Malnutrition in Intensive Care Units: An Important Risk Factor for Intensive Care Unit-Acquired Infections

Yoğun Bakım Ünitesinde Malnütrisyon: Yoğun Bakım Ünitesinde Kazanılmış Enfeksiyonlar için Önemli Bir Risk Faktörü

Kürşat Gündoğan[1], Adnan Bayram[2], Emine Alp[3]

[1]Erciyes Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Yoğun Bakım Bilim Dalı, Kayseri, Türkiye
[2]Erciye Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Kayseri, Türkiye
[3]Erciyes Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Kayseri, Türkiye

Abstract

Intensive care units have the highest prevalence of nosocomial infections in hospitals. Good nutritional support is essential to prevent nosocomial infections. However, malnutrition is a common and important problem in intensive care units, especially in developing countries. For the prevention of malnutrition, a team approach is needed. Immunonutrition is nutrition that affects the immune response in various ways and increases the strength of the immune system. Pharmaconutrition is the administration of immunonutrients over the daily recommended doses that act like pharmacological agents and drugs. The major immunonutrients are glutamine, arginine, omega-3 fatty acids, nucleotides, antioxidants (selenium, vitamin E, vitamin C, zinc, copper, and N-acetyl cysteine), probiotics, prebiotics, and synbiotics. The aim of this review is to highlight the pathophysiology and role of malnutrition in intensive care unit-acquired infections (ICU-AIs) and the use of immunonutrients to prevent ICU-AIs.
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Key words: Malnutrition, intensive care unit, immunonutrition, pharmaconutrition, nosocomial infection

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Özet

Yoğun bakım üniteleri, hastane kökenli enfeksiyonların en sık görüldüğü yerlerdir. İyi beslenme desteği hastane enfeksiyonlarını önlemek için gereklidir. Bununla birlikte, özellikle gelişmekte olan ülkelerde malnütrisyon yoğun bakım ünitelerinde önemli ve yaygın bir problemdir. Malnütrisyonun önlenmesi için ekip çalışmasına ihtiyaç vardır. İmmünonütrisyon, hastanın savunma sistemini etkileyerek savunma sisteminin gücünün arttıran bir beslenmedir. Farmakonütrisyon ise, savunma sistemini etkileyen besinlerin günlük önerilen dozların üzerinde bir farmakolojik ajan ve ilaç gibi yüksek dozda verilmesidir. Temel immün nütrientler glutamin, arjinin, omega-3 yağ asitleri, nükleotidler, antioksidanlar (selenyum, vitamin E, vitamin C, çinko, bakır ve N- asetil sistein) probiyotikler, prebiyotikler ve sinbiyotiklerdir. Bu derlemede, malnütrisyonun patofizyolojisini, yoğun bakım ünitelerinde kazanılmış enfeksiyonlardaki rolünü ve bu enfeksiyonlardan korunmak için immün nütrientlerin kullanımını anlatmayı amaçladık.
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Anahtar sözcükler: Malnütrisyon, yoğun bakım ünitesi, immün nütrisyon, farmakonütrisyon, hastane kökenli enfeksiyon

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Introduction

Nosocomial infection is one of the leading causes of mortality and morbidity in intensive care units (ICUs) (1). Several factors (age, underlying diseases, severity of illness, poor infection control, etc.) cause intensive care unit-acquired infections (ICU-AIs), and malnutrition is one of the most common and severe reasons. Good nutritional support can result in improved immune system function, gastrointestinal structure and function, and low ICU-AIs (2)-. The aim of this review is to highlight the pathophysiology and role of malnutrition in ICU-AIs and the use of immunonutrients to prevent ICU-AIs.

