REVIEW

Metabolism of Proteins and Amino Acids in Critical Illness: From Physiological Alterations to Relevant Clinical Practice

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Abstract: The clinical impact of nutrition therapy in critically ill patients has been known for years, and relevant guidelines regarding nutrition therapy have emphasized the importance of proteins. During critical illness, such as sepsis or the state following major surgery, major trauma, or major burn injury, patients suffer from a high degree of stress/inflammation, and during this time, metabolism deviates from homeostasis. The increased degradation of endogenous proteins in response to stress hormones is among the most important events in the acute phase of critical illness. Currently published evidence suggests that adequate protein supplementation might improve the clinical outcomes of critically ill patients. The role of sufficient protein supplementation may even surpass that of caloric supplementation. In this review, we focus on relevant physiological alterations in critical illness, the effects of critical illness on protein metabolism, nutrition therapy in clinical practice, and the function of specific amino acids.

Keywords: critical illness, protein, metabolism, amino acid

Introduction

Nutrition therapy has been recognized as a pivotal component of critical care medicine for years. Malnutrition appears to alter patient outcomes and is associated with a higher rate of complications, increased mortality, longer hospital length of stay (LOS) and increased hospital costs.[1,2] According to the 2019 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, all critically ill patients staying for more than 48 hours in the intensive care unit (ICU) should be considered at risk for malnutrition, and nutrition therapy should be administered to all patients staying in the ICU.[3] Proteins are undoubtedly among the most important macronutrients in nutrition therapy. Current cumulative evidence indicates the importance of protein administration and its impact on the clinical outcomes of critically ill patients.[4,5] The adequate delivery of proteins might have a higher impact than caloric delivery.[4]

Critical illness, such as major trauma or sepsis, is characterized by a high degree of stress/inflammation. Stress induces neuroendocrine changes, and inflammatory-related cytokine effects further modulate human metabolism.[6,7] Normal metabolism is shifted to a hypercatabolic status, especially during the acute phase.[8] The accelerated degradation of body reserves, including proteins, may cause malnutrition and organ dysfunction during the later stage under inappropriate management.

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The increased degradation of endogenous proteins in response to stress hormones is among the most important events.[8] Several currently published studies suggest that correctly timed adequate protein supplementation improves the clinical outcomes of critically ill patients.[9,10]

In this article, we review the neuroendocrine and inflammatory responses in critical illness and their effects on protein and amino acid metabolism. Then, we focus on the clinical practice of nutrition therapy and protein administration. In addition, the effects of several specific amino acids on immune modulation are elucidated.

Physiological Impact of Critical Illness

Critical illness resulting from sepsis, trauma, burns or major surgery shifts normal metabolism to a dynamic state to address different demands during different phases of the disease. Metabolic conditions can be divided into different stages. During the acute phase, the patient encounters the ebb phase, which includes the initial 24 to 48 hours, and the flow phase, which extends until 7 days.[11] After the acute phase, some patients may enter the recovery stage, while other patients remain in a stage of prolonged critical illness.[3] During the ebb phase, the metabolic status responds to tissue hypoperfusion and vasoconstriction and shifts to a status of decreased overall metabolism.[12] The most prominent metabolic change during the ebb phase is glycogenolysis, which occurs in the liver in response to a catecholamine surge.[13] After the ebb phase (ie, during the flow phase), the catabolic response increases, and the degradation of human stored components, including proteins, occurs. According to the current guidelines for nutrition therapy, we call the "flow phase" the "late period of the acute phase", which is when hypercatabolism occurs, and both the recovery stage and prolonged critical illness stage are considered the post-acute phase.[3] In the following paragraphs, we discuss the metabolic changes in proteins and amino acids that occur during the late period of the acute phase and the post-acute phase. Regarding the post-acute phase, we mention metabolic changes in both patients in the recovery stage and those with prolonged critical illness.

