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Diagnostic and Prognostic Value of Hyperammonemia in Patients with Liver Cirrhosis, Hepatic Encephalopathy, and Sarcopenia (Experts' Agreement)

Maria Yu. Nadinskaia[1]*, Marina V. Maevskaya[1], Igor G. Bakulin[2], Elena N. Bessonova[3], Alexey O. Bueverov[1,4], Maria S. Zharkova[1], Sergey V. Okovityi[5], Anna S. Ostrovskaya[1], Kseniya A. Gulyaeva[1], Vladimir T. Ivashkin[1]

[1] *I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation*
[2] *North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russian Federation*
[3] *Sverdlovsk Regional Clinical Hospital No. 1, Yekaterinburg, Russian Federation*
[4] *M.F. Vladimirsky Moscow Regional Research and Clinical Institute, Moscow, Russian Federation*
[5] *Saint Petersburg State Chemical Pharmaceutical University, Saint Petersburg, Russian Federation*

Introduction. In cirrhotic patients, hyperammonemia develops due to impaired ammonia detoxification and portosystemic blood shunting and is most commonly associated with hepatic encephalopathy and sarcopenia. Currently, there are questions regarding the diagnosis of hyperammonemia and the effect of ammonia-lowering therapy on disease outcomes.
Materials and methods. The Russian Scientific Liver Society selected a panel of seven experts in liver cirrhosis research and management of patients with this disease to make reasoned statements and recommendations on the issue of diagnostic and prognostic value of hyperammonemia in patients with liver cirrhosis, hepatic encephalopathy and sarcopenia.
Results. The Delphi panel identified the most relevant topics, in the form of PICO questions (patient or population, intervention, comparison, outcome). The Delphi panel made six questions relevant to clinical practice and gave reasoned answers, framed as 'clinical practice recommendations and statements' with evidence-based comments. The questions and statements were based on the search and critical analysis of medical literature by keywords in English- and Russian-language databases. The formulated questions could be combined into four categories: hepatic encephalopathy, sarcopenia, hyperammonemia, and ammonia-lowering therapy.
Conclusions. The results of the experts' work are directly relevant to the quality management of patients with liver cirrhosis, and their recommendations and statements can be used in clinical practice.
Keywords: PICO, ammonia measurement methods, hyperammonemia, hepatic encephalopathy, sarcopenia, hyperammonemia treatment, lactulose, rifaximin, L-ornithine-L-aspartate, LOLA, branched-chain amino acids, BCAA
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Диагностическое и прогностическое значение гипераммониемии у пациентов с циррозом печени, печеночной энцефалопатией и саркопенией (соглашение специалистов)

М.Ю. Надинская[1]*, М.В. Маевская[1], И.Г. Бакулин[2], Е.Н. Бессонова[3], А.О. Буеверов[1,4], М.С. Жаркова[1], С.В. Оковитый[5], А.С. Островская[1], К.А. Гуляева[1], В.Т. Ивашкин[1]

[1] *ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Российская Федерация*

[2] *ФГБОУ ВО «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Российская Федерация*

[3] *ГАУЗ Свердловской области «Свердловская областная клиническая больница № 1», Екатеринбург, Российская Федерация*

[4] *ГБУЗ МО «Московский областной научно-исследовательский клинический институт им. М.Ф. Владимирского», Москва, Российская Федерация*

[5] *ФГБОУ ВО «Санкт-Петербургский государственный химико-фармацевтический университет» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Российская Федерация*

