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Nutrition for critically ill patients: The role of glutamine in nutritional immunomodulation

[1,2]Miomir Jović, [1]Vladimir Savić

[1]Dedinje Cardiovascular Institute, Clinical Department for Anesthesia and Intensive Therapy, Milana Tepica 1, Belgarde, Serbia
[2]Faculty of Medicine, University of Belgrade, Doktora Subotića 8, Belgrade, Serbia

Corresponding author:
Prof Miomir Jović MD, PhD
Dedinje Cardiovascular Institute, Milana Tepića 1, Belgrade, Faculty of Medicine, University of Belgrade
E-mail address: miomir.jovic@gmail.com

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Abstract

Glutamine is a nonessential amino acid, conditionally essential in stressful conditions (catabolism/hyper catabolism). The lungs, liver, brain, and skeletal muscles take part in specific glutamine synthesis pathways. Plasma concentration of this amino acid is about 50% of total amino acid concentration and about 60% of free amino acids in the body. It is a significant source of energy for all cells, including immune cells. Glutamine can be used as a substrate for nucleotide synthesis. In the last few decades, advanced technology significantly changed the treatment of critically ill patients. Mechanical ventilation, blood products transfusion, renal replacement therapy, invasive monitoring, and many other technical procedures prolong the life of patients by changing and modulating homeostasis and developing new pathways and mechanisms of adaptation – allostasis. Systemic inflammatory response and immunomodulatory activity are part of complex underlying mechanisms involved in allostasis. Nutrition is an important part of the strategy for the treatment of critically ill patients. Based on recently published results, few nutrients (omega-3 fatty acids, arginine, glutamine), when added to the standard formula for enteral and parenteral nutrition, reduce intensive care unit (ICU) stay, infection rate, and the duration of mechanical ventilation in critically ill patients. Glutamine has a high immunomodulatory capacity, as fuel for muscles and a "shuttle" for nitrogen, protecting lung and gut function as well as the function of immunocompetent cells. The most vulnerable systems in COVID-19 patients are respiratory and renal. Despite no universally accepted strategy, treatment with glutamine could have an important role in protecting the cellular integrity of immune cells, alveolar-capillary, and enteral membrane.

Key words: *Critically ill patients; Nutrition; Immunomodulation; Glutamine; COVID -19.*

INTRODUCTION

Surgical, non-surgical, and poly traumatized critically ill patients often need prolonged intensive care treatment, Critically ill patients, some of them, surgical and non-surgical as well as poly-traumatized need prolonged intensive care treatment.. This is dependent on the type and extensity of surgery or trauma and individual functional reserve of cardiovascular, respiratory, and other organ systems. During the intraoperative and immediate postoperative period, these patients are exposed to hypotension, hypoperfusion, and hemodilution with subsequent deterioration in tissue perfusion and oxygenation. Eventual hypothermia, excessive blood loss with extensive volume replacement, blood and blood products transfusion with volume distribution misbalance often take part in the complex postoperative period.

Treatment of these patients demands different modalities of respiratory support and mechanical lung ventilation, invasive hemodynamic monitoring [1,2], fluid balance, and a wide spectrum of noninvasive diagnostic and therapeutic procedures. All of these procedures trigger the systemic inflammatory stress response of the organism. Trauma (surgical procedure), mechanical lung ventilation, and different invasive diagnostic and therapeutic procedures, alongside hypoperfusion and hypoxia, considerably increase infection

risk. Immuno-insufficiency with infection is a predilection for the development of sepsis and multiorgan failure. This triggers a series of compensatory mechanisms of allostasis, an endeavor to maintain homeostasis in completely disturbed regulatory mechanisms of critically ill patients, primarily directed to improve and optimize tissue perfusion/oxygenation ratio.