Late Period of the Acute Phase of Critical Illness

Humans do not need proteins as a fuel but need proteins to increase their body cell mass during growth, recovery,

or adaptation under steady-state conditions.[14] However, proteins become the main energy substrate during the catabolic phase of critical illness.[2] The human body does not have any "reserved protein storage"; all proteins in the body exist for structural or functional purposes.[2] A rapid net catabolism of body proteins, which occurs particularly in skeletal muscle, has been demonstrated.[15] Muscle loss is thought to be due to amino acid transport from the periphery to vital organs in the splanchnic area, especially the gut and liver, for gluconeogenesis, protein synthesis (acute phase proteins), and substrates for immune cells.[16,17] Gamrin et al conducted a study investigating skeletal degradation.[18] By obtaining muscle biopsies from 20 critically ill patients (APACHE II scores of 11 to 30) and 17 metabolically healthy patients, these authors demonstrated that the total free amino acids in skeletal muscle decreased by 59% and the skeletal muscle glutamine concentration decreased by 72% in critically ill patients. A recent study conducted by Puthucheary et al (MUSCLE study) further recognized an acute wasting of skeletal muscle that occurred early and rapidly during the first week of critical illness and was highly correlated with the disease severity.[19] Puthucheary's findings revealed that patients with critical illness suffer from acute protein breakdown and a decrease in protein synthesis during the acute phase of critical illness, and a 15% decrease in the muscle amount occurs in patients with multiple organ failure. Then, Puthucheary et al extended their study to the relationship between bioenergetics changes and skeletal muscle wasting.[20] Vastus lateralis muscle biopsies and serum samples (ICU admission days 1 and 7) were obtained from the same 63 intensive care patients in the MUSCLE study. Puthucheary's findings revealed a reduction in the mitochondrial beta-oxidation enzyme concentrations and intramuscular ATP content and an increase in intramuscular tumor necrosis factor receptor 1 and IL-10 from days 1 to 7, indicating that a relationship exists between an impaired bioenergetic status and acute muscle wasting during early critical illness.

The nitrogen balance is another indicator of protein utilization. Sakurai et al demonstrated an increased consumption of proteins by observing the nitrogen balance.[21] Each 6.25 grams of proteins contain 1 gram of nitrogen, and a negative nitrogen balance can be observed in patients with critical illness by observing the nitrogen balance or using a constant essential amino acid tracer infusion method. Using a radioisotope technique to label

the essential amino acid leucine, Jackson et al demonstrated that both nonoxidative leucine disposal and leucine oxidation/metabolic clearance rates were increased in patients with critical illness.[22] Jackson's study revealed that both an increase in the proteolysis and synthesis of acute phase proteins and an increase in protein turnover contribute to an increase in the metabolism of proteins.

In summary, the overall consumption of proteins is significant during critical illness. The net effect of multiple factors, including the sympathetic response, the neuroendocrine response, and inflammatory cytokines, contributes to this metabolic phenomenon (Figure 1). The consumption of proteins is significant during the acute phase of critical illness.

Protein Metabolism During the Post-Acute Phase: Recovery vs Prolonged Critical Illness

Patients who survive the acute phase of critical illness enter the post-acute phase, ie, either the recovery stage or prolonged critical illness. If the etiology of the critical illness is properly addressed and eliminated, the patient enters the recovery stage. Currently, over 70% of ICU patients recover within 1 week.[23] When a patient enters the recovery stage, both the energy requirement and the protein requirement increase to replace the body mass lost during the acute phase. This phenomenon has been proven by Uehara et al immediately before this century by measuring energy expenditure and body composition.[24] Anabolism is observed during this stage of critical disease.

