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REVIEW ARTICLE

Nutritional supports in sepsis cases

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ABSTRACT

Sepsis is defined as life-threatening organ dysfunction resulting from unregulated host effect on the infection. Despite new advances in treatments, the morbidity and mortality of sepsis continues to be high today. One of the main causes of septic cells morbidity and death is cardiac and vascular rupture and consequent generalized tissue hypoxia. Sepsis, which is one of the most common causes of non-cardiac deaths in intensive care units in developed countries, increases the number of secondary infections with immunosuppression and thus increases the cost. Since most sepsis symptoms are nonspecific, the diagnosis of sepsis may be delayed. However, there is no specific treatment that has proven effective for sepsis. Patients with sepsis need more nutrients and energy. As a result of insufficient energy intake in sepsis, malnutrition occurs in the individual due to the lack of energy and nutrients for cells in organ systems. Nutritional support should be provided in patients with sepsis due to increased energy consumption, acceleration in catabolism and hyperdynamic circulation. In addition, drug treatments applied to patients also cause an increase in energy requirement. With nutritional support, carbohydrates and fats are provided as energy sources. Proteins, amino acids, vitamins and minerals are also used in nutritional support for cell building blocks and functions. Appropriate nutritional intervention should be performed depending on whether the gastrointestinal system of the individual with sepsis is functioning or not. Enteral nutrition is the safest way of feeding the patient. In patients with severe and prolonged catabolic period, parenteral nutrition is applied in cases where enteral nutrition cannot be performed due to the deterioration of the anatomical or functional integrity of the gastrointestinal system. Malnutrition can be corrected in these patients by providing effective and comprehensive early nutritional therapy. It is aimed to prevent increased destruction, secondary infections, multi-organ failure, morbidity and mortality with nutritional support to individuals with sepsis. In this review, types of sepsis and nutritional treatments in patients with sepsis will be evaluated.

Keywords: *sepsis, nutritional support, micronutrients*

INTRODUCTION

Sepsis is a disease that affects many systems, causes hemodynamic cells, can lead to shock, organ dysfunction and organ failure (1). The Third International Consensus Definitions for

Sepsis and Septic Shock "Sepsis-3" was published in 2016 and the SIRS definition that has been in use since 1992 was removed from the sepsis definition (2). The results of the sepsis consensus meetings in 1992 and 2003 were renamed as "Sepsis-1" and "Sepsis-2". "Sepsis-3" is defined sepsis as life-threatening organ dysfunction resulting from an abnormal host response to infection. According to the most current definition, sepsis is a negative and unresolved response to infection that causes organ dysfunction (3). Sepsis continues to be a disease with a high mortality rate despite the increase in new and advanced treatment methods over time (4). One of the reasons why mortality is so common is that this disease has a complex pathophysiology. The fact that most of the conditions that define sepsis are nonspecific may cause delays in the diagnosis (5).

Epidemiological studies on sepsis have different and contradictory results regarding incidence and mortality rates (6). The incidence of severe sepsis in the United States is thought to be 300 cases per 100,000 population (7). In Turkey, sepsis is known as a very important infection problem in hospitalized patients, especially in the Intensive Care Unit, and a significant number of patients die due to sepsis. There is a decrease in the quality of life in living patients (8). The incidence of sepsis and septic shock has been increasing since the 1930s, and scientific research indicates that this increase will continue (9). It is difficult to accurately determine the incidence of sepsis-related clinical manifestations in Turkey. A relative decrease was observed in sepsis seen in the community, while an increase in nosocomial sepsis cases was noted. In a study conducted at the Fırat University Medical Faculty Hospital, the rate of sepsis was reported as 17.2% in the Thoracic and Cardiovascular Surgery, Anesthesia and Reanimation ICU (Intensive Care Unit), and 13.0% in the Dokuz Eylul University Internal Medicine ICU (8).

Sepsis can be caused by bacteria, fungi, viruses or parasites or it can be seen in non-infectious intra-abdominal conditions such as sepsis, severe trauma, pneumonia, pancreatitis (10). Host control of the extent observed in sepsis is complicated by both pathogen-related variables that exacerbate the disease and immune cell-mediated inflammatory responses that can have adverse consequences in the early or advanced stages of the disease (11). Although gram-negative septic agents were common in the past with the increase in hospital-acquired infections and invasive procedures, the number of gram-positive microorganisms has increased over the years (12). Although studies have shown an increase in the incidence of gram-positive organisms, a study conducted in Europe reported an equal prevalence of gram-positive and gram-negative microorganisms (13). Gram-positive microorganisms produce exotocin, Which causes sepsis through cell wall components (14). The pathogenesis of sepsis consists of many complex events and chains of events (15). Microorganisms or their products that pass from the source of infection to the systemic circulation cause bacteremia (16). Almost half of the patients with sepsis die within 28 days. The death of cells one by one plays an important role in the pathophysiology of sepsis. Apoptosis and necrosis are the main types of cell death (17).

