

Features of energy and protein supply in patients with sepsis: a retrospective observational study

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Abstract

INTRODUCTION: Sepsis remains an actual problem of modern medicine. Among other treatment options, timely prescribed optimal nutritional-metabolic support is one of the priority methods of intensive treatment for this category of patients. **OBJECTIVE:** To study the severity of metabolic dysfunction in sepsis and determine the parameters of optimal substrate supply for this category of patients. **MATERIALS AND METHODS:** The study included 166 patients with sepsis. We studied the severity of systemic metabolic dysfunction and the impact of various options for energy and protein supply on the course of the disease and its outcome. Energy expenditure and the severity of the catabolic reaction of the body were studied by dynamic evaluation of indicators of indirect calorimetry, actual losses of nitrogen and nitrogen balance. **RESULTS:** Actual energy expenditure in sepsis reaches its maximum values by the 5–6th day of the disease (33.5 ± 1.8 kcal/kg/day or 2366 ± 126 kcal/day). The average energy consumption in sepsis is 2226 ± 96 kcal/day or 30.9 ± 1.4 kcal/kg/day. Energy supply in sepsis less than 25 kcal/kg/day leads to a significant increase in mortality. Protein losses in sepsis reach their maximum values by the 5–6th day of the disease (1.93 ± 0.12 g/kg/day). The average loss of protein in sepsis is 1.68 ± 0.06 g/kg/day. Protein provision of this category of patients with more than 1.5 g/kg/day contributes to a significant decrease in mortality, relative to patients receiving less protein per day. **CONCLUSIONS:** Energy supply in the range of 25–35 kcal/kg/day, as well as protein supply of more than 1.5 g/kg/day, significantly contribute to better survival of patients with sepsis.

Особенности энергетического и белкового обеспечения больных при сепсисе: ретроспективное наблюдательное исследование

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Реферат

АКТУАЛЬНОСТЬ: Сепсис остается актуальной проблемой современной медицины. Своевременно назначенная оптимальная нутритивно-метаболическая терапия является одним из приоритетных методов интенсивного лечения данной категории больных. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Изучить выраженность метаболической дисфункции при сепсисе и определить параметры оптимального субстратного обеспечения данной категории больных. **МАТЕРИАЛЫ И МЕТОДЫ:** В исследование вошли 166 пациентов с сепсисом. Изучались выраженность системной метаболической дисфункции и влияние различных вариантов энергетического и белкового обеспечения на течение заболевания и его исход. Энергетические затраты и выраженность катаболической реакции организма исследовались путем динамической оценки показателей непрямой калориметрии, фактических потерь азота и азотистого баланса. **РЕЗУЛЬТАТЫ:** Действительные энергозатраты при сепсисе достигают максимальных значений к 5–6-м суткам заболевания ($33,5 \pm 1,8$ ккал/кг/сут, или 2366 ± 126 ккал/сут). Средние показатели энергозатрат при сепсисе составляют 2226 ± 96 ккал/сут, или $30,9 \pm 1,4$ ккал/кг/сут. Энергетическое обеспечение при сепсисе менее 25 ккал/кг/сут приводит к достоверному увеличению летальности. Потери белка при сепсисе достигают максимальных значений к 5–6-м суткам заболевания ($1,93 \pm 0,12$ г/кг/сут). Средние потери белка при сепсисе составляют $1,68 \pm 0,06$ г/кг/сут. Белковое обеспечение данной категории больных более 1,5 г/кг/сут достоверно способствует снижению летальности у пациентов, получающих меньшее количество белка в сутки. **ВЫВОДЫ:** Энергетическое обеспечение в диапазоне 25–35 ккал/кг/сут, так же как и белковое обеспечение более

KEYWORDS: sepsis, nutritional support, requirements of protein, requirements of energy, nitrogen loss, enteral nutrition, parenteral nutrition

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1,5 г/кг/сут, достоверно способствуют лучшей выживаемости пациентов с тяжелым сепсисом.

КЛЮЧЕВЫЕ СЛОВА: сепсис, нутритивная поддержка, потребность в белке, потребность в энергии, потери азота, энтеральное питание, парентеральное питание

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Introduction

Today sepsis remains an actual problem of modern medicine because of high morbidity and mortality rates.

