https://doi.org/10.15360/1813-9779-2023-4-2329

Nutritional Status of Patients with Chronic Critical Illness

Ivan V. Sergeev[1]*, Marina V. Petrova[1,2], Alexander E. Shestopalov[1,3], Mikhail M. Kanarsky[1], Oleg B. Lukyanets[1], Irina A. Yarotskaya[4], Yulia Yu. Nekrasova[1]

[1] Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, 25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia
[2] Peoples Friendship University of Russia, 6 Miklukho-Maclaya Str., 117198 Moscow, Russia
[3] Russian Medical Academy of Continuous Professional Education, Ministry of Health of Russia, 2/1 Barricadnaiay Str., Bldg. 1, 125993 Moscow, Russia
[4] Konchalovsky City Clinical Hospital, Moscow City Health Department, 2 Kashtanovaya alley, bld. 1,124489 Moscow, Zelenograd, Russia

For citation: *Ivan V. Sergeev, Marina V. Petrova, Alexander E. Shestopalov, Mikhail M. Kanarsky, Oleg B. Lukyanets, Irina A. Yarotskaya, Yulia Yu. Nekrasova.* Nutritional Status of Patients with Chronic Critical Illness. *Obshchaya Reanimatologiya = General Reanimatology.* 2023; 19 (4): 4–11. https://doi.org/10.15360/1813-9779-2023-4-2329 [In Russ. and Engl.]

***Correspondence to:** Ivan V. Sergeev, dr.1vansergeev@yandex.ru

Summary

Objective: to assess the nutritional status of patients with chronic critical illness.

Material and methods. We examined 23 patients with chronic critical illness who were in a minimally conscious state (MCS) with 10.9±2.5 scores on the FOUR (Full Outline of Unresponsiveness) Score Coma Scale. Indicators of carbohydrate, lipid, protein and energy exchange metabolism were evaluated using specimens sampled in the morning hours. Nutritional support was provided by isocaloric isonitrogenic mixtures.

Results. Blood biochemistry showed decreases in total protein and albumin levels in 86.9% and 91.3% of patients, respectively. The tests also revealed decreased concentrations of several amino acids, including essential amino acids: histidine (38.3±13.07 μmol/L), methionine (12.68±3.81 μmol/L), threonine (61.6 [58.5; 87.7] μmol/L), tryptophan (33.06±15.95 μmol/L), and non-essential amino acids: arginine (40.50 [22.2; 46.9] μmol/L), glutamic acid (124.5±39.29 μmol/L), tyrosine (37.97±10.12 μmol/L). Some correlations between the concentrations of individual amino acids and other indicators were revealed, such as histidine and CRP (r=–0.68, P=0.043), tryptophan and CRP (r=–0.86, P=0.002), histidine and leukocyte count (r=–0.76, P=0.015), methionine and lysine (r=0.88, P=0.008), methionine and patient's weight (r=–0.68, P=0.042). A relationship between threonine concentration and the level of consciousness on the FOUR scale (r=–0.73, P=0.037) was also found. All patients demonstrated significant alterations of carbohydrate and lipid metabolism.

Conclusion. Alteration of adequate protein metabolism seems to be the most affected constituent in the nutritional status of patients with chronic critical illness. It is manifested by a decrease in the concentration of total protein and a number of essential and non-essential amino acids, which implies the importance of high-protein nutritional support and correction of the amino acid profile.

Keywords: nutritional status; critical illness; protein metabolism; amino acid profile; amino acids; prolonged disturbance of consciousness

Conflict of interest. The authors declare no conflict of interest.

Introduction

The number of patients surviving critical illness caused by exposure to a significant damaging factor is steadily rising due to advancements in medical care, the development of new technologies and equipment, as well as manipulations and therapies. Unfortunately, the prevalence of late complications and prolonged critical illness (PCI), which is linked to a lower quality of life and a less effective rehabilitation, is also rising [1].

The most frequent side effects of prolonged ICU stays are muscular and neurological deficits, which increase the risk of chronic critical illness and poor outcomes in this patient population [2].

Many patients with intact consciousness still experience respiratory problems, muscle weakness, and decreased exercise tolerance years after being discharged from the intensive care unit. Psychological issues like depression, sexual dysfunction, and social isolation frequently coexist with the medical conditions in these patients [3, 4].

This extensive list of symptoms and conditions is known as post-intensive care (PIC) syndrome [5].

As a result, many patients leave the unit for only a brief time because of commonly required readmission [6].

Further investigation is needed into the predictors, treatment, and, most importantly, prevention of PIC syndrome and chronic critical illness.

Adequate nutritional support is one of the most important aspects of therapy. Unfortunately, the optimal nutritional support strategy in the ICU remains an unsolved issue. There are numerous guidelines on nutritional support for patients written by ESPEN (European Society of Parenteral and Enteral Nutrition), ASPEN (American Society of Parenteral and Enteral Nutrition), RSPEN (Russian National Association of Clinical Nutrition and Metab-

olism), and other national organizations, but their implementation in clinical practice remains difficult [7–9]. The choice of the proper nutritional support is further complicated by the quantitative and qualitative variations in metabolite levels that depend on the type of prolonged disorders of consciousness and circadian phases [10].

