The importance and dosage of amino acids in nutritional support of various pathological conditions in ICU patients

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Background. Normal adults require twenty L-amino acids (AA) for protein synthesis. Functional AA regulate key metabolic pathways that are necessary for maintenance, growth, reproduction and immunity. Dietary supplementation with one or a mixture of these AA may be beneficial for ameliorating health problems at various stages of the life cycle and for optimizing of the efficiency of metabolic transformations. During disease, other amino acids also become essential. The principal goal of protein/amino acid administration in various pathological conditions in intensive care unit (ICU) patients is to provide the precursors of protein synthesis in tissues with high turnover and to protect skeletal muscle mass and function. Amino acid requirements in parenteral nutrition (PN) are higher when the patient is stressed/traumatized/infected than in the unstressed state. In severely ill ICU patients a higher provision of protein and amino acids has been associated with a lower mortality.

Methods and Results. An overview of the effects and dosage of amino acids in nutritional support of various pathological conditions in ICU patients is presented.

Conclusion. It was demonstrated that 2.0–2.5 g protein substrate/kg normal body weight/day is safe and could be optimal for the most critically ill adults to decrease the risk of morbidity and mortality in some pathological conditions.

Key words: amino acids, nutritional support, ICU patiens

Received: January 29, 2014; Accepted with revision: June 6, 2014; Available online: June 25, 2014
http://dx.doi.org/10.5507/bp.2014.034

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INTRODUCTION

Amino acids (AA) are not only cell signaling molecules but are also regulators of gene expression and the protein phosphorylation cascade. AA are key precursors for the synthesis of hormones and low-molecular weight nitrogenous substances. Some AA regulate key metabolic pathways are necessary for maintenance, growth, reproduction, and immunity. They are called functional AA, which include arginine, cysteine, glutamine, leucine, proline, and tryptophan. Dietary supplementation with one or a mixture of these AA may be beneficial for (1) ameliorating health problems at various stages of the life cycle (e.g., fetal growth impairment, neonatal morbidity and mortality, weaning-associated intestinal dysfunction and wasting syndrome, obesity, diabetes, cardiovascular disease, the metabolic syndrome, and infertility); (2) optimizing efficiency of metabolic transformations to enhance muscle growth and athletic performance, while preventing excess fat deposition and reducing adiposity1.

Normal adults require twenty L-amino acids for protein synthesis, although only leucine, isoleucine, valine, lysine, threonine, phenylalanine, methionine and tryptophan cannot be synthesised and so are essential (Table 1). The minimal daily requirement in a normal healthy adult is about 0.25 g/day of tryptophan (the requirement for tryptophan decreases with age, the minimum daily requirement for an adult is 3 mg/kg/day or about 160 mg/day in females and 250 mg/day in males[2,3]). Assuming a mean total protein requirement of 0.66 g/kg/day, intakes of about 0.18 g/kg/day and 0.48 g/kg/day of indispensable and dispensable amino acids, respectively, or preformed α-amino nitrogen (28 mg nitrogen/kg/day and 78 mg nitrogen/kg/day, respectively), should be sufficient to maintain body nitrogen homeostasis in healthy adults[4].

The branched-chain amino acids (BCAA) of leucine, isoleucine and valine are unique in that they bypass the liver and are metabolised almost exclusively by the skeletal muscle. Leucine also stimulates skeletal muscle protein synthesis and inhibits muscle proteolysis (even during sepsis). During disease, other amino acids are also essential (e.g. histidine, cystine/cysteine, glutamine, arginine and tyrosine). Histidine is essential in infants and in patients who have renal failure. Cysteine is essential in premature infants and in critically ill patients. Glutamine is a precursor for renal ammonia production and a crucial substrate for the rapidly dividing cells of both the gastrointestinal mucosa and the immune system. It is also required for the production of the major cellular antioxidant glutathione, a requirement which is increased in the critically ill patient. Arginine is required in sufficient amounts to convert ammonia to urea and is the precursor for endo-

thelium derived relaxing factor (i.e., nitric oxide); it may also enhance cell mediated immunity5.

The hypoaminoacidemia of critical illness appears to represent a state of increased amino acid uptake by the rapid turn over of central proteins, which is constrained by the maximum rate of amino acids released from the muscle. This is a portrayal of acute central protein deficiency, and it suggests that sufficient exogenous amino acid provisions could improve clinical outcomes, both early by increasing central protein synthesis, optimizing the inflammatory response, and mitigating the extensive loss of muscle protein characteristic of the first week of catabolic critical illness and in the long term by minimizing the muscle atrophy that commonly occurs in protracted critical illness. The recommendation for metabolically normal hospitalized adults is the same as for healthy people: 0.8 g of protein/kg normal body weight/day. The most common recommendation in critical illness lies between 1.2 and 1.5 g protein/kg normal body weight/day. What is the real need of sufficient protein/amino acids which will reduce the risk of morbidity and mortality of critical illness patients? We carried out a review of the clinical literature of amino acids with the optimum and safe upper limit of protein provision in nutritional support in various pathological conditions in ICU patients.

The conditionally essentials amino acids

Nutrients such as arginine (Arg), refined menhaden oil, and RNA have been found to have immune-stimulating properties[7]. There is compelling evidence that Arg regulates interorgan metabolism of energy substrates and the function of multiple organs. The results of both experimental and clinical studies indicate that Arg is a nutritionally essential AA for spermatogenesis, embryonic survival, fetal and neonatal growth, as well as maintenance of vascular tone and hemodynamics[8]. Arginine plays an important role in many physiologic and biologic processes beyond its role as a protein-incorporated amino acid[9]. It has multiple metabolic fates and thus is one of the most versatile amino acids. Not only is it metabolically interconvertible with the amino acids proline and glutamate, but it also serves as a precursor for the synthesis of protein, nitric oxide (NO), creatine, polyamines, agmatine, and urea. These processes do not all occur within each cell but are differentially expressed according to cell type, age and developmental stage, diet, and state of health or disease[10].

The speculation that arginine may pose a threat to critically ill patients is mainly based on the concept that critically ill patients are often hemodynamically unstable and that this population is in a state in which

Table 1. Protein L-amino acid requirements in adults (modified by ref.[4,5,6]).

