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# Nutritional support in sepsis and septic shock

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## Abstract

Sepsis is *a life-threatening organ dysfunction caused by a dysregulated host response to infection*. Its incidence is increasing worldwide. Sepsis and septic shock are associated with changes in metabolism. So far, research into nutrition and metabolism in sepsis has shown inconsistent results. Inadequate nutrition (both malnutrition and overfeeding) is detrimental for the patient. According to current recommendations, the treatment of choice in patients with sepsis is enteral nutrition, which is associated with many benefits. In the absence of enteral nutrition or the inability to provide the patient's energy requirements, total or partial parenteral nutrition is indicated. *ESPEN guideline on clinical nutrition in the intensive care unit* recommends for critically ill mechanically ventilated patients to assess energy expenditure by indirect calorimetry - in this case, hypocaloric nutrition is recommended in the early acute phase, and gradual introduction of isocaloric nutrition at a later stage. For critically ill patients, a progressive supply of 1.3 g/kg BW protein equivalents per day is recommended. The amount of carbohydrates should not exceed 5 mg/kg BW/ min. Intravenous lipid emulsions in parenteral nutrition should not exceed 1.5 g lipids/kg BW/day and should

be adequate to the patient's tolerance. There is no clear evidence of the effect of supplementation with fish oil, antioxidants and glutamine on the results of treatment in patients with sepsis, none of these substances is indicated for routine use. More research is needed into the metabolism and nutrition of patients with sepsis.

**Key words:** sepsis, nutrition, metabolism, septic shock

## Introduction

According to the definition of sepsis established higher average age of patients in 2016 by the European Society of Intensive Care Medicine and Society of Critical Care Medicine, it is *a life-threatening organ dysfunction caused by a dysregulated host response to infection*. [ HYPERLINK \l "MSi16" 1 ] The incidence of sepsis is increasing worldwide, which is considered as the result of immunosuppression, multi-drug resistant infections and higher average age of patients.2] In studies conducted in Poland, symptoms of sepsis were found in about 34% of patients treated in intensive care units (ICUs), including 16% with severe sepsis symptoms and 6% with septic shock symptoms. [ HYPERLINK \l "Küb07" 3 ] Sepsis is characterized by an initial hypermetabolic state, followed by a hypometabolic state.4] However, research into the prevention and alleviation of sepsis gives an inconsistent results. [ HYPERLINK \l "Coh18" 5 ] Appropriate therapeutic management includes nutrition adequate to the patient's energy needs. To maintain a proper balance of energy and macronutrients, it is necessary to assess the requirement.

## Feeding route

According to current recommendations, enteral nutrition (EN) is the treatment of choice for patients in sepsis.6] The main contraindication for the use of this method is gastrointestinal insufficiency. However, enteral nutrition is not contraindicated in the early stages of septic shock. The risk associated with enteral nutrition is impairment of visceral perfusion (reporting of intestinal ischemia associated with this type of nutrition is not high). Hypotension is an additional risk factor for this disorder, therefore enteral nutrition should only be implemented after stabilization of perfusion pressure. [ HYPERLINK \l "Sin19" 6 ]7] Enteral nutrition, as a physiological feeding route, has many advantages. These include maintaining the integrity of the intestinal epithelium [ HYPERLINK \l "Kud01" 8 ], stimulating peristalsis, which causes distal movement of bacteria and limiting their numbers, and supporting the physiological intestinal microbiota, which prevents colonization by pathogens and promotes the metabolism of some bacterial toxins.9] In addition, physiological intestinal microbiota is involved in the fermentation of dietary fiber. Its effect is the production of short chain fatty acids, including butyrate, which by stimulating receptors in the large intestine regulates oxidative stress and inflammation. [ HYPERLINK \l "Ina00" 10 ] 11] Enteral nutrition also stimulates the secretion of IgA antibodies that prevent bacteria from adhering to the intestinal wall [ HYPERLINK \l "Kud01" 8 ] 11] [ HYPERLINK \l "Kud02" 12 ] and supports the process of "educating" naive CD4 helper lymphocytes by exposing them to bacterial antigens in the intestinal lumen (Figure 1).11] In cases where enteral nutrition is contraindicated, parenteral nutrition should be implemented. [ HYPERLINK \l "Sin19" 6 ]5] Complementary parenteral nutrition is also possible in situations where enteral nutrition is not able to cover the total energy and nutrient requirements. [ HYPERLINK \l "Coh18" 5 ]