There are two most important pathophysiological processes in sepsis: a strong systemic inflammatory reaction and a long-lasting systemic metabolic dysfunction that is characterized by hypermetabolism and hypercatabolism and rapidly growing protein-energy malnutrition. Therefore it is crucial to prescribe optimal nutritional-metabolic support for this group of patients in order to reduce the period of the hypermetabolic-hypercatabolic syndrome and minimize the incidence of complications and, as the result, to increase the effectiveness of treatment. It is important to determine the route of administration, the nature and amount of nutritional substrate according to the intensity and prevalence of organ failure, to the level of consciousness, to the dysphagia, to the baseline nutritional status and to the absorption and digestion disorders [1–19].

The management and the amount of substrates needed for this type of patients, especially during the first week of their disease, are still under discussion [20].

Objective: to search the severity of metabolic dysfunction among septic patients and to define the criteria for optimal substrate supply for this category of patients.

The objectives of the study:

1. To search how energy losses of the septic patients depend on the terms and duration of the infectious process.
2. To evaluate the structure of the oxidable nutritious substrates according to the respiratory exchange ratio.
3. To search the level and the duration of the hypercatabolic reaction in connection with the system inflammatory reaction and the organ dysfunction.
4. To define the amount of energy and protein to provide to septic patients.

Materials and methods

To solve the mentioned problems, we conducted a retrospective study of 166 septic patients treated in the intensive care unit (ICU) of the Saint-Petersburg I.I. Dzhanelidze Research Institute of Emergency Care from October 2016 to June 2020.

Patients with sepsis, both male and female, aged from 18 to 80, who required nutritional support (enteral, parenteral, or both) were included in the study. The exclusion criteria were established as follows: the period of nutritional support less than 10 days; extensive combined cytoreductive surgery for grade IV tumors; serious comorbidities in decompensation (chronic cardiovascular insufficiency, chronic kidney disease, liver cirrhosis); community-acquired infections (tuberculosis, acquired immunodeficiency syndrome); patients > 80 years of age.

The statistical analysis of the collected data was conducted using the criteria of Kolmogorov–Smirnov. We used the Student's *t*-test to confirm the normal distribution and to assess the statistical significance of the average samples. When there were no signs of normal distribution, we used the chi-square criterion. We used the Fisher's exact test to compare relative indexes. The 95 % probability level was accepted as the critical *p*-level (*p* = 0.05).

The distribution of patients by gender, age and body mass index (BMI) is shown in Table 1.

There was no significant age or BMI difference between men and women.

Some laboratory test values at the admission to the ICU are represented in Table 2.

The majority of patients developed hypoalbuminemia (100 %), leukocytosis (96.9 %), hypoproteinemia

(96.4 %), anemia (90.3 %). Less often septic patients developed hyperglycemia (57.8 %), lymphopenia (55.4 %), uremia (46.9 %), leukocytopenia (2.4 %). All patients had high levels of C-reactive protein and low levels of cholinesterase, which is an indirect marker of the synthetic ability of the liver.

It is worth mentioning, that the hypoalbuminemia level, usually associated with the severity of sepsis, turned out to be a predictor of the disease outcome. A significantly lower mortality (*p* < 0.01) was in the group of patients whose albumin level was 25 g/L and more (7.1 %). When the albumin level was between 20–25 g/L, the mortality rate raised up to 38.2 %, and up to 43.1 % — when the albumin level decreased < 20 g/L.

The severity of organ dysfunction was assessed at the admission to the ICU with the Sequential Organ Failure Assessment (SOFA) scale: 4.44 ± 2.4 scores (43.4 % of patients had less than 4 scores, 17.9 % — 5–6 scores and 38.8 % — had over 6 scores). The patients' average level of consciousness, assessed by Glasgow Coma Scale was 11.7 ± 3.1 days. The average length of stay in the ICU was 25.4 ± 11 days and the average duration of mechanical ventilation (ALV) — 17.5 ± 16.1 days.

The distribution of patients by type of sepsis and mortality is shown in Table 3.

Table 1. Characteristics of patients (*n*) by gender, age and body mass index

Gender	<i>n</i> (%)	Average age, years	Average BMI, kg/m ²
Female	60 (36.1)	56.1 ± 18.8	23.75 ± 4.0
Male	106 (63.9)	51.0 ± 15.7	23.60 ± 3.7
	166 (100)	52.8 ± 17.0	23.63 ± 3.8

Table 2. Laboratory parameters of patients at the time of admission to the ICU

Average value at admission	Normal range	Value (<i>M</i> ± <i>m</i>)
Haemoglobin, g/L	130–160	93.4 ± 19.8
Lymphocytes, $\times 10^9$ /L	1.2–3	1.17 ± 0.6
Leukocytes, $\times 10^9$ /L	4–9	12.2 ± 6.3
General protein, g/L	64–83	49.6 ± 7.9
Albumin, g/L	35–55	21.85 ± 4.4
Urea, mmole/L	< 8.3	12.25 ± 6.3
Creatinine, micromole/L	60–120	118 ± 45.6
Glucose, mmole/L	3.05–6.38	8.5 ± 3.7
Cholinesterase, unit/L	6400–15 500	2311 ± 972
C-reactive protein, mg/L	< 5	165.7 ± 131