Essential		
Indispensable	WHO/FAO recommendation (mg/kg/day)	Dispensable
Valine	26	Alanine
Isoleucine	20	Asparagine
Leucine	39	Aspartic acid
Lysine	30	Glutamic acid
Methionine	10.4	Glycine
Phenylalanine	25*	Proline
Threonine	15	Serine
Tryptophan	4	

Essential during disease		
Amino acid	WHO/FAO recommendation* (mg/kg/day)	Note
Histidine	10	Essential in infants and in patients who have renal failure
Arginine	Not given	Essential for the synthesis of the increased amounts of reparative collagen required for wound healing, and it decreases some of the negative aspects of the metabolic responses to injury
Cysteine	4.1	Essential in premature infants and in critically ill patients
Tyrosine	25*	Affects the synthesis of thyroidal hormones and intensity of basal metabolism
Glutamine	Not given	Essential in critically ill patients

*Recommendation given as total aromatic amino acid, sum of phenylalanine and tyrosine

inducible NO-synthase (iNOS) is commonly upregulated. Consequently, delivering supplemental arginine as the substrate for upregulated iNOS will result in increased NO. This increased NO could result in vasodilation and hypotension, leading to greater hemodynamic instability. An alternate, equally valid argument would be that controlled vasodilation would be beneficial in critical illness and sepsis. Unfortunately, few human studies have evaluated arginine as a single agent in critically ill populations. It can be extrapolated from several studies that the 15–30 g of enteral supplemental arginine, which is the amount commonly given when a critically ill patient is being fed enterally at goal rates with immune-modulating formula, is safe and appears to meet the needs of the patient. The appropriate and safe level in the critically ill or hypermetabolic patient in which a proinflammatory state exists is much more difficult to determine. From review of the available animal and human data, arginine appears to be safe and potentially beneficial at doses delivered in immune modulation formulas for most of the hemodynamically stable ICU populations able to tolerate enteral feeding. This would include medical and surgical ICU patients, trauma patients, major surgical patients, postmyocardial infarction, and those with pulmonary hypertension. In major elective surgical patients expected to be admitted to the ICU postoperatively, arginine given before the surgical procedure has been shown to be beneficial. Hemodynamically unstable ICU patients with poor gut perfusion are not candidates for supplemental arginine. If enteral feeding is pursued in patients during hemodynamically unstable periods, it should be done with extreme caution, so as not to result in mesenteric ischemic injury[11].

Dietary supplementation of Arg can enhance wound healing, regulate endocrine activity and potentiate immune activity (Table 2). These finding have led to the use of Arg supplementation as part of an immune-enhancing dietary regimen to help combat the immune suppression seen in such patients[9]. Moreover, a growing body of evidence clearly indicates that dietary supplementation or intravenous administration of Arg is beneficial in improving reproductive, cardiovascular, pulmonary, renal, gastrointestinal, liver and immune functions, as well as facilitating wound healing, enhancing insulin sensitivity, and maintaining tissue integrity (Table 3) (ref.[8]). Arginine supplementation may enhance or preserve immune function in high-risk surgical patients and theoretically improve the host's capacity to resist infection[12]. Critically ill patients fed a high-protein diet enriched with Arg, fiber, and antioxidants had a significantly lower catheter-related sepsis rate than patients fed a standard high-protein diet. There were no differences in mortality or ICU and hospital length of stay[13]. Another study suggests that postoperative enteral nutrition with supplemental Arg, RNA, and omega-3 fatty acids instead of a standard enteral diet significantly improved immunologic, metabolic, and clinical outcomes in patients with upper gastrointestinal malignancies who were undergoing major elective surgery[14].

Table 2. Effect of supplementation of arginine on organ function.

Author	Effect of supplementation
Efron et al.[9]	Enhancing wound healing, regulating endocrine activity and potentiating immune activity
Wu et al.[8]	Beneficial in improving reproductive, cardiovascular, pulmonary, renal, gastrointestinal, liver and immune functions, as well as facilitating wound healing, enhancing insulin sensitivity, and maintaining tissue integrity
Daly et al.[12]	Enhancing or preserving immune function in high-risk surgical patients and theoretically improving the host's capacity to resist infection
Caparrós et al.[13]	Significantly lower catheter-related sepsis rate
Daly et al.[14]	Improving immunologic, metabolic, and clinical outcomes

Table 3. Studies in which arginine was given i.v. for various disease conditions (modified by ref.[15]).

Author	Disease	I.v. dose	Outcome
Barbul et al.[16]	Surgical wound	28 g/day	↑ Collagen deposition
Facchinetti et al.[17]	Preterm labor	1 g/min for 30 min	↓ Uterine contractions
Campisi et al.[18]	Cardiac	0.66 g/min for 45 min	Normalized vasomotor tone in smokers
Mehta et al.[19]	Pulmonary hypertension	0.5 g/kg	↓ Pulmonary hypertension
Luiking et al.[20]	Sepsis	1.2 μmol/kg/min for 72 h	No adverse hemodynamics
Komorowska-Timek[21]	Free flap blood flow	30 g/day	↑ Blood flow, ↓ Flap loss
Berard et al.[22]	Surgical ICU	Total parenteral nutrition enriched with arginine (129.2 mmol/L vs. 86.1 mmol/L)	↑ Nitrogen balance, ↓ Protein myofibrillar catabolism

Taurine is a sulfonated β-amino acid derived from methionine and cysteine metabolism. It is present in high concentrations in most tissues and in particular in proinflammatory cells such as polymorphonuclear phagocytes. Role for this amino acid has been found in membrane stabilization, bile salt formation, antioxidation, calcium homeostasis, growth modulation, and osmoregulation[23]. Intracellular and plasma taurine levels are high and although cellular taurine is tightly regulated, plasma levels are known to decrease in response to surgical injury and numerous pathological conditions including cancer, trauma and sepsis. Decreased plasma concentrations can be restored with supplementary taurine[24]. In human sepsis, levels of taurine are directly and significantly related to levels of glutamate, aspartate, β-alanine and phosphoethanolamine (and unrelated to other amino acids). Levels of these amino acids increased simultaneously with increasing doses of leucine, isoleucine and valine in total parenteral nutrition (TPN). Decreasing taurine was associated with increasing lactate, arteriovenous O_2 concentration difference and respiratory index, and with decreasing cholesterol and cardiac index[25]. Taurine plays a role in the modulation of intracellular free calcium concentration, and although it is one of the few amino acids not incorporated into proteins, taurine is one of the most abundant amino acids in the brain, retina, muscle tissue, and organs throughout the body. All ocular tissues contain taurine. In the retina, taurine is critical for photoreceptor development and acts as a cytoprotectant against stress-related neuronal damage and other pathological conditions[26]. Taurine supplementation might help forestall the age-related decline in cognitive functions through interaction with the GABAergic system[27]. Gonzales- Contreras's study shows hepatoprotective effect of i.v. dose 22.41 +/– 3.57 mg/kg/day of taurine[28].