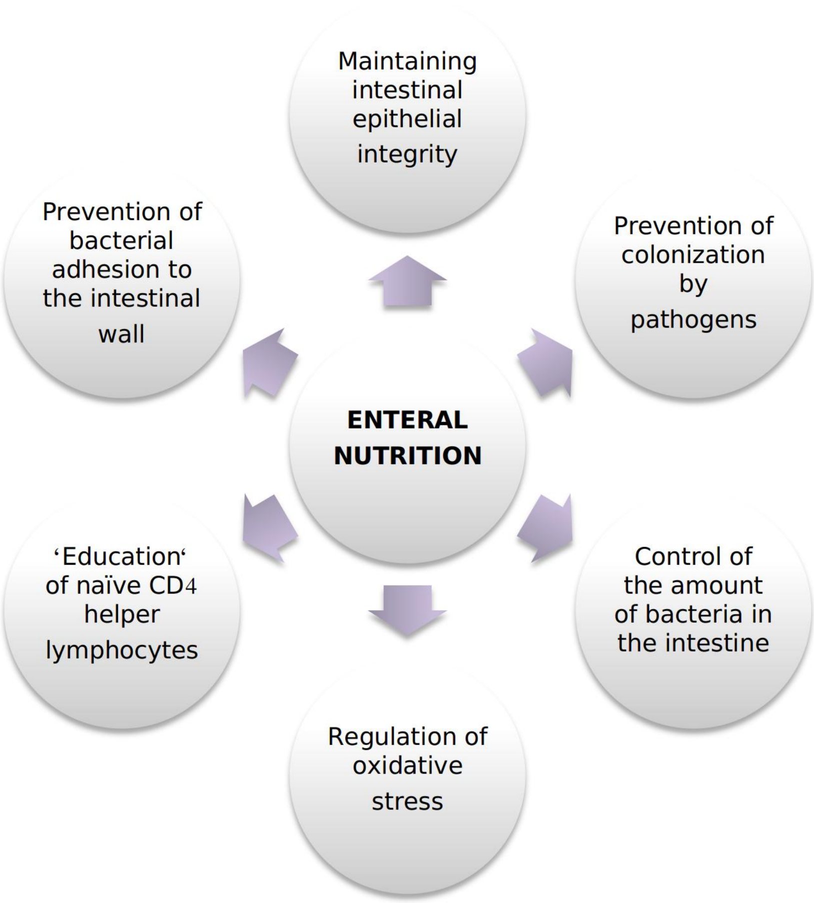


*Figure 1. Benefits of enteral nutrition 11*

**Underfeeding, overfeeding and refeeding syndrome**

Nutrients are necessary because of their energetic and building role but oxidation processes, essential for their transformation, intensifies oxidative stress. Reactions, which are the source of oxidative stress, are located mainly in mitochondria. For critically ill patients, the adaptability of mitochondria depends on the supply of oxygen and energy substrates, the proper efficiency of oxidative phosphorylation, hormonal balance and mitochondrial protease activity. Clinically, excessive energy supply leads to hyperglycaemia, an increased risk of infection, prolonged mechanical ventilation, and hospital stay. A relationship between insufficient energy supply, and an increased number of complications and an increase in mortality have also been demonstrated (Figure 2).13 For both enteral and parenteral nutrition, inadequate planned nutritional treatment may be the cause of inadequate energy and nutrient supply. In addition, in the case of enteral nutrition, patients may be malnourished due to poor food tolerance by the digestive system.5 Another dangerous nutrition disorder is the patient's refeeding syndrome, which includes electrolyte imbalance such as hypophosphatemia, hypokalaemia and hypomagnesemia, which can lead to haemolysis, myocardial dysfunction and neuromuscular dysfunction - including rhabdomyolysis and respiratory disorders. 14

**Overfeeding**

- hyperglycaemia
- fatty liver
- increased risk of infection
- prolonged mechanical ventilation
- prolonged hospital stay