Table 3. Distribution of patients (*n*) by type of sepsis and mortality

Type of sepsis	<i>n</i> (%)	Mortality, %
Abdominal	85 (51.2)	34.1
Pulmonary	51 (30.8)	47.1
Soft-tissue infection	15 (9.0)	40.0
Sepsis-associated encephalopathy	15 (9.0)	40.0

The data represented in Table 3 show that the majority of patients developed the abdominal type of sepsis (51.2% of all cases), which is associated with the lowest mortal-

ity rate. The overall mortality rate in the study was 39.16% (40.0% — male and 38.7% — female). The patients who died were significantly older than those who survived (Table 4).

Table 4. Mortality of patients (*n*) depending on age

Outcome	<i>n</i>	Mortality, %	Age, years
Recovery	101	39.16	49.7 ± 17.7*
Death	65		57.3 ± 15.1
Total	166		52.8 ± 17.0

* The difference between the compared parameters in groups are statistically significant ($p < 0.01$).

It is also worth mentioning, that the highest mortality rate was in the group of patients who suffered from energy-protein malnutrition (42.5%) and from marasmic kwashiorkor (35.5%) at baseline, and the lowest mortality was in the group of patients with nutritional marasmus (20%).

Management goals for nutrition in sepsis were as follows: calories 20–25 kcal/kg/day, protein 1–1.2 g/kg/day — in case the condition of the patient was unstable; and calories 25–35 kcal/kg/day, protein 1.3–2 g/kg/day for those, who were stable. The micronutrient supply was provided in the amount indicated by the daily deficiency needs. The total amount of nutritional support was gradually increased during 3–4 days (500 kcal/day and more) with the regular check up of the metabolic response. For patients with overweight and obesity the nutrition delivery doses are calculated regarding the ideal body weight, for undernourished and eutrophic patients — regarding the actual body weight.

The primary objective of the nutritional support of septic patients was early enteral nutrition that started in the first 24–48 hours upon admission to the ICU. If the nutrition goals could not be achieved enterally, additional parenteral nutrition was prescribed within 5 days. If it seemed to be impossible to feed the patient enterally in the first 5–7 days (it was typical for patients with abdominal sepsis), we began parenteral nutrition in the first 48–72 hours and gradually increased its volume keeping in check the rate of administration of nutritional substrates.

There were several contraindications for nutritional support: toxic shock syndrome, severe arterial hypoxemia (the oxygen partial pressure in arterial blood was less than 50 mm Hg), the decompensated hyperchloremic acidosis (hyperlactatemia 4 mmol/L and more), hypercapnia (the di-oxide carbon partial pressure > 80 mm Hg, pH < 7.2), intolerance to feeding formulas.

The actual energy expenditure (AEE) was calculated by indirect calorimetry (metabolimeter Qvark-RMR produced by CosMed, Italy). The catabolic reaction and protein needs were assessed by calculating the daily nitrogen losses and the nitrogen balance.

The indirect calorimetry was carried out in the first 2–3 days, then on the 5–6, 10–11 and 15–16 days in the intensive care unit. The average level of basal metabolic rate (BMR) during the whole period of treatment in the ICU was 2226 ± 96 kcal/day or 30.9 ± 1.4 kcal/kg/day, average respiratory ratio rates — 0.69 ± 0.04 , which is a sign of predominating lipid peroxidation.

Along with that, we measured daily nitrogen losses in the above time limits for all the patients without kidney or liver failure. Then we calculated the ratio between nitrogen losses in grams and the obtained AEE values in kilocalories, as well as the ratio between nitrogen losses and non-protein energy expenditure. The collected data were brought into correlation with the severity of organ dysfunction.

