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RECOMMENDATIONS FOR SPECIALIZED NUTRITIONAL-METABOLIC TREATMENT OF THE CRITICAL PATIENT

Recommendations for specialized nutritional-metabolic treatment of the critical patient: Sepsis and septic shock. Metabolism and Nutrition Working Group of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC)☆

Recomendaciones para el tratamiento nutrometabólico especializado del paciente crítico: sepsis y shock séptico. Grupo de Trabajo de Metabolismo y Nutrición de la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC)

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Introduction

The published studies on the nutritional management of patients with sepsis are very few, and the existing publications moreover have important deficiencies referred to methodology, applicability, editorial independence, the participation of parties with invested interests, and rigor in conduction of the studies. Another important issue is the prior nutritional status of the patient. Recent studies in patients with sufficient nutritional reserves have reported favorable outcomes at the start of low-dose nutritional support in the acute phase of the disease, but this strategy is probably not advisable in malnourished septic patients. In the context of an exacerbated inflammatory response, and in addition to immune response dysregulation and probable inhibition of autophagia, intense metabolic disturbances occur that predispose to increased patient morbidity. Furthermore, sepsis is usually characterized by gastrointestinal dysfunction that can limit or impede adequate enteral feeding, as well as by changes in the intestinal barrier and microbiome.

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Questions

¿Do the energy and protein requirements of patients with sepsis and septic shock differ from those of the rest of critical patients?

No studies of sufficient methodological quality have precisely established optimum macronutrient intake in critical patients, and even less so in septic patients. With regard to the energy requirements, Kreymann et al.,[1] in a study of 30 patients (15 diagnosed with sepsis, 11 with severe sepsis, and 8 with septic shock), concluded that energy expenditure was elevated in the first two groups but was lower in the last group. A study involving septic patients subjected to mechanical ventilation (MV)[2] has evidenced variability in the energy requirements in the context of common maneuvers in the Intensive Care Unit (ICU), with a significant increase in the energy requirements during weaning periods, because of increased work of breathing (2.090 ± 489 kcal/day versus 1.910 ± 579 kcal/day at the end of weaning). Furthermore, this increase takes place at the expense of the consumption of carbohydrates rather than of fat. In the case of patients with normal nutritional status, it has been shown that so-called ''trophic'' hypocaloric nutrition (10 kcal/kg/day) during the first days of the disease process (in the acute phase) offers advantages, and that the calculated total provision may be postponed if necessary for about 5–7 days.[3,4] However, there is no evidence referred to malnourished patients (body mass index [BMI] < 17 kg/m^2), since these patients have been excluded from the studies.

With regard to protein supply, the limitations are similar to those referred to calorie supply, and it is not possible to provide specific recommendations referred to sepsis in its different stages. In an observational study of 886 critical patients, of which 129 were septic individuals,[5] reaching the predetermined calorie and protein requirements with 1.2 g/kg/day reduced mortality after 28 days by 50%, except among the septic patients.

Is it safe to administer early enteral nutrition in septic shock patients?

Very few studies are available on this subject, and the existing publications moreover have two important limitations: firstly, most of the available series correspond to general shock patients, and secondly, all of the series on septic shock patients are of a retrospective nature; the drawing of conclusions is therefore a delicate issue. With regard to the appearance of major complications, non-occlusive mesenteric ischemia and non-occlusive intestinal necrosis are not described in all studies, particularly in those involving a larger number of patients. Rai et al.,[6] in a retrospective study of 43 septic individuals, of which 33 presented septic shock, did not find the presence of shock to have an impact upon the time of introduction of nutritional support; indeed, the latter was even seen to start earlier (1.3 ± 1.7 versus 1.7 ± 1.3 days). The presence of shock did not significantly influence the amount of nutritional support (69% versus 77%). The difference in patients between the two groups represented an important study limitation. Khalid et al.,[7] in another prospective study on ICU patients subjected to MV and vasopressor treatment, studied mortality in the ICU and in hospital in two groups of patients: one receiving early (<48 h) enteral nutrition (EN) versus another group in which EN was started later. Mortality in the ICU and in hospital was lower in the early EN group (22.5% versus 28.3%; $p = 0.03$; 34.0% versus 44.0%; $p < 0.001$). These results were more notorious among the more seriously ill patients, but unfortunately only 76 cases of sepsis were documented in the early EN group versus 61 in the later EN group, and the authors did not detail mortality according to subgroups. In another retrospective study in 299 patients, Mancl and Muzevich[8] analyzed the tolerance and safety of the concomitant administration of EN and vasopressors in 346 episodes. Most episodes corresponded to septic shock ($n = 167$). The authors concluded that the tolerance of EN under vasopressor therapy is inversely related to the administered maximum noradrenalin dose (12.5 μg/min in the case of tolerance to EN versus 19.4 μg/min among the non-tolerant patients; $p = 0.0009$). It must be noted that the authors considered a gastric residual volume of ≥300 ml to be a cause of intolerance. This series included three cases of intestinal ischemia/perforation, but it was not specified whether these were septic shock cases or patients with other types of shock. Patel et al.,[9] in another retrospective study of 66 patients with septic shock and subjected to MV, established three groups: 15 patients without EN; 37 with EN and the supply of <600 kcal/day; and 14 patients with EN and the supply of >600 kcal/day. The group administered <600 kcal/day experienced fewer days of stay ($p < 0.001$) and a shorter duration of MV ($p < 0.001$) compared with the other two groups. In the adjusted analysis, the duration of stay was 2.33-fold longer in the group without EN (95% confidence interval [95%CI] 1.36–3.97; $p < 0.003$) and 1.58-fold longer in the group administered >600 kcal/day (95%CI 1.28–1.97; $p < 0.001$). In turn, the duration of MV was 2.41-fold greater (95%CI 1.20–4.08; $p < 0.014$) in the group without EN and 1.49-fold greater in the group administered >600 kcal (95%CI 1.14–1.95; $p < 0.004$), when compared with the group administered <600 kcal/day. The mortality rate and number of complications were similar in all three groups. No cases of non-occlusive mesenteric ischemia or non-occlusive intestinal necrosis were recorded.

