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REVIEW ARTICLE

Nutrition in critically ill adult patients

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Summary

Nutrition is a crucial component of critically ill patients' treatment. The key questions to address are when to initiate nutrition therapy, how to determine the optimal route, the appropriate amounts of macro and micronutrients, and the precise energy requirements for each patient.

Critical illness has three phases: early period (previously "ebb phase") lasting 1-2 days; late period (previously "flow" phase) lasting for 3-7 days; late phase (Phase Rehabilitation or Chronic Phase). Each of the above-mentioned phases has its characteristics. During the first phase, severe catabolism is increased, and it gradually proceeds to anabolism during the following 3 to 4 days. The recommendations for critically ill patients' nutrition have been formed based on these phases.

Early nutrition therapy, especially early parenteral nutrition with high energy and protein intake, should be avoided in the first three days of critical illness. Reaching the nutritional goal should be initiated only 3 to 4 days upon the onset of critical illness. According to ESPEN recommendations, daily calorie intake should be initiated at 20-25 kcal/kg/day, while daily protein intake should be initiated at 0.8g/kg/day with a gradual increase to 1.3 g/kg/day. On the other hand, ASPEN recommends 12-25kcal/kg/day of daily calorie intake with daily protein intake at 1.2-2 g/kg/day. The optimal route of feeding is enteral whenever possible. Alternatively, parenteral route should be used. Indirect calorimetry serves as a basis for determining nutritional needs in critically ill patients.

Conclusion: Nutritional therapy is essential for critically ill patients. Nutrition should be obtained through enteral route whenever possible. Energy and protein intake should be gradually introduced in critically ill patients' treatment. Nutritional therapy prescription should be adapted to the patients' needs.

Keywords: critically ill, enteral nutrition, intensive care, parenteral nutrition

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INTRODUCTION

It has been widely accepted that nutrition not only serves as support, but is also a therapy on its own, one that evidently affects patients' treatment outcome. Similar to other treatment methods, such as antibiotics or vasopressors, nutritional therapy has specific indications and contraindications that are dependent on the type of formula, its components and ingredients. The dosage of micro and macronutrients in various types of formulas is well known. Nutrition therapy applied to critically ill patients has surpassed a universal prescription. Nowadays nutritional therapy is particularly prescribed according to the patient's diagnosis, stage of the disease and nutritional status. It can be described as being individually tailored. The precise moment of the induction of nutritional therapy, its duration and the interval of implementation are individually determined. All these components have a significant impact on morbidity, mortality, quality of life, time of recovery and, finally, to the positive economic impact (1-3).

How do we define a critically ill patient? The definition is certainly hard to find. It is a patient who has developed or is under the risk of developing an acute severe or multiple organ failure. Likewise, it can also be a patient with other comorbidities and under the risk of further deterioration. A common denominator among all the above is that they are patients requiring constant monitoring, whether invasive or non-invasive, with 24-hour care and comprehensive individualized treatment. For example, such a patient would require invasive or non-invasive respiratory support, as well as the need for vasoactive drugs, nutritional therapy, continuous renal replacement therapy, and/or purification processes **(Figure 1)**.

Organ dysfunction can be monitored using the Sequential Organ Failure Assessment (SOFA) score, a scoring system that also provides insights into the level of inflammation and organ impairment. SOFA score enables us to trace the degree of respiratory system dysfunction based on the PaO_2/FiO_2 ratio. Furthermore, we can detect the coagulation system dysfunction based on platelet count, the liver dysfunction based on bilirubin values, the cardiovascular system dysfunction based on the values of mean arterial pressure and/or the use of vasoactive drugs, the central nervous system dysfunction based on Glasgow Coma Score (GCS), and renal dysfunction based on the values of creatinine and/or diuresis (4, 5).

EPIDEMIOLOGY

A significant number of post-surgery patients have been hospitalized after experiencing substantial weight loss