L-cysteine is now widely recognized as a conditionally essential (or indispensible) sulphur amino acid. Cysteine-rich proteins, such as keratin, may have advantages over the simple amino acid or its derivatives, such as nutraceuticals, to safely and beneficially improve antioxidant status in health and disease. Cysteine and glutathione (GSH) metabolism is impaired in neonates and the critically ill.

Table 4. Effect of supplementation of glutamine on organ fuction.

Author	Effect of supplementation
Osowska et al.[36]	Improving protein status
Smith et al.[31]	Increasing protein synthesis and decreasing protein degradation in skeletal muscle and stimulating glycogen synthesis in the liver
Houdijk et al.[35]	Decreasing the number of infections, a low frequency of pneumonia, sepsis, and bacteraemia
Bollhalder et al.[37]	Reducing infections, length of stay and mortality

Table 5. Different effects of various doses of glutamine (modified by ref.41).

Authors	L-Gln / Gln dipeptide	Glutamine dose	Results
Schulman et al.[42]	L-glutamine	0.60 g/kg/day, enteral	Did not influence the acquisition of characteristics of infections
Garrel et al.[43]	L-glutamine	26 g/day, enteral	Reduced blood infections and decreased mortality in burn patients
Hall et al.[44]	L-glutamine	20 g/l/day, enteral	Did not reduce the incidence of infections in patients with pulmonary ventilation
Schulman et al.[45]	L-glutamine	0.6 g/kg/day, enteral	Did not improve survival and the rate of infections
Juang et al.[46]	L-glutamine	0.52 g/kg/day, enteral	Did not reduce infectious complications
Décholette et al.[39]	Glutamine dipeptide	0.50 g/kg/day, parenteral	Reduced rate of infections
Ziegler et al.[47]	Glutamine dipeptide	0.50 g/kg/day, parenteral	Decreased rate of infections
Tang et al.[48]	L-glutamine (combined with recombined human Growth hormone)	0.30 g/kg, parenteral	Improved imune function and intestinal integrity
Estivariz et al.[49]	Glutamine dipeptide	0.5 g/kg/day, parenteral, alanyl-glutamine dipeptide	Reduced infections in surgical intensive care unit SICU patients
Fuentes-Orozco et al.[50]	Glutamine dipeptide	0.50 g/kg, parenteral	Decreased rate of infections
Wischmeyer et al.[51]	L-glutamine	0.57 g/kg, parenteral	Reduced bacteremic episodes

Enteral nutrition enriched with cysteine can decrease cysteine catabolism and improve GSH status[29]. Cysteine is essential in premature infants and in critically ill patients[5].

Glutamine (Gln) is normally an abundant amino acid in the body. It has many important metabolic roles, which may protect or promote tissue integrity and enhance the immune system[30]. It is the most abundant free amino acid in circulation and in intracellular pools and a precursor for the synthesis of amino acids, proteins, nucleotides, and many other biologically important molecules. It is the most important precursor for ammoniagenesis in the kidney, the major end product of ammonia-trapping pathways in the liver, a substrate for gluconeogenesis, and an oxidative fuel in rapidly proliferating cells and tissues[31].

Gln has many important metabolic roles that may protect or promote tissue integrity and enhance the immune system[32]. Gln also has a number of important regulatory roles, such as increasing protein synthesis and decreasing protein degradation in skeletal muscle and stimulating glycogen synthesis in the liver. When glutamine concentrations decrease, the tissue glutamine metabolism increases markedly in many catabolic, stressful disease states and has led to a reconsideration of the classification of glutamine from a nonessential amino acid to the alternative hypothesis that glutamine may be a conditionally essential nutrient[31].

During stress the body's requirements for Gln appear to exceed the individual's ability to produce sufficient amounts of this AA. Standard formulation of enteral nutrition contains 2–4 g/l of glutamine. However, this dose is insufficient to normalize glutamine plasma concentration. Plasma concentration of glutamine is low in many patients with critical illness and a low level is an independent risk factor for mortality[33].

Provision of supplemental glutamine in specialized enteral or parenteral feeding may improve protein status and immunocompetence, enhance nutritional management, reduce the number of infections and augment recovery of the seriously ill while minimizing hospital stay (Table 4) (ref.[30,32,34,35,37]). The effect of Gln is dose dependent (Table 5). High doses of glycyl-glutamine or alanyl-glutamine dipeptide are feasible and safe in patients with polytrauma and are not associated with any relevant renal substrate loss[38,39].

Of all studies involving glutamine supplementation by enteral or parenteral route, there are virtually no reports of adverse or harmful effects. The only condition known to be accompanied by very high plasma glutamine concentrations is acute liver failure, whereas chronic liver failure is not accompanied by high plasma glutamine levels. The pathophysiology behind these high concentrations is not well characterized. There is no literature reporting, that high glutamine concentrations are associated with any of the symptoms of acute liver failure or the prognosis[40].

The conditionally essential amino acids with omega-3 fatty acids

Immunonutrition in composition of the "conditionally essential" amino acids arginine, glutamine, cysteine, and taurine with omega-3 fatty acids can enhance the immune response in critically ill patients. This is due to the immunomodulating properties of these nutrients[52].

Omega-3 fatty acids increase bleeding time; decrease platelet aggregation, blood viscosity, and fibrinogen; and increase erythrocyte deformability, thus decreasing the tendency of thrombus formation[53]. It has been increasingly reported that administration of omega-3 fatty acids is beneficial in patiens with inflammatory processes. This effect is most likely caused by different biological characteristics, including an immunomodulating effect of the products derived from omega-3 fatty acids through eicosanoid metabolism. Weiss et al. observed shorter postoperative periods in the intensive care unit and on the regular medical wards, as well as lower rates of severe infections. The results suggest that perioperative administration of omega-3 fatty acids may have a favourable effect on the outcome of patients with severe surgical interventions by lowering the magnitude of inflammatory response and by modulating the immune response[54]. Fish oil -supplemented PN initiated at the onset of sepsis to improve survival, beneficially altering the lipid profile in plasma and erythrocyte membrane, modulate immune function, and regulate inflammatory response in a rat model[55].

Branched-chain amino acids

The metabolic response to severe tissue injury and sepsis releases a flood of amino acids from their muscle reservoir, especially ketogenic amino acids valine, leucine, isoleucine. The supplementation of BCAA appears to be beneficial.