Pathophysiology of Malnutrition

Intensive care unit patients are considered to be malnourished when their food (protein, carbohydrates, and lipids) supply is not enough to meet their metabolic requirements (3). The causes of malnutrition in patients in ICU are multifactorial. Underlying diseases and invasive procedures done in ICUs increase the stress on their body and metabolic requirements, thus leading to the deficiency of various nutrients (4). The mechanisms of disease-related malnutrition are the interference of adequate absorption, digestion, infection-dependent changes in the metabolism of food, loss of appetite, and disease-specific catabolism. However, there are also many other major causes, such as poor dental health,

Address for Correspondence / Yazışma Adresi: Kürşat Gündoğan, MD, Erciyes Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Yoğun Bakım Bilim Dalı, Kayseri, Türkiye.
Phone: +90 352 207 66 66 e.mail: kgundogan@erciyes.edu.tr
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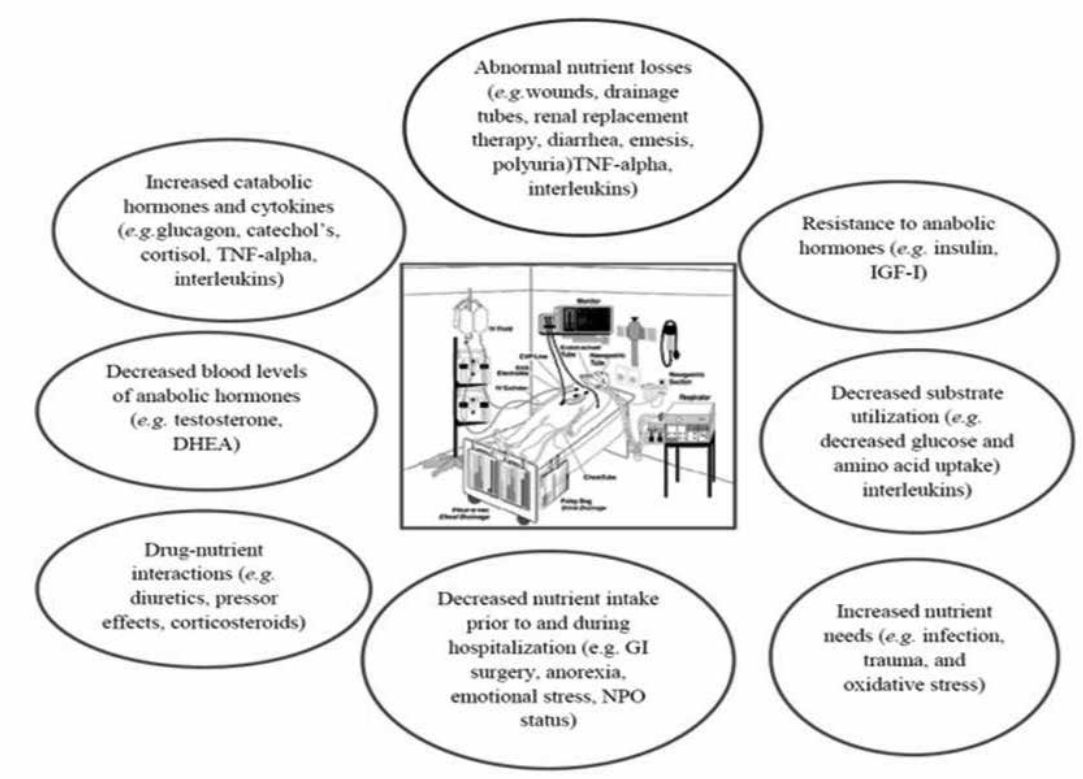

