown by chest radiography), by a pulmonary-artery wedge pressure < 18 mmHg, and by a Pao_2/Fio_2 ratio (P/F) < 200. Insight into the molecular basis of the inflammatory process and lung injury has significantly deepened in recent years. Accordingly, new strategies have been designed and are being implemented to care for patients with ARDS. An important component of those new strategies is nutritional support. The results of a prospective, multicenter, double-blinded, randomized, controlled trial involving 146 patients with ARDS were reported recently [27]. The patients were randomized to receive, for at least 4–7 days, either enteral tube-feeding with eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA) or an isonitrogenous isocaloric standard diet. Patients on EPA + GLA had significantly fewer neutrophils per bronchoalveolar lavage, a significantly improved P/F oxygenation ratio, and lower ventilatory variable (FiO_2, positive end-expiratory pressure [PEEP], minute ventilation) values, as compared with those on the standard diet (the control group). Furthermore, patients on EPA + GLA spent fewer days on ventilator support and in the ICU. In addition, only 8% of the patients on EPA + GLA developed multiorgan system failure. Their antioxidants modulated neutrophil-mediated lung injury; the mechanism of action was thought to involve the anti-inflammatory and vasodilator properties of EPA and GLA. The benefits of EPA + GLA have been supported by other studies [28].

One recent study involving patients with sepsis or those in septic shock found that nutrient-rich special formulas with high doses of omega-3 fatty acids, fish oil, nucleosides, nucleotides, vitamins, and other nutrients were beneficial [29]. In that study, the 28-day mortality rate was significantly reduced in the study group on a special formula, as compared with the control group. In addition, the study group had more ventilator-free days (mean, 13.4 ± 1.2 days), as compared with the control group (mean, 5.8 ± 1.0) ($p < 0.001$). The study group also had significantly fewer ICU days (mean, 10.8 ± 1.1 days), as compared with the control group (mean, 4.6 ± 0.9 days) ($p < 0.001$). Furthermore, as in the initial ARDS[74] clinical study, the study group had a significantly lower incidence of new organ dysfunction (38%), as compared with the control group (81%) ($p < 0.001$).

In conclusion, nutritional support with immune-modulating formulas is an important part of the treatment

of patients with acute lung injury and ARDS; it has become the standard of care in recent years. A recent executive summary of the Society of Critical Care Medicine (SCCM) and ASPEN recommended immune-modulating enteral formulations for patients undergoing major elective surgery, for patients with trauma, burns, and head and neck cancer, and for critically ill patients on mechanical ventilation. They also recommended placing patients with ARDS or severe acute lung injury on enteral formulations characterized by an anti-inflammatory lipid profile and antioxidants [30].

Summary

The biology of nutritional support has become much better understood, although we are far from knowing all that we need to know in this complex and ever-advancing field. Serial assessment of nutritional status should be a routine component of ICU care. Nutritional support is indicated either when return to a full diet is expected to be delayed or when postoperative complications further impair nutritional status. With increased knowledge of the altered regulation of nutrient metabolism in critically ill and trauma patients, the formulation and administration of more effective parenteral and enteral therapeutic feeding regimens are inevitably evolving. To prevent and reverse pathophysiologic alterations, early optimal nutritional support with immune-enhancing, immune-modulating, or other yet-to-be-identified formulas is obligatory, in order to significantly improve outcomes.

Conflict of interest statement

The authors declare that there is no actual or potential conflict of interest in relation to this article.