In another retrospective study of 120 adult patients subjected to vasopressor drug treatment, Merchan et al.[10] evaluated tolerance to EN starting in the first 48 h after septic shock onset, and found 62% of the patients to tolerate enteral feeding – this parameter being related to a noradrenalin dosage of ≤0.14 μg/kg/min. No cases of non-occlusive mesenteric ischemia were recorded, and the duration of stay in the ICU and in hospital, as well as in-ICU mortality, were similar in the groups with and without tolerance. However, in-hospital mortality was significantly greater in the tolerant group. It must be noted that the authors considered a residual gastric volume of >250 ml to be indicative of intolerance to EN.

What is the best administration route? When is parenteral nutrition indicated?

A recent meta-analysis published by Elke et al.[11] involving 2880 critical patients and 10 studies from 1983 to 2014

concluded that EN versus parenteral nutrition (PN) has no effect on patient mortality but shortens ICU stay and the number of infectious complications. This meta-analysis did not explicitly address patients with sepsis, evaluated studies carried out 20 or 30 years ago, and was based on the multicenter CALORIES trial.[12] The latter involved 2400 critical patients admitted to 33 hospitals in the United Kingdom, and the results obtained revealed no differences in mortality or in the incidence of infection between the two groups – though the PN group showed a decrease in hypoglycemia rate (3.7% versus 6.2%; $p = 0.006$) and vomiting (8.4% versus 16.2%; $p < 0.001$). The study did not specify how many patients with sepsis were included. Two important prospective studies not contemplated in the meta-analysis provided conclusions that should be taken into account. Doig et al.,[13] in a randomized multicenter trial involving 1372 patients with relative contraindications to the start of EN over the short term, explored the effects of early PN from the first 24 h of admission to the ICU versus standard nutritional support according to the protocol in force in each individual center. The mortality rate at 60 days was not modified, in the same way as the duration of stay in the ICU and in hospital – though the duration of MV was seen to decrease. Another study[14] likewise involving a prospective, randomized and controlled design examined the effect of complementary PN upon nosocomial infections in 305 critical patients who on day three of admission received less than 60% of their energy requirements through EN. The results evidenced a decrease in nosocomial infections in the complementary PN group. However, only 24 of the global subjects were septic patients.

What is the best formula for the specialized nutritional management of these patients? Do diets enriched with arginine and other pharmaconutrients play a role?

Glutamine was once regarded as an essential component in the nutrition of septic patients, but became questioned as a result of the REDOX trial[15] (though only 30% of the included patients were septic cases), which recorded an increase in patient mortality after the early administration of inappropriately high doses of glutamine in individuals with shock or multiorgan dysfunction. In a randomized, controlled, double-blind prospective study involving 55 patients with sepsis, supplementation with glutamine and antioxidants for 24 h had no impact upon the final patient outcome, though an earlier decrease was noted in the Sequential Organ Failure Assessment (SOFA) score.[16] The MetaPlus study,[17] a randomized, double-blind, parallel-group international trial, analyzed the effects of hyperproteic EN versus a similar diet but supplemented with glutamine, omega-3 fatty acids and antioxidants upon 301 critical patients subjected to MV, of which only 66 suffered sepsis. The study diet did not reduce the incidence of infections, but an increase in the 6-month adjusted mortality rate was observed, which a priori could be regarded as a deleterious effect. However, there are many elements that deserve to be commented in relation to these findings, such as for example the fact that most of the patients had normal baseline glutamine levels (with the exception of the trauma patients), or the fact that the theoretical calorie and protein requirements were not covered – thereby limiting interpretation of the results. At present, no specific recommendations can be made regarding the use of enteral glutamine in septic patients. Few studies are available on parenteral glutamine supplementation in patients with sepsis. Koksal et al.[18] recorded improvement of the nutritional parameters and nitrogen balance in malnourished septic patients administered enteral and parenteral nutrition supplemented with glutamine. The recommendations on the use of glutamine via the parenteral route in septic patients would arise from extrapolation of the data referred to the general critical patient population and the absence of harmful effects associated with its administration.