Energy and nutrient requirements in patients with sepsis

Patients with septic shock have a higher basal metabolic rates (BMR) than patients with sepsis. Therefore, the energy expenditure of patients with sepsis is observed at different levels (18). Malnutrition affects all patients in the intensive care unit, and its negative consequences are more risky, especially in patients with sepsis (19). In the case of stress seen in sepsis, the need for various nutrients in the gastrointestinal system, immune system cells, kidneys and other organs increases. In cases where the intake of nutrients needed by the cells is less than their consumption, the stores in the body are emptied. This causes a deficiency of proteins and other important building blocks of the

body (20). The aim of nutritional support is to prevent or limit malnutrition and its consequences and to correct immediate metabolic deficiencies, which can be common factors in sepsis-related morbidity and mortality (21). Indirect calorimetry or Harris-Benedict formula can be used when calculating energy. The energy requirement increases in patients with sepsis and is approximately 25-35 kcal/kg/day. However, there is evidence that low-calorie diets are better than high-calorie diets (22). Zusman *et al.* in a retrospective study examining the calorie and protein consumption applied to 1171 critically ill patients, the BMR of the patients were measured by indirect calorimetry (IC). The result was related to the percentage of calories administered divided by BMR. This study has proven that both undernutrition and overfeeding are harmful. Calories/BMR administered greater than 70% showed increased mortality and was associated with longer ventilation time and length of stay in ICU (23). In a study, 834 adult patients with sepsis and septic shock hospitalized in the ICU during 4 years, their mortality were observed to decrease as protein or energy amount increased in the first week of sepsis onset in critically ill patients with sepsis (24). Daily BMR measurement is the most useful way to measure the ever-changing and dynamic needs of patients with sepsis. Daily changes are important and it is recommended to measure BMR twice a week (25). Hyperglycemia is very common in sepsis patients. One of the main causes of this condition is insulin resistance in peripheral tissues, which is associated with high levels of various hormones in the blood. In addition, hyperglycemia is detected when parenteral glucose is given in excess (20).

Carbohydrates: In the early stages of sepsis, it should provide 150-180 g of glucose daily to support glucose-dependent tissues and maintain blood glucose levels to prevent amino acid degradation with deficient glucose administration. The recommended glucose dose for sepsis patients is 3-5 g/kg/day, and it has been shown to be triggered when acute stress exceeds 6 g/kg/day (20). In the early stages of sepsis (first 2-4 days), 200-300 g of glucose per day, together with electrolytes and vitamin supplements, is sufficient to feed glucose-dependent tissues. The amount of glucose given in a day should not exceed 600 grams. The course of sepsis can be very different. While some patients may die very quickly from Multiple Organ Failure (MOF), some patients experience a stationary but catabolic phase. At this stage, the benefits of nutrition can be seen. Nosocomial infections and MOF development can be prevented with the right nutritional support to be applied at this stage (26). The Sepsis Survival Campaign, published in 2021, recommends starting insulin therapy for adults with sepsis or septic shock when their blood glucose level is 180 mg/dL or higher (27).

Fats: It has been reported that 20% to 35% of the energy needs of patients with sepsis should be met with lipids (20). The importance of fats and fatty acids as a fuel source in critical illness is emphasized by classical metabolic studies in intensive care patients. These studies show that glucose utilization is significantly reduced in severe sepsis and critical illness, and free fatty acid (FFA) metabolism is accelerated and is the main energy source (28). Infusion of long chain fatty acids (LCT) should not exceed 1 mg/kg/min (1.4 g/kg/day) since ketogenesis is impaired in sepsis patients. The amount of oil emulsion should be maximum 2.5-3.5 g/kg per day. Oil emulsions in nutrient solutions are either LCT alone or a combination of LCT/MCT and the essential fatty acids linoleic and linolenic acids should be administered to the patient. In a study of critically ill normal-weight and obese patients, normal-weight patients used free fatty acids (FFA) for more than half of their BMR, while obese patients used amino acid metabolism instead of FFAs for BMR. that's why they lost their lean body mass (LBM) faster than normal weight patients (29). In a study of critically ill patients with severe