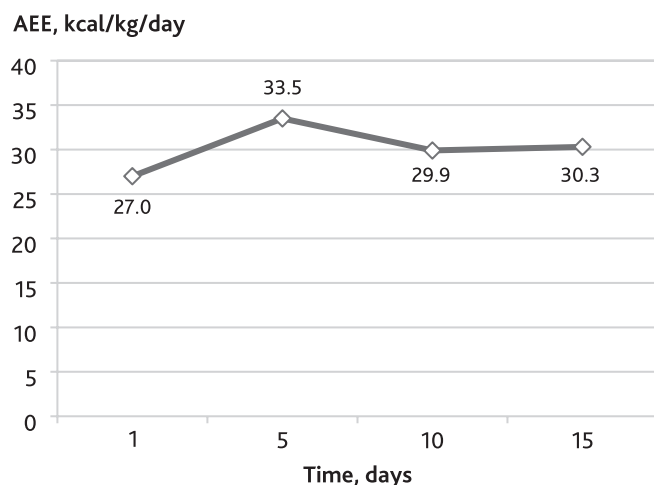


Fig. 1. Dynamics of the actual energy expenditure depending on the timing of the development of sepsis

Results

Dynamics of average energy expenditure and nitrogen losses is shown in Table 5.

The average energy expenditure at the beginning of the septic process was 27.0 ± 2.1 kcal/kg/day, reached the peak on the 5–6 day (33.5 ± 1.8 kcal/kg/day) and then flattened out at 30.0 ± 3.6 kcal/kg/day (Fig. 1).

The average day nitrogen loss during the whole research period was 18.8 ± 0.6 g/day (0.27 ± 0.01 g/kg/day),

1.68 ± 0.06 g/kg/day of protein, respectively. The protein loss reached its maximum on the 5th day of the disease (1.93 ± 0.12 g/kg/day) and later stood at 1.56 ± 0.13 g/kg/day.

The association between average energy expenditure, nitrogen losses, the ratio of lost nitrogen to total and non-protein energy expenditure (NP kcal) depending on the severity of organ dysfunction, are displayed in Table 6.

We divided septic patients into three groups to assess the effects of different types of energy supply. The first group was supplied with 25 kcal/kg/day, the second group — 25–30 kcal/kg/day, and the third — > 30 kcal/kg/day. We divided patients into groups retrospectively, considering the average daily level of energy supply during the whole period of treatment (Table 7). There were no significant differences in the severity of organ dysfunction (measured with the SOFA scale) between groups.

As shown in Table 7, the lowest mortality was in the group of patients who received > 30 kcal/kg/day. It was decreased by 50 % in comparison with the patients who received < 25 kcal/kg/day. Among patients who received 25–30 kcal/kg/day mortality was also significantly lower (1.5 times) than in the first group (< 25 kcal/kg/day), but 1.4 times higher than in the third group of patients (> 30 kcal/kg/day). However, there was no statistically significant difference between the 2nd and the 3rd group.

Patients in the study were also divided into groups (Table 8) according to the amount of protein that they

Table 5. Dynamics of AEE and nitrogen losses depending on the timing of sepsis

Day of sepsis	<i>n</i>	SOFA, score	AEE, kcal/day	AEE, kcal/kg/day	Nitrogen losses, g/day	Nitrogen losses, g/kg/day
2–3	166	4.33 ± 2.4	1930 ± 115	27.0 ± 2.1	20.6 ± 1.5	0.28 ± 0.01
5–6	158	3.89 ± 2.3	2366 ± 126	33.5 ± 1.8	20.8 ± 1.4	0.32 ± 0.02
10–11	122	3.96 ± 2.8	2247 ± 175	29.9 ± 2.4	18.1 ± 1.3	0.25 ± 0.01
15–16	90	2.91 ± 1.8	2328 ± 411	30.3 ± 5.4	17.0 ± 1.2	0.24 ± 0.1

AEE — actual energy expenditure; *n* — number of patients; SOFA — Sepsis-Related organ Failure Assessment score.

Table 6. Average energy expenditure (AEE), nitrogen losses, the ratio of lost nitrogen to total and non-protein energy expenditure (NP kcal) depending on the severity of organ dysfunction

SOFA, score	Average SOFA	AEE, kcal/day	AEE, kcal/kg/day	Nitrogen losses, g/day	NP kcal	Nitrogen, g: AEE, kcal	Nitrogen, g: NP kcal
4 and more	$5.9 \pm 0.17^*$	2159 ± 165	28.8 ± 1.7	21.1 ± 1.3	1691 ± 159	1:109	1:85
1–3	$2.2 \pm 0.06^*$	2171 ± 134	29.8 ± 1.9	16.8 ± 0.8	1723 ± 138	1:143	1:104

* The differences of the parameters, compared in the groups, are significant ($p < 0.05$).