Figure 1. Pathophysiology of malnutrition in intensive care unit

poorly fitting false teeth, social isolation, gastrointestinal symptoms, addiction, poverty/lack of money, mental illness (e.g., depression, dementia), swallowing disorders, changes in taste perception, complex medication, or an individual's inability to purchase or prepare food. Systematic early evaluation and the resulting treatment of potential underlying causes are essential medical tasks that are part of the suitable treatment of patients at risk of under-/malnutrition (5, 6). In ICUs, malnutrition can be aggravated in multiple ways: response to trauma and infection and alteration of metabolism and absorption or assimilation of nutrients. Mechanical obstructions in the gastrointestinal tract may lead to reduced food intake by causing nausea, vomiting, pain, or discomfort induced by the passage of food. Any disorder, whether chronic or acute, has the potential to aggravate malnutrition (7). Some mediators, like glucocorticoids, catecholamines, certain cytokines (interleukin 1, interleukin 6, and tumor necrosis factor alpha), and deficiency of insulin growth factor-1, have been shown to be catabolic in previous studies, but the relation between them has not yet been shown (8). In some cancers, proteolysis-inducing factor (PIF) (9) and lipid-mobilizing factor (LMF) (10, 11) have been identiŞed to play major roles in the pathogenesis of malnutrition. Adverse effects of certain drugs (e.g., morphine derivatives, sedatives, neuroleptics, antibiotics, anti-histaminic, chemotherapy, digoxin captopril, etc.) may interfere with the ingestion of food and lead to anorexia. Dementia, immobilization, anorexia, and poor dentition in geriatric patients can further worsen the situation (12, 13). The metabolic changes that occur in response to stress lead to an increase in protein catabolism. Therefore, a significant loss of lean body mass is seen, which increases complications, especially infections, wound dehiscence, and unfavorable outcomes (14) (Figure 1).

Nutritional Assessment in the ICU (15)

- Review of past medical-surgical history and history/tempo of current illness
- Physical examination
- Body weight history
- Dietary intake pattern
- Gastrointestinal tract function
- Functional status
- Biochemical tests in blood (electrolytes, blood glucose, organ function tests, and selected specific nutrients)
- Estimate energy (calorie), protein, and micronutrient needs
- Enteral/parenteral access for nutrient delivery

Malnutrition Prevalence in the ICU

Poor nutritional status is an important problem, especially in ICUs. The problem is huge in developing countries. Poor nutritional status includes under-nutrition and malnutrition states. It has been reported that the prevalence of malnutrition in acutely hospitalized adults is approximately 50% in these countries (3, 16). Malnutrition is an important problem that increases mortality and morbidity. Since malnutrition increases the length of the hospital stay, nosocomial infections are mostly seen in these patients (17, 18).

Malnutrition is more common in ICUs than in other clinics and depends on the socioeconomic status of the countries. Nicolo et al. (19) found that 15.7% of acutely ill patients had moderate malnutrition, while 16.7% of acutely ill patients had severe malnutrition in the United States. Malnutrition was associated with acute illness more in ICUs than in non-ICU settings.