Current international clinical guidelines favor enteral nutrition (EN) for critically ill patients when feasible. The physiological benefits, side effects of parenteral nutrition (PN), and increased cost of PN have led to the dominance of the EN concept. Often, EN alone is not sufficient to provide adequate energy and substrate to the patient, especially in the critically ill, due to the severity of illness and energy cost, marked catabolism, and gastrointestinal dysfunction [11–13].

It is important to maintain adequate levels of precursors of large molecules other than macronutrients, such as proteins, fats, and carbohydrates, which play an equally important role in ensuring adequate levels of metabolism, transition from catabolism to anabolism, and improved outcomes. In particular, an adequate supply of amino acids, which are components of protein structures, helps to reduce inflammation and loss of muscle mass, and increases resistance to oxidative stress [14].

In addition to macronutrients, micronutrients are also important in correcting protein-energy deficiencies. The necessity of micronutrient administration is determined by their participation in the normal functioning of cells and molecular structures. The presence of antioxidant properties in some micronutrients is extremely important, as their deficiency can provoke oxidative stress, especially in critical illness [15]. Oxidative stress, in turn, plays a crucial role in the pathophysiology of critical illnesses such as acute respiratory distress syndrome, reperfusion syndrome, and multiorgan failure [16].

It is important to emphasize that there are still problems in formulating a fully balanced amino acid solution for parenteral nutrition. In particular, all parenteral nutrition formulations do not contain sufficient concentrations of cysteine because it is not stable in solution [17]. Providing adequate concentrations of tyrosine and glutamine is also challenging due to their poor solubility. N-acetylated tyrosine, a water-soluble derivative of tyrosine, is used in some amino acid solutions, but this is associated with side effects because it takes a long time to convert to tyrosine in humans and is poorly reabsorbed by the kidneys [18].

At present, solutions containing some amino acids are unbalanced due to the unique characterstics of their metabolism. Thus, the adequate maintenance and supply of protein to a critically ill patient remains both a scientific and clinical problem.

In this regard, the dynamic control of macro- and micronutrients in patients throughout all stages of treatment may represent a necessary approach to adequate nutritional support.

The aim of this study was to evaluate the nutritional status of chronically critically ill patients.

Materials and Methods

An observational, prospective, single-center study included chronically critically ill patients after severe brain injury treated in the intensive care units of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (FRCCICMR) in 2022. The patients' condition was assessed during the first 3 days after admission for treatment and rehabilitation.

The study was approved by the Ethics Committee of the FRCCICMR, protocol 4/21/9 dated 29.09.2021.

The study included 23 chronically critically ill patients with a mean age of 46.91±15.09 years, ranging from 24 to 79 years. The age of most patients ranged from 30 to 60 years.

Among the patients, 12 were male (52%) and 11 were female (48%).

The level of consciousness according to the FOUR (Full Outline of Unresponsiveness) scale was 10.9±2.5 points.

Inclusion criteria were

- time from exposure to the initial damaging factor to admission to the FRCCICMR units more than 30 days;
- minimal consciousness;
- breathing through a tracheostomy tube.

Exclusion criteria were:

- vasopressor or intravenous support;
- drug sedation;
- hepatic or renal failure;
- diabetes mellitus.

All patients received isocaloric isonitrogenous formulas. The mean caloric intake was 1673.91±243.49 kcal/day, with protein 1.2±0.12 g/kg/day, carbohydrate 3.1±0.38 g/kg/day, and fat 1.01±0.12 g/kg/day.

Patient assessment protocol:

1. Anthropometric measurements (height, weight, body mass index calculation).

2. Complete blood count parameters (hemoglobin, red blood cells, white blood cells, WBC differential, platelets).

3. Serum biochemistry (total protein, albumin, glucose, cholesterol, triglycerides, C-reactive protein).

4. Amino acid profile: alanine (Ala), alpha-aminobutyric acid (Aba), arginine (Arg), asparagic acid (Asp), asparagine (Asn), citrulline (Cit), gamma-aminobutyric acid (GABA), glutamic acid (Glu), glutamine (Gln), glycine (Gly), histidine (His), hydroxyproline (Hyp), isoleucine (Ile), leucine (Leu), lysine (Lys), methionine

Table 1. Biochemical parameters of patients

Parameter	Values		Reference range	Number of patients with values outside the reference range, *N* (%)
	M±*m* / *Me* [*Q1*; *Q3*]	min–max		
Total protein, g/L	54.61±7.77	40.3–70.7	66.0–83.0	20 (86.9)
Albumin, g/L	29.88±5.2	22.3–38.8	35.0–52.0	21 (91.3)
Glucose, mmol/L	5.87 [5.3; 6.4]	3.56–9.0	4.1–5.9	5 (21.7)
Triglycerides, mmol/L	1.46±0.73	0.66–2.6	0.0–1.7	7 (30.4)
Total cholesterol, mmol/L	3.61±0.94	1.62–5.28	0.0–5.2	1 (4.3)

(Met), ornithine (Orn), phenylalanine (Phe), pipecolic acid (PA), proline (Pro), sarcosine (Sar), threonine (Thr), tryptophan (Trp), tyrosine (Tyr), valine (Val).