Few studies are available on the use of arginine as an isolated substrate in septic patients. Luiking et al.[19] administered arginine as an intravenous infusion in 8 patients with septic shock, and although an increase in nitric oxide (NO) production was recorded, there were no effects of any kind upon the hemodynamic parameters, and secondarily protein catabolism was seen to improve. Another randomized double-blind study involving 30 critical medical patients receiving EN supplemented with arginine[20] recorded no deleterious effects or increase in infections or immune disorders.

With regard to septic patients and omega-3 fatty acids, only two studies have been published to date. The first was a randomized, controlled trial[21] involving 60 septic patients administered omega-3 fatty acids via the parenteral route added to standard nutritional support versus a control group only administered the mentioned standard nutrition. The authors recorded a decrease in the incidence of new fatalities, but there were no differences in relation to ICU stay or mortality, with the exception of the subgroup of less severe septic patients. The second study involved a randomized, open-label and multicenter design,[22] and examined the effects of omega-3 fatty acid supplementation in 132 patients with sepsis and acute respiratory distress syndrome. The authors concluded that supplementation did not reduce the days of MV or the incidence of infections, but did shorten ICU stay. In a recent meta-analysis,[23] supplementation with omega-3 fatty acids had no beneficial impact upon mean stay or mortality among septic patients following administration via the enteral or the parenteral route – though a decrease in the number of days of MV was recorded.

Is supplementation with selenium and other micronutrients indicated?

From the biochemical perspective it has been reported that selenium or other micronutrients could play a relevant role as oxidative stress regulators or as inflammatory response modulators. The idea that selenium has immune modulating properties was reinforced by initial studies that found patients with low selenium levels to be at an increased risk of nosocomial infections and have a greater inflammatory profile. However, selenium supplementing has not been found to exert a significant influence upon septic patient clinical outcome. Few clinical trials have exclusively focused on septic patients, and most of the existing publications involve fewer than 100 subjects per arm. Interpretation

of the results is strongly limited by the scant statistical power of the studies. Of note is the study published by Bloos et al.,[24] involving 1089 patients with severe sepsis or septic shock, in which no modifications in outcome were observed. In fact, the mortality rate after 28 days was 28.3% (95%CI 24.5–32.3) in the selenium treatment group versus 25.5% (95%CI 21.8–29.4) in the placebo group. Valenta et al.[25] likewise reported no significant modifications in either the inflammatory profile or in the outcomes of 150 septic patients following the administration of selenium. A meta-analysis published by Manzanares et al.[26] further analyzed these variables, without finding evidence supporting the idea that selenium – in any of these therapeutic regimens – is able to modify the outcome of critical patients.

With regard to micronutrients in general, the mentioned REDOX trial[15] recorded no beneficial effects with the administration of antioxidants, either isolatedly or combined with glutamine.

Regarding other specific micronutrients with potential effects in septic patients (mainly vitamins C and D, and zinc), the existing experience remains anecdotal; their use therefore cannot be recommended, except in patients known to have low levels of these nutrients.

Recommendations

- It is advisable for calorie supply in the acute phase of the septic process to be no greater than 20 kcal/kg/day (level of evidence: low).
- The early administration of enteral nutrition (both trophic and complete) is safe in septic shock patients, provided close monitoring is ensured (level of evidence: moderate).
- It is advisable for septic patients to receive a protein supply of at least 1.2 g/kg/day (level of evidence: low).
- The administration of parenteral nutrition is safe in the septic patient (level of evidence: moderate).
- It is advisable to consider administering enteral diets enriched with mixtures of pharmaconutrients, together with the administration of omega-3 fatty acids, in septic patients (level of evidence: low).
- It is advisable to consider administering arginine in septic patients (level of evidence: low).
- Selenium supplementing in septic patients is not recommended (level of evidence: high).
- Systematic specific supplementing of micronutrients in septic patients is not advised (level of evidence: low).

Conflicts of interest

Dr. Ortiz-Leyba declares that he has no conflicts of interest. Dr. Valenzuela has received payment from Vegenat for participation in training activities. Dr. Yébenes-Reyes has received payment from Fresenius Kabi, Abbott and Vegenat for participation in training activities.

Note to supplement

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