sepsis or septic shock who required mechanical ventilation and were able to tolerate enteral feeding, a low-carbohydrate, high-fat enteral formula rich in antioxidants and containing a blend of oils with EPA and GLA had significantly lower mortality rates. It has been found to be related to (30). In a study, 25 patients with sepsis or systemic inflammatory response syndrome who were thought to need parenteral nutrition were administered half a medium chain fatty acid and soybean oil combination or a 50:40:10 medium chain oil combination. Addition of fish oil to parenteral nutrition in septic intensive care patients increases plasma eicosapentaenoic acid, creates differences in inflammatory cytokine levels and improves gas exchange. This change is associated with a tendency to shorten hospital stays (31).

Proteins: Protein replacement is given enterally or parenterally to provide and increase muscle protein production to prevent or reduce muscle wasting in critically ill patients and to accelerate neuromuscular reaffirmation time. However, an optimum protein intake during critical illness is hotly debated. The dose, timing, and risk-benefit of protein supplementation at different stages of sepsis are largely unknown (32). One remains that includes 834 patients with sepsis and septic shock, the myth of 0.1 g/kg/day in protein intake in the first week of sepsis onset, could be achieved with a 6% reduction in mortality in the group with a high mNUTRIC score. In addition, increased daily energy intake was associated with reduced 30-day mortality, particularly in the high mNUTRIC score group (24). Allingstrup et al. With increasing protein intake, patients with low (0.79 g/kg), moderate (1.06 g/kg), and high (1.46) had 10-day survival rates with 50%, 78%, and 87% less mortality, respectively. reported that it is relevant (33). The normal human's first response to hunger is gluconeogenesis to maintain blood sugar. However, proteins are used in gluconeogenesis as glycogen reserves are depleted in 2-3 days. A number of adaptive mechanisms have evolved to stop or slow down the consumption of proteins: These include ketone metabolism by glucose-dependent tissues, slowing of basal metabolism, oxidation of fat stores for energy production. This mechanism is different in patients with sepsis. Due to the increase in the activity of the sympathetic nervous system and the increase in catecholamine and glucagon levels, the state of destruction in the body is more pronounced. Oxidation of fat reserves does not increase and basal metabolism accelerates. Therefore, gluconeogenesis results in a negative nitrogen balance as a result of protein degradation (34).

Elements of immunonutrition for patients with sepsis

Glutamine should have the greatest effect in critically ill patients with sepsis and organ failure, that is, in patients with maximum glutamine deficiency. In addition, glutamine deficiency is associated with increased mortality in intensive care units (35). The most abundant free amino acid in the human body is glutamine, and its stores are quickly depleted in the muscles. For example, in burns that cause trauma, sepsis, and catabolic stress, the stores are rapidly depleted. For this reason, glutamine is classified as a conditionally essential amino acid (36). In experimental models of sepsis, glutamine has been shown to reduce the inflammatory response, improve lung function, and improve survival (37). In a randomized controlled, double-blind study conducted with 30 intensive care patients with sepsis and enteral nutrition, half of the patients were given 30 g/day glutamine supplementation, and the remaining half were supplemented with calcium caseinate at the same gram. In the blood samples checked after 5 days, it was observed that the lymphocyte count increased and lipid peroxidation decreased in the patients who received glutamine supplementation (38). In the Sepsis Survival Campaign in 2016, it was reported that they were against the administration of glutamine supplementation to patients with sepsis and septic shock (39).

Arginine is an amino acid involved in many metabolic processes. It initiates the production of polyamine and hydroxyproline, which play a role in the repair of connective tissue, and also nitric oxide, which is a very important signal molecule (40). Studies on the use of arginine in sepsis have shown that this amino acid produces different results according to the period of sepsis, and it can increase the risk of mortality, especially in the later periods, while creating good results in mild cases (41). In a study examining the short-term (8 hour) dose response in 8 severely ill patients with septic shock; Protein degradation was found to be increased initially, and both protein degradation and protein synthesis were decreased with arginine infusion. As a result, adding arginine at a level that can increase plasma arginine 4 times in sepsis; It has been found that it can regulate resynthesized arginine and nitric oxide doses and reduce total body protein breakdown without affecting hemodynamic parameters (42). In the 2016 Sepsis Survival Campaign, it was reported that they were against the use of arginine in the treatment of patients with sepsis and septic shock (39).