Calculation of Glu/Gln index.

5. Daily urinary nitrogen losses and nitrogen balance.

Biochemical parameters were measured by AU480 biochemical analyzer (Beckman Coulter, USA), blood was taken from patients at 6:00 am.

Blood amino acid concentration was measured by AB Sciex QTRAP 5500 (AB Sciex, Concord, ON, Canada).

Indirect calorimetry was performed using a Medgraphics Ultima CPX gas exchange analyzer (MGC Diagnostics Corporation, USA).

Daily urinalysis to determine nitrogen losses was performed on an AU480 analyzer (Beckman Coulter, USA). Due to the presence of non-urea nitrogen losses with urine, its excretion with stool and through the skin, 4 g were added to the obtained values [19].

The data obtained were analyzed using Statistica 12.5 software (TIBCO Software, USA).

Normality of the distribution was checked using the Shapiro-Wilk criterion. For data with normal distribution, values were presented as mean±standard deviation, otherwise median and 1 and 3 quartiles were reported.

Correlations with normal distribution were evaluated by Pearson's test. For non-normal distribution, Spearman's criterion was used. The results of statistical analysis were considered significant at $P \leqslant 0.05$.

Results

A decrease in the levels of total protein and albumin was found in almost 90% of the studied patients (Table 1). Abnormal triglyceride, cholesterol and glucose levels were observed in almost 30% of patients.

According to indirect calorimetry, the level of resting energy expenditure was 1400.5±370.0 kcal/day, with a positive nitrogen balance of 4.25±2.05 g/day.

The amino acid profile indicated a reduction in the levels of several essential amino acids, including histidine, methionine, threonine, and tryptophan. Moreover, there was a decrease in the levels of non-essential amino acids, with arginine, glutamic acid, and tyrosine being notably affected (Table 2).

Table 2. Amino acid profile of patients

Parameter	Values		Reference range	Number of patients with values outside the reference range, *N* (%)
	M±*m* / *Me* [*Q1*; *Q3*]	min–max	значения	
Alanine, μmol/L	210.4±82.88	80.3–344.1	160.0–530.0	5 (21.7)
Alpha–aminobutyric acid, μmol/L	17.80 [8.6;18.5]	6.6–19.9	10.2–40.1	10 (43.5)
Arginine, μmol/L	40.50 [22.2;46.9]	16.0–107.2	35.0–125.0	10 (43.5)
Asparagic acid, μmol/L	16.10 [14.3; 16.4]	10.6–28.4	<15.0	8 (34.8)
Asparagine, μmol/L	36.4±12.83	19.7–61.2	20.0–80.0	3 (13)
Citrulline, μmol/L	15.8±5.93	8.9–26.3	21.4–48.8	18 (78.3)
Gamma–aminobutyric acid, μmol/L	0.4±0.2	0.0–0.6	0.0–5.0	0 (0)
Glutamic acid, μmol/L	124.5±39.29	72.6–178.2	15.0–130.0	10 (43.5)
Glutamine, μmol/L	515.78±127.96	337.0–703.0	311.6–732.2	0 (0)
Glycine, μmol/L	260.76±45.47	199.80–348.5	140.0–420.0	0 (0)
Histidine, μmol/L	38.3±13.07	22.1–56.5	52.8–88.5	20 (86.9)
Hydroxyproline, μmol/L	9.40 [7.5; 9.6]	2.5–24.2	5.0–40.0	3 (13)
Isoleucine, μmol/L	55.36±17.23	32.0–84.4	30.0–120.0	0 ()
Leucine, μmol/L	92.46±22.06	58.9–117.7	60.0–180.0	3 (13)
Lysine, μmol/L	131.87±42.81	80.0–220.8	85.0–230.0	5 (21.7)
Methionine, μmol/L	12.68±3.81	7.5–19.3	15.0–40.0	18 (78.3)
Ornithine, μmol/L	56.48±22.02	33.9–100.6	25.0–110.0	0 (0)
Phenylalanine, μmol/L	47.96±15.21	30.1–73.0	25.0–80.0	0 (0)
Pipecolic acid, μmol/L	0.60 [0.5; 1.3]	0.5–5.3	<3.1	3 (13)
Proline, μmol/L	116.63±33.54	74.7–182.4	90.0–350.0	5 (21.7)
Sarcosine, μmol/L	8.92±1.63	5.7–11.1	2.0–19.4	0 (0)
Serine, μmol/L	98.06±27.47	50.2–130.3	60.0–170.0	5 (21.7)
Threonine, μmol/L	61.6 [58.5; 87.7]	53.5–243.6	67.2–211.1	15 (65.2)
Tryptophan, μmol/L	33.06±15.95	10.5–52.5	25.0–80.0	10 (43.5)
Tyrosine, μmol/L	37.97±10.12	22.7–53.7	35.0–110.0	13 (56.5)
Valine, μmol/L	155.91±36.71	102.2–206.2	120.0–320.0	5 (21.7)
Glutamic acid / Glutamine	0.25±0.1	0.141–0.466	0.22–0.88	10 (43.5)