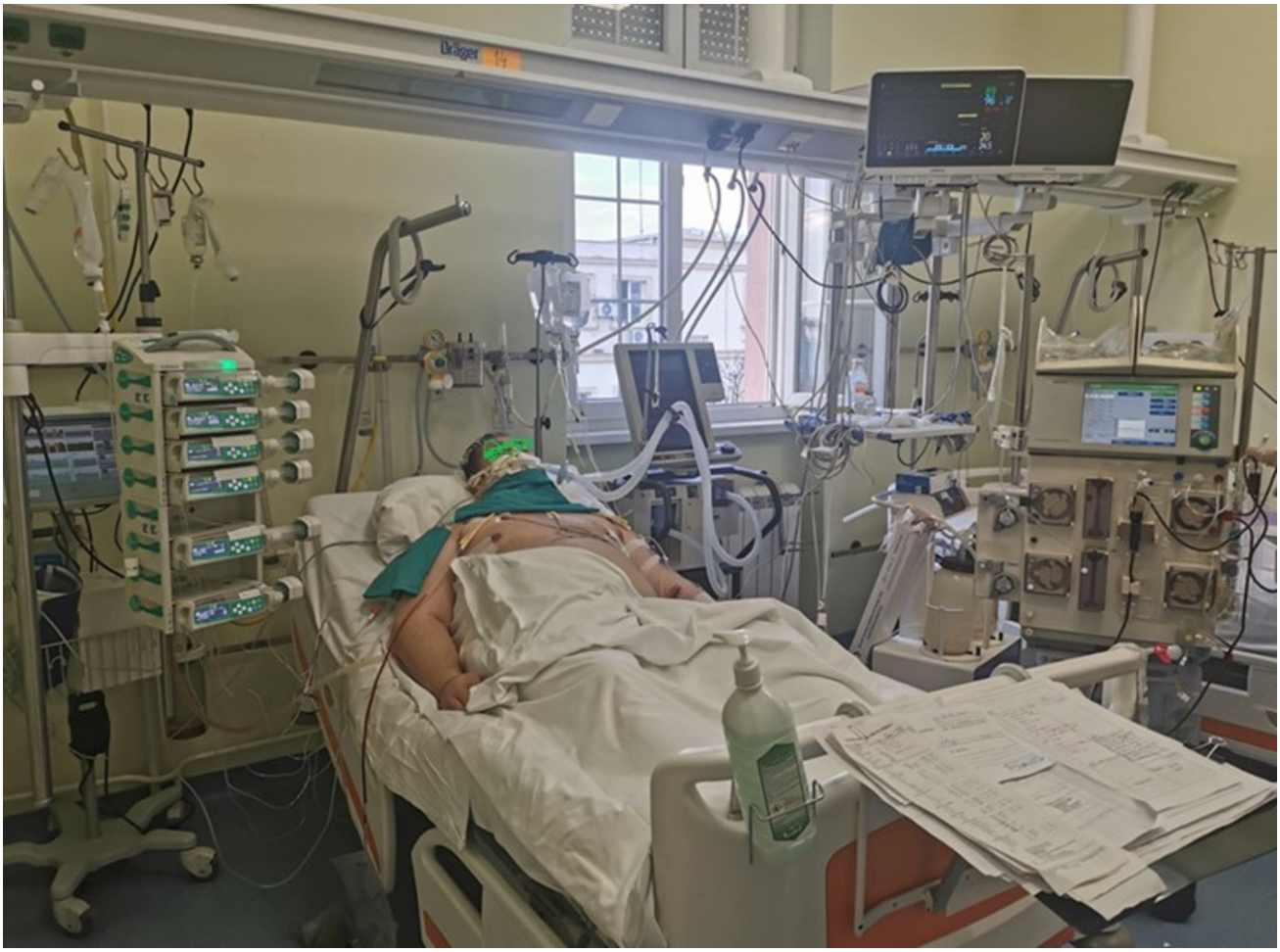

Figure 1. Critically ill patient in the intensive care unit (author's personal archive)

(over 10 kg) within the past six months. At the Clinic for Digestive Surgery, University Clinical Centre of Serbia (UCCS), this percentage amounted to 53.3% in 2008, while in Europe, in 2006, it reached 33%. The starvation trend continues after hospital admission, because some patients suffered from loss of appetite (28.95%), 12.28% had difficulties swallowing food, while an astonishing 45.6% did not receive food orally due to diagnostic interventions and preparations for upcoming surgical procedures. Hospitalized patients evidentially have problems with food intake, which places them in need of nutritional therapy. The Clinic for Digestive Surgery UCCS has, therefore, made the nutritional therapy an integral component of the patients' treatment during their preoperative preparation and other procedures. As a result, there were 26.31% of patients on parenteral nutrition in 2008, 13,51% of patients on enteral nutrition, and 2.63% of patients who received specialized nutrition with the introduced protein supplements amounting to 0.88% cases. This systemic assessment of nutritional problems has resulted in the formation of a nutritional therapy team and the evaluation of nutritional risk following patients' admission into hospital, through the implementation of Nutritional Risk Screening 2002(NRS 2002) (6-8).

NUTRITIONAL RISK ASSESSMENT

Nutritional risk assessment is a critical matter. The implementation of it, in practice, enables us to identify patients that are under a greater risk of complications due to prolonged fasting. Two most common scoring systems that have been used in the Intensive Care Unit (ICU) are mNUTRIC (modified Nutrition Risk in Critically Ill Score) and NRS 2002 (Nutritional Risk Screening). The mNUTRIC takes the following into account: the age, APACHE II (Acute Physiology and Chronic Health Evaluation II), SOFA score (Sepsis-Related Organ Failure Assessment), comorbidities and days since the time of hospital admission and to the ICU. Score ≤ 4 is defined as low risk, whereas score ≥ 5 is defined as high risk. NRS 2002 is composed of age, BMI (body mass index), percentage of weight loss, energy intake compared with energy requirement and severity of disease. Nutrition risk classification is scored as: < 3: No risk, ≥ 3: At risk, ≥ 5: High risk. Nutritional risk assessment in critically ill patients could be very challenging, since those patients are at a great nutritional risk considering the fact that they are in a critical condition as soon as they enter the ICU, being in severe catabolism and inflammation and requiring nutritional therapy. As a result, the scoring systems mentioned above could not be applied to critically ill patients. It is considered that the most useful tool to assess the nutritional risk of patients in the ICU is NUTRIC (Nutrition Risk in Critically Ill Score), that has all the same parameters as the mNUTRIC with the exception of interleukin-6; score ≤ 5 is considered as low risk; score ≥ 6 is considered as high risk (9). Patients with the NRS score ≥ 3 have a significantly longer hospital stay (24 vs 14 days) and a significantly higher number of complications (57.1% vs. 13.3%) compared to patients with an NRS score <3. Postoperative morbidity was increased 3.84 times for each positive response to the initial four screening questions (10).

EFFECTS OF NUTRITION

Nutrition is certainly a crucial part of therapy for critically ill patients. The impact of nutrition on reducing morbidity and mortality in critical illness has been confirmed. Alberda's multicentre study reached interesting conclusions (11). Critically ill patients received amounts of energy (15,0-30,9 kcal/kg/day) and protein (1,0-1,4 g/kg/day) intake based on their BMI. 69.0% of patients received enteral nutrition (EN), 8.0% received parenteral nutrition (PN), 17.6% received EN plus PN, and 5.4% received neither EN nor PN. The results indicated that increased energy and protein intake improved the treatment outcome of critically ill patients, especially those with BMI below 25 and greater than 35. On the other hand, the increased energy and protein intake did not enhance the outcome of patients with BMI 25-35 (11). In a multicentre study, Compher et al. divided critically ill patients into two groups: patients with NUTrition Risk score < 5 and patients with NUTrition Risk score ≥ 5. By analyzing mortality on the 4th day of critical illness, it was observed that there was no change in odd ratio when it comes to mortality or an increase in energy intake for the group of patients with high nutritional risk. However, by analyzing interaction between NUTRIC category, energy intake and mortality on the 12th day of critical illness, the study noted that the odds of death were significantly reduced by 11.6% with each 10% increase in delivery of goal energy intake but not in the low-risk patients. A similar result was obtained in relation to the goal protein intake. Increasing protein intake on the 4th day of critical illness does not reduce the odds of mortality in patients with a high Nutrition Risk, but on the 12th day of critical illness in patients in the group with an increased Nutrition Risk, the odds of death decreased significantly by 10.1% with each 10% increase in protein intake relative to goal but not significantly in the low-risk patients. In conclusion, patients with higher nutritional risk at the ICU admission may benefit from greater protein and energy intake, especially during longer ICU stays, while patients with lower nutritional risk have no benefit from greater intake (12).