Micronutrients were found effectively based on a before-after their supplementation (43). Patients with severe sepsis and septic shock received 6 g daily supplementation of vitamin C, thiamine (400 mg daily), and hydrocortisone (200 mg daily) and compared with patients in the control group. In this study, significant benefits were observed on the mortality rate and vasopressor administration time in the patient. Several randomized clinical trials with a total of 1239 sepsis patients reported that omega-3 supplementation did not affect important foods after death, but was able to reduce the length of stay in the ICU and mechanical ventilation. However, the use of this supplement in sepsis is not certain due to the lack of sufficient evidence for the application of omega-3 fatty acids supplementation in the routine treatment of sepsis (44). The Sepsis Survival Campaign, published in 2016, recommended that omega-3 fatty acids not be used as immune support for severely ill patients with sepsis or septic shock (39). In the Sepsis Survival Campaign published in 2021, intravenous vitamin C supplementation is not recommended for patients with sepsis or septic shock, and sodium bicarbonate therapy is recommended for adults with septic shock and severe metabolic acidemia ($pH \leq 7.2$) and acute kidney injury in the same campaign (27). As a result, it was concluded that the type of immunonutrition used in the studies improved the outcome only in patients with mild sepsis (APACHE<15), this effect may disappear as the disease progresses and may even be harmful in critical cases. Such preparations should not be used in these patients as they are associated with potentially increased mortality in severe sepsis (45).

Route of delivery of nutritional supports in patients with sepsis

Although the way in which nutritional support is given to patients with sepsis is important, experts do not have a common view on which route should be applied to patients with sepsis in the intensive care unit. Although ASPEN guidelines state that EN therapy should be initiated within 1-2 days of confirmation of a diagnosis of severe sepsis or septic shock in critically ill patients, the use of private PN or supplemental PN with EN should be avoided. In addition, there is no conclusive evidence that EN applied to patients with sepsis or septic shock is better associated with mortality than PN (46). In another study, patients with sepsis were divided into three groups as (1) EN, (2) PN, and (3) EN with additional PN. These separated groups were compared for 1-year mortality. This comparison showed that additional PN and EN in the first week of sepsis were better than EN in improving 1-year mortality, even after adjustment for energy intake (24). In a retrospective secondary analysis of another sepsis study, 353 patients with severe sepsis who received stable or reduced vasopressors, more than half received EN+PN, some received EN,

and few received PN. Average caloric intake was 918 kcal/day (EN), 1.210 kcal/day (PN), and 1,343 kcal/day (EN+PN). After 3 months, mortality was less in EN compared to EN+PN (47). Despite strong reasons to doubt the therapeutic benefits of aggressive and early nutritional support for patients with sepsis, recommendations for nutritional support are still lacking. The Surviving Sepsis Campaign recommends avoiding early parenteral nutrition based on low to moderate quality studies, but encourages early initiation of progressive enteral nutrition (39). In addition, ASPEN guidelines recommend initiation of EN therapy within 1-2 days of the diagnosis of sepsis in hemodynamically stable patients (46). A study was conducted to investigate the relationship between nutrition and morbidity-mortality with 399 patients with severe sepsis or septic shock in university hospitals, university-affiliated hospitals, general hospitals and others in Germany. The overall hospital mortality in this study was 55.2%. Hospital mortality was significantly higher in patients receiving only parenteral (62.3%) or mixed nutrition (57.1%) than patients receiving only enteral nutrition (38.9%) (48).

Enteral Nutrition (EN)