In the early 80s, many new concepts have been introduced in the everyday clinical management of critically ill patients. Girard and Raffin [3] introduced the term chronic critical illness syndrome – CCIS, the concept based on the net of previously unknown compensatory mechanisms, initiated to restore the balance of different levels of neuro-humoral regulators. In chronically critically ill patients, horizontal and vertical synchronization of complex regulatory mechanisms is impaired: hypothalamus–pituitary, corticotropic releasing factor – an adrenocorticotropic hormone, catecholamine, glucagon, growth factor, and vasopressin. Macrophages/monocytes stimulate tumor necrosis factor (TNF-α) secretion. Hyper catabolism and water retention due to hypercorticism as well as peripheral hypothyroidism and resistance to insulin with subsequent glycogenolysis, gluconeogenesis, and lipolysis are part of complex hormonal misbalance. Shoemaker and coworkers, at the same time, emphasized the importance of balanced perfusion and oxygenation in tissue during the management of the critically ill, optimizing oxygen delivery, and consumption [4].

Despite the increased concentration of plasma nutrients during the treatment, its consumption is limited by insulin resistance and lipoprotein lipase inhibition. In parallel, due to the action of cytokines (TNF-α, interleukine-1, interleukine-6) and glucocorticoids, liver function is reprogramed into the direction to produce acute phase reactants (C-reactive protein, fibrinogen, and immunoglobulin).

The critical illness, associated with a broad spectrum of clinical signs, can be divided into four stages regarding the changes during allostasis: acute critical illness, prolonged acute critical illness, chronic critical illness, and recovery from critical illness. The most critical subsets of patients are those in acute (first 3 days) and prolonged acute critical illness (3-10 days of intensive treatment) [5). During the chronic stage of critical illness (after 14 days of intensive treatment), the patient is mechanically ventilated, tracheotomy is performed, and suffers complex disorders with hypoalbuminemia, anasarca, and stress-induced hypoglycemia, vitamin D deficiency and severe polyneuropathy and myopathy induced by critical illness.

Recently it became clear that intensive metabolic support (IMS) represents the cornerstone of CCIS treatment. Consistent blood sugar control, intensive insulin treatment, adequate nutritive treatment based on the knowledge about allostasis and nutritive pharmacology are essential for IMS [5].

NUTRITION FOR CRITICALLY ILL PATIENTS

The old surgical principle "if the bowels work, use them" is still valid today with specific modifications, unless it is limited by the nature of the disease or surgical treatment of esophagus, intestine, or upper respiratory tract burns. The energy demands and uptake depend on the patient's condition, catabolism degree, presence and stage of infection, and inflammatory response. There are many enteral and parenteral nutrition products, standard or adjusted for patients with different conditions such as diabetes, renal, and liver damage. Nutrition of patients is directed towards two treatment goals to achieve the acquired deficiency correction and modulate systemic stress response [6].

Basic principles

It has been known that respiratory muscle work depends on nutrition, electrolyte, and hormonal levels, oxygen transport, and other metabolic factors. Protein catabolism and musculature weakening are often seen in critically ill patients [7]. Regular hypoxic and hypercarbic ventilatory response can be disturbed during starving. On the other side, hyperalimentation can prolong the weaning of mechanical ventilation by excessive CO_2 production. Bicarbonate excretion as a result of hyperventilation (relatively frequent in patients with COPD) can thwart the process of weaning of mechanical ventilation because patients have decreased hypercarbia compensation capacity.

Numerous disorders can be the cause of respiratory muscle dysfunction. Phosphate and magnesium deficiency can cause respiratory muscle weakness and prolonged weaning. Hyperthyroidism, insulin, glucagon, and corticosteroid misbalance may remarkably deteriorate the optimal muscular function and delay early patient mobilization.

There is no consensus in clinical practice: when to start the nutrition and on what regime; what is the optimal caloric intake, and if treatment duration and outcome depend on caloric intake and administration route [8]. There is an impression that it has been accepted that a critically ill patient's daily energetic requirements are 25 -30 kcal/kg/day and that the enteral route of nutrition is the most efficient [9]. Before enteral nutrition (EN) starts, the possibility of ischemic bowel disease and hypoperfusion should be ruled out because food intake during hypotension or inotropic support can trigger bowel ischemia [6]. As a general principle, it has been accepted that the enteral route of nutrition in an unstable patient should be avoided as long as inotropic agents maintain pressure and perfusion hemodynamics.