NUTRITIONAL RECOMMENDATIONS

Should one start nutritional therapy in critically ill patients? And if so, what would be the right time for

introducing it? There is no doubt that nutrition proved beneficial during critically ill patients' therapy. Studies have shown that nutrition improves the outcome of the treatment and a proper timing is crucial. Determining the right moment for the beginning of nutritional therapy and the right amount of energy and nutrient intake are crucial. The European Society for Clinical Nutrition and Metabolism (ESPEN) has given the following recommendations: every critically ill patient is considered to be at risk of malnutrition if the length of stay in the ICU is longer than 48 hours. Oral intake of food and water is preferable. However, as this is often not feasible in critically ill septic patients with the intact gastrointestinal tract, enteral nutrition is recommended whenever possible, especially within the first 72 hours. Furthermore, if there are any cases in which enteral nutrition is not achievable while the patient is at a high nutritional risk (NRS score greater than 5), parenteral nutrition should be introduced gradually, taking into account all the risks it carries (occurrence of overfeeding and refeeding). Early full EN and PN are to be prescribed within three to seven days. The recommendation is to use indirect calorimetry to assess the energy requirements of critically ill patients, especially in cases involving mechanical ventilation. If predictive equations are used to determine the energy requirement of a critically ill patient (20 to 25 kcal/kg/day), a hypocaloric intake (below 70% of the calculated needs) is recommended. This recommendation should be used during the first seven days of critical illness (13-15). American Society for Parenteral and Enteral Nutrition (ASPEN) states that there is no significant difference in the applied amount of energy in the first days of critical illness, but they recommended the intake of 12 to 25 kcal/kg/day during the first days of critical illness (8, 16).

What is the appropriate protein intake for a critically ill patient? This is yet another important question that requires our attention, and it is as crucial as the issue of energy-per-day parameters which are connected to the critically ill patients' treatment outcome. According to ESPEN recommendations, daily protein intake should be initiated at 0,8g/kg/day with a gradual increase to 1.3 g/kg/day, while ASPEN recommends 1.3 g/kg/day past 24-48h, upon hemodynamic stabilization. The amount of protein intake depends on the severity of critical illness. For instance, in patients with burns, additional protein intake should be administered (up to 2g/kg/day) (8-14).

How did we establish these recommendations and their undeniable necessity for an individual approach to the patients' needs? While the exact amount of nutrients and energy intake is well known, it should be pointed out that the "breaking point" for reaching the nutritional goal comes only after the 3-4th day from the onset of critical illness. The question is why it is so.

PATHOPHYSIOLOGICAL BASIS OF THE RECOMMENDATION

Critical illness has three phases: early period (previously known as "ebb" phase) lasting for 1-2 days, late period (previously known as "flow" phase) lasting for 3-7 days, late phase (Phase Rehabilitation or Chronic Phase) (8,14,15,17,18).

Early period is characterized by hypermetabolism, a severe increase in catabolism, muscle wasting, protein and amino acid degradation, production of glucose and acute-phase proteins, insulin resistance and finally, hemodynamic instability. It is important to remember that 500 to 1400 kcal of endogenous energy is produced during this phase and that any addition of energy through nutrition will lead to overfeeding and all its negative outcomes.

Late period is characterized by organism slowly turning towards catabolism (third day) which in turn causes a decrease of endogenous energy production. In this period, we gradually increase energy along with the protein uptake.

Late phase (Phase Rehabilitation or Chronic Phase) marks a period when anabolism begins to overtake catabolism triggering the patients' rehabilitation. In certain cases, however, some patients fail to recover, leaving them in a late persistent catabolism and resulting in prolonged hospitalization.

ESTABLISHING A SET OF RECOMMENDATIONS

Over the past decades a great amount of previous studies were conducted with a goal of determining the exact protein and energy daily intake in critically ill patients, avoiding the negative impact on morbidity and mortality at the same time.

Casear et al. (2011) have published a randomized, multicentre study on the impact of early (within 48h) versus late initiation (starting 8 days later) of parenteral nutrition in critically ill patients as an addition to enteral nutrition targeted to reach the caloric goal. The results were in favor of late implementation of parenteral nutrition with an aim of reaching the caloric goal **(Table 1)**. Late parenteral nutrition initiation has proven to be superior due to patients' shortened length of stay in the ICU, as well as a lowered number of infections and renal complications. The latter indicates that the lower protein intake positively correlates with the lower renal stress. As a conclusion, late PN initiation has evidently contributed to a faster recovery, followed by a reduced number of complications as compared to the early PN initiation (19).