Table 7. Mortality in severe sepsis depending on the average daily level of energy supply (ES) ($n = 166$)

ES, kcal/kg/day	Outcome	<i>n</i>	Mortality, %	Average ES, kcal/kg/day
< 25	discharge	49	46*	20.2 ± 0.5
	death	43		20.2 ± 0.5
25–30	discharge	39	31#	27.0 ± 0.2
	death	18		27.2 ± 0.3
> 30	discharge	13	23#	33.5 ± 0.9
	death	4		31.2 ± 0.9

n — number of patients.

* The differences in comparison with all groups are significant ($p < 0.05$).

The differences in comparison with the first group are significant ($p < 0.05$).

Table 8. Outcomes of severe sepsis depending on the average daily protein supply (PS) ($n = 166$)

PS, g/kg/day	Outcome	<i>n</i>	Mortality, %	Average PS, g/kg/day
< 1.2	discharge	42	46.2#	1.01 ± 0.02
	death	36		0.98 ± 0.02
1.2–1.5	discharge	38	39.7#	1.33 ± 0.01
	death	25		1.36 ± 0.02
> 1.5	discharge	21	16.0*	1.63 ± 0.02
	death	4		1.73 ± 0.09

n — number of patients.

The differences in comparison with the last group are significant ($p < 0.05$).

* The differences in comparison with all groups are significant ($p < 0.05$).

Table 9. Positive nitrogen balance at different stages of sepsis with different protein supply

Protein supply, g/kg/day	Positive nitrogen balance, % from all the examined patients		
	5–6 day	10–11 day	15–16 day
< 1.2	18.7	11.1#	37.5#
1.2–1.5	13.0	18.7#	33.3#
> 1.5	20.0	46.1*	72.7*

The differences in comparison with the last group are significant ($p < 0.05$).

* The differences in comparison with all groups are significant ($p < 0.05$).

received. There were no significant differences in the severity of organ dysfunction (measured with the SOFA scale) between groups.

The data in Table 8 show the statistically significant lowest mortality rate between patients who received more than 1.5 g/kg/day of protein. The mortality rate in this group was by 2.9 lower, than in the group with protein supply < 1.2 g/kg/day and by 2.5 lower than in the group with 1.2–1.5 g/kg/day. There was no statistically significant difference in mortality between the 1st and the 2nd groups.

The nitrogen balance was significantly different (to a better extent) in the group of patients who received a high amount of protein (more than 1.5 g/kg/day) during the whole study. The ratio between patients with pos-

itive nitrogen balance and the total amount of examined patients different stages of sepsis with different protein supply is shown in Table 9.

When protein supply was in the amount more than 1.5 g/kg/day, almost half of the patients reached positive values of nitrogen balance on day 10–11, and 73 % of patients on day 15–16, (significantly faster, than patients who received less protein supply).

Relationship between mortality and nitrogen balance at different stages of sepsis development is displayed in Table 10.

The data in Table 10 show, that if positive nitrogen balance is achieved at any stage of the development of sepsis, then mortality significantly decreases.

Table 10. Relationship between mortality and nitrogen balance at different stages of sepsis development

Nitrogen balance	5–6 day of sepsis		10–11 day of sepsis	
	<i>n</i>	Mortality, %	<i>n</i>	Mortality, %
Negative	108	38.9*	69	44.9*
Positive	16	18.7*	30	30*

n — number of patients.

* The differences in comparison with a corresponding group are significant ($p < 0.05$).

Discussion

The route, type and amount of nutritional support for septic patients, especially during the first week upon admission to hospital, are still under discussion [20]. The international guidelines for management in severe sepsis and septic shock (published in 2012) [21] are based on the results of three randomized studies [22–24], where there were no significant differences in mortality rates between trophic (400–500 kcal/day) and full-energy (1300–1500 kcal/day) enteral nutrition within the first week of the disease. Thus, it is recommended to choose the strategy of initial trophic enteral feeding [25]. This statement is contrary to Canadian guidelines published in 2013 [26] and the results of the analysis of a large nutrition database, carried out by Elke G [27, 28]. The analysis included pooled data collected prospectively from international nutrition studies (13,630 patients in 730 ICU in 33 countries included in the dataset, 2270 patients met the study inclusion criteria). Mechanically ventilated patients received a mean amount of 1057 kcal/day (14.5 kcal/kg/day) and 49 g protein/day (0.7 g/kg/day) by enteral nutrition in the first week. An increase of 1000 kcal was associated with reduced 60-day mortality and more ventilation-free days, as was an increase of 30 g protein per day.