BCAA of isoleucine, leucine and valine are unique in that they bypass the liver and are principally metabolized extrahepatically in the skeletal muscle. Leucine also stimulates skeletal muscle protein synthesis and inhibits muscle proteolysis - even during sepsis[5,56,57]. Plasma concentrations of the BCAA are more prominently affected than the concentrations of other amino acids by changes in dietary-caloric, protein, fat, and carbohydrate-intake in man[58]. It is concluded that amino acids, particularly the branched-chain ones, increase the sensitivity of muscle protein synthesis to insulin[59,60]. But in critically ill septic patients, une modulation consistently improve either survival or morbidity. BCAA are recommended in treatment of liver failure. The rationale for recommendation is based on their unique pharmacologic properties, stimulatory effect on ammonia detoxification to glutamine, and decreased concentrations in liver cirrhosis[61]. Potential areas of further research may include the combination of BCAA supplements with other anabolic factors (e.g. growth hormone (GH)) in managing patients with catabolic disease states[56]. Specific amino acids, such as arginine, lysine and ornithine, can stimulate GH release when infused intravenously or administered orally[62]. The chronic BCAA effects on plasma levels of GH and plasma levels of GH binding protein might suggest an improvement of muscle activity through protein synthesis[63]. For a list of clinical trials evaluating branched- chain amino acids therapy, see Table 6.

Studies both in vivo and in vitro have shown that leucine at a very high dose can stimulate muscle protein

synthesis, an effect that is enhanced in vivo by insulin secreted in response to the leucine dose. High levels of leucine can also inhibit protein degradation in skeletal muscle, as well as in the liver. In contrast, at normal physiological levels, increasing leucine concentration by infusion stimulates muscle protein synthesis by enhancing its sensitivity to insulin[73]. Leucine was demonstrated to positively affect protein synthesis in an experimental model of sepsis or burn. BCAA supplementation in septic patients also demonstrated an improvement in patients' nutritional status and outcome[57].

Doi et al. reports of isoleucine stimulating glucose uptake in rat skeletal muscle in vivo, and these results indicate that there might be a relation between the reduction in blood glucose and the increase in skeletal muscle glucose uptake that occur with isoleucine administration in rats. The alterations in glucose metabolism caused by isoleucine may result in an improvement of the availability of ATP in the absence of increases in AMP-activated protein kinase activity in skeletal muscle[74].

The dosing of amino acids in critically ill patiens

For the The European Society's for Clinical Nutrition and Metabolism (ESPEN) guidelines for enteral and parenteral nutrition in critically ill patients, see Table 7 (ref.[75-76]).

Other studies suggest that a protein intake of 1.2 g/kg/day is currently recommended for inactive healthy individuals, whereas guidelines recommend up to 1.5 g/kg/day in patients with severe systemic inflammation, such as those affected by critical illness or cancer (Table 8). High protein intake accelerates progression of chronic renal insufficiency but does not affect renal function in healthy individuals[79]. During chronic renal failure (CRF), the aims of nutritional interventions are to minimize uremic toxicity, avoid malnutrition and delay progression of kidney disease. BCAA and Branched chain keto acids (BCKA) supplements have been proposed to decrease further protein intake while maintaining satisfactory nutritional status. Protein restriction together with keto acids and/or essential AAs has been reported to improve insulin sensitivity and hyperparathyroidism and to be compatible with a preservation of nutritional status[80]. Acute renal failure (ARF) is associated with fundamental alterations of metabolism and immunocompetence with the induction of a pro-oxidative and proinflammatory state. A nutritional program for a patient with ARF must consider not only the specific metabolic consequences associated with renal failure and with the underlying disease process but also the profound alterations in nutrient balances induced by replacement therapy. For most patients with ARF requiring nutrition support, evidence suggests that

Table 6. Clinical trials evaluating branched- chain amino acids therapy (modified by ref.[56]).

Author	Disease	Dose	Outcome
Fan et al.[64]	Resection of hepatocellular carcinoma	14 days perioperative *parenteral nutrition* + 35% BCAA + *oral* diet	Reduced morbidity, 34% vs 55%, mainly due to fewer infections
Vente et al.[65]	Traumatized and septic	BCAA-enriched *parenteral nutrition*	BCAA not associated with any benefits relating to nitrogen metabolism
Von Meyenfeldt et al.[66]	Traumatized and septic	BCAA-enriched *parenteral nutrition,* 0.56 g/kg	No significant difference in mortality or morbidity
Okada et al.[67]	Gastrectomy for cancer	BCAA-enriched *parenteral nutrition*	Urinary-3- methylhistidine lower in the BCAA group: no significant differences in concentrations of secretory proteins
Cerra et al.[68]	Surgical patients within 24 hours of the onset of major general surgery, polytrauma, or sepsis	*parenteral nutrition,* 0.7 g/kg/day	Improving nitrogen retention, an elevation of their absolute lymfocyte count
Wahren et al.[69]	Liver cirrhosis and acute hepatic encephalopathy	*intravenous infusion,* 40 g/day in 5% glucose	Reduces the concentrations of aromatic amino acids but neither improves cerebral function nor decreases mortality
Plaitakis et al.[70]	Amyotrophic lateral sclerosis	*orally*, 1 received daily 12 g L-leucine, 8 g L-isoleucine, 6.4 g L-valine, one-year	Significant benefit in terms of maintenance of extremity muscle strength and continued ability to walk
Muto et al.[71]	Decompensated cirrhosis	*orally* 12 g/day 2 years	Improves event-free survival, serum albumin concentration, and QOL
Garcia de Lorenzo et al.[72]	Septic patients	*Parenteral nutrition* Total parenteral nutrition,1.1 - 1.5 g/kg/day 45% branch-chain amino acids	The length of stay in the ICU did not change. Reduced mortality rate, plasma levels of leucine and isoleucine levels increased

Table 7. The ESPEN's guidelines for enteral and parenteral nutrition in critically ill patients.