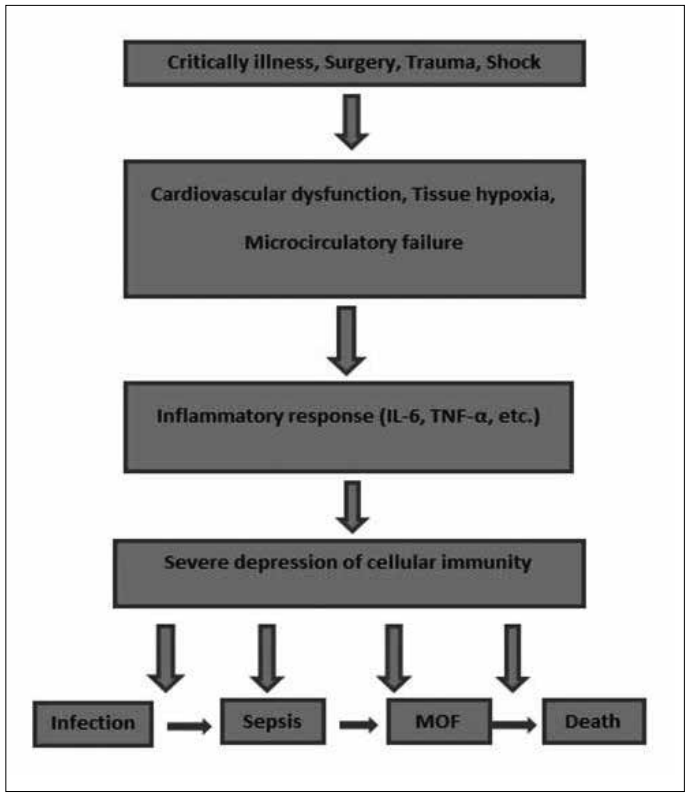

Figure 2. Pathophysiology of critically illness and infections

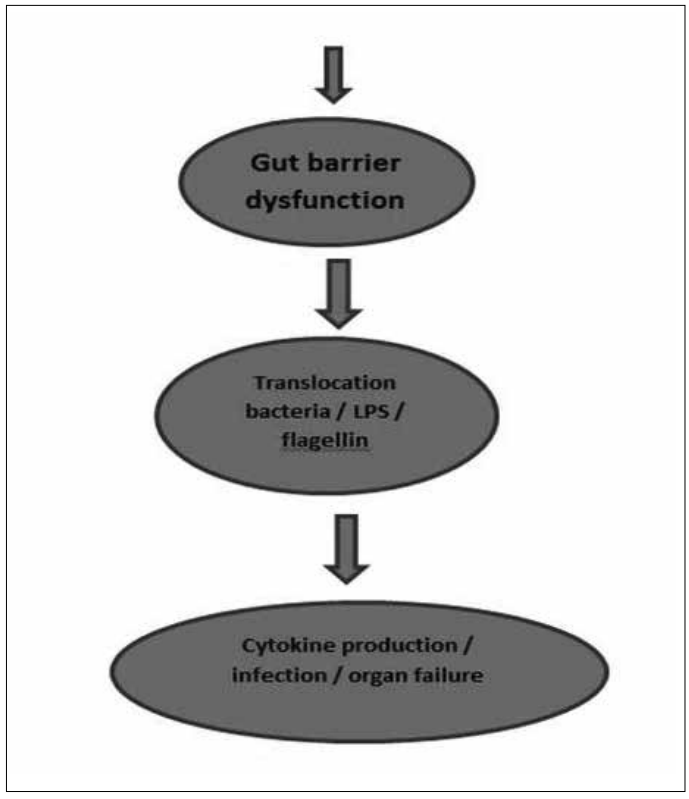

Figure 3. Malnutrition and gut barrier dysfunction

Korfali et al. (16) conducted a multicenter observational prospective study to assess the nutritional risk of hospitalized patients in Turkey. Thirty-four hospitals from 19 cities contributed data from 29,139 patients. It was found that 15% of patients had nutritional risk upon admission. Nutritional risk was common (52%) in ICU patients and lowest (3.9%) in otorhinolaryngology patients.

Another observational, prospective study was performed by Chakravarty et al. (3), in which the prevalence of malnutrition and its grade among patients who were admitted in a mixed ICU of a tertiary care hospital in India were considered. Five hundred sequential patients who were admitted to the ICU were screened on admission for malnutrition over a 1-year period. Of the total, 198 (39.6%) patients were malnourished, including 1 patient who qualified as severely malnourished.

De Souza Menezes et al. (20) performed a prospective cohort study in which 385 children who were admitted to the ICU of a teaching hospital in Brazil were assessed over a 2-year period for nutritional status at admission and clinical outcomes. One hundred seventy-five patients (45.5%) were found to be malnourished upon admission. Malnutrition was also found to be associated with greater length of mechanical ventilation and length of ICU stay but not with mortality in the univariate analysis. Malnutrition was associated with greater length of ventilation in multiple logistic regression models, as well.

Malnutrition and Infection

Depending on the severity of the hyperinflammation during critical illness, impairment in cellular immune function, oxidative stress, and mitochondrial dysfunction may occur. As a result of inadequate oral intake and stress response in critically ill patients, nutrient deficiency can develop rapidly. Deficiency of nutrients increases the intensity of hyperinflammation and predisposes one to infections. On the other hand, poor nutritional status depresses the immune system, which increases the patient's risk of infection. Depending on the severity and duration of this process, sepsis, multiorgan failure, and death may be observed (Figure 2) (21, 22).

Also, malnutrition mainly affects gut barrier dysfunction. Long-lasting starvation (especially patients who can not be fed orally) causes atrophic changes in intestinal villi, microorganisms located on the intestinal wall migrate to the bloodstream, and infections occur (Figure 3) (23).