**Underfeeding**

- increase in the number of complications
- increase in mortality

**Refeeding syndrome**

- hypophosphatemia
- hypokalaemia
- hypomagnesemia
- haemolysis
- myocardial dysfunction
- rhabdomyolysis
- respiratory disorders

*Figure 2. The effects of inadequate energy supply*

**Energy requirement**

Numerous metabolic complications of sepsis are known. These include, but are not limited to, hyperglycaemia, hypoglycaemia, electrolyte imbalance, hyperuricemia, lipid disorder, elevated transaminases and osteopenia. This is accompanied by a severe condition of the patient and severe inflammation.14 For this reason, both assessing the nutritional status of a patient suffering from sepsis and determining his nutrient requirements is a major challenge. As already mentioned, improper qualitative and quantitative nutrition planning can lead to malnutrition, overfeeding or refeeding syndrome. 14 In the past, due to the initial hypermetabolic phase, the goal of nutritional treatment was to reverse catabolism and achieve a positive nitrogen balance, which is why patients were given up to 4,000 kcal / day. However, as it was later demonstrated, the energy requirement of patients is much lower - it rarely exceeds 30-35 kcal/kg BW/day. It has also been proven that excessive glucose supply can increase carbon dioxide production, which increases the need for mechanical ventilation. In addition, it has been shown that excessive energy supply increases energy expenditure (so-called thermic effect of nutrition (TEN)).15 ESPEN guideline on clinical nutrition in the intensive care unit from 2019 recommends critically ill patients with mechanically ventilated assessment of energy expenditure (EE) by indirect calorimetry. If this method is not available, EE should be assessed using VO2 (oxygen consumption) from pulmonary arterial catheter or VCO2 (carbon dioxide production) derived from the ventilator. These methods allow the assessment of EE with greater accuracy than predictive equations. 6 If indirect calorimetry is used, hypocaloric nutrition (not exceeding 70% of EE) is recommended in the early acute phase of the disease, after this stage isocaloric nutrition should be gradually implemented (after 3 days 80-100% EE). However, if predictive equations were used to calculate energy expenditure, hypocaloric nutrition is recommended for the first week of stay at the ICU.6 As previously mentioned, the enteral route is the route of choice. For patients who do not tolerate the full planned dose during the first week in the ICU, the safety and benefit of parenteral nutrition should be considered on a case by case basis. However, starting parenteral nutrition is not recommended before attempting to increase enteral nutrition tolerance. 6

**Nutrient requirements**

According to ESPEN guideline on clinical nutrition in the intensive care unit from 2019, in critically ill patients, a progressive supply of 1.3 g/kg BW protein equivalents per day is recommended. The amount of glucose (in parenteral nutrition) or carbohydrates (in enteral nutrition) should not exceed 5 mg/kg BW/min. Intravenous lipid emulsions should be a part of parenteral nutrition, however they should not exceed 1.5 g lipid/kg BW/day (including non-nutritional lipid sources) and should be well tolerated by the patient.6