Heidegger (2013) published the results of a controlled, randomized study, in which a parenteral nutrition supplemented the already existing enteral nutrition with an aim of optimizing energy intake in critically ill patients. The nutritional goal was at 25kcal/kg/day of ideal bodyweight for women and 30kcal/kg/day of ideal body-

Table 1. The main results of early and late supplemental parenteral nutrition implementation (prepared according to the reference (19))

	Late initiation group (n=2328)	Early initiation group (n=2312)	p Value
Discharged alive from the ICU within 8 days no (%)	1750 (75.2)	1658 (71.7)	0.007
Death in ICU no (%)	141 (6.1)	146 (6.7)	0.76
Death in hospital no (%)	242 (10.4)	251 (10.9)	0.63
Death within 90 days upon enrolment no (%)	257 (11.2)	255(11.2)	1.00
Nutrition related complication no (%)	423 (18.2)	434(18.8)	0.62
Length of stay in the ICU	3 (2-7)	4 (2-9)	0.02
Infection no (%)	531 (22,8)	605 (26,2)	0,008
Mechanical ventilation; median duration (days)	2 (1-5)	2 (1-5)	0,02

weight for men. During the first three days, all patients received enteral nutrition after which one group continued receiving enteral nutrition, while the other group received enteral nutrition with supplemental parenteral nutrition (Figure 2). Both groups had a target of reaching the nutritional caloric goal. Those patients who received enteral nutrition exclusively were less susceptible to nosocomial infections, as they did not always manage to reach the caloric goal. Mortality was reduced in patients who received supplemental parenteral nutrition (ICU mortality 5 vs7%, p= 0.211and general mortality 13% vs 18%; p=0.119). The conclusion of this study was that the individually optimized energy supplementation with supplemental parenteral nutrition starting 4 days after ICU admission should be considered as a strategy to improve clinical outcome in patients in the ICU for whom enteral nutrition is insufficient (20). In other words, there is no need to rush with implementing of parenteral nutrition with an aim of reaching the caloric goal during the first 3-4 days of the onset of critical illness. Furthermore, enteral nutrition should be introduced as early as possible, with a gradual increase of caloric intake up to 25 kcal/kg/day. In those cases where this goal is impossible to reach, after four days supplemental parenteral nutrition should be considered (21).

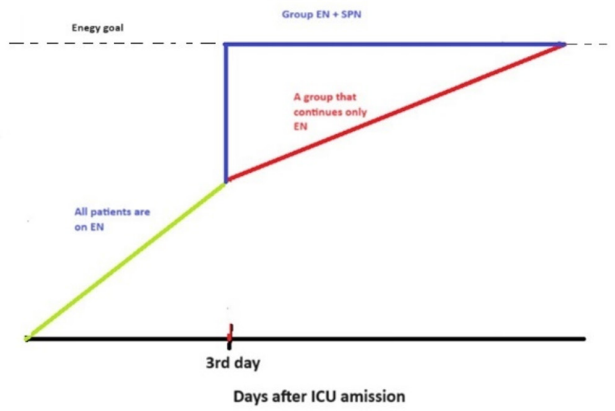

Figure 2. Study design (Prepared according to the reference (20))

Prospective cohort study published in 2012 set the initial calorie (25-30 kcal/kg/day) and protein goal (1.2 – 1.5 g/kg/day) in critically ill patients. They hypothesized that securing the protein intake improves the outcome of the critically ill patients' treatment. Ten-day mortality was the lowest in the group of patients with the highest amount of proteins (1.46+0.29 g/kg/day). The conclusion of this study suggested that the increase of proteins and amino acids figures as more important to the recovery of critically ill patients than the increased caloric intake alone (22). Weijs et al. monitored four groups of critically ill patients during their treatment with nutritional therapy. The first group included patients who did not reach either the caloric or the protein goal, while the second group reached both of these goals. The third group was comprised out of patients who had reached only the caloric goal, and the fourth group included the patients who had reached only the protein goal. The results have shown that in those patients who had only reached the protein goal within 1.2g/kg/day the 28-day mortality was lowered, as well as the hospital mortality and the ICU mortality. The best results with regards to mortality were shown in the group that had reached both the caloric and the protein goal. Reaching the caloric goal exclusively (1600 kcal/kg/day) did not impact mortality (23). Zusman et al.'s retrospective observational study showed that nutritional therapy which was commenced within the first 4 hours of the admission in the ICU had resulted in the lowest mortality rates providing that 70% of the total caloric needs (energy expenditure) were met. The protein intake was 1.3g/kg/day. Ultimately, this study excludes the thesis that 100% of calorie intake fares as necessary for the patient's recovery and highlights the indirect calorimetry as an essential factor for the assessment of patient's caloric needs (24).

In a prospective cohort study (**PROTINVENT**), critically ill patients were divided according to calorie intake in three groups: hypocaloric (less than 80% caloric needs), normocaloric (80-100% caloric needs), and hypercaloric intake (more than 110% caloric needs), with a desired protein intake from 1.5 up to 2g/kg/day. The conclusion of this study was that late medium protein and late high energy intake were associated with survival benefit in septic patient; on the other hand, early high protein intake was associated with higher 6-month mortality, while late protein intake higher than 0.8g/kg/day was proven to be beneficial (25). In an EFFORT Protein international, randomized, multicentre study the pro-

tein intake was initiated within 96 hours of ICU admission. The patients were divided into two groups; the first group was receiving high doses of proteins (at least 2.2g/kg/day, or more), while the second group was receiving the usual doses of proteins (1.2g/kg/day or less). Calorie intake was not controlled. In conclusion, it was highlighted that the protein intake of 1.2g/kg/day was reasonable and safe for critically ill patients, while delivery of higher doses of protein to mechanically ventilated critically ill patients did not improve the time-to-discharge-alive from hospital and might have worsened outcomes for patients with acute kidney injury and high organ failure scores (26). Reignier et al. hypothesized that early protein and energy restriction in critically ill patients in comparison with a standard intake could improve treatment outcome, but the results were surprising. There were fewer complications in the group with restricted intake, but without impact on mortality. The conclusion was that low caloric and protein intake (6 kcal/kg/day; 0.2 – 0.4 g/kg/day) compared to standard caloric and protein intake (25 kcal/kg/day; 1.0 -1.3 g/kg/day) during the acute phase of critical illness led to a faster recovery with fewer complications, without affecting mortality (27).

WHY LESS PROVIDES MORE?