Malnutrition Prevention in ICU

Malnutrition increases hospital costs, infection rates, morbidity, and mortality in ICUs. Therefore, nutrition therapy has vital importance in ICUs and is recommended to be done by a professional nutrition team. Generally, this team consists of a doctor, nutritionist, pharmacist, and nutrition nurse. Upon admission, ICU patients should be evaluated for the risk of malnutrition by a nutritionist, and the caloric needs and the shape of the patient's nutrition should be determined; the nutritional formula of the patient and interactions with other drugs should be considered by a pharmacist. A nutrition nurse is involved in the provision of the administration route of the nutrition product (EN or PN). Studies have shown that hospitals with nutrition teams have patients with improved nutritional statuses, lower hospital costs, and reduced morbidity and mortality (24-27).

In order to avoid malnutrition in ICUs, training of healthcare personnel is also an important point. Studies show that after training, the ICU team is more sensitive about nutrition (28, 29). According to ESPEN guidelines, enteral feeding should be initiated within the first 24 hours to all of the patients who are adopted in intensive care who are hemodynamically stable (30).

Immunonutrition in the ICU

Immunonutrition is nutrition that affects the immune response in various ways and increases the strength of the immune system. Pharmaconutrition is the administration of immunonutrients that act like pharmacological agents and drugs over the daily recommended doses.

Table 1. Mechanism of immunonutrients (30, 31)

Immunonutrients	Mechanism of action
Omega-3 fatty acids (EPA and DH)	Anti-inflammatory effect due to suppression of pro-inflammatory cytokine production; reverses immunosuppression.
Glutamine	Nutrient for gut immune cells, improves gut barrier function, precursor for glutathione.
Arginine	Precursor for nitric oxide, increases T lymphocyte production and function, precursor for praline, stimulates growth hormone production.
Sulfur amino acids, their precursors and other thiol compounds (methionine, cysteine, N-acetyl cysteine (NAC), L-2-oxothiazolidine-4-carboxylate lipoic acid (OTZ; procysteine).	Enhances antioxidant defenses via glutathione synthesis or 'protection' of available glutathione (GSH) through provision of other sulfhydryl groups to interact with oxidant molecules.
Nucleotides	RNA and DNA precursors, improves T lymphocyte function.
Probiotics, prebiotics, and synbiotics	Immunomodulatory (increases productions of secretory IgA, regulates the response of T helper cells)

The major immunonutrients are glutamine, arginine, omega-3 fatty acids, nucleotides, antioxidants (selenium, vitamin E, vitamin C, zinc, copper, and N-acetyl cysteine), probiotics, prebiotics, and synbiotics. The mechanisms of immunonutrients are shown in Table 1.

Glutamine

Glutamine is an amino acid that has a number of vital metabolic functions. It is the most abundant free amino acid in circulation under normal circumstances; however, under conditions of stress, such as critical illness or chronic gastrointestinal disorders, glutamine levels may be inadequate to meet the body's demands and are thus classified as conditionally essential (31, 32).

Glutamine plays an essential role in renal ammonia genesis and nitrogen transport within the body; it is a fuel for rapidly dividing cells, such as lymphocytes, enterocytes, and colonocytes; is a precursor to a key antioxidant (glutathione) (33); and is an important substrate for purine and pyrimidine synthesis of DNA and mRNA during immune cell proliferation (34). Glutamine is predominantly important in the intestine as the favored fuel source of enterocytes and immune cells within gut-associated lymphoid tissue (GALT), where up to 50% of available glutamine is metabolized following enteral feeding. Activated immune cells, such as lymphocytes and macrophages, also use glutamine as a source of energy (35-37).