We identified correlations between the lowest amino acid levels and other patient data. We observed a negative relationship between histidine levels and CRP concentration (r=–0.68, P=0.043), as well as with WBC count (r=–0.76, P=0.015). There was a strong association between methionine and lysine (r=0.88, P=0.008), and between methionine and patient weight (r=0.68, P=0.042). Furthermore, we observed a weaker negative association between threonine and the level of consciousness on the FOUR scale (r=–0.73, P=0.037). Additionally, a negative relationship was found between tryptophan and CRP levels (r=–0.86, P=0.002).

Discussion

We found significant abnormalities in the amino acid profile, indicating a predominant disturbance in protein metabolism in chronically critically ill (CCI) patients.

We would like to pay special attention to the amino acids whose levels were reduced more than others.

Citrulline is almost entirely produced by intestinal cells and its plasma level is regarded as a biomarker of the functional capacity of small intestinal enterocytes. Given the existing protein-energy deficiency in CCI patients and the inability to correct it through adequate enteral administration of both micro- and macronutrients, the decrease in citrulline concentration suggests impaired absorption of these elements. Because citrulline is converted into arginine in the kidneys, which play a crucial role in the regulation of citrulline metabolism, an increase in citrulline may also be a sign of renal failure. There was no evidence of renal failure in the patients studied [20, 21].

The kidneys metabolize 83 percent of all citrulline absorbed from the intestine, «consuming» about 1.5 g of citrulline from the blood per day, or about 35 percent of total circulating citrulline [22]. The kidneys can provide all the arginine the body needs, given adequate renal function and citrulline intake. An increase in muscle protein synthesis was observed in a study of aged mice given citrulline, suggesting that it may directly stimulate protein synthesis in myofibrils and sarcoplasm [23]. Furthermore, oral citrulline supplementation of healthy subjects increased muscle protein synthesis even when they were consuming a low protein diet compared to an isonitrogenic diet group [24]. Therefore, supplementation with this amino acid appears promising in CCI patients.

Another deficient amino acid was histidine, which plays an important role in nutritional status by participating in iron binding to hemoglobin and myoglobin and by being an active regulatory component of metalloenzymes (anhydrase, cytochromes, etc.). The histidine-rich glycoprotein present in the plasma of vertebrates is essential for the immune function [25].

Histidine deficiency does not involve a sudden development of negative nitrogen balance. Instead, the body compensates for histidine deficiency by activating the catabolism of hemoglobin and muscle tissue resulting in their decrease [26]. In earlier studies conducted at FRCCICMR, a decrease in iron levels and also a severe reduction in muscle mass in patients with severe brain injury were noted, which may also be due to low histidine levels [27].

Histidine has an important role in maintaining a positive nitrogen balance, but after a longer period of time, which has been demonstrated in both mice and humans. For example, a prolonged deficiency followed by a histidine-rich diet has been shown to increase nitrogen balance parameters even with a low-protein diet [28].

Methionine is an essential amino acid and although it is essential for survival, its limited intake in mammals results in beneficial effects such as reduced likelihood of obesity, increased insulin sensitivity, decreased inflammation and oxidative stress, and ultimately increased survival [29].

Protein-bound methionine and its oxidized form, methionine sulfoxide, play an important role in regulating the antioxidant system as a buffer, although elevated methionine sulfoxide is considered undesirable and associated with decreased survival. Activation of sulfoxidation upregulates various transcription factors in response to a stimulus, modulating the activity of signaling protein kinases and cytoskeletal changes. Mutual conversion of methionine and methionine sulfoxide provides stability of proteins and their interactions [30, 31].

The observed decrease in methionine levels in CCI patients may reflect the characteristic severe dysfunction of many organs and systems.

Threonine is necessary to ensure optimal development and function of the animal's immune system. The function of the intestinal wall, its ability to digest and absorb nutrients, and the normal performance of the intestinal cell barrier are critically dependent on an adequate intake of threonine. Both deficiency and excess of threonine can have negative effects on the immune and digestive systems. In addition, threonine plays an important role in neuropsychiatric health, adequate response to physiological stress, and anti-inflammatory response [32]. The observed decrease in threonine, as well as citrulline, in CCI patients may indicate digestive disorders.

Tryptophan is also important for nutritional status, and both its elevation and depletion can have negative consequences due to the production of toxic metabolites from excessive tryptophan oxidation. Tryptophan is one of three aromatic amino acids, along with phenylalanine and tyrosine. These amino

acids have potent antioxidant effects [33]. According to some studies, when tryptophan metabolism is activated through the kynurenine pathway, the activity of chronic inflammation increases [34, 35].