If the etiology of critical illness cannot be solved, the patient enters a phase of prolonged critical illness. The physiological response during this stage greatly differs from that during the acute phase. In neuroendocrine aspects, a decrease in function is the major presentation. The major pathways of the neuroendocrine system involved in metabolism, including the growth hormone axis, pituitary–thyroid axis, pituitary–adrenocortical axis, are generally suppressed.[23] Under the aforementioned effects, patients with prolonged critical illness suffer
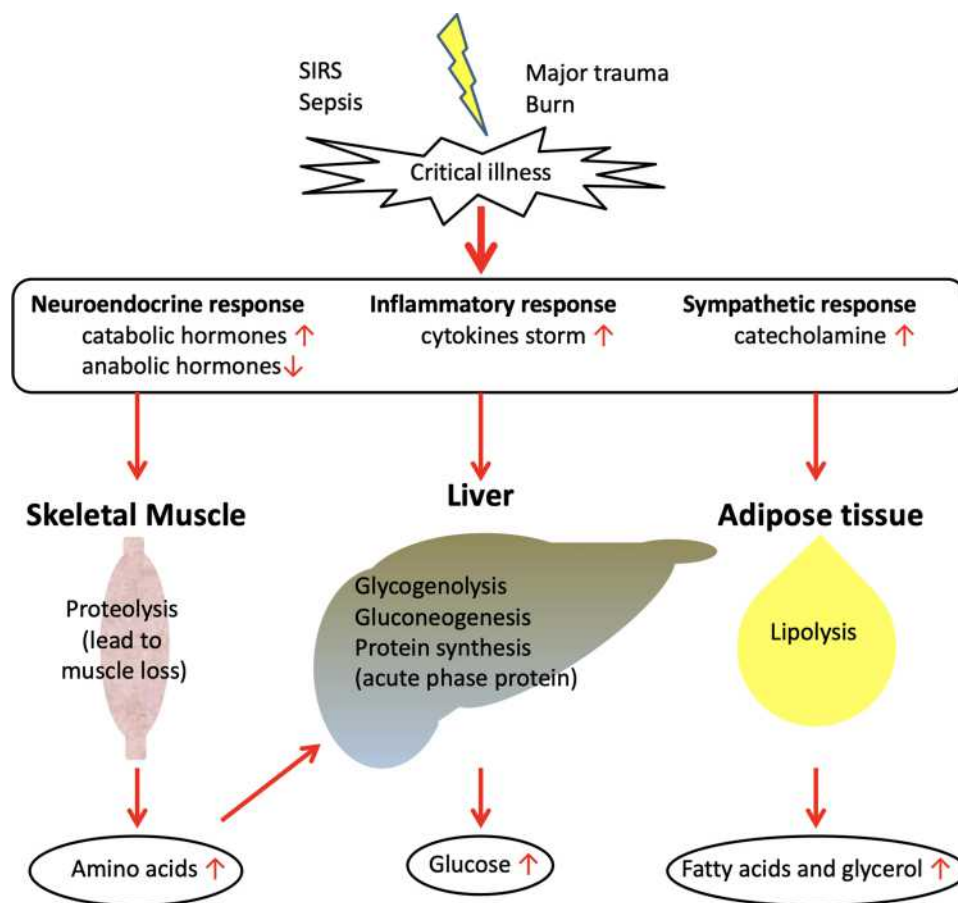
Figure 1 Metabolic response during the acute phase of critical illness: protein consumption.

from catabolism rather than anabolism and the restoration of body structure and lost body mass.[3] The cytokine immune response affects metabolism, and its effect cannot be overemphasized during the acute phase; its functional alteration in prolonged critical illness also has an impact.[6,15] While the initial cytokine storm characterizes the acute phase of critical illness, the immune status usually returns to homeostasis during the recovery stage. However, patients suffer from prolonged critical illness, and their immune system enters a specific condition, ie, persistent inflammation/immunosuppression and catabolism syndrome (PICS).[25] PICS is characterized by markedly increased C-reactive protein concentrations, neutrophilia, and the release of immature myeloid cells.[26] Rosenthal et al demonstrated that patients with PICS presented with persistent inflammatory conditions (elevated IL-6 and IL-8 levels) and immunosuppression (decreased lymphocyte count).[27] The restoration of metabolic homeostasis failed, and catabolism persisted as demonstrated by relevant biomarkers, including higher glucagon-like peptide and a higher 1,3-methylhistidine/creatinine ratio. In addition, the persistent synthesis of acute phase proteins, such as persistently elevated C-reactive protein, was also noted. In summary, patients with PICS suffer from persistent low-grade inflammation that drives catabolism and blocks anabolism.[28]