Our data show that the energy expenditure of septic patients reach the maximum on the 5–6 day of the disease (33.5 ± 1.8 kcal/kg/day or 2366 ± 126 kcal/day in absolute data values). Mean energy expenditure values are around 2226 ± 96 kcal/day or 30.9 ± 1.4 kcal/kg/day. If the amount of energy nutrition provided to these patients in the ICU is less than 25 kcal/kg/day, the mortality rate significantly increases. Reaching optimal energy targets (30 kcal/kg/day and more) is associated with a decrease in mortality by 50 %.

Optimal protein support of critically ill patients remains a question for further discussion. There is a number of recent studies showing that nourishing a patient with high quantities of nitrogen shortens the period of mechanical ventilation, decreases the number of infectious complications, reduces the length of stay in the ICU and mortality [27, 29–32].

For example, the results of a randomized study, conducted in 2016 by S. Ferrie et al. show that higher protein provision for critically ill patients (> 1.2 g/kg/day compared with < 0.8 g/kg/day) is associated with positive changes of somatometric parameters. At the same time there was no difference in mortality and length of stay in the ICU [33]. The authors of the other study proved that skeletal muscle wasting occurs early and rapidly in critical illness and

is not associated with nutrition support [34]. According to the results of M.P. Casaer et al., a higher dose of calories and protein administered parenterally in the first week and combined with low-energy enteral nutrition is associated with more intensive muscle wasting and more delayed recovery [35]. The group of patients with early combined (enteral-parenteral) feeding received 1576 ± 368 kcal/day and 47.2 ± 15.1 g protein/day from the 3rd to the 7th day after admission, and the group with low-energy enteral nutrition received 594 ± 345 kcal/day and 14.2 ± 14.6 g protein/day. At the end of the first week the amount of nutrition support became equal in both groups.

In the next multicenter study data were collected from 2772 patients on mechanical ventilation in 167 ICUs from 37 countries. It was shown that the provision of higher calories (> 1500 kcal/day) and protein (> 60 g/day) was associated with a significant overall reduction in 60-day mortality. The largest mortality reduction was obtained at 1900 kcal/day and 90 g protein/day [29].

M.J. Allingstrup et al. [36] conducted a prospective observational cohort study of 113 ICU patients, mainly (88.5%) septic. They registered the lowest mortality rate (16%) when protein supply reached 1.46 ± 0.29 g/kg/day. In the groups of patients with protein supply 0.79 ± 0.29 and 1.06 ± 0.23 g/kg/day, mortality rate was 27% and 24% correspondingly. At the same time, there was no association found between higher provision of energy and the disease outcome.

Our findings demonstrate that in septic patients protein losses measured with daily nitrogen losses achieve the highest values (1.93 ± 0.12 g/kg/day) on the 5–6th day of the disease. Mean protein losses in septic patients are around 1.68 ± 0.06 g/kg/day. Supplying these patients with > 1.5 g/kg/day of protein results in a significant reduction of mortality rate, compared to patients who receive less protein per day.

Our findings show that it is reasonable to use a personalized approach when choosing the strategy of energy and protein supply of septic patients. It is necessary to consider the severity of organ dysfunction (assessing it with the SOFA scale). With equal energy expenditure values, when SOFA scores are 1–3 and 4 and more (29.8 ± 1.9 and 28.8 ± 1.7 kcal/kg/day correspondingly),

because of the growing nitrogen losses and the aggravation of organ dysfunction, the balance between nitrogen and non-protein kilocalories changes (1:104 when SOFA scores are 1–3, and 1:85 when SOFA scores are 4 and more). It is advisable to consider these differences during nutrition support of septic patients in order to optimize the energy and protein supply.

Conclusion

The hypermetabolism-hypercatabolism in septic patients is the most intensive on the 5th day:

- Energy expenditure reaches 33.5 ± 1.8 kcal/kg/day, and protein loss — 1.93 ± 0.12 g/kg/day.
- Mean values of actual energy expenditure (measured by indirect calorimetry) are around 30.9 ± 1.4 kcal/kg/day, average respiratory ratio rates — 0.67 ± 0.01 , which is a sign of predominating lipid peroxidation in septic patients.
- Average daily nitrogen losses in septic patients are around 18.8 ± 0.6 g/day (0.27 ± 0.01 g/kg/day), or 1.68 ± 0.06 g/kg/day of protein correspondingly.
- Supplying a septic patient with 30–35 kcal/kg/day definitely leads to better survival rates compared with patients who receive less energy.
- The septic patients should receive more than 1.2 g/kg/day of protein, because lower protein supply results in increased mortality. Providing septic patients with more than 1.5 g/kg/day of protein ensures the highest survival rates.