Particularly in studies conducted after the 2000s, the addition of glutamine to the nutritional solutions of patients in critical care or undergoing surgery was shown to reduce the rates of infectious complications and mortality (38-41). These studies were conducted on homogeneous groups of patients. Patients who had liver and renal failure, who were hemodynamically unstable, who had uncontrolled sepsis or severe head trauma, and who were receiving immunosuppressive agents were excluded from the study. In these patients, glutamine was administered parenterally, with a maximum dose of <0.5 mg/kg/day. However, in two recently conducted large, randomized, controlled studies, the addition of high-dose glutamine to nutritional solutions was shown not to reduce infectious complications and mortality but, on the contrary, led to increased mortality rates (42, 43). In the REDOX study performed by Heyland et al. (42) in 1223 patients (All patients were admitted to medical, surgical and trauma intensive care units), patients with an APACHE II score >25, who were in a state of shock (approximately 65% being septic shock), and who had multiple organ failure were included in the study, and they were treated with high-dose parenteral glutamine (0.8 mg/kg/day), administered together with antioxidant treatment. When Heyland et al. (44) reanalyzed the data that they had obtained in that study, they reported that the mortality rate was particularly higher in patients with renal failure who were receiving glutamine and antioxidant treatment. Van Zanten et al. (43), in their Meta Plus study, in which they included trauma, medical, and surgical intensive care patients with SOFA scores >8 and APACHE II scores >22, determined no significant difference in terms of nosocomial infection between groups receiving and not receiving immunonutrition; additionally, they reported a higher 6-month mortality rate in medical intensive care patients receiving immunonutrition.

As a conclusion, in critical patients whose APACHE II and SOFA scores are not high and who are hemodynamically stable, low-dose enteral and parenteral glutamine (0.3-0.5 mg/kg/day) may be utilized in order to reduce infectious complications.

Arginine

Arginine is another conditionally essential amino acid that plays an important role in a number of metabolic pathways (45). In acutely ill patients with catabolic diseases, serum arginine levels decrease due to a number of factors, such as reduced dietary intake; increased uptake in the endothelium, liver, and intestine; and increased overall metabolism (46). These levels, however, increase, following the development of sepsis and as the duration of the catabolic event increases (47).

Arginine plays a vital role in the urea cycle, as it is derived from argininosuccinate and is further metabolized to produce urea and the amino acid ornithine. It also stimulates the release of essential peptide hormones, such as growth hormones, prolactin, and insulin. Arginine has also been found to stimulate the production of T cells and enhances T cell function (48).

There are not so many studies investigating the effect of adding arginine to nutritional solutions on infectious complications in critically ill patients. In a prospective and multi-center study (49), when the group in which the enteral nutritional solution was prepared by the addition of arginine, fiber, and antioxidant and was enriched with high proteins was compared with the control group, the rate of catheter-related sepsis was found to be lower in the group receiving arginine, fiber, and anti-

oxidant. However, arginine has been also claimed to worsen the clinical state in patients with sepsis, first being converted to citrulline and then to nitric oxide. As a result of the studies conducted until now, adding arginine to the diet of critically ill patients is not recommended.

Omega -3 (ω-3) Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids that can not be synthesized by mammals and are, therefore, essential dietary compounds (50).They are isolated from cold-water fish species (such as salmon, herring, and mackerel), flaxseed, and canola oil (50). These fatty acids are known for their proposed anti-inflammatory properties, the most important of which are α-linolenic acid (ALA), eicosapentanoic acid (EPA), and docosahexanoic acid (DHA) (51).

Omega-3 fatty acids are readily incorporated into inflammatory cell membrane phospholipids, often at the expense of omega-6 fatty acids, like arachidonic acid. Consequently, this competitive binding reduces the production of pro-inflammatory eicosanoids derived from omega-6 fatty acids (such as leukotriene B4, thromboxane A2, and prostaglandin E2) and increases the production of less inflammatory eicosanoids derived from omega-3 fatty acids (such as thromboxane A3, prostaglandin E3, and leukotriene B5), thus resulting in anti-inflammatory effects (51).

Omega-3 fatty acids have been reported to reduce the incidence of infectious complications in critically ill patients (52, 53). In a multicenter, randomized, double-blind study in which EPA, ALA, and antioxidant were added to enteral nutritional solutions, fewer patients were reported to develop severe sepsis and septic shock (52). In another study in patients who had developed septic shock related to intra-abdominal infection, adding fish oil to the parenteral nutritional solutions in the early period was reported to be unable to reduce organ failure (53). As a conclusion, studies on omega-3 treatment for the reduction of infectious morbidity in critically ill patients are insufficient, and its routine use is not recommended in the intensive care unit.