Total parenteral nutrition (TPN) is widely accepted as part of a critically ill patient's treatment and brings lower morbidity, complication, and mortality rate. Ac-

cording to the American Society for Parenteral and Enteral Nutrition (ASPEN, https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Clinical_Guidelines/) and European Society for Clinical Nutrition and Metabolism (ESPEN, https://www.espen.org/guidelines-home/ guidelines espen-guidelines) guidelines, EN should be started in the early postoperative stage. In patients with good nutritive status, TPN should not be initiated in the first 5–7 days and if it is not expected to be used for more than 7 days. In patients who require EN in the early postoperative stage, early initiation of immunomodulatory formulas is recommended, especially based on arginine and fish oil [8]. Abunnaja *et al.* recommend early implementation of immunomodulation based on glutamine [11].

NUTRITION AND IMMUNOMODULATION

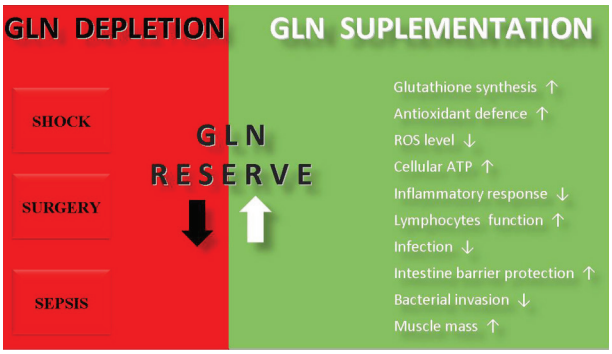
During the last decades, we have been facing more severe cases of intrahospital infections caused by multidrug-resistant bacteria, associated with increased morbidity and mortality rates. Numerous clinical studies have examined the effect of omega-3 fat acid, arginine, glutamine, and nucleotides added to standard nutrition formulas on critically ill patient's treatment outcomes [10]. The authors reported lower infection incidence, shorter general intensive care unit (ICU) and in-hospital stay, shorter mechanical ventilation time in patients treated with nutrients with immunomodulatory potential, and lower treatment expenses.

Immunonutrition and gastrointestinal system

In recent years integrity of the enteral barrier and its protection by enteral nutrition (at least 500 kcal/day) has been requested. In both, liberal and conservative approach, correction of intestine hypoperfusion and hypoxia alongside EN is essential to prevent bacterial translocation and bacterial endotoxin intoxication. If treatment to maintain the enteral barrier is unsuccessful, cytokine and systemic hormones should be activated. The gastrointestinal system is extremely vulnerable to hypoxia and hypoperfusion and has a unique role in the immune response. The small intestine and colon metabolize large amounts of glutamine, where glutamine as a source of energy is more important than glucose. The inflammatory response triggered by surgery results in the realese of inflammatory cytokines (TNF, IL-1, and IL-6), adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), catecholamine, and cortisol. Acute response to stress leads to hyper catabolism and skeletal muscle degradation, amino acid mobilization, and an increase of glutamine and alanine levels in the systemic amino acid depot. Critically ill patients usually lose 5-10% of their body mass during one week in the ICU.

Glutamine – essential "nonessential" amino acid

Glutamine has a role in maintaining cellular sodium pump, thereby cellular osmolality. It represents a "source of energy for muscles" and "nitrogen transporter" in the process of muscle regeneration and glycogen depot restoration during the stress, as well as an alternative energy source for the myocardium [12]. The nonessential amino acid that becomes essential in stress conditions is often termed "conditional" essential amino acid. In healthy persons, it is distributed in all tissues (average 70–80 g). It is synthesized from glutamate by glutamine synthetase, mostly in skeletal muscle, lungs, liver, and brain. It constitutes 50% of plasma amino acids (500–800 μM/l) and up to 60% of all body amino acids. Glutamine is a remarkable source of energy during stem cell and some immune cell division [11, 13]. In the central nervous system, it represents the substratum for neurotransmitter (gamma-aminobutyric acid – GABA) synthesis. It has been recently confirmed that astrocytes have a role in the resorption of an excessive amount of glutamine and its recycling out of the synaptic space. Glutamine has an important role in ammonia detoxification and glucose metabolism regulation, alongside glycemia regulation (**Scheme 1**).