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Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

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References

- [1] Клинические рекомендации по диагностике и лечению тяжелого сепсиса и септического шока в лечебно-профилактических организациях Санкт-Петербурга 2016 года. Санкт-Петербургское общество специалистов по сепсису [Электронный ресурс]. URL: http://www.spbseps.ru/wp-content/uploads/Protocols_24.11.2016.pdf (дата обращения: 12.05.2022) [Clinical guidelines for the diagnosis and treatment of severe sepsis and septic shock in medical institutions in St. Petersburg, 2016. St. Petersburg Society of Sepsis Specialists [Elektronnyj resurs]. URL: http://www.spbseps.ru/wp-content/uploads/Protocols_11/24/2016.pdf (accessed 12.05.2022) (In Russ)]
- [2] Основы клинического питания. Материалы лекций для курсов Европейской ассоциации парентерального питания. Под ред. Л. Сobotki: пер. с англ. М., 2015. [Fundamentals of clinical nutrition. Lecture materials for the courses of the European Association for Parenteral Nutrition. Ed. L. Sobotki. M., 2015. (In Russ)]
- [3] Сепсис в начале XXI века. Классификация, клинико-диагностическая концепция и лечение: Практич. рук-во. Под ред. В.С. Савельева, Б.Р. Гельфанда. М.: Литтерра, 2006. [Sepsis at the beginning of the XXI century. Classification, clinical diagnostic concept and treatment: Practical guide. Eds. V.S. Saveliev, B.R. Gelfand. M.: Litterra, 2006. (In Russ)]
- [4] Хирургические инфекции: Практич. рук-во. Под ред. И.А. Ерюхина, Б.Р. Гельфанда, С.А. Шляпникова. Изд. 2-е, перераб. и доп. М.: Литтерра, 2006. [Surgical infections: Practical guide. Eds. I.A. Eryukhin, B.R. Gelfand, S.A. Shlyapnikov. 2nd ed., revised and enlarged. M.: Litterra, 2006. (In Russ)]
- [5] Интенсивная терапия: Национальное рук-во. Краткое издание. Под ред. Б.Р. Гельфанда, И.Б. Заболотских. 2-е изд., перераб. и доп. М., ГЭОТАР-Медиа, 2019. [Intensive care: National leadership. Brief edition. Eds. B.R. Gelfand, I.B. Zabolotskikh. 2nd ed., revised and additional. M.: GEOTAR-Media, 2019. (In Russ)]
- [6] Парентеральное и энтеральное питание: Национальное рук-во. Под ред. М.Ш. Хубутия, Т.С. Поповой, А.И. Салтанова. М., ГЭОТАР-Медиа, 2014. [Parenteral and enteral nutrition: National guidelines. Eds. M. Sh. Khubutia, T.S. Popova, A.I. Saltanov. M.: GEOTAR-Media, 2014. (In Russ)]
- [7] Руководство по клиническому питанию. Под ред. В.М. Луфта. СПб.: Арт-Экспресс, 2016. [Clinical Nutrition Guide. Ed. by V.M. Luft. St. Petersburg: Art-Express, 2016. (In Russ)]
- [8] Basics in Clinical Nutrition. Fifth edition. Editor in chief L. Sobotka. Publishing House Galén. 2019.
- [9] Fontaine E., Muller M.J. Adaptive alterations in metabolism: practical consequences on energy requirements in the severely ill patient. *Curr Opin Clin Nutr Metab Care*. 2011; 14: 171–5. DOI: 10.1097/MCO.0b013e328328342bad4
- [10] Zauner C., Schuster B.I., Schneeweiss B. Similar metabolic responses to standardized total parenteral nutrition of septic and nonseptic critically ill patients. *Am J Clin Nutr*. 2001; 74: 265–70. DOI: 10.1093/ajcn/74.2.265
- [11] Hoffer L.J., Bistrian B.R. Why critically ill patients are protein deprived. *JPEN J Parenter Enteral Nutr*. 2013; 37: 300–9. DOI: 10.1177/0148607113478192
- [12] Lightfoot A., McArdle A., Griffiths R.D. Muscle in defense. *Crit Care Med*. 2009; 37: S384–S390. DOI: 10.1097/CCM.0b013e3181b6f8a5
- [13] Soeters P.B., Grimble R.F. Dangers, and benefits of the cytokine mediated response to injury and infection. *Clin Nutr*. 2009; 28: 583–96. DOI: 10.1016/j.clnu.2009.05.014
- [14] Correia M.I., Waitzberg D.L. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr*. 2003; 22: 235–9. DOI: 10.1016/S0261-5614(02)00215-7
- [15] Jensen G.L., Mirtallo J., Compher C., et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *JPEN J Parenter Enteral Nutr*. 2010; 34: 156–9. DOI: 10.1177/0148607110361910
- [16] Heyland D.K., Dhaliwal R., Drover J.W., et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003; 27: 355–73. DOI: 10.1177/0148607103027005355
- [17] McClave S.A., Martindale R.G., Vanek V.W., et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2009; 33: 277–316. DOI: 10.1177/0148607115621863
- [18] Singer P., Berger M.M., Van den Berghe G., et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr*. 2009; 28(4): 387–400. DOI: 10.1016/j.clnu.2009.04.024
- [19] McClave S.A., Heyland D.K. The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutr Clin Pract*. 2009; 24: 305–15. DOI: 10.1177/0884533609335176
- [20] Koekkoek K.W.A.C., van Zanten A.R.H. Nutrition in the critically ill patient. *Curr Opin Anesthesiol*. 2017; 30: 178–185. DOI: 10.1097/ACO.0000000000000441
- [21] Dellinger R.P., Levy M.M., Rhodes A., et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013; 41: 580–637. DOI: 10.1097/CCM.0b013e31827e83af
- [22] Arabi Y.M., Tamim H.M., Dhar G.S., et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *Am J Clin Nutr*. 2011; 93: 569–77. DOI: 10.3945/ajcn.110.005074
- [23] Rice T.W., Mogan S., Hays M.A., et al. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Crit Care Med*. 2011; 39: 967–74. DOI: 10.1097/CCM.0b013e31820a905a
- [24] Rice T.W., Wheeler A.P., Thompson B.T., et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012; 307: 795–803. DOI: 10.1001/jama.2012.137
- [25] Sondheimer J.M. A critical perspective on trophic feeding. *J Pediatr Gastroenterol Nutr*. 2004; 38: 237–8. DOI: 10.1097/00005176-200403000-00001
- [26] Dhaliwal R., Cahill N., Lemieux M., Heyland D.K. The canadian critical care nutrition guidelines in 2013: an update on current recommendations and implementation strategies. *Nutr Clin Pract*. 2014; 29: 29–43. DOI: 10.1177/0884533613510948