The kynurenine/tryptophan ratio is a biomarker of age-related changes. It is known to increase with age, with tryptophan decreasing and kynurenine increasing [36]. Given the observed low tryptophan level, we can assume the activation of chronic inflammation in the studied patients, which is also evidenced by the increased CRP concentration (55.6± 39.5 mg/l) and WBC count (8.8±4.7 thousand) compared to reference values.

Arginine turnover depends on citrulline metabolism and their concentrations are closely correlated. Arginine is implicated in the regulation of vascular tone and is a metabolite involved in the production of nitric oxide by the vascular endothelium [37]. Prolonged plasma arginine deficiency leads to oxidative stress, degradation of intracellular arginine and inhibition of its production from the precursor citrulline, resulting in vasospasm due to insufficient nitric oxide formation [38]. In addition, arginine plays an important protective role in ammonia metabolite intoxication and participates in muscle development [39]. Correction of low citrulline levels in CCI patients may be required before restoring arginine levels.

Glutamate (glutamic acid) is essential for mammalian brain function. It is both an excitatory neurotransmitter and a precursor of the inhibitory neurotransmitter gamma-aminobutyric acid, an important structural component of proteins, an energy substrate, and can also be a neurotoxin [40]. It appears that the decrease in the concentration of this amino acid is due to impaired neurotransmitter metabolism and nervous system regulation.

Tyrosine is produced from phenylalanine. Due to its special structure, it is able to be both an electron and proton donor in the reactions of enzyme metabolism and therefore can be found in the active part of many enzymes, both oxidases and reductases [41]. Studies have found that additional tyrosine supplementation reduces the risk of developing type 2 diabetes and also affects the functioning of neurotransmitters such as dopamine [42]. Reduced tyrosine level with no decrease in phenylalanine in CCI patients could indicate a greater expenditure of tyrosine for the formation and functioning of enzymes, and their greater loss is due to the existing chronic inflammation and dysregulation of organs and systems resulting from brain disorders.

High plasma glutamate concentrations and elevated glutamate-to-glutamine ratios are associated with an increased risk of heart failure, cancer, immunodeficiency virus infection, and indicate a risk of loss of cell mass in healthy individuals [43, 44]. Glutamate potentiates oxidative stress and induces apoptosis, whereas glutamine is involved in myocardial metabolism and exerts potent antioxidant and anti-inflammatory effects by inducing the expression of hemoxygenase-1, heat shock proteins (HSP) and glutathione [45, 46]. Glutamate and glutamine are also involved in energy metabolism. Low values of their ratio indicate the possibility of hyperammonemia or vitamin B1 deficiency [47, 48].

Lack of predetermined sample size was the limitation of our study.

Conclusion

The study found that the most common defect in the nutritional status of chronically critically ill patients is inadequate protein metabolism. No significant disturbances in carbohydrate or lipid metabolism were observed.

Abnormal levels of both essential and non-essential amino acids were also revealed, suggesting the importance of protein-rich nutritional support and correction of the amino acid profile.

References

1. *Wischmeyer P.E., San-Millan I.* Winning the war against CU-acquired weakness: new innovations in nutrition and exercise physiology. *Crit Care.* 2015; 19 Suppl 3 (Suppl 3): S6. DOI: 10.1186/cc14724. PMID: 26728966.
2. *Desai S.V., Law T.J., Needham D.M.* Long-term complications of critical care. *Crit Care Med.* 2011; 39 (2): 371–379. DOI: 10.1097/CCM.0b013e3181fd66e5. PMID: 20959786.
3. *Herridge M.S., Tansey C.M., Matté A., Tomlinson G., Diaz-Granados N., Cooper A., Guest C.B., et al.*; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 2011; 364 (14): 1293–1304. DOI: 10.1056/NEJMoa1011802. PMID: 21470008.
4. *Cheung A.M., Tansey C.M., Tomlinson G., Diaz-Granados N., Matté A., Barr A., Mehta S., et al.* Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006; 174 (5): 538–544. DOI: 10.1164/rccm.200505-693OC. PMID: 16763220.
5. *Needham D.M., Davidson J., Cohen H., Hopkins R.O., Weinert C., Wunsch H., Zawistowski C., et al.* Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med.* 2012; 40 (2): 502–509. DOI: 10.1097/CCM.0b013e318232da75. PMID: 21946660.
6. *Puthucheary, Z.A., Rawal, J., McPhail, M., Connolly B., Ratnayake G., Chan P., Hopkinson N. S., et al.* Acute skeletal muscle wasting in critical