Protein Absorption in Critical Illness

To maintain body proteins, it is important to provide adequate nutritional intake of proteins. However, whether the human body can absorb and metabolize nutritional proteins during critical illness remains uncertain. Gastrointestinal failure was observed in 10.4% of critically ill adults in a retrospective study.[29] Gastrointestinal symptoms/failure is also associated with an increased risk of mortality.[30] Gastrointestinal dysfunction indicates functional impairment of the alimentary tract that may include disturbances in motility or absorption, breaches in the mucosal integrity, changes in the microbiome, increased intraabdominal pressure, impaired mesenteric perfusion and an impaired local immune response in the bowel.[31] Therefore, the digestion of proteins and absorption of amino acids could be affected under the circumstances of critical disease and lead to protein malabsorption.

Compared with glucose or lipids, evidence regarding protein digestion and absorption during critical illness is scarce. Liebau et al established a method for quantifying the effect of enteral protein feeding in critically ill patients

receiving early enteral nutrition.[32] These authors reported that the uptake of labeled ^{13}C-phenylalanine from diet could be detected in plasma after nasogastric feeding in most adult elderly critically ill patients. However, the isotope–labeled amino acid plasma concentration was much lower than that in the healthy volunteers. This result showed that critically ill patients could digest and absorb proteins from enteral feeding but might be affected by impaired digestion or absorption or greater splanchnic extraction.

Splanchnic extraction represents the fraction of ingested amino acids taken up by the splanchnic organs (gut or liver) that is not available systemically, eg, not available to muscles.[33,34] This phenomenon is greater among the elderly and presents substantial variability during critical illness.[33,35] This variation is correlated with the protein amount provided in enteral nutrition. It seems that the lower the protein intake, the higher the fractional splanchnic extraction presented.[36,37] These studies suggest that splanchnic organs extract the amino acids required for regional metabolism during feeding and then release the remainder to the central circulation. Another small sample size randomized trial also reported that a full dose of enteral nutrition delivered more amino acids to the central circulation than a half dose of enteral nutrition and led to a more positive protein balance in adult critically ill patients.[36] In summary, since the digestion of proteins and absorption of amino acids are affected in critical illness, our goal is to supply adequate proteins to these patients to deliver more amino acids to the systemic circulation.

Protein Deficiency and Clinical Outcomes
Protein Deficiency

In ICU patients, the nutritional status should be assessed after admission. Idrissi et al reported that 42.9% of patients had low plasma levels of prealbumin, 73.6% of patients had low plasma albumin and 99% of patients had low plasma transferrin upon admission to the ICU.[38] However, laboratory data alone may not be reliable for nutrition assessments under the circumstances of a critical illness, and multiple monitoring, including laboratory and other clinical aspects, is necessary.[39] Since net protein consumption results in muscle wasting, the change in the body composition is also an important observation related to the nutrition status,[40] especially in the case of a protein

deficiency. The composition of the human body is divided into lean mass, containing water plus all proteins, and fat mass, containing mainly fat-energy stores. A change in the body composition is a characteristic of patients with critical illness, and this change is due to protein breakdown. The rapid net catabolism of body proteins, which occurs particularly in skeletal muscle,[15] renders muscle loss an indicator of protein deficiency in critically ill patients. A loss of more than 10% of lean body mass decreases immunity and increases the risk of infection, while a loss of more than 20% of lean body mass decreases wound healing and increases muscle weakness.[41] Furthermore, notably, with a loss of 30% or more of lean body mass, the wound healing rate is decreased until lean mass is restored.[42] In a study of measurements of muscle wasting during critical illness, significant reductions in the rectus femoris cross-sectional area were observed on day 10 (−17.7% [95% CI, −20.9% to −4.8%], p < 0.001).[19] Therefore, the loss of muscle is a characteristic phenomenon of protein deficiency and a predictor of clinical outcomes.[43–47]

Short-Term Outcomes
In critically ill patients, malnutrition and protein deficiency are important issues because they are associated with increased morbidity, mortality, LOS, use of healthcare resources and costs.[48] Protein-energy malnutrition also causes impaired wound healing and the development of chronic wounds and infections.