Reviewing the above mentioned studies, it is suggested that in the first days of critical illness a reduced amount of energy and protein is needed in order to achieve the best possible results in the treatment of these patients. It could be said that less is more. This could be explained by more expressed catabolism, produced endogenous energy and muscle protein degradation in the first days of critical illness. Nutritional therapy during that period could lead to overfeeding and renal stress, which could be accompanied by further renal damage in patients with impaired renal function (18). Additionally, reduced energy intake and fasting have been shown to be the most potent physiological triggers for activating autophagy, which is essential for defending the body against microorganisms and for eliminating damaged or dead cells. Parenteral nutrition itself leads to suppression of autophagy, which has been proven in experiments on rabbits. Autophagy is greatly reduced in the liver by parenteral nutrition, which is a pillar of the body's defence against detritus and pathogenic microorganisms. Early parenteral nutrition, especially with an increased amount of amino acids and lipids, reduces the body's defence and should therefore be avoided during the early phase of critical illness. Intraoperative administration of amino acids together with lidocaine and magnesium has been shown to reduce the postoperative inflammatory response, as measured by inflammation parameters. That being said, the strategy of fasting under the first 2 to 3 days of critical illness could be justified (28-31). One of the reasons for nutritional therapy in early stages of critical illness is an attempt to salvage the muscles from catabolism, as well as to maintain muscle mass. Unfortunately, this could not be possible during a critical illness, provided that muscle strength is reduced while myofibrils are replaced by fat tissue; moreower, during an early parenteral nutrition this process is more expressed. Hence, the above mentioned could be the reason why the early parenteral nutrition should be avoided during the early stages of critical illness (32).

During a critical illness, the urea-creatinine level is increased in response to muscle wasting, which is more expressed in traumatized patients; the higher the ratio, the longer is the stay in the ICU and the higher is the mortality rate. Increased load of amino acids leads to worsening of critical illness and deterioration of renal function. With this in mind, the protein intake should be reduced in the first days of critical illness in order to reduce the urea-creatinine ratio as an indicator of catabolism. This could explain why the use of glutamine in critically ill patients has not given the expected satisfactory results, on the contrary, glutamine use led to liver overload. Glutamine is well known as the amino acid with the most potential of producing urea and glycogen, which significantly overloads the liver and kidneys (14, 33,34). Nutritional therapy is known to suppress ketogenesis, while fasting activates lipolysis and ketogenesis. Ketogenesis is of great importance in critical illness for the following reasons: ketone bodies are a great alternative to glucose in the brain and cardiomyocytes during the first days of critical illness, they have a signaling role in activating an immune response, autophagy, activating muscle regeneration, as well as having anti-inflammatory features. Therefore, ketone bodies that are produced during fasting represent an evolutionary mechanism of body defense (35). It could be concluded that early nutrition therapy, especially early parenteral nutrition with high energy and protein intake, should be avoided in the first three days of critical illness on the account of introducing overfeeding, protein, amino acid and carbohydrate overload, muscle catabolism, reduced production of ketone bodies, which all lead to higher morbidity and mortality. In short, less is more.

OTHER REQUIREMENTS

There are two key issues that nutritional therapy of critically ill patients ought to resolve – the starting time for nutrition, and the exact amounts of protein/energy intake. These have, evidently, had the most impact on the mortality and morbidity of critically ill patients. Alongside the specific energy and amino acid needs, nutritional therapy requires the implementation of glucose and lipids or fatty acids. These amounts are added into the daily energy needs of critically ill patients. Lipids are introduced intravenously, through emulsions. It is important to highlight that the daily energy intake must include

all the lipids, together with those introduced through the anesthetic propofol. Taking all these lipid (or fatty acid) sources into account, the total daily value should not exceed 1.5 g/kg/day. Daily amounts of fatty acids have to be adjusted individually, according to each patient's needs. Consequently, their triglyceride and cholesterol values require monitoring. If the values rise, the intake has to be either adjusted accordingly, or terminated completely.

Lipid emulsions used in parenteral nutrition may contain polyunsaturated fatty acids of fish oil, olive or soybean oil and their immunomodulatory role in critically ill and septic patients has been proven. Thus, soybean oil-based fatty acids (omega-6 fatty acids) should be avoided in septic patients because of their pro-inflammatory effect. Fatty acids based on fish oil (omega-3 fatty acids) have an anti-inflammatory effect, while olive oil-based fatty acids (omega-9, monounsaturated fatty acids) have a relatively neutral effect on the inflammatory response. Knowing all this, the immune response in critically ill patients could be modified by using certain fatty acids. Implementing omega-3 fatty acids in critically ill septic patients' nutrition therapy has been proven to be beneficial in some aspects, such as improved gas exchange and earlier weaning from mechanical ventilation. However, their positive impact in critical illness has not shown obvious proofs (36). On the other hand, all of the three above mentioned fatty acids are essential, meaning they are not endogenously synthetized, therefore, their intake during critical illness is crucial. Essential fatty acids are necessary for synthesizing eicosanoids, from which biologically active substances are produced (prostaglandins, leukotrienes, thromboxane). These substances modulate the coagulum production, regulating circulation and affect immune processes (14-16,27,37). Nowadays, there are lipid emulsion formulas that contain all these three essential fatty acids.

Glucose is a necessary macronutrient, as it is a basic source of energy. Daily dose of glucose should not exceed 5mg/kg/min or 150g/day, respectively. During the first two days it is necessary to monitor the glucose level every 4 hours. If the values of glucose exceed 10mmol/L, insulin should be implemented in therapy (14-16,27,37).

Vitamins (hydrophilic and lipophilic) and micronutrients have an important role in metabolic processes, immune response and as antioxidants in gene synthesis and reparation. Therefore, it is necessary to supplement them daily, either orally or parenterally (14-16).