ESPEN Guidelines for adult parenteral nutrition	
Intensive care	– a balanced amino acid mixture should be infused at approximately 1.3-1.5 g/kg/day (ideal body weight) – in ICU patients the amino acid solution should contain 0.2-0.4 g/kg/day of L-glutamine (ref.[75])
Surgery	In illness/stressed conditions a daily nitrogen delivery equivalent to a protein intake of 1.5 g/kg ideal body weight (or approximately 20% of total energy requirements) is generally effective to limit nitrogen losses (ref.[76]).
ESPEN Guidelines on adult enteral nutrition	
Intensive care	– during the acute and initial phase of critical illness: in excess of 20-25 kcal/kg/day may be associated with a less favourable outcome – during the anabolic recovery phase, the aim should be to provide 25-30 kcal/kg/day (ref.[77])
Surgery	– use enteral nutrition preferably with immuno-modulating substrates (arginine, omega-3 fatty acids and nucleotides) perioperatively independent of the nutritional risk for patiens after severe trauma (ref.[78])

both essential and nonessential amino acids should be employed. However, there appears to be a therapeutic role for small quantities of essential amino acids, without nonessential amino acids, in selected patients. Data supports the importance of proactive measures to prevent fluid and electrolyte imbalances in patients with ARF (ref.[81,82]). Nutritional therapy in these patients should not depend on the impairment of renal function but on the severity of multiple organ failure (MOF). ARF, per se, does not affect energy expenditure. Energy requirements in these patients are the same as in other MOF patients. 30 to 35 kcal/kg/day should be administered as carbohydrate and lipid solutions/emulsions, and the serum concentration of glucose and triglycerides controlled. In contrast to patients with chronic renal failure, in ARF patients nitrogen administration of approximately 1.5 to 1.7 g amino acids/kg/day is necessary to diminish protein catabolism. No clinical data exist about the best composition of the administered amino acids, but a mixture of essential and nonessential amino acids seems sensible; the exclusive administration of essential amino acids is obsolete. New dialysis techniques such as continuous renal replacement therapy offer the opportunity to adapt nutrition to each individual patient's needs. Using these techniques, there is no reason to reduce nutrition because of fluid restriction, as is often necessary in intermittent hemodialysis[83]. Nevertheless, PN may be necessary in renal failure in patient groups with acute or chronic renal failure (ARF or CRF) and additional acute diseases but without extracorporeal renal replacement therapy, or in patients with ARF or CRF with additional acute diseases on extracorporeal renal replacement therapy, haemodialysis therapy (HD), peritoneal dialysis or continuous renal replacement therapy, or in patients on HD therapy with intradialytic PN. The substrate requirements of acutely ill, non-hypercatabolic patients with CRF correspond to those of patients with ARF who are not receiving any renal replacement patients therapy (utilisation of the administered nutrients has to be monitored carefully). In ARF patients and acutely ill CRF patients on renal replacement therapy, substrate requirements depend on disease severity, type and extent/frequency of extracorporeal renal replacement therapy, nutritional status, underlying disease and complications occurring during the course of the disease. Patients under HD have a higher risk of developing malnutrition. Intradialytic PN should be used if causes of malnutrition cannot be eliminated and other interventions fail[84].

Strack van Schijndel and colleagues have observed an improvement in survival when patients reach the calorie target according to indirect calorimetry and a protein intake of greater than 1.2 g/kg/day (ref.[85]). And the study of Atkinson and Worthley suggest that in the acutely ill patient, the minimal quantity of protein required is unknown, although it is unlikely to exceed 50-60 g/day, in patients who have no external protein loss[5]. The meta-analysis of Hoffer and Bistrian showed that 1.2-1.5 g protein/kg normal body weight/day is low and it was demonstrated that 2.0-2.5 g protein substrate/kg normal body weight/day is safe and could be optimum for most critically ill adults to decrease the risk of morbidity and mortality in some pathological conditions. The main conclusion of this systematic review is that nitrogen balance improves with increasing protein provision up to the highest studied dose of 2.5 g/kg/day. Some studies suggest that higher levels of protein provision increase the rate of wholebody protein synthesis. During the early phase of critical illness, the body's priority is central protein synthesis at the expense of protein loss from the skeletal muscle compartment. Exogenous protein could increase protein synthesis in the small, but crucial, central compartment, with benefit to the patient, without necessarily requiring a commensurate reduction in muscle protein catabolism. Sufficient protein provision mitigates nitrogen loss by promoting central and peripheral protein synthesis. This is clearly preferable when the body's priority is to mobilize peripheral amino acids in support of central protein synthesis[86].

Table 8. Dosing of amino acids in critical condition in various studies.

Studies	Route of administration	Dose of amino acids in critical condition per day
Braga et al.[76]	Parenteral	1.5 g/kg/day (ideal body weight)
Singer et al.[77]	Parenteral	1.3 - 1.5 g/kg/day (ideal body weight)
Atkinson, Worthley[5]	Parenteral	50 - 60 g/day
Guadagni et al.[79]	Undistinguished	1.5 g/kg/day
Singer et al.[85]	Undistinguished	more than 1.2 g/kg/day
Allingstrup, 2012 (ref.[2])	Undistinguished	1.5 g/kg/day
Hoffer, Bistrian[86]	Undistinguished	2.0 - 2.5 g/kg/day
Society of Critical Care Medicine (ref.[86])	Undistinguished	2.0 - 2.5 g/kg/day
The American Society for Parenteral and Enteral Nutrition (ref.[86])	Undistinguished	2.0 - 2.5 g/kg/day
The European Society's for Clinical Nutrition and Metabolism (ref.[86])	Undistinguished	1.3 - 1.5 g/kg/day

CONCLUSION

The principal goal of protein/amino acid administration in critical illness is to provide precursors for protein synthesis in tissues with a high turnover and to protect skeletal muscle mass and function. In physiological conditions, intravenous amino acid administration leads to stimulation of the whole body and muscle protein synthesis, while insulin and glucose infusions preferentially inhibit proteolysis. In critical illness, stress hormones and inflammatory mediators inhibit insulin and amino acid anabolic efficiency, and lean tissue loss is unavoidable in patients with severe trauma or sepsis despite aggressive nutritional support. Acceleration of muscle proteolysis plays a pivotal role in the catabolic response to critical illness[75]. In severely ill ICU patients, a higher provision of protein and amino acids has been associated with a lower mortality[87].

Dietary supplementation of arginine can enhance wound healing, regulate endocrine activity and potentiate immune activity[9]. Cysteine is essential in critically ill patients[5]. Supplementation of glutamine may improve protein status and immunocompetence, enhance nutritional management, reduce the number of infections and augment recovery of the seriously ill while minimizing hospital stay[30,32,34-37]. Leucin stimulates skeletal muscle protein synthesis and inhibits muscle proteolysis, even during sepsis[5,56,57].

The prevalent opinion in modern critical care nutrition is that 1.2-1.5 g protein/kg normal body weight/day is sufficient and hence not usually exceeded. At the present time, most critically ill adults receive less than half the current recommendation, 1.5 g protein/day, for the first week or longer of their ICU stay. The limited amount and poor quality of the available evidence preclude conclusions or clinical recommendations but it has been demonstrated, that 2.0-2.5 g of protein/kg normal body weight/day is safe and could be optimum for most critically ill adults to decrease the risk of morbidity and mortality in some pathological conditions. It is important to note, that it is commonly assumed, that the weight of the amino acids in a parenteral amino acid mixture equals the amount of protein they provide, although the molecular weight of free amino acids is 18mass units greater than when they are protein bound. Hoffer concluded that amino acid mixtures provided 17% less protein and energy than is now widely assumed. Clinicians who aim to provide 0.8-1.5 g protein/kg must administer 1.0-1.8 g mixed amino acids/kg (ref.[88]).