The nutritional status of critically ill patients is a significant predictor of survival. According to a cohort study involving 6518 ICU patients, the nonspecific malnutrition 30-day mortality odds ratio (OR) was 1.17 (95% confidence interval [CI], 1.01–1.37), and protein malnutrition increased the 30-day mortality with an OR of 2.10 (95% CI, 1.70–2.59).[49] A prospective observational cohort study involving 113 ICU patients also reported that the low-protein/amino-acid provision group was associated with a higher 28-day mortality than the high-protein/amino-acid provision group.[50] Elke et al studied 2270 critically ill patients with a diagnosis of sepsis/pneumonia who were admitted to the ICU for ≥3 days, mechanically ventilated within 48 hours of ICU admission and only received enteral nutrition.[51] The results showed that the provision of an additional 30 grams of protein per day decreased the 60-day mortality and days of ventilator use. Another multicenter international study conducted by Nicolo et al reported a cohort of 1584 patients who stayed

in the ICU ≧12 days.[4] The authors reported that the time to discharge alive (TDA) was shorter in patients who were prescribed adequate proteins (intake ≥80% goal amount) compared with those patients who were not (hazard ratio [HR], 1.25; 95% CI, 1.04–1.49). In summary, protein deficiency in critically ill patients might be associated with a higher mortality rate and a worse prognosis and restoring the protein deficiency may improve the clinical outcomes.

Long-Term Outcomes
In addition to the increased short-term mortality rate, malnutrition and protein deficiency also have a negative impact on long-term survival and post-discharge outcomes. Mogensen et al reported an observational cohort of 23,575 patients who received critical care and then survived hospitalization.[52] Mogensen's study revealed that the 90-day post-discharge mortality in patients at risk of malnutrition, nonspecific malnutrition, and protein-energy malnutrition fully adjusted relative to patients without malnutrition was 1.77, 2.51, and 3.72, respectively. Furthermore, the ORs of 365-day post-discharge mortality in patients at risk for malnutrition, nonspecific malnutrition, and protein-energy malnutrition compared with that in patients without malnutrition was 1.14, 1.70, and 3.75, respectively. In addition, the ORs of 30-day re-admission in patients at risk for malnutrition, nonspecific malnutrition, and protein-energy malnutrition was 1.08, 1.20, and 1.67, respectively, compared with that of patients without malnutrition. Therefore, the overall clinical impact of protein deficiency is negative according to current evidence. Furthermore, malnutrition also has an influence in the social-economic aspect. For example, the British Association for Parenteral and Enteral Nutrition (BAPEN 2005) described that malnutrition costs the UK more than £7.3 billion per annum; £3.8 billion was spent on treating malnourished patients in the hospital, and £2.6 billion were spent on long-term care facilities.[48]

In summary, protein deficiency in patients with critical illness results from both excessive breakdown during the acute phase and inadequate protein provision. The negative impact of protein deficiency is extensive. Clinical management should attempt to reverse this condition after the initial acute phase. Therefore, nutrition therapy interventions are an important management tool used to improve clinical outcomes.

Protein Delivery in Critically Ill Patients

Timing and Amount of Protein Administration: Acute Phase

The importance of protein supplementation in critically ill patients is currently well known, but how to deliver sufficient protein to ICU patients is still debatable In general, enteral nutrition (EN) is considered superior to parenteral nutrition (PN), and EN should be initiated early (within 48 hours) in critically ill adult patients.[3,53] Calorie/protein targets are determined to gradually achieve more than 70% of the resting energy expenditure (REE) but not 100% during the acute phase of critical illness.[3]