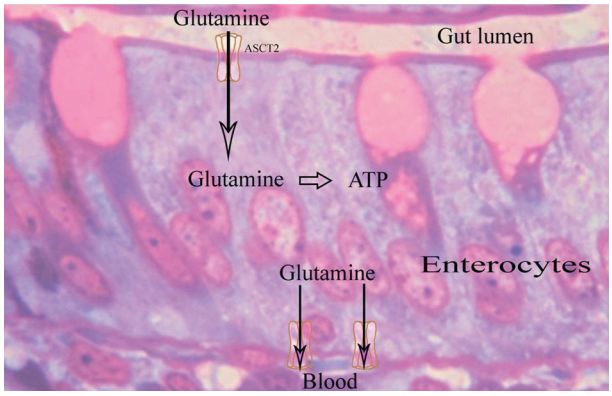


Scheme 1. Potential effects of glutamine supplementation in critically ill patients.

The liver has a special role in glutamine synthesis, as well as in consumption. Glutamine has an important role in stimulating the liver's detoxification role (fatty acid metabolism, chemotherapy, cirrhosis). The absorption capacity of hepatocytes is determined by urea cycle intensity, whereas blood pH and NH_3 metabolism are regulated.

Enterocytes represent a vulnerable glutamine-dependent system as glutamine derived from food intake is the principal energy source for enterocytes and immune cells, initiating underlying mechanisms for their fast regeneration. Based on a great variety of mutually interdependent mechanisms: glutathione stimulation, NO, polyamine, nucleotides, and some amino acids (alanine, citrulline, and proline) synthesis. Protection and stimulation of enteral integrity and stability are among the underlying principles in colitis, Crohn's disease

diarrhea, and chemotherapy-induced colitis treatment by applying Glutamine 20 g/day [13] (**Scheme 2**).



Scheme 2. Glutamine absorbtion in gastrointestinal system.

The extreme effort, infection, stress, and trauma may provoke glutamine deficiency in critically ill patients, thereby deficiency of energy source for many of their cells (lymphocytes, macrophages, and T-cells). Daily substitutional dose in healthy persons is 2-5 g/day, and in severely ill patients (AIDS and bone marrow transplanted) up to 40 g/day [14]. Glutamine neutralizes inflammatory mediators and raises cell immune response and level of anti-inflammatory agents. It is a precursor of glutathione – the most important intracellular antioxidant. Glutamine has a role in intestinal barrier maintenance [15], insulin-mediated utilization of glucose, increased arginine synthesis in kidneys, and increased taurine plasma level (which is vital for cell volume regulation).

CLINICAL EXPERIENCES

Conventional amino acid solutions do not contain glutamine because of its instability in solution and insolubility at high concentrations. Glutamine is synthesized and used in the form of dipeptides L-alanyl-L-glutamine and glycyl-L-glutamine, which are stable in solution and, after intravenous implementation, can be rapidly degraded by hydrolysis in plasma. Despite many publications, debates, and studies, there is no clear consensus. Numerous clinical trials have been conducted with the purpose of examining whether glutamine-rich TPN and EN contribute to better treatment outcomes. A meta-analysis of 355 elective surgery patients treated by glutamine-rich TPN showed a significant reduction in postoperative infection rate and hospital stay [16]. A meta-analysis of 14 randomized control studies that outreached 751 critically ill patients after elective surgery showed that high glutamine doses, more than 0.20 g/kg/day, significantly reduce infection rate, hospital stay, and mortality. In contrast, low doses of glutamine had no effect on those parameters [17]. A randomized control trial was conducted in 20 patients with a head injury (Glasgow coma score 5-12]; divided into two groups: -control group (10 patients) fed by standard enteral formula, and study group fed by a standard enteral formula with the addition of glutamine 30 g/day and probiotic (fermented milk with *Lactobacillus johnsonii*). The number of days on mechanical ventilation was lower in the study group (no statistically significant difference) with a significant reduction in the infection rate and duration of the ICU stay [18].