COMPLICATIONS AND MONITORING OF NUTRITIONAL THERAPY

Nutritive therapy complications arise due to two reasons: poor planning or poor monitoring. Monitoring prevents complications that result from nutritive therapy treatment, such as metabolic, infectious or mechanic complications, as well as thrombosis. Electrolyte imbalance is particularly significant since it could lead to refeeding syndrome. For that reason, a careful daily monitoring of electrolyte and biochemical panel prevents any further electrolyte imbalance as well as increased urea and creatinine levels. Refeeding syndrome is a metabolic disorder that occurs during the transition from the fasting state to a state of food intake during the initial phase of nutritional therapy in patients who are severely malnourished or are in a state of stress due to a critical illness. That being the case, gradual intake of food with daily electrolyte monitoring should be carefully planned. Particular attention should be paid to the potassium, sodium, phosphorus and magnesium levels. Main refeeding syndrome symptoms include arrhythmias, decompensated heart failure, breathing disorders, vision disorders, and neurological disorders. Potassium, sodium, phosphorus, magnesium and thiamine supplementation should be applied from the first day of nutritional therapy in patients who are at a risk of developing refeeding syndrome. Thiamine is an essential vitamin that has a role as a coenzyme in the Krebs cycle and is necessary for the conversion of glucose into adenosine triphosphate (ATP). Along with other vitamins, thiamine should be given 200 to 300 mg per os, or intravenously daily (8,31,37-39). During the fasting phase, a decomposition of cells begins since there is no energy that would activate the Na-K pump whose role maintains osmotic equilibrium between intracellular and extracellular space. Once the Na-K pump ceases to function, cellular death occurs. The beginning of food intake, whether enterally or parenterally, the organism receives the necessary nutrients for cell reconstruction and energy for activating Na-K pump. In order to create energy, sufficient amounts of thiamine and phosphorus are needed. As a result, phosphorus starts building up in this energetic carrier, as well as in cell membranes, all of which leads to hypophosphatemia. With the appearance of ATP a large number of Na-K pumps are activated, with the aim of maintaining the newly created cells that pump potassium into the cell. This results in hypokalaemia and hypomagnesemia.

Hyperbilirubinemia and acalculous cholecystitis are frequent complications that occur after a long-term application of parenteral nutrition, although these complications can arise shortly after implementing the therapy. It is a result of certain components' toxicity, as well as overfeeding. The main symptoms are abdominal pain and discomfort followed by elevated transaminase and lactate dehydrogenase levels. Furthermore, elevated levels of bilirubin have been recorded. Acalculous cholecystitis is presented as a gallbladder dysfunction and its etiological factors may include critical illness, fasting, weight loss, and total parenteral nutrition. Best course of action is to terminate parenteral nutrition and make a transition to enteral nutrition or at least to exclude fatty acids from the therapy. Hyperbilirubinemia and acalculous cholecystitis can, however, also occur in case of enteral nutrition (40, 41).

Nutritive therapy monitoring is based on the laboratory and biochemical panel monitoring, as well as energy needs and protein catabolism monitoring. The optimal practice for energy needs monitoring of patients is indirect calorimetry. If such an approach is not available, the nitrogen balance offers the best way to find out if the patient's energy needs are met. This practice allows us to calculate the ratio of nitrogen input versus output. If nitrogen output is greater than the input, the patient's energy needs have not been met yet, leaving the organism to consume its proteins for energy production. When nitrogen input is greater than the output, the patient has met their energy needs and the organism no longer needs to consume its proteins for energy production (8, 15,37,39).

CONCLUSION

Nutritional therapy is essential for critically ill patients. The optimal route of feeding is enteral whenever possible. Alternatively, parenteral route should be used. The basis of nutritional therapy prescription is to determine the necessary energy and protein amounts. Hypocaloric and hypoproteinemic intake during the first 2 to 3 days of critical illness is recommended. Additionally, indirect calorimetry serves as a basis for determining nutritional needs in critically ill patients.

Author Contributions

Conception, design of the manuscript; final approval of the version to be published, analysis, interpretation of data: Ivan Palibrk

Analysis, interpretation of data, Marija Đukanović

Drafting, revising manuscript critically: Dona Stefanović

Co-first author: Marija Đukanović and Dona Stefanović have contributed equally to this work and they share first authorship.