During the late period of the acute phase (ie, the flow phase), full EN or PN should be gradually achieved within three to seven days. The protein targets should gradually reach 1.3 g/kg or 1.2 to 2.0 g/kg protein per day, which is recommended for critically ill patients in the current guidelines (Table 1).[3,54–56] Over the past several years, some experts have suggested that delivering more proteins is better for patients with critical illness and that even up to 2.0–2.5 g/kg/day is safe and optimum.[57,58] However, some studies, including several randomized controlled trials (RCTs), revealed that a higher protein formula has no impact on mortality in critically ill patients. Doig et al compared intravenous high-amino-acid therapy (2.0 g/kg/day) to standard nutrition care and reported no difference in mortality.[59] A higher protein formula also had no effect on the ICU LOS, hospital LOS or duration of mechanical ventilation in critically ill patients.[60] Thiessen et al explained that this phenomenon may be caused by the increasing amino acid levels during critical illness stimulating glucagon and resulting in more hepatic amino acid breakdown and ureagenesis.[16] In conclusion, energy and protein delivery to critically ill patients should be established in a stepwise method to achieve the target (80–100% energy expenditure and 1.3 g/kg/day protein) after day 3 in the acute phase to avoid overfeeding.

Amino Acid Provision in Supplemental PN

If a patient cannot tolerate an oral diet or EN or an oral diet or EN is contraindicated in a patient, the current consensus suggests that PN should be implemented within three to seven days. Parenteral amino acid therapy should be considered at this time. Ferrie et al compared PN solutions containing amino acids at 1.2 g/kg/day to those containing amino acids at 0.8 g/kg/day and reported no effect on mortality, ICU and hospital LOS or mechanical ventilation duration in critically ill patients. However, this study revealed better handgrip strength on study day 7, a lower fatigue

Table 1 Protein Delivery Recommendations According to the Current Practice Guidelines

	ESPEN Guideline (2019)[3]	ASPEN Guideline (2016)[56]	Canadian Guideline (2015, 2021)[54,84]
Daily protein administration	1.3 g/kg protein equivalents per day.	1.2–2.0 g/kg actual body weight per day.	Insufficient data to make a recommendation.
Branched Chain Amino Acids (BCAAs)	NA	No evidence of benefit for patients with hepatic encephalopathy. Guideline suggested standard enteral formulations to be used in ICU patients with acute and chronic liver disease.	BCAA was associated with a trend towards a reduction in mortality of critical ill patients, but insufficient data to make a recommendation.
Arginine	NA	Immune-modulating enteral formulations (including arginine and glutamine) should not be used routinely in the medical ICU; reserved for patients with trauma and perioperative patients in the surgical ICU.	Diets supplemented with arginine used for critically ill patients is not recommended.
Glutamine (EN)	Suggested for trauma and burn patients but should not be used in other ICU patients.	Should not be added to an EN regimen.	Not recommended for use in critically ill patients. However, may benefit patients with burn or trauma.
Glutamine (PN)	Should not be used.	Should not be used.	Should not be used.

Abbreviations: ESPEN, European Society for Clinical Nutrition and Metabolism; ASPEN, American Society for Parenteral and Enteral Nutrition; EN, enteral nutrition; PN, parenteral nutrition; NA, not available; ICU, intensive care unit.

score and greater forearm muscle thickness on ultrasound.[5] Parenteral amino acid provision can be an alternative to enteral formula, and the recommended dosage is similar.

## Timing and Amount of Protein Administration: Post-Acute Phase

As mentioned in the section regarding the recovery stage of the post-acute phase, both energy requirements and protein requirements increase to replace the body mass lost during the acute phase. During this post-acute phase, activity and exercise increase. Therefore, the target calorie intake might increase to 125–150% of the predicted values, and the protein intake goal might increase to 1.5–2.5 g/kg/day.[10,61] During this time, patients are often discharged from the ICU and start oral intake. Therefore, clinicians should monitor the patient's oral intake amount to avoid insufficient protein intake. Ensuring that the feeding tube is not removed too early or providing oral nutrition supplemental products might resolve these problems.[61] However, if the etiology of the critical illness cannot be resolved, the patient enters a phase of prolonged critical illness, and PICS might develop. As mentioned above, patients with PICS suffer from prolonged low-grade inflammation and catabolism with a loss of lean body mass. Nutritional support in these patients is similar to that in patients with sarcopenia or cancer cachexia, and the provision of 1.5–2.0 g/kg/day

protein might be appropriate.[28] A summary of the protein delivery in each specific phase is provided in Figure 2.