Numerous studies were conducted in recent years, with various methodologies, inclusion criteria, IMS regime, and glutamine time of administration, dosage, and treatment duration.

Stehle *et al.* conducted a meta-analysis of randomized controlled studies that examined the effect of parenteral nutrition with glutamine dipeptide regime on infection rate, hospital stay, and mortality [19]. Glutamine administration was performed by current guidelines (0, 3-0,5 g/kg/day, up to 30% of nitrogen demands) in combination with adequate nutrients. Sixteen studies were analyzed (842 critically ill patients with multiple conditions: sepsis, secondary peritonitis, severe acute peritonitis, multiple traumas, and severe burns without liver/kidney failure, thermodynamically stable) with no coherent methodological approach in regard to the duration of mechanical ventilation, duration of hospital stay, and ICU mortality. Despite these differences, the authors reported that: those meta-analysis results strongly suggest the benefit of glutamine dipeptide usage as a supplement to parenteral nutrition. Guidelines for glutamine dosage 0, 3-0,5 g/kg/day (it should be less than 30% of daily protein requirement) should be followed. The use of glutamine as a supplement was related to lower infection rates and in-hospital mortality. Studies that compared hospital stay and mechanical ventilation duration, ICU stay duration, and mechanical ventilator support usage concluded that glutamine usage improved these parameters. It has also been shown that glutamine supplementation led to treatment cost reduction [19].

It has also been investigated which route of administration of glutamine, enteral or parenteral, is more beneficial. According to the results, it seems that both routes have some advantages. Parenteral route causes faster effect onset and broader organ outreach. The enteral route had emphasized the local effect on preserving physical and enteral immune system integrity by protecting enterocytes and regional lymphatic-immune system. In comparison, glutamine administrated by enteral route reaches the systemic circulation in smaller doses.

Within the elaborate illness presentation of COVID-19 patients, malnutrition and negative nitrogen balance dominate and thereby impact treatment outcome without coordinated treatment strategy. There is no consensus, but due to recent publications, it is

recommended to use nutritive support as an important part of treatment [20, 21]. The most vulnerable systems in COVID-19 patients are respiratory and renal. Based on the aforementioned clinical experience in CCIS, glutamine could have an important role in the protection and restoration of cellular integrity of the alveolar-capillary and enteral membrane [22, 23]. First, efforts to make protocols and guidelines for COVID-19 patients management and nutrition are made. Algorithms support early enteral nutrition via the gastric route, hypocaloric nutrition in the first 5-7 days, protein delivery of at least 1.2 g/kg/day, while consideration is given to pandemic nutrition resourcing and planning [24]. In a recently published review article, authors concluded that nutritional therapy, together with pharmacological therapy, undoubtedly helps the COVID patient to overcome the acute phase of the disease first and to shorten recovery times [25].

CONCLUSION AND PERSPECTIVE

Survival, proliferation, and function of immune cells in many ways depend on glutamine availability. During catabolic/hypercatabolic processes in critically ill patients, glutamine stores are depleted, decreasing its availability. However, the low glutamine blood level is not always detected in all critically ill patients or patients with metabolic disturbance. There is no unique ground point, but the impression that the level of its availability should individualize glutamine therapy prevails. New studies are needed so we could examine and eventually set the guidelines for this matter. At the same time, there is no consensus about the dosage and regime of administration. On the basis of recent studies, ASPEN, and ESPEN guidelines, the nutritive immunomodulation is based on arginine, glutamine, omega-3 acids (eicosapentaenoic acid – EPA and docosahexaenoic acid – DHA), and omega-6 fatty acids. The most common opinion is that protein recoupment in the early postoperative stage should be 1,2–2,0 g/kg/day with the addition of glutamine 0,3–0,5 g/kg/day or 30% of daily protein requirements.