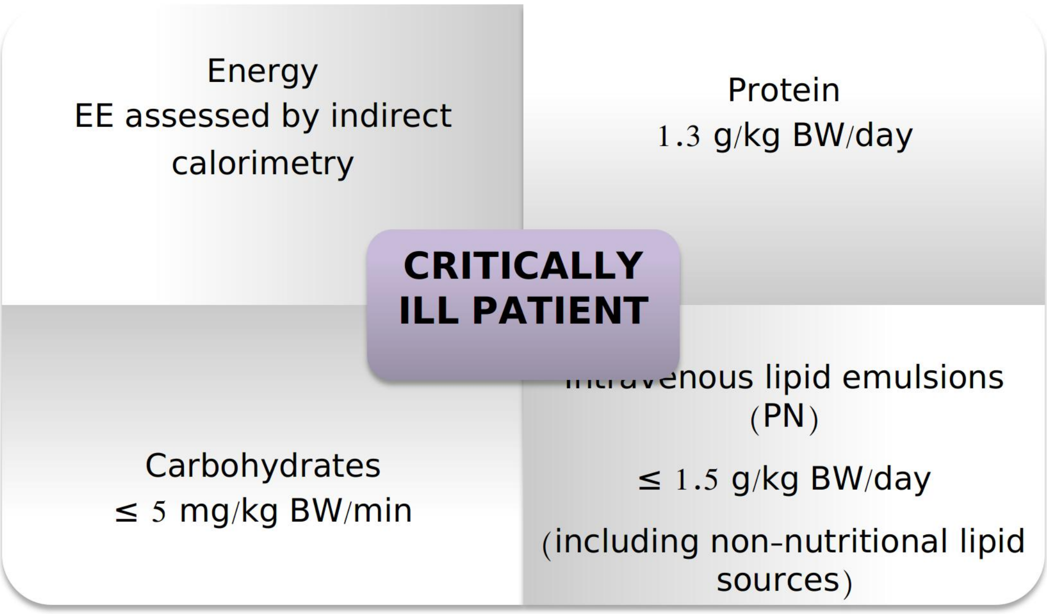


*Figure 3. Energy and nutrient requirements for a critically ill patient 6*

**Nutritional supplementation**

Supplements mentioned as potentially beneficial for patients with sepsis include omega-3 polyunsaturated fatty acids, antioxidants and glutamine.5 The research results, regarding the usefulness of these compounds, are not conclusive. The literature on fish oil supplementation in patients with sepsis shows inconsistent results. The prospective, randomized study demonstrated that the enrichment of enteral feeding with -linolenic acid, eicosapentaenoic acid (EPA) and anti-oxidants among patients with early septic results in milder course of sepsis. In addition, fewer cardiovascular and respiratory failure and shorter hospital stays at the ICU have been reported in patients receiving supplementation. There were no differences in mortality assessed over 4 weeks. 16 Different results were obtained in another large, randomized study in which EPA, -linolenic acid and antioxidant supplementation did not reduce the incidence of organ failure and did not improve gas exchange in critically ill patients with sepsis and acute lung injury or ARDS. There was also no effect on the incidence of infectious complications, while shorter ICU stays were reported for patients receiving EPA and -linolenic acid supplementation.17 *ESPEN guideline on clinical nutrition in the intensive care unit* allows the administration of nutritional doses of omega 3 fatty acids, however high doses of omega-3 enriched enteral formulas should not be given on a routine basis. Parenteral nutrition can use parenteral lipid emulsions enriched with EPA and DHA.6 It has been shown that in patients with sepsis, enteral nutrition supplemented with glutamine and antioxidants improves parameters associated with organ failure, however, the results of these studies could also be affected by higher protein supply in the studied group. 18 According to ESPEN guideline on clinical nutrition in the intensive care unit, glutamine is recommended for patients after burns and critical injuries, however, in the other groups, its administration is not recommended. 6 Oxidant supplementation appears to be beneficial because sepsis increases the production of reactive oxygen species, which affects inflammation. However, no clear relationships were found in the studies.5 According to *ESPEN guideline on clinical nutrition in the intensive care unit*, antioxidants as high dose monotherapy should not be used unless deficiency has been proven. 6

## Conclusions

Available studies on nutrition and metabolism in sepsis has shown inconsistent results. Inadequate nutrition (both malnutrition and overfeeding) is detrimental for the patient. According to current recommendations, the treatment of choice for patients with sepsis is beneficial enteral nutrition. In the absence of enteral nutrition or the inability to provide the patient's energy requirements, total or partial parenteral nutrition is indicated. *ESPEN guideline on clinical nutrition in the intensive care unit* recommends for critically ill mechanically ventilated patients to assess energy expenditure by indirect calorimetry - in this case, hypocaloric nutrition is recommended in the early acute phase, and gradual introduction of isocaloric nutrition at the later stage. For critically ill patients, a progressive supply of 1.3 g/kg BW protein equivalents per day is recommended. The amount of carbohydrates should not exceed 5 mg/kg BW/ min. Intravenous lipid emulsions in parenteral nutrition should not exceed 1.5 g lipids/kg BW/day and should be adjusted to patient's tolerance. There is no clear evidence of the effect of supplementation with fish oil, antioxidants and glutamine on the results of treatment among patients with sepsis, none of these substances is indicated for routine use. More research is needed into the metabolism and nutrition of patients with sepsis.

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