Special Considerations of Amino Acids in Critical Care
Branched-Chain Amino Acids

A branched-chain amino acid (BCAA) is an amino acid that has an aliphatic side-chain with a branch. The three BCAAs are valine, leucine and isoleucine. All three BCAAs are essential amino acids for humans. The use of BCAAs in the treatment of hepatic failure and hepatic encephalopathy is based on enhanced detoxification of ammonia in skeletal muscle and the promotion of liver regeneration.[62] According to some studies, BCAA supplementation appears to be associated with the prevention of progressive hepatic failure and a decreased frequency of complications of cirrhosis.[63,64] However, BCAA supplementation may lead to enhanced ammonia production from glutamine breakdown in the gut and kidneys and, thus, has adverse effects on hepatic encephalopathy.[65] Due to controversial evidence, the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines suggest that standard enteral formulations (not BCAA formulas) may be used in ICU patients with acute and chronic liver disease.[56] In trauma patients without liver disease, a previous study also
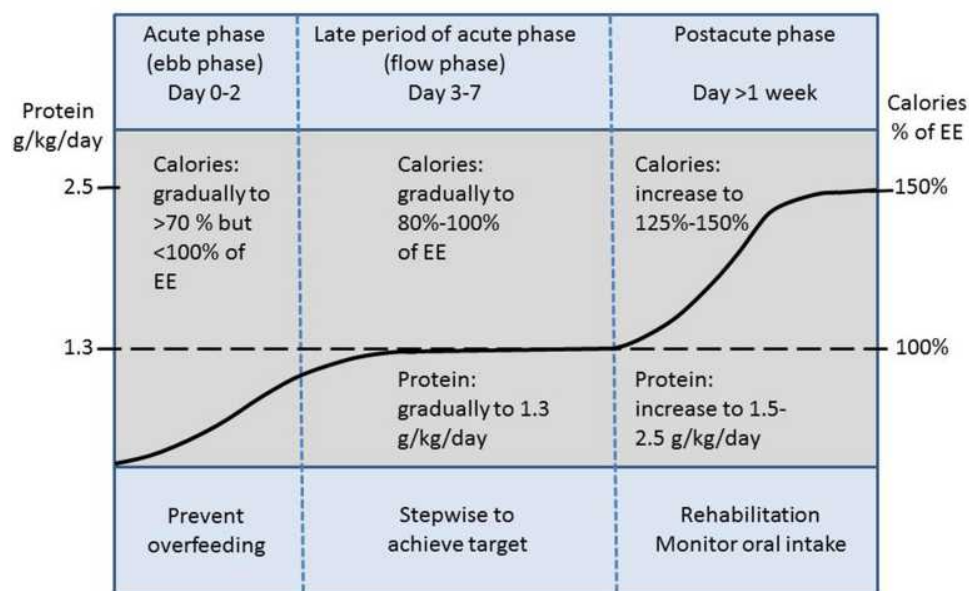
Figure 2 Protein delivery recommendations in critical illness. Adapted from. Figure 1 in Zanten et al Critical Care (2019) 23:368: Nutrition therapy and critical illness: Practical guidance for the ICU, post-ICU, and long-term convalescence phases.[61]
Abbreviation: EE, energy expenditure.

reported no effect on mortality or the LOS in the ICU when a BCAA-enriched (45%) parenteral solution was added to standard EN.[66]

Arginine

Arginine is classified as a nonessential amino acid in healthy individuals. However, arginine can become a conditionally essential amino acid during metabolic or traumatic stress because the endogenous arginine supply is inadequate to meet physiological demands.[67] Arginine depletion during critical illness may have several important effects, including reduced NO production, poor wound healing, impaired microcirculatory blood flow, immunosuppression (T-cell dysfunction), and impaired muscle function.[67,68] However, evidence of a benefit of arginine administration in ICU patients is still lacking.[69] Tadié et al showed that early enteral L-arginine administration does not reverse immunosuppression or inflammation in medical ICU (MICU) patients.[70] Luiking et al also reported no effect on global hemodynamics, organ function parameters or protein metabolism by L-arginine infusion in severe sepsis patients.[71] However, a previous study reported that using an arginine-supplemented diet in perioperative patients reduced infection and the hospital LOS but had no significant effect on mortality.[72] Therefore, the ESPEN guidelines for nutrition in critical illness had no recommendations related to arginine use. The 2016 Society of Critical Care Medicine (SCCM)/ASPEN nutrition therapy guidelines also suggest that immune-modulating enteral formulations (including arginine and glutamine) should not be used routinely in the MICU and that these formulations should be reserved for patients with trauma and perioperative patients in the surgical ICU (SICU).[56]

Glutamine

Glutamine is among the most abundant amino acids and is classified as a nonessential amino acid in the human body. However, glutamine may become a conditionally essential amino acid during stress. Glutamine is an important oxidative fuel for rapidly proliferating cells, including those in the gastrointestinal tract and immune system, and mainly serves as a precursor in the synthesis of other amino acids and glucose for energy.[68] In addition, glutamine seems to be a potent enhancer of stress-induced heat shock protein expression, which can decrease cell death and organ injuries in several models of cellular stress.[73]

Numerous studies investigating the effects of glutamine have been published over the past years. Two major meta-analyses illustrated the positive effect of glutamine before 2014. Bollhalder et al analyzed forty randomized clinical trials and reported no significant reduction in short-term mortality but found reduced infection and hospital LOS with parenteral glutamine supplementation in severely ill patients.[74] Wischmeyer et al also analyzed 26 RCTs and reported that parenteral glutamine supplementation was associated with a significant reduction in hospital mortality and the hospital LOS.[75] However, this beneficial effect was only observed in single-center studies and not in multicenter studies during the subgroup analysis.

Since 2013, several strong studies investigating the negative influence of glutamine have been published. One multicountry, multicentered large RCT (1223 critically ill patients in 40 ICUs who received supplements of glutamine, antioxidants, both, or placebo), the REDOXS study, reported that the early provision of glutamine did not improve survival and was associated with an increase in mortality among critically ill patients with multiorgan failure.[76,77] Another MetaPlus study compared high-protein EN enriched with immune-modulating nutrients (IMHP, including glutamine, omega-3 fatty acids, and antioxidants) to standard high-protein EN (HP) in mechanically ventilated critically ill patients. The results showed that the IMHP group did not show improvements in infectious complications but had a higher 6-month mortality rate than the medical subgroup.[78] A recent meta-analysis also reported that enteral glutamine provision resulted in no significant difference in mortality or the length of hospitalization.[79]

However, some evidence has proven that glutamine has benefits in subgroups of critical patients. Glutamine-supplemented EN could be associated with a reduction in hospital mortality and bacteremia in burn patients and a reduction in infectious complications in multiple-trauma patients.[80,81] Finally, Stehle et al published a meta-analysis (15 RCTs involving 842 patients) of studies that enrolled only hemodynamically stable patients without liver or renal failure. The conclusion showed that parenteral glutamine dipeptide supplementation significantly reduced infectious complications, the ICU LOS, the hospital LOS, and the mechanical ventilation duration and lowered the hospital mortality rate by 45% but had no effect on ICU mortality.[82] In conclusion, supplemental glutamine might be used cautiously in surgical patients with burns or multiple traumas and stable medical patients.[83] The current published nutritional guidelines

also have conservative recommendations for glutamine use in critical patients (Table 1).

Conclusion

Amino acid and protein metabolism are altered when the human body faces stress, such as sepsis, trauma or major surgery. Under such a clinical setting, protein-energy malnutrition results in an increased mortality rate and several other negative influences on the hospital LOS and long-term outcomes. Understanding these changes and issues could help clinicians provide adequate and appropriate nutrition therapy to critically ill patients, especially during the late acute phase and post-acute phase. While several specific amino acids, including arginine and glutamine, may have immunomodulatory effects, the current level of evidence is still weak. During clinical practice for patients with critical illness, giving protein supplementation to the right patient at the right time in an adequate amount may optimize the overall clinical outcome.

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