A recent, unexpected tsunami of coronavirus (COVID-19) pandemic overstrained the healthcare system worldwide. We are seeing an increasing number of patients with complex clinical conditions with a great variety of clinical symptoms, from very mild to severe respiratory, renal, circulatory, and gastrointestinal insufficiency as a consequence of underlying more or less severe immune deficiency. Without consensus in treatment and management worldwide, with frequent changes, sometimes opposite recommendations, intensifies the need to use previous experience in the management of critically ill patients. Based on that experience, immunonutrition based on micronutrients with immunomodulatory capacity might be part of treatment in these patients. So far, there is no consensus regarding dosage, timing, and the most important, early administration of glutamine, besides vitamin C, vitamin D, vitamin E, zinc, and other supportive therapies. Still, some reports, based on initial experience, offer promising results. Clinicians need to tailor the management of COVID-19 patients based on experience with similar multiorgan failure conditions in the critically ill. Time will open new questions and dilemmas before us.

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Ishrana kritično obolelih pacijenata: Uloga glutamina u imunomodulaciji ishranom

[1,2]Miomir Jovic, [1]Vladimir Savic

[1]Institut za kardiovaskularne bolesti "Dedinje", Klinika za anesteziju i intenzivno lečenje, Milana Tepica 1, Beograd, Srbija

[2]Medicinski fakultet Univerziteta u Beogradu, Doktora Subotića 8, Beograd, Srbija

Kratak sadržaj

Glutamin je neesencijalna aminokiselina koja postaje esencijalna u uslovima stresa (katabolizma /hiperkatabolizma) te se često naziva „uslovno" esencijalna aminokiselina. Sintetiše se iz glutamata dejstvom glutamin sintetaze, pre svega u skeletnim mišićima kao i u plućima, jetri i mozgu. Glutamin čini do 50% aminokiselina u plazmi i do 60% slobodnih aminokiselina u telu. Supstrat je za sintezu nukleotida a predstavlja i značajan izvor energije za sve ćelije uključujući imunske ćelije. Tokom poslednjih decenija značajno se promenila strategija lečenja kritično oboleleih. Invazivne dijagnostičke i terapijske procedure kao što su mehanička ventilacija, transfuziona terapija, supstituciona terapija bubrežne funkcije i invazivni hemodinamski monitoring značajno su promenile i produžile život modulirajući mehanizme homeostaze, inicirajući nove forme i mehanizme adaptacije – alostazu. Sistemski inflamatorni odgovor i imunomodulacija su deo komleksnih mehanizama uključenih u alostazu. Vrlo važan deo strategije lečenja kritično obolelih je ishrana. Skorašnja istraživanja pokazuju da neki nutrijenati (omega-3 masne kiseline, arginin, glutamin) kada se dodaju standardnoj formuli za enteralnu i parenteralnu ishranu, doprinose kraćem lečenju kritično obolelih u jedinici intenzivnog lečenja, nižoj učestalosti infekcija i kraćem trajanju mehaničke ventilacije. Glutamin poseduje visok imunomodulatorni kapacit, kao izvor energije za mišiće i „transporter" azota, ima ulogu u protekciji funkcije pluća, creva i imunokompetentnih ćelija. Najosetljiviji sistemi organa kod COVID-19 pacijenata su respiratorni i bubrežni. Iako ne postoji univerzalno prihvaćena strategija za lečenje COVID-19 pacijenata, smarta se da glutamin može imati važnu ulogu u zaštiti integriteta imunskih ćelija kao i enteralne i alveolarno-kapilarne membrane.

Ključne reči: *Kritično oboleli pacijenti; Ishrana; Imunomodulacija; Glutamin; COVID-19.*