EN should be the method of choice for patients with a functional gastrointestinal tract (49). It is safer and has a better prognosis. It has been reported that enteral nutrition protects intestinal physiology, prevents intestinal atrophy, reduces intestinal permeability, protects against ischemia-reperfusion injury by stimulating intestinal perfusion, protects intestinal barrier against various injuries, improves local and systemic immune responses, and increases epithelial proliferation (49). In the Surviving Sepsis Campaign guide published in 2017, early trophic or low-calorie EN is recommended for severely ill patients with sepsis and septic shock (39). More recently, the ESPEN guidelines report that there is no evidence of EN in septic shock and that the reduced perfusion caused by shock can potentially worsen with EN administration (50). In cases where there are no contraindications, it is more correct to feed with enteral nutrition, which is the physiological way. If the gastrointestinal tract is normal but oral intake is insufficient, enteral tube feeding is recommended. Although enteral feeding may be associated with some complications, it has a lower incidence of sepsis, requires less follow-up, and is less expensive than PN (20). In the Sepsis Survival Campaign published in 2016, early PN alone or PN with EN is not recommended for patients with sepsis or sepptic shock. Early EN is recommended instead (39). In another study, early EN administration is evaluated in severely ill patients and the results were compared with patients in the late EN onset. (51). It was observed that patients in the group treated with early EN and ventilated in the ICU had a longer hospital stay, higher incidence of pneumonia and infection, and developed diarrhea at a higher rate than patients in the late EN group,

Parenteral Nutrition (PN)

PN is an important tool that provides nutrition to patients with reduced gastrointestinal absorption capacity, dysfunctional or enteral feeding problems. Correct use has a positive effect on patient clinical outcomes, but misuse leads to increased infectious complications, metabolic abnormalities, and increased healthcare costs (52). In patients with severe sepsis and septic shock, early and dominant use of parenteral nutrition in combination with enteral nutrition resulted in higher caloric intake and longer ICU stay compared to early enteral nutrition alone (47). Glucose is used as the carbohydrate source for the PN solution. It is determined that the amount of glucose administered will meet approximately 60% of the non-protein calorie requirement. However, hyperglycemia is seen in more than half of the patients, depending on insulin resistance, diabetes, severity of the underlying disease, concomitant steroid therapy, and glucose level given in critically ill patients. In this case, insulin therapy is started and, if

necessary, the glucose level given to the patient is restricted. The aim of treatment is to have a blood glucose level between 80 and 145 mg/dL (53). The level of fat given to the patient should be such that it meets 40% of non-protein calories. A lipid solution low in saturated fat and containing essential fatty acids (soy-based long chain triglycerides, medium chain triglycerides or mixed types) should be administered or it can be applied to the patient at levels of 0.7-1.5 g/kg/day. The aim of clinical follow-up is to keep serum triglyceride levels below 400 mg/dL (54).

Peripheral Parenteral Nutrition (PPN)

PPN is a form of PN usually used for short periods of time in well-nourished patients and used as a mediator for transition to EN or central parenteral nutrition. Patients who cannot receive enteral nutrition for a long time, have hypercatabolism and high calorie needs that are not suitable for PPN. This form of nutrition can be recommended to patients with good nutritional status who need nutritional support in a short period of time and do not require excess calories (55). The use of short peripheral catheters should be avoided when performing PPN. The osmolality of the applied solution should not exceed 600 mOsm/L. Solutions containing calcium should be administered with caution. Peripheral catheters should be placed in large veins for maximum dilution and checked frequently for phlebitis (55).

Central Parenteral Nutrition (CPN)

Patients without nutritional distress may not need enteral or parenteral nutritional support for up to one week after hospitalization. It may be appropriate for such patients to have a daily glucose supplement of 2-3 g/kg/day. A persistent negative energy balance has been reported to be associated with increased infectious complications (particularly sepsis), longer mechanical ventilation, longer ICU stays, longer antibiotic use, and other complications in critically ill patients (56). In high-risk patients, flushing with heparin or isotonic fluid to prevent blockage following central catheter placement, removal of the catheter for catheter-related sepsis, administration of appropriate antibiotics and daily subcutaneous heparin therapy are recommended for patients at high risk of thrombosis (57).

CONCLUSION

Sepsis has a high mortality rate caused many organ failures and intense can lead to care unit deaths. Nutrition of patients with sepsis according to the data obtained, treatment has an important place in the healing process. A low proportion of sepsis patients participating in nutrition studies in the intensive care unit, and associated with sepsis that determines or interferes with nutritional processes inflammation, metabolic changes, immune reactivity and organ dysfunction. Therefore, nutritional assessment and management of sepsis are critical. Providing nutrition to critically ill and especially septic patients. It is always assumed that something is appropriate. Septic patients calories and protein transport is difficult to predict. Because patients are hypometabolic or may be hypermetabolic and their energy needs increase over the time. Evidence in nutritional management of sepsis, enteral route use and supplementing nutritional formulas with immuno-nutrients suggest that it may affect the incidence and course of sepsis. However, more studies and information on nutrition are needed to express a clear view on treatment.

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