illness. *JAMA*. 2013; 310 (15): 1591–1600. DOI: 10.1001/jama.2013.278481. PMID: 24108501.
7. *Singer P., Blaser A.R., Berger M.M., Alhazzani W., Calder P.C., Casaer M.P., Hiesmayr M., et al.* ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019; 38 (1): 48–79. DOI: 10.1016/j.clnu.2018.08.037. PMID: 30348463.
8. *McClave S.A., Taylor B.E., Martindale R.G., Warren M.M., Johnson D.R., Braunschweig C., McCarthy M.S., et al.;* Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. 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*. 2016; 40 (2): 159–211. DOI: 10.1177/0148607115621863. PMID: 26773077.
9. *Mooi N.M., Ncama B.P.* Evidence on nutritional therapy practice guidelines and implementation in adult critically ill patients: a systematic scoping review. *Curationis*. 2019; 42 (1): e1–e13. DOI: 10.4102/curationis.v42i1.1973. PMID: 31833375.
10. *Орлова А.А., Кондратьева Е.А., Дубровский Я.А., Дрягина Н.В., Вербицкая Е.В., Кондратьев С.А., Костарева А.А., и др.* Метаболомное профилирование крови пациентов с хроническим нарушением сознания. *Общая реаниматология*. 2022; 18 (2): 22–36. [*Orlova A.A., Kondrat'eva E.A., Dubrovskii Y.A., Dryagina N.V., Verbitskaya E.V., Kondratev S.A., Kostareva A.A.,et al.* Metabolomic profiling of the blood of patients with chronic consciousness disorders. *General Reanimatology/ Obshchaya Reanimatologya*. 2022; 18 (2): 22–36. (In Russ.).] DOI: 10.15360/1813-9779-2022-2-22-36.
11. *Heyland D.K., Schroter-Noppe D., Drover J.W., Jain M., Keefe L., Dhaliwal R., Day A.* Nutrition support in the critical care setting: current practice in Canadian ICUs-opportunities for improvement? *JPEN J Parenter Enteral Nutr*. 2003; 27 (1): 74–83. DOI: 10.1177/014860710302700174. PMID: 12549603.
12. *Hill A., Heyland D.K., Ortiz Reyes L.A., Laaf E., Wendt S., Elke G., Stoppe C.* Combination of enteral and parenteral nutrition in the acute phase of critical illness: an updated systematic review and meta-analysis. *JPEN J Parenter Enteral Nutr*. 2022; 46 (2): 395–410. DOI: 10.1002/jpen.2125 PMID: 33899951.
13. *Пасечник И.Н.* Нутритивная поддержка больных в критических состояниях (обзор). *Общая реаниматология*. 2020; 16 (4): 40–59. *[Pasechnik I.N.* Nutritional support for critically ill patients (Review). *General Reanimatology / Obshchaya Reanimatologya*. 2020; 16 (4): 40–59. (In Russ.)]. DOI: 10.15360/1813-9779-2020-4-40-59.
14. *Wandrag L., Brett S.J., Frost G., Hickson M.* Impact of supplementation with amino acids or their metabolites on muscle wasting in patients with critical illness or other muscle wasting illness: a systematic review. *J Hum Nutr Diet*. 2015; 28 (4): 313–330. DOI: 10.1111/jhn.12238. PMID: 24807079.
15. *Bailey R.L., West K.P. Jr, Black R.E.* The epidemiology of global micronutrient deficiencies. *Ann Nutr Metab*. 2015; 66 Suppl 2: 22-33. DOI: 10.1159/000371618. PMID: 26045325.
16. *Koekkoek W.A.C.K., van Zanten A.R.H.* Antioxidant vitamins and trace elements in critical illness. *Nutr Clin Pract*. 2016; 31 (4): 457–474. DOI: 10.1177/0884533616653832. PMID: 27312081.
17. *Yarandi S.S., Zhao V.M., Hebbar G., Ziegler T.R.* Amino acid composition in parenteral nutrition: what is the evidence? *Curr Opin Clin Nutr Metab Care*. 2011; 14 (1): 75–82. DOI: 10.1097/MCO.0b013e328341235a. PMID: 21076291
18. *Hoffer L.J., Sher K., Saboohi F., Bernier P., MacNamara E.M., Rinzler D.* N-acetyl-L-tyrosine as a tyrosine source in adult parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2003; 27 (6): 419–422. DOI: 10.1177/0148607103027006419. PMID: 14621123.
19. *Mackenzie T.A., Clark N.G., Bistrian B.R., Flatt J.P., Hallowell E.M., Blackburn G.L.* A simple method for estimating nitrogen balance in hospitalized patients: a review and supporting data for a previously proposed technique. *J Am Coll Nutr*. 1985; 4 (5): 575–581. DOI: 10.1080/07315724. 1985.10720100. PMID: 3932497.
20. *Crenn P., Messing B., Cynober L.* Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. *Clin Nutr*. 2008; 27 (3): 328–339. DOI: 10.1016/j.clnu.2008.02.005. PMID: 18440672.
21. *Crenn P., Cynober L.* Effect of intestinal resections on arginine metabolism: practical implications for nutrition support. *Curr Opin Clin Nutr Metab Care*. 2010; 13 (1): 65–69. DOI: 10.1097/MCO.0b013e328333c1a8. PMID: 19915459.
22. *van de Poll M.C.G., Soeters P.B., Deutz N.E.P., Fearon K.C.H., Dejong C.H.C.* Renal metabolism of amino acids: its role in interorgan amino acid exchange. *Am J Clin Nutr*. 2004; 79 (2): 185–197. DOI: 10.1093/ajcn/79.2.185. PMID: 14749222.
23. *Osowska S., Duchemann T., Walrand S., Paillard A., Boirie Y., Cynober L., Moinard C.* Citrulline modulates muscle protein metabolism in old malnourished rats. *Am J Physiol Endocrinol Metab*. 2006; 291 (3): E582–E586. DOI: 10.1152/ajpendo.00398.2005. PMID: 16608884.