ABBREVIATIONS

AA, amino acids; AMP, adenosine monophosphate; ARF, acute renal failure; ARG, arginine; ATP, adenosine triphosphate; BCAA, branched-chain amino acids; BCKA, branched-chain keto acids; CRF, chronic renal failure; ESPEN, The european society's for clinical nutrition and metabolism; FAO, Food and Agriculture organisation; GABA, gamma-aminobutyric acid; GH, growth hormone; Gln, glutamine; GSH, gluthathion; HD, hemodyalysis; ICU, intensive care unit; iNOS, inducible; MOF, multiple organ failure; NO, nitric oxide; NO-synthase; PN, parenteral nutrition; QOL, quality of life; RNA, ribonucleic acid; SICU, surgical intensive care unit; TPN, total parenteral nutrition; WHO, World Health Organisation.

ACKNOWLEDGEMENTS

The authors are grateful to Lucie Vitkova for assistance with the manuscript. Supported without sponsors by MH CZ - DRO (UHHK, 00179906), PRVOUK P40 and Faculty of Pharmacy (SVV 267 003) are gratefully acknowledged.

Authorship contributions: PPA: literature search, manuscript writing, tables; PPA, MH: conception and design; MH, ZZ: final approval.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Wu G. Amino acids: metabolism, functions, and nutrition. Amino acids 2009;37:1-17.
2. Sidransky H., Tryptophan: Biochemical and Health Implications. Boca Raton: CRC Press LLC; 2002.
3. Braverman E.R., The Healing nutrients within: Facts, findings, and New research on aminoacids. Laguna Beach: Basic Health Publications, Inc.; 2003.
4. WHO/FAO/UNU, Protein and amino acid requirements in human nutrition. Geneva: WHO; 2007.
5. Atkinson M, Worthley LIG. Nutrition in the Critically Ill Patient: Part I. Essential Physiology and Pathophysiology. Critical care and resuscitation 2003;5:109-20.
6. Seifter E. Arginine: an essential amino acid for injured rats. Surgery 1978;84:224-30.
7. Cerra FB, Lehmann S, Konstantinides N, Dzik J, Fish J, Konstantinides F, LiCari JJ, Holman RT. Improvement in immune function in ICU patients by enteral nutrition supplemented with arginine, RNA, and menhaden oil is independent of nitrogen balance. Nutrition 1991;7:193-9.
8. Wu G, Bazer FW, Davis TA, Kim SW, Li P, Rhoads JM, Satterfield MC, Smith SB, Spencer TE, Yin Y. Arginine metabolism and nutrition in growth, health and disease. Amino acids 2009;37:153-68.
9. Efron D, Barbul A. Role of arginine in immunonutrition. J Gastroenterol 2000;35:20-3.
10. Morris SM. Arginine Metabolism: Boundaries of Our Knowledge. J Nutr 2007;137:16025-95.
11. Zhou M, Martindale RG. Arginine in the critical care setting. J Nutr 2007;137: 1687S-92S.
12. Daly JM, Reynolds J, Sigal RK, Shou J, Liberman MD. Effect of dietary protein and amino acids on immune function. Crit Care Med 1990;18:S86-93.
13. Caparrós T, Lopez J, Grau T. Early Enteral Nutrition in Critically III Patients With a High-Protein Diet Enriched with Arginine, Fiber, and Antioxidants Compared With a Standard High-Protein Diet. The Effect on Nosocomial Infections and Outcome. JPEN J Parenter Enteral Nutr 2001;25:299-309.
14. Daly JM, Lieberman MD, Goldfine J, Shou J, Weintraub F, Rosato EF, Lavin P. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. Surgery 1992;112:56- 67.
15. Zhou M, Martindale RG. Arginine in the critical care setting. J Nutr 2007;137:16875-925.
16. Barbul A, Fishel RS, Shimazu S, Wasserkrug HL, Yoshimura NN, Efron G. Intravenous hyperalimentation with high arginine levels improves wound healing and immune fiction. J Surg Res 1985;38:328-34.
17. Facchinetti F, Neri I, Genazzani AR. L-arginine infusion reduces preterm uterine contractions. J Perinat Med 1996;24:283-5.
18. Campisi R, Czernin J, Schoder H, Sayre JW, Schelbert HR. l-Arginine Normalizes Coronary Vasomotion in Long-Term Smokers. Circulation 1999;99:491-7.
19. Mehta S, Stewart DJ, Langleben D, Levy RD. Short-term Pulmonary Vasodilation With L-Arginine in Pulmonary Hypertension. Circulation 1995;92:1539-45.
20. Luiking YC, Poeze M, Dejong CH, Ramsay G, Deutz Ne. Sepsis: an arginine deficiency state? Crit Care Med 2004;32:2135-45.
21. Komorowska-Timek E, Timek TA, Brevetti LS, Zhang F, Lineaweaver WC, Buncke HJ. The effect of single administration of vascular endothelial growth factor or L-arginine on necrosis and vasculature of the epigastric flap in the rat model. Br J Plast Surg 2004;57:317-25.
22. Berard MP, Zazzo JF, Condat P, Vasson MP, Cynober L. Total parenteral nutrition enriched with arginine and glutamate generates glutamine and limits protein catabolism in surgical patients hospitalized in intensive care units. Crit Care Med 2000;28:3637-44.