- [27] *Elke G., Wang M., Weiler N., et al.* Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. *Crit Care*. 2014; 18: R29. DOI: 10.1186 / cc13720
- [28] *Elke G., Heyland D.K.* Enteral nutrition in critically ill septic patients—less or more? *JPEN J Parenter Enteral Nutr*. 2015; 39: 140–2. DOI: 10.1177/0148607114532692
- [29] *Alberda C., Gramlich L., Jones N., et al.* The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med*. 2009; 35: 1728–37. DOI: 10.1177/0148607114532692
- [30] *Weijs P.J., Stapel S.N., de Groot S.D.* Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. *JPEN J Parenter Enteral Nutr*. 2012; 36: 60–8. DOI: 10.1177/0148607111415109
- [31] *Nicolo M., Heyland D.K., Chittams J., et al.* Clinical outcomes related to protein & delivery in a critically ill population: a multicenter, multinational observation study. *JPEN J Parenter Enteral Nutr*. 2016; 40: 45–51. DOI: 10.1177/0148607115583675
- [32] *Mehta N.M., Bechard L.J., Zurakowski D., et al.* Adequate enteral protein intake is inversely associated with 60-d mortality in critically ill children: a multicenter, prospective, cohort study. *Am J Clin Nutr*. 2015; 102: 199–206. DOI: 10.3945 /ajcn.114.104893
- [33] *Ferrie S., Allman-Farinelli M., Daley M., Smith K.* Protein requirements in the critically ill: a randomized controlled trial using parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2016; 40: 795–805. DOI: 10.1177/0148607115618449
- [34] *Puthucheary Z.A., Rawal J., McPhail M., et al.* Acute skeletal muscle wasting in critical illness. *JAMA*. 2013; 310: 1591–600. DOI: 10.1001/jama.2013.278481
- [35] *Casaer M.P., Wilmer A., Hermans G., et al.* Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. *Am J Respir Crit Care Med*. 2013; 187: 247–55. DOI: 10.1164 /rccm.201206-0999OC
- [36] *Allingstrup M.J., Esmailzadeh N., Wilkens Knudsen A., et al.* Provision of protein and energy in relation to measured requirements in intensive care patients. *Clin Nutr*. 2012; 31(4): 462–8. DOI:10.1016/j.clnu.2011.12.006