REFERENCES

1. Muscaritoli M, Krznaric Z , Barazzoni R, Cederholm T, Golay A, Van Gossum A, et al. Effectiveness and efficacy of nutritional therapy e A cochrane systematic review. Clin Nutr 2017;36(4):939-957.doi: 10.1016/j.clnu.2016.06.022. PMID: 27448948.
2. Lambell KJ Babet O T, Chapple L, Gantner D, Ridley EJ..Nutrition therapy in critical illness: a review of the literature for clinicians. Crit Care. 2020;4;24(1):35. doi: 10.1186/s13054-020-2739-4. PMID: 32019607.
3. Palibrk I, Veličković J, Pantić Palibrk V, Arsenijević V, Tanović B, Ugrinović Đ. Preoperative preparation for patients with nutritional disorders. Acta Chir Iugosl. 2011;58(2):163-168. DOI: 10.2298/aci1102163p. PMID: 21879667.
4. Vincent, J.-L., Creteur, J. The Critically Ill Patient.In: Critical Care Nephrology.3rd Ed.Elseviaer;2019. doi:10.1016/b978-0-323-44942-7.00001-7
5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. TheThirdInternationalConsensusDefinitions for Sepsis andSepticShock(Sepsis-3). JAMA.2016;315(8):801-810. doi:10.1001/jama.2016.0287. PMID: 26903338.
6. Palibrk I, Matić M, Peško P, Ranković V, Tomašević Lj, Milenković M, Nenadić B, Maširević V. Nutrition day in Serbia. 30th Congress of ESPEN, Florence, Italy September 13-16, 2008. Clinical Nutrition.2008;3 Suppl 1:P 110. doi.org/10.1016/S1744-1161(08)70172-8
7. Palibrk I, Pantić-Palibrk V, Matić M, Milenković M, Maširević V, Ranković V. Nutrition day 2009 in one hospital in Serbia – what should we do? 31th Congress of ESPEN, Vienna, Austria. August 29-01 September, 2009. Clinical Nutrition.2009;4 Suppl 2:P 069. doi.org/10.1016/S1744-1161(09)70119-X
8. Palibrk I, Pantić Palibrk V, Đukanović M, Ivošević T, Đurašić Lj, Lađević N. NUTRITION SUPPORT IN INTENSIVE CARE UNIT. SJAIT2013;3-4:141-152. Nutrition support in intensive care unit (ceon.rs)
9. Cattani A, Eckert IC, Brito JC, Tartari RF, Silva FM. Nutritional risk in critically ill patients: how it is assessed, its prevalence and prognostic value: a systematic review. Nutr Rev. 2020;78(12):1052-1068. doi: 10.1093/nutrit/nuaa031. PMID: 32529226.
10. Veličkovic J, Palibrk I, Žnidaršič M, Zec S, Marnic M, Đukanovic M. SUN-P198 NUTRITIONAL RISK ASSESSMENT IN PATIENTS UNDERGOING GASTROINTESTINAL SURGERY: CAN NRS 2002 SCORE BE SIMPLIFIED? Clinical Nutrition.2017;36 Suppl 1:S127.doi.org/10.1016/S0261-5614(17)30430-2
11. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med. 2009;35(10):1728-37.doi: 10.1007/s00134-009-1567-4. PMID: 19572118.
12. Compher C, Chittams J, Sammarco T,Nicolo M, Heyland DK. Greater Protein and Energy Intake May Be Associated With Improved Mortality in Higher Risk Critically Ill Patients: A Multicenter, Multinational Observational Study. Critical Care Medicine 2017;45(2):156-163. DOI: 10.1097/CCM.0000000000002083. PMID: 28098623.
13. Palibrk I, Đukanović M. Osnove enteralne ishrane. SJAIT 2015;1-2:15-19. 2217-77441502015P.pdf (ceon.rs)
14. Singer P, Reintam Blaser A, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clinical Nutrition 2019;38:48-79. doi.org/10.1016/j.clnu.2018.08.037. PMID: 30348463
15. Singer P, Blaser AR, Berger MM, Calder PC Michael Casaer M, Michael Hiesmayr ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit. Clinical Nutrition 2023;42: 1671-1689. DOI: 10.1016/j.clnu.2023.07.011. PMID: 37517372
16. Compher C, Bingham AL, McCall M, Patel J, Rice TW, Braunschweig C McKeever L. Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and EnteralNutrition. J Parenter Enteral Nutr.2022;46:12–41. doi.org/10.1002/jpen.2267. PMID: 34784064.
17. Wischmeyer PE. Nutrition Therapy in Sepsis. Crit Care Clin 2018;34(1):107-125.doi: 10.1016/j.ccc.2017.08.008 PMID: 29149933.
18. Fiaccadori E, Sabatino A, Barazzoni R, Carrero JJ, Cupisti A, De Waele E, Jonckheer J, Singer P, Cuerda C. ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. Clinical Nutrition 2021;40:1644-1668. doi.org/10.1016/j.clnu.2021.01.028. PMID: 33640205.
19. Casaer MP ,Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt,G. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506-17. doi: 10.1056/NEJMoa1102662. Epub 2011 Jun 29. PMID: 21714640.
20. Heidegger CP , Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013; Feb 2;381(9864):385-93. doi: 10.1016/S0140-6736(12)61351-8. PMID: 23218813