23. Redmond HP, Stapleton PP, Neary P, Bouchier-Hayes D. Immunonutrition: the role of taurine. Nutrition 1998;14:599-604.
24. Stapleton PP, Charles RP, Redmond HP, Bouchier-Hayes DJ. Taurine and human nutrition. Clinical nutrition 1997;16:103-8.
25. Chiarla C, Giovannini I, Siegel JH, Boldrini G, Castagneto M. The Relationship between Plasma Taurine and Other Amino Acid Levels in Human Sepsis, J Nutr 2000;130:2222-7.
26. Ripps M, Shen W. Review: Taurine: A "very essential" amino acid. Mol Vis 2012;18:2673-86.
27. Idrissi AEI, Shen ChH, L'Amoreaux WJ. Neuroprotective role of taurine during aging. Amino acids 2013;45:735-50.
28. Gonzales- Contreras J, Villalobos Gámez JL, Gómez-Sánchez AI, García-Almeida JM, Enguix Armanda A, Rius Díaz F, Lucena González MI. Cholestasis induced by total parenteral nutrition; effects of the addition of Taurine (Tauramin (R)) on hepatic function parameters; possible synergistic action of structured lipids (SMOFlipid (R)). Nutr Hosp 2012;27:1900-7.
29. McPherson RA, Hardy G. Clinical and nutritional benefits of cysteine-enriched protein supplements. Curr Opin Clin Nutr 2011;14:562-8.
30. Jones Ch, Palmer TEA, Griffiths RD. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. Nutrition 1999;12:108-15.
31. Smith JR. Glutamine Metabolism and Its Physiologic Importance. JPEN J Parenter Enteral Nutr 1990;14:40-44.
32. Griffiths RD. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 1997;13:295-302.
33. Wernerman J. Glutamine supplementation. Ann Intensive Care 2011;1:25-31.
34. Lacey MJ, Douglas W. Is Glutamine a Conditionally Essential Amino Acid? Nutr Rev 1990;48:297-309.
35. Houdijk APJ, Rijnsburger ER, Jansen J, Wesdorp RIC, Weiss JK, McCamish MA, Teerlink T, Meuwissen SGM, Haarman HJThM, Thijs LG, van Leeuwen PAM. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet 1998;352:772-6.
36. Osowska S, De Bandt JP, Chaib S, Neveux N, Bérard MP, Cynober L. Efficiency of a cysteine-taurine-threonineserine supplemented parenteral nutrition in an experimental model of acute inflammation. Intensive Care Med 2003;29:1798-1801.
37. Bollhalder L, Pfeil AM, Tomonaga Y, Schwenkglenks M. A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation. Clinical Nutrition 2013;32:213-23.
38. Weingartmann G, Fridrich P, Mauritz W, Götzinger P, Mittlböck M, Germann P, Karner J, Roth E. Safety and efficacy of increasing dosages of glycyl-glutamine for total parenteral nutrition in polytrauma patients. Wien Klin Wochenschr 1996;108:683-8.
39. Déchelotte P, Hasselmann M, Cynober L, Allaouchiche B, Coëffier M, Hecketsweiler B, Merle V, Mazerolles M, Samba D, Guillou YM, Petit J, Mansoor O, Colas G, Cohendy R, Barnoud D, Czernichow P, Bleichner G. L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: The French controlled, randomized, double-blind, multicenter study. Crit Care Med 2006;34:598-604.
40. Wernerman J. Clinical use of glutamine supplementation. J Nutr 2008;138:2040S-44S.
41. Oliveira GP, Dias CM, Pelosi P, Rocco PRM. Understanding the mechanisms of glutamine action in critically ill patients. An Acad Bras Cienc 2010;82:417-430.
42. Schulman A, Willcutts KF, Claridge JA, O'donnell KB, Radigan AE, Evans HL, McElearney ST, Hedrick TL, Lowson SM, Schirmer BD, Young JS, Sawyer RG. Does Enteral Glutamine Supplementation Decrease Infectious Morbidity? Surg Infect (Larchmt) 2006;7:29-35.
43. Garrel D, Patenaude J, Nedelec B, Samson L, Dorais J, Champoux J, D'Elia M, Bernier J. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: A prospective, controlled, randomized clinical trial. Crit Care Med 2003;31:2444-9.
44. Hall JC, Dobb G, de Sousa R, Brennan L, McCauley R. A prospective randomized trial of enteral glutamine in critical illness. Intensive Care Med 2003;29:1710-16.
45. Schulman A, Willcutts KF, Claridge JA, Evans HL, Radigan AE, O'Donnell KB, Camden JR, Chong TW, McElearney ST, Smith RL, Gazoni LM, Farinholt HMA, Heuser CC, Lowson SM, Stuart M, Schirmer BD, Young JS, Sawyer RG. et al. Does the addition of glutamine to enteral feeds affect patient mortality? Crit Care Med 2005;33:2501-6.
46. Juang P, Fish DN, Jung R, MacLaren R. Enteral Glutamine Supplementation in Critically Ill Patients with Burn Injuries: A Retrospective Case-Control Evaluation. Pharmacotherapy 2007;27:11-19.
47. Ziegler TR, Ogden LG, Singleton KD, Luo M, Fernandez-Estivariz C, Griffiths DP, Galloway JR, Wischmeyer PE. Parenteral glutamine increases serum heat shock protein 70 in critically ill patiens. Intensive Care Med 2005;31:1079-86.