Введение. У пациентов с циррозом печени в результате нарушения процессов обезвреживания аммиака и портосистемного шунтирования крови может развиваться гипераммониемия, которая наиболее часто ассоциирована с печеночной энцефалопатией и саркопенией. На сегодняшний день остаются вопросы по диагностике гипераммониемии и влиянию гипоаммониемической терапии на исходы заболевания.
Материалы и методы. Российское общество по изучению печени объединило семь экспертов в области изучения цирроза печени и ведения пациентов с этим заболеванием для вынесения аргументированных рекомендаций и положений по проблеме «Диагностическое и прогностическое значение гипераммониемии у пациентов с циррозом печени, печеночной энцефалопатией и саркопенией».
Результаты. Эксперты работали по упрощенному дельфийскому методу, определение наиболее актуальных проблем осуществляли по принципу PICO (patient or population, intervention, comparison, outcome). Эксперты сформулировали шесть актуальных для клинической практики вопросов и дали на них аргументированные ответы, оформленные как «рекомендации и положения для клинической практики» с комментариями на основе доказательной медицины. В основу формулировки вопросов, рекомендаций и положений лег критический анализ медицинской литературы, найденной по ключевым словам в англоязычных и русскоязычных базах данных. Объединить сформулированные вопросы можно в четыре категории: печеночная энцефалопатия, саркопения, гипераммониемия, гипоаммониемическая терапия.
Выводы. Результаты работы экспертов имеют прямое отношение к качественному ведению пациентов с циррозом печени, сформулированные ими рекомендации и положения могут использоваться в клинической практике.
Ключевые слова: PICO, методы измерения аммиака, гипераммониемия, печеночная энцефалопатия, саркопения, лечение гипераммониемии, лактулоза, рифаксимин, L-орнитин-L-аспартат, LOLA, аминокислоты с разветвленной боковой цепью, BCAA
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Introduction

Ammonia is a toxic substance that is mainly present in the blood as ions (NH^{4+}). Under fasting conditions, healthy people have low concentrations of ammonia in the blood (from 8 to 60 μmol/L). It should be noted that the upper normal limit for blood ammonia concentrations is not defined by international standards and may vary depending on the blood sampling site (arterial, venous, or capillary blood) and laboratory test method [1].

Liver cirrhosis (LC) is characterized by fibrosis and transformation of normal liver structure into abnormal nodules, representing the end stage of most diffuse liver diseases. Hyperammonemia may occur during the course of cirrhosis and is due to impaired ammonia detoxification in the liver and portosystemic blood shunting. In clinical studies of patients with LC, hyperammonemia is defined as venous blood ammonia concentration > 50 μmol/L [2–4] or > 60 μmol/L [5, 6] and arterial blood ammonia concentration > 60 μmol/L [7].

Approximately one third of patients with LC develop a fatal outcome directly associated with its complications [8]. One of the most common complications of cirrhosis associated with hyperammonemia is hepatic encephalopathy (HE): overt HE at disease onset is observed in 10–20 % [9–12], in 30–40 % of patients, it develops during the disease course and is a marker of decompensation [13–16]; while covert HE is diagnosed in 20–80 % of patients depending on the diagnostic method [17–21].

Another common complication of cirrhosis is sarcopenia: its prevalence is 25–70 %, increasing with the severity of cirrhosis [22–24]. Ammonia is neutralized in the skeletal muscles in patients with LC, therefore, sarcopenia is a risk factor for HE [25, 26]. Both experimental and clinical studies have shown that hyperammonemia can exacerbate sarcopenia [27].

Approximately one in four patients with cirrhosis is diagnosed with HE and sarcopenia simultaneously [28, 29]. This combination is unfavourable: both conditions aggravate each other, forming a *circulus vitiosus*, and have a negative synergistic effect on patients' quality of life and prognosis [30].

Recent studies have demonstrated the prognostic value of hyperammonemia in patients with LC: increased ammonia levels have been identified as an independent risk factor for hospitalization, morbidity, and mortality [31, 32].

However, it is currently not known whether it is necessary to measure blood ammonia levels in patients with HE and/or sarcopenia before the

use of pathogenesis-based ammonia-lowering therapy, whether alternative therapeutic options for these complications are available, and how the use of ammonia-lowering therapy is going to affect the outcomes, what the best method to measure the ammonia concentration is, and some others.

The answers to these questions are directly related to the quality management of patients with LC in clinical practice. The questions could be combined into four categories: hepatic encephalopathy, sarcopenia, hyperammonemia, and ammonia-lowering therapy