21. Vincent JL, Preiser JC. When should we add parenteral to enteral nutrition?Lancet 2013;381:354. doi: 10.1016/S0140-6736(12)61893-5. PMID: 23218814.
22. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Jensen TH, Wiis J, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr. 2012 Aug;31(4):462-8.doi: 10.1016/j.clnu.2011.12.006. PMID: 22209678
23. Weijs P, Stapel S, de Groot SDW, Driessen RH, de Jong E, Girbes ARJ, et al. ptimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. JPEN J Parenter Enteral Nutr. 2012 Jan;36(1):60-8. doi: 10.1177/0148607111415109. PMID: 22167076.
24. Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. Crit Care. 2016; Nov 10;20 (1):367.doi: 10.1186/s13054-016-1538-4. PMID: 27832823.
25. de Koning MSL, Koekkoek VACK, Kars JCNHK, van Zanten ARH. Association of PROtein and CAloric Intake and Clinical Outcomes in Adult SEPTic and Non-Septic ICU Patients on Prolonged Mechanical Ventilation: The PROCASEPT Retrospective Study. JPEN J Parenter Enteral Nutr. 2020; Mar;44(3):434-443.doi: 10.1002/jpen.1663. PMID: 31172544
26. Heyland D, Patel J,Compher C, Rice TW, Bear DE, Lee ZY,et al. The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial. Lancet 2023 Feb 18;401(10376):568-576.doi: 10.1016/S0140-6736(22)02469-2. PMID: 36708732
27. Reignier J, Plantefeve G, Mira JP, Argaud L , AsfarP, Aissaoui N. et al. Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group trial (NUTRIREA-3). Lancet Respir Med. 2023 Jul;11(7):602-612. doi: 10.1016/S2213-2600(23)00092-9. PMID: 36958363.
28. Kroemer G, Marin G,Levine B. Autophagy and the Integrated Stress Response. Mol Cell 2010;40:280-93. DOI 10.1016/j.molcel.2010.09.023. PMID: 20965422
29. Derde S,Vanhorebeek I,Güiza F, Derese I, Gunst J, Fahrenkrog B, et al. Early Parenteral Nutrition Evokes a Phenotype of Autophagy Deficiency in Liver and Skeletal Muscle of Critically Ill Rabbits. Endocrinology 2012; 153: 2267–2276. doi: 10.1210/en.2011-2068. PMID: 22396453.
30. Sarenac O, Lazovic R, Vukcevic B, Lazovic J, Palibrk I. Impact of Perioperatively Administered Amino Acids, Lidocaine, and Magnesium on Inflammatory Response and Pain Associated with Abdominal Surgery: A Prospective Clinical Study Med Sci Monit, 2023; 29: e939204. DOI: 10.12659/MSM.939204. PMID: 36703508
31. Ivan Palibrk. Rastvori aminokiselina i glukoze i emulzije masti. U: M. Jović, P. Stevanović, KME, Medicinski fakultet - Beograd editor. Lečenje infuzionim rastvorima. Kontinuirana medicinska edukacija, Medicinski fakultet, Univerziteta u Beogradu, DAS anesteziološke sveske No VI;2008.p. 97-111.ISBN 978-86-904891-4-5
32. Hermans G, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T ,Derde S, Meersseman P,et al.Effect of tolerating macronutrient defi cit on the development of intensive-care unit acquired weakness:a subanalysis of the EPaNIC trial.Lancet Respir Med 2013; Oct1(8):621-629. DOI: 10.1016/S2213-2600(13)70183-8. PMID: 24461665.
33. Haines RW, Zolfaghari P, Wan Y, Pearse RM, Puthucheary Z, Prowle JR.. Elevated urea-to-creatinine ratio provides a biochemical signature of muscle catabolism and persistent critical illness after major trauma. Intensive Care Med 2019; Dec;45(12):1718-1731.doi: 10.1007/s00134-019-05760-5. PMID: 31531715.
34. Heyland DK, Elke G, Cook D, Berger MM, Wischmeyer PE, Albert M, et al. Glutamine and Antioxidants in the Critically Ill Patient: A Post Hoc Analysis of a Large-Scale Randomized Trial.JPEN . 2015; may39 (4):401-409. doi.org/10.1177/0148607114529994. PMID: 23594003.
35. De Bruyn A, Gunst J, Goossens C , Vander Perre S, Guerra GG, Verbruggen S, et al Effect of withholding early parenteral nutrition in PICU on ketogenesis as potential mediator of its outcome benefit. Critical Care 2020;24:536doi.org/10.1186/s13054-020-03256-z. PMID: 32867803.
36. Koekkoek WK, Panteleon V, Rh van Zanten A. Current evidence on ω-3 fatty acids in enteral nutrition in the critically ill: A systematic review and meta-analysis. Nutrition 2019; Mar:59:56-68. doi: 10.1016/j.nut.2018.07.013. PMID: 30419501.
37. Ivan Palibrk. Komplikacije: Poremećaji serumskih elektrolita i glukoze. U. P. Peško,P. Stevanović, M. Jović, V. Bumbaširević., KME, Medicinski fakultet- Beograd editor. Osnovi kliničke nutricije. Kontinuirana medicinska edukacija, Medicinski fakultet, Univerziteta u Beogradu, DAS anesteziološke sveske NoV;2007.p.343-380.ISBN 978-86-904891-3-8
38. Reber E, Friedli N, Vasiloglou MF, Schuetz P, Stanga Z Management of Refeeding Syndrome in Medical Inpatients. J Clin Med. 2019; Dec 13;8(12):2202. doi: 10.3390/jcm8122202. PMID: 31847205.
39. Palibrk I, Veličković J, Djukanović M. Ishrana hirurškog bolesnika. U Hirurgija sa anesteziologijom. Simić A, Grujičić D, Spasovski D. Ed. 383-390. Medicinski fakultet Univerziteta u Beogradu, Beograd, 2023.ISBN 978-86-7117-677-4
40. Żalikowska-Gardocka M, Przybyłkowski A. Review of parenteral nutrition-associated liver disease.Clin Exp HEPATOL 2020;6, 2: 65–73./doi.org/10.5114/ceh.2019.95528. PMID: 32728621.
41. Jones MW; Ferguson T, editors. Acalculous Cholecystitis [monograph on the Internet]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan [cited 2024 May 9]. Available from: Acalculous Cholecystitis - StatPearls - NCBI Bookshelf (nih.gov)

ISHRANA KOD KRITIČNO OBOLELIH ODRASLIH BOLESNIKA

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Sažetak

Ishrana je sastavni deo terapije kritično obolelog bolesnika. Postavlja se pitanje kada je započeti, na koji način i koje količine makro i mikronutrienata treba primeniti, a svakako je najvažnije pitanje koja količina energije je potrebna takvom bolesniku.

Kritična bolest ima tri faze: *early* period (ranije *ebb*) u trajanju od 1 do 2 dana, *late* period (ranije *flow phase*) u trajanju od 3 do 7 dana i *late phase* (*phase rehabilitation* ili *chronic phase*). Svaka faza ima svoje karakteristike. U prvoj fazi je izražen jak katabolizam, koji od 3. do 4. dana polako prelazi u anabolizam. Na osnovu toga su napravljene i preporuke za ishranu kritično obolelog.

Prvih dana kritične bolesti ne preporučuje se pun energetski i proteinski unos hrane. Dosezanje nutritivnog cilja treba započeti tek posle 3-4 dana od početka kritične bolesti. Energetski unos treba da se kreće od 20 do 25 kcal/kg/dan, a proteinski od 0,8g/kg/dan uz postepeno povećanje do 1,3 g/kg/dan po ESPEN-u. Po ASPEN-u energetski unos treba da je od 12 do 25 kcal/kg/dan , a proteinski od 1,2 do 2 g/kg/dan. Preporučuje se enteralni unos hrane kada god je moguće, a ako on nije moguć onda se primenjuje parenteralni način ishrane.

Rani, puni energetski i proteinski unos može rezultovati povećanim morbiditetom i mortalitetom kod kritično obolelog.

Za određivanje energetskih potreba kritično obolelog bolesnika preporučuje se korišćenje indirektne kalorimetrije.

Zaključak: Kritično obolelog treba hraniti. Koliko god je moguće ishrana treba da bude enteralnim putem. Bilo da je ona enteralna ili parenteralna, unos energije i proteina treba da je postepen. Preskripcija nutritivne terapije treba da je individualna, prilagođena potrebama bolesnika.

Ključne reči: kritična bolest, enteralna ishrana, intenzivno lečenje, parenteralna ishrana

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