24. *Jourdan M., Nair K.S., Carter R.E., Schimke J., Ford G.C., Marc J., Aussel C., et al.* Citrulline stimulates muscle protein synthesis in the post-absorptive state in healthy people fed a low-protein diet — a pilot study. *Clin Nutr.* 2015; 34 (3): 449–456. DOI: 10.1016/j.clnu.2014.04.019. PMID: 24972455.
25. *Poon I.K., Patel K.K., Davis D.S., Parish C.R., Hulett M.D.* Histidine-rich glycoprotein: the Swiss Army knife of mammalian plasma. *Blood.* 2011; 117 (7): 2093–2101. DOI: 10.1182/blood-2010-09-303842. PMID: 20971949.
26. *Сергеев И.В., Петрова М.В., Шестопалов А.Е., Радутная М.Л., Хижняк Т.И., Ветшева М.С., Лукьянец О.Б. и др.* Саркопения у пациентов после тяжелых повреждений головного мозга. *Неотложная медицинская помощь. Журнал им. Н.В. Склифосовского.* 2022; 11 (3): 402–411. [*Sergeev I.V, Petrova M.V, Shestopalov A.E, Radutnaya M.L, Khizhniak T.I, Vetsheva M.S, Lukyanets O.B, et al.* Sarcopenia in patients after severe brain injury. *Russian Sklifosovsky Journal «Emergency Medical Care» / Zhurnal im. N.V. Sklifosovskogo «Neotlozhnaya Meditsinskaya Pomoshch»*. 2022; 11 (3): 402–411. (In Russ.)]. DOI: 10.23934/2223-9022-2022-11-3-402-411
27. *Петрова М.В., Сергеев И.В., Шестопалов А.Е., Лукьянец О.Б.* Метаболические нарушения у пациентов, находящихся в хроническом критическом состоянии, обусловленном последствиями черепно-мозговой травмы. *Вопросы питания.* 2021; 90 (4): 103–111. [*Petrova M.V., Sergeev I.V., Shestopalov A.E., Lukyanets O.B.* Metabolic disorders of chronically critically ill patients caused by consequences of traumatic brain injury. *Problems of Nutrition / Voprosy pitaniia.* 2021; 90 (4): 103–111. (In Russ.)]. DOI: 10.33029/0042-8833-2021-90-4-103-111.
28. *Cho E.S., Anderson H.L., Wixom R.L., Hanson K.C., Krause G.F.* Long-term effects of low histidine intake on men. *J Nutr.* 1984; 114 (2): 369–384. DOI: 10.1093/jn/114.2.369. PMID: 6693997.
29. *Wanders D, Hobson K, Ji X.* Methionine restriction and cancer biology. *Nutrients.* 2020; 12(3): 684. DOI: 10.3390/ nu12030684 PMID: 32138282.
30. *Drazic A., Miura H., Peschek J., Le Y., Bach N.C., Kriehuber T., Winter J.* Methionine oxidation activates a transcription factor in response to oxidative stress. *Proc Natl Acad Sci U S A.* 2013; 110 (23): 9493–9498. DOI: 10.1073/pnas.1300578110. PMID: 23690622.
31. *Aledo J.C.* The role of methionine residues in the regulation of liquid-liquid phase separation. *Biomolecules.* 2021; 11 (8): 1248. DOI: 10.3390/biom11081248. PMID: 34439914.
32. *Mao X., Zeng X., Qiao S., Wu G., Li D.* Specific roles of threonine in intestinal mucosal integrity and barrier function. *Front Biosci (Elite Ed).* 2011; 3 (4): 1192–1200. DOI: 10.2741/ e322. PMID: 21622125.
33. *Yusufu I., Ding K., Smith K., Wankhade U.D., Sahay B., Patterson G.T., Pacholczyk R., et al.* Tryptophan-deficient diet induces gut microbiota dysbiosis and increases systemic inflammation in aged mice. *Int J Mol Sci.* 2021; 22 (9): 5005. DOI: 10.3390/ijms22095005. PMID: 34066870.
34. *Cervenka I., Agudelo L.Z., Ruas J.L.* Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health. *Science.* 2017; 357 (6349): eaaf9794. DOI: 10.1126/science. aaf9794. PMID: 28751584
35. *Franceschi C., Garagnani P., Parini P., Giuliani C., Santoro A.* Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol.* 2018; 14 (10): 576–590. DOI: 10.1038/s41574-018-0059-4. PMID: 30046148.
36. *Sorgdrager F.J.H., Naudé P.J.W., Kema I.P., Nollen E.A., Deyn P.P.* Tryptophan metabolism in inflammaging: from biomarker to therapeutic target. *Front Immunol.* 2019; 10: 2565. DOI: 10.3389/fimmu.2019.02565. PMID: 31736978.
37. *Berkowitz D.E., White R., Li D., Minhas K.M., Cernetich A., Kim S., Burke S., et al.*. Arginase reciprocally regulates nitric oxide synthase activity and contributes to endothelial dysfunction in aging blood vessels. *Circulation.* 2003; 108 (16): 2000–2006. DOI: 10.1161/01.CIR.0000092948.04444.C7. PMID: 14517171.
38. *Rashid J., Kumar S.S., Job K.M., Liu X., Fike C.D., Sherwin C.M.T.* Therapeutic potential of citrulline as an arginine supplement: a clinical pharmacology review. *Paediatr Drugs.* 2020; 22 (3): 279–293. DOI: 10.1007/s40272-020-00384-5. PMID: 32140997.
39. *Meijer A.J., Lamers W.H., Chamuleau R.A.* Nitrogen metabolism and ornithine cycle function. *Physiol Rev.* 1990; 70 (3): 701–748. DOI: 10.1152/physrev.1990.70.3.701. PMID: 2194222.
40. *Bak L.K., Schousboe A., Waagepetersen H.S.* The glutamate/ GABA-glutamine cycle: aspects of transport, neurotransmitter homeostasis and ammonia transfer. *J Neurochem.* 2006; 98 (3): 641–653. DOI: 10.1111/j.1471-4159.2006.03913.x. PMID: 16787421.
41. *Yu Y., Lv X., Li J., Zhou Q., Cui C., Hosseinzadeh P., Mukherjee A., et al.* Defining the role of tyrosine and rational tuning of oxidase activity by genetic incorporation of unnatural tyrosine analogs. *J Am Chem Soc.* 2015; 137 (14): 4594–4597. DOI: 10.1021/ja5109936. PMID: 25672571.
42. *Jäger S., Cuadrat R., Wittenbecher C., Floegel A., Hoffmann P., Prehn C., Adamski J., et al.* Mendelian randomization study on amino acid