Antioxidants

Antioxidants are substances that can protect tissues from the destructive effects of oxidative stress caused by excessive amounts of reactive oxygen species and reactive nitrogen-oxygen species. Oxidative stress is central to the development of organ failure in critically ill patients. In such patients, reduced stores of antioxidants lead to an increase in free radical generation, which stimulates the systemic inflammatory response. This, in turn, leads to cell injury, tissue damage and, ultimately, organ failure (54).

Selenium has been found to be an essential trace mineral antioxidant. It is incorporated into the amino acid selenocysteine and is an important cofactor in at least 25 selenoproteins, which include essential immune, endocrine, and antioxidant enzymes (55). The most recognized role of selenium is the antioxidant function of glutathione.

There are studies performed with selenium in infectious complications in critically ill patients (56, 57). In a study, high-dose selenium treatment was shown to reduce the incidence of ventilator-associated pneumonia (56). In the study by Andrews et al. in critically ill patients, adding selenium to parenteral nutritional solutions was reported to reduce the development of new infections (57). However, adding selenium to nutritional solutions was reported to be unable to reduce oxidative injury and mortality in various studies (58, 59). As a conclusion, the number of studies on antioxidants, particularly selenium, is not sufficient, and further studies are needed to evaluate its routine utilization in critically ill patients.

Prebiotics, Probiotics, and Synbiotics

Probiotics are living bacteria or fungal microorganisms created by humans. It is believed that they are beneficial when added to dietary food (60).

Prebiotics are fibers in the soluble regimen and are fermentable, like inulin and oligosaccharides. They are known as beneficial bacteria and are metabolized by intestinal microbiomes (61).

Synbiotics are nutritional products that include probiotics and prebiotics. The purpose of their administration is to increase immune resistance (61).

Recent research has focused on the proposed immunomodulatory effects of pre- and probiotics through GALT, which contains up to 70% of the immune cells in the body (62, 63). Studies have shown that the prolonged use of PN reduces the number of Peyer's patches, lamina propria lymphocytes, mucosal Th2 cytokines, mucosal secretory immunoglobulin-A (sIgA) transport protein, and polymeric immunoglobulin receptors (pIgRs) (64-66). This results in a reduction of luminal sIgA, thus contributing to the loss of a major limb of specific immunity in gastrointestinal luminal fluid. sIgA prevents bacterial mucosal attachment through bacterial opsonization. The presence of sIgA inhibits the expression of virulence factors by gut bacteria and thus has an anti-inflammatory effect (67). Certain prebiotic and probiotic mixtures can enhance the effect of tissue anti-inflammatory cytokines and advance macrophage activation and antigen presentation, thus normalizing the parameters of GALT functioning and stimulating the release of sIgA on the gut lumen (68, 69). In a study conducted in the children of pregnant mothers, consuming probiotic foods by increasing the production of IL-27 has been shown to protect from allergic diseases (61). A double-blind, randomized, controlled pilot trial showed that synbiotic therapy decreased microbial translocation and inflammation and improved immunological status (increased CD4+ T lymphocytes) in HIV patients (70).

O'Sullivan et al. (71) performed a study in elderly patients and found that probiotics and prebiotics altered the intestinal microbiota after post-antibiotic therapy.

In a meta-analysis, it was shown that the administration of probiotics in critically ill adult patients was unable to reduce the intensive care requirement and general mortality; however, it was able to reduce the incidence of hospital-acquired pneumonia and the duration of stay in the intensive care unit (72). In a case report, fungal sepsis-related death in a burn patient who was treated in the intensive care unit was reported (73). In another randomized, double-blind study, prophylactic administration of probiotics in critically ill patients was reported to be unable to reduce intensive care-acquired infections and catheter-related bloodstream infections (74). In patients with severe trauma, when synbiotics were administered, the incidences of the development of infection, severe sepsis, and mortality were shown to be reduced in that group (75). As can be seen from the studies above, the studies on probiotics/prebiotics and synbiotics in critically ill patients are not sufficient. Therefore, their routine clinical utilization is not recommended.

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