References

1. Latifi R, Caushaj PE. Nutrition support in critically ill patients: current status and practice. J Clin Ligand Assay 1999; 22:279–84.
2. Essén P, McNurlan MA, Gamrin L, Hunter K, Calder G, Garlick PJ, Wernerman J. Tissue protein synthesis rates in critically ill patients. Crit Care Med 1998;26:92–100.
3. Latifi R, Dudrick SJ, eds. Surgical nutrition: strategies in critically ill patients. Austin, TX: Springer-Verlag/R.G. Landes, 1995.
4. Dudrick SJ, Latifi R. Amino acids in critically ill patients: current concepts. In: Latifi R, Dudrick SJ, eds. Surgical nutrition: strategies in critically ill patients. Austin, TX: Springer-Verlag/R.G. Landes, 1995:31–47.
5. Souba WW, Klimberg VS, Plumley DA, Salloum RM, Flynn TC, Bland KI, Copeland EM 3rd. The role of glutamine in maintaining a healthy gut and supporting the metabolic response to injury and infection. J Surg Res 1990;48:383–91.
6. Wischmeyer PE, Lynch J, Liedel J, Wolfson R, Riehm J, Gottlieb L, Kahana M. Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control. Crit Care Med 2001;29:2075–80.
7. Barbul A. Arginine and immune function. Nutrition 1990;6:53–62.
8. Luiking YC, Poeze M, Ramsay G, Deutz NEP. The role of arginine in infection and sepsis. J Parenter Enteral Nutr 2005;29(suppl):S70–S74.
9. Blackburn GL, Moldawer LL, Usui S, Bothe A Jr, O'Keefe SJ, Bistrian BR. Branched chain amino acid administration and metabolism during starvation, injury, and infection. Surgery 1979;86:307–15.
10. García-de-Lorenzo A, Ortíz-Leyba C, Planas M, Montejo JC, Núñez R, Ordóñez FJ, Aragón C, Jiménez FJ. Parenteral administration of different amounts of branch-chain amino acids in septic patients: clinical and metabolic aspects: randomized controlled trial. Crit Care Med 1997;25:418–24.
11. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma: a prospective, randomized study. J Trauma 1986;26:874–81.
12. Alexander JW, Macmillan BG, Stinnett JD, Ogle CK, Bozian RC, Fischer JE, Oakes JB, Morris MJ, Krummel R. Beneficial effects of aggressive protein feeding in severely burned children. Ann Surg 1980;192:505–17.
13. Martindale RG, McClave SA, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. Crit Care Med 2009;37:1757–61.
14. Latifi R, Dudrick SJ, eds. The biology and practice of current nutrition support, 2nd edn. Georgetown, TX: Landes Bioscience and Eurekah.com, 2003.
15. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma–reduced septic morbidity. J Trauma 1989;29:916–22.
16. Jeejeebhoy KN. Total parenteral nutrition: potion or poison? Am J Clin Nutr 2001;74:160–3.
17. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, Kuhl MR, Brown RO. Enteral versus parenteral feeding. Effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg 1992;215:503–11.
18. Gould KL, Martucci JP, Goldberg DI, Hess MJ, Edens RP, Latifi R, Dudrick SJ. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. A potential noninvasive marker of healing coronary endothelium. Circulation 1994;89:1530–8.
19. Battistella FD, Widergren JT, Anderson JT, Siepler JK, Weber JC, MacColl K. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. J Trauma 1997;43:52–8.
20. Alexander JW. Immunonutrition: the role of omega-3 fatty acids. Nutrition 1998;14:627–33.
21. Latifi R, Burns GA. Nucleic acids and nucleotides in nutritional support. In: Van Way C, ed. Nutrition secrets. Philadelphia: Hanley & Belfus Inc., 1999:173–7.
22. Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, Van Buren CT, Rothkopf MM, Daly JM, Adelsberg BR. Early enteral administration of a formula (Impact) supplemented

with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit Care Med 1995;23:436–49.
23. Kudsk KA, Minard G, Croce MA, Brown RO, Lowrey TS, Pritchard FE, Dickerson RN, Fabian TC. A randomized trial of isonitrogenous enteral diets after severe trauma. An immune-enhancing diet reduces septic complications. Ann Surg 1996;224:531–43.
24. Senkal M, Mumme A, Eickhoff U, Geier B, Späth G, Wulfert D, Joosten U, Frei A, Kemen M. Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. Crit Care Med 1997;25:1489–96.
25. Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Crit Care Med 1998;26:1164–72.
26. Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. Ann Surg 1999;229:467–77.
27. Gadek JE, DeMichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, Van Hoozen C, Wennberg AK, Nelson JL, Noursalehi M. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Crit Care Med 1999;27:1409–20.
28. Pacht ER, DeMichele SJ, Nelson JL, Hart J, Wennberg AK, Gadek JE. Enteral nutrition with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants reduces alveolar inflammatory mediators and protein influx in patients with acute respiratory distress syndrome. Crit Care Med 2003;31:491–500.
29. Pontes-Arruda A, Aragão AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med 2006;34:2325–33.
30. The American Society for Parenteral and Enteral Nutrition Practice Recommendations Task Force and the Board of Directors. ASPEN enteral nutrition practice recommendations. J Parenter Enteral Nutr 2009;33:122–67.

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