metabolism suggests tyrosine as causal trait for type 2 diabetes. *Nutrients*. 2020; 12 (12): 3890. DOI: 10.3390/nu12123890. PMID: 33352682.

43. *Papandreou C., Hernández-Alonso P., Bulló M., Ruiz-Canela M., Li J., Guasch-Ferré M., Toledo E., et al.* High plasma glutamate and a low glutamine-to-glutamate ratio are associated with increased risk of heart failure but not atrial fibrillation in the Prevención con Dieta Mediterránea (PREDIMED) study. *J Nutr*. 2020; 150 (11): 2882–2889. DOI: 10.1093/jn/ nxaa273. PMID: 32939552.
44. *Wang X., Yang R., Zhang W., Wang S., Mu H., Li H., Dong J., et al.* Serum glutamate and glutamine-to-glutamate ratio are associated with coronary angiography defined coronary artery disease. *Nutr Metab Cardiovasc Dis*. 2022; 32 (1): 186–194. DOI: 10.1016/j.numecd.2021.09.021. PMID: 34906414.
45. *Ramadan S., Lin A., Stanwell P.* Glutamate and glutamine: a review of in vivo MRS in the human brain. *NMR Biomed*. 2013; 26 (12): 1630–1646. DOI: 10.1002/nbm.3045. PMID: 24123328.
46. *Kimura M., Oda Y., Hirose Y., Kimura H., Yoshino K., Niitsu T., Kanahara N., et al.* Upregulation of heat-shock protein HSP-70 and glutamate transporter-1/glutamine synthetase in the striatum and hippocampus in haloperidol-induced dopamine-supersensitivity-state rats. *Pharmacol Biochem Behav*. 2021; 211: 173288. DOI: 10.1016/j.pbb.2021.173288. PMID: 34653399.
47. *Цепкова П.М., Артюхов А.В., Бойко А.И., Алешин В.А., Мкртчян Г.В., Звягинцева М.А., Рябов С.И., и др.* Тиамин индуцирует долгосрочные изменения аминокислотного профиля и активностей дегидрогеназ 2-оксоадипата и 2-оксоглутарата мозга крысы. *Биохимия*. 2017; 82 (6): 954–969. *[Tsepkova P.M., Artiukhov A.V., Boyko A.I., Aleshin V.A., Mkrtchyan G.V., Zvyagintseva M.A., Ryabov S.I., et al.* Thiamine induces long-term changes in amino acid profiles and cctivities of 2-oxoglutarate and 2-oxoadipate dehydrogenases in rat brain. *Biochemistry (Mosc)*. 2017; 82 (6): 723–736. (In Russ.)]. DOI: 10.1134/S0006297917060098. PMID: 28601082
48. *Cooper A.J.L, Jeitner T.M.* Central role of glutamate metabolism in the maintenance of nitrogen homeostasis in normal and hyperammonemic brain. *Biomolecules*. 2016; 6 (2): 16. DOI: 10.3390/biom6020016. PMID: 27023624.

Received 19.03.2023
Accepted 22.06.2023