48. Tang ZF, Ling YB, Lin N, Hao Z, Xu RY. Glutamine and recombinant human growth hormone protect intestinal barrier function following portal hypertension surgery. World J Gastroenterol 2007;21:2223-8.
49. Estivariz CF, Griffith DP, Luo M, Szeszycki EE, Bazargan N, Dave N, Daignault NM, Bergman GF, McNally T, Battey CH, Furr CE, Hao L, Ramsay JG, Accardi CR, Cotsonis GA, Jones DP, Galloway JR, Ziegler TR. Efficacy of Parenteral Nutrition Supplemented With Glutamine Dipeptide to Decrease Hospital Infections in Critically Ill Surgical Patients. JPEN J Parenter Enteral Nutr 2008;32:389-402.
50. Fuentes-Orozco C, Cervantes-Guevara G, Mucino-Hernández I, López-Ortega A, Ambriz-González G, Gutiérrez-de-la-Rosa JL, Gómez-Herrera E, Hermosillo-Sandoval JM, González-Ojeda A. L-Alanyl-L-Glutamine-Supplemented Parenteral Nutrition Decreases Infectious Morbidity Rate in Patients With Severe Acute Pancreatitis. JPEN J Parenter Enteral Nutr 2008;32:403-11.
51. 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.
52. Grimm H, Kraus A. Immunonutrition – supplementary amino acids and fatty acids ameliorate immune deficiency in critically ill patients. Langenbecks Arch Surg 2001;386:369-76.
53. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. Am J Clin Nutr 1991;54:438-63.
54. Weiss G, Meyer F, Matthies B, Pross M, Koenig W, Lippert H. Immunomodulation by perioperative administration of n-3 fatty acids. Br J Nutr 2002;87:89-94.
55. Cao S, Ren J, Sun L, Gu G, Yuan Y, Li J. Fish oil-supplemented parenteral nutrition prolongs survival while beneficially altering phospholipids' fatty acid composition and modulating immune function in rat sepsis. Shock 2011;36:184-90.
56. Platell C, Kong SE, McCauley R, Hall JC. Branched-chain amino acids. J Gastroenterol Hepatol 2000;15:706-17.
57. De Bandt JP, Cynober L. Therapeutic Use of Branched-Chain Amino Acids in Burn, Trauma, and Sepsis. J Nutr 2006;136:3085-3135.
58. Adibi SA. Metabolism of branched-chain amino acids in altered nutrition. Metabolism 1976;25:1287-1302.
59. Freund HR, Ryan JA, Fischer JE. Amino Acid Derangements in Patients With Sepsis: Treatment With Branched Chain Amino Acid Rich Infusions. Ann Surg 1978;188:423-9.
60. Garlick PJ, Grant I. Amino acid infusion increases the sensitivity of muscle protein synthesis in vivo to insulin. Effect of branched-chain amino acids. Biochem J 1988;254:579- 84.
61. Holeček M. Branched-chain amino acids and ammonia metabolism in liver disease: Therapeutic implications. Nutrition 2013;29:1186-91.
62. Chromiak JA, Aotnio J. Use of amino acids as growth hormone-releasing agents by athletes. Nutrition 2002;18:657-61.
63. De Palo EF, Gatti R, Cappellin E, Schiraldi C, De Palo CB, Spinella P. Plasma lactate, GH and GH-binding protein levels in exercise following BCAA supplementation in athletes. Amino acids 2001;20:1-11.
64. Fan ST, Lo CM, Lai EC, Chi KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med 1994;8: 1547-52.
65. Vente JP, Soeters PB, von Meyenfeldt MF, Rouflart MM, van der Linden CJ, Gouma DJ. Prospective randomized double-blind trial of branched chain amino acid enriched versus standard parenteral nutrition solutions in traumatized and septic patients. World J Surg 1991;15:128-32.
66. Von Meyenfeldt MF. Effect of branched chain amino acid enrichment of total parenteral nutrition on nitrogen sparing and clinical outcome of sepsis and trauma: A prospective randomized double blind trial. Br J Surg 1990;77:924-9.
67. Okada A. Branched-Chain Amino Acids Metabolic Support in Surgical Patients: A Randomized, Controlled Trial in Patients with Subtotal or Total Gastrectomy in 16 Japanese Institutions. JPEN J Parenter Enteral Nutr 1988;12:332-7.
68. Cerra FB, Mazuski JE, Chute E, Nuwer N, Teasley K, Lysne J, Shronts EP, Konstantinides FN. Branched chain metabolic support. A prospective, randomized, double-blind trial in surgical stress. Ann Surg 1984;199:286-91.
69. Wahren J, Denis J, Desurmont P, Eriksson LS, Escoffier JM, Gauthier AP, Hagenfeldt L, Michel H, Opolon P, Paris JC, Veyrac M. Is Intravenous Administration of Branched Chain Amino Acids Effective in the Treatment of Hepatic Encephalopathy? A Multicenter Study. Hepatology 1983;3:475-780.
70. Plaitakis A, Mandeli J, Smith J, Yahr MD. Pilot trial of branched-chain aminoacids in amyotrophic lateral sclerosis. Lancet 1988;331:1015-18.
71. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Hiquchi K, Nishiquchi S, Kumada H. Effects of Oral Branched-Chain Amino Acid Granules on Event-Free Survival in Patients With Liver Cirrhosis. Clin Gastroenterol Hepatol 2005;3:705-13.
72. Garcia de Lorenzo A, Ortiz Leyba C, Planas M, Montejo J, Nunez R, Ordonez FJ, Aragon C, Jimenez F. Parenteral administration of different amounts of branch-chain amino acids in septic patients: Clinical and metabolic aspects. Crit Care Med 1997;25:418-424.
73. Garlick, PJ. The Role of Leucine in the Regulation of Protein Metabolism. J Nutr 2005;135:15535-65.
74. Doi M, Yamako I, Nakayama M, Mochizuki S, Sugahara K, Yoshizawa F. Isoleucine, a Blood Glucose-Lowering Amino Acid, Increases Glucose Uptake in Rat Skeletal Muscle in the Absence of Increases in AMP-Activated Protein Kinase Activity. J Nutr 2005;135:2103-8.
75. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, Griffiths R, Kreyman G, Levere X, Pichard C. ESPEN Guidelines on Parenteral Nutrition: Intensive care. Clinical nutrition 2009;28:387-400.
76. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN Guidelines on Parenteral Nutrition: Surgery. Clinical nutrition 2009;28:378-86.
77. Kreymann KG, Berger MM, Deutz NEP, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, Ebner C, Hartl W, Heymann C, Spies C. ESPEN Guidelines on Enteral Nutrition:Intensive care. Clinical nutrition 2006;25:210-23.
78. Weimann A, Braga M, Harsanyi L, Laviano A, Ljumgqvist O, Soeters P, Jauch KW, Kemen M, Hiesmayr JM, Horbach T, Kuse ER, Vestweber KH. ESPEN Guidelines on Enteral Nutrition: Surgery including Organ Transplantation. Clinical nutrition 2006;25:224-44.
79. Guadagni M, Biolo G. Effects of inflammation and/or inactivity on the need for dietary protein. Curr Opin Clin Nutr 2009;12:617-22.
80. Cano NJ, Fouque D, Leverve XM. Application of branched-chain amino acids in human pathological states: renal failure. J Nutr 2006;136:299S-307S.
81. Druml W. Nutritional management of acute renal failure. J Ren Nutr 2005;15:63-70.
82. Kopple JD. The nutrition management of the patient with acute renal failure. JPEN J Parenter Enteral Nutr 1996;20:3-12.
83. Kierdorf HP. The nutritional management of acute renal failure in the intensive care unit. New Horiz 1995;3:699-707.
84. Druml W, Kierdorf HP. Parenteral nutrition in patients with renal failure - Guidelines on Parenteral Nutrition, Chapter 17. Ger Med Sci 2009;7:Doc11.
85. Singer P. Toward protein-energy goal-oriented therapy? Crit Care 2009;13:188-189.
86. Hoffer J, Bistrian B. Appropriate protein provision in critical illness: a systematic and narrative review. Am J Clin Nutr 2012;591-600.
87. Allingstrup MJ, Esmailzadeh N, Knudsen AW, Espersen K, Jensen TH, Wiis J, Perner A, Kondrup J. Provision of protein and energy in relation to measured requirements in intensive care patients. Clinical Nutrition 2011;31:462-8.
88. Hoffe LJ. How much protein do parenteral amino acid mixtures provide? Am J Clin Nutr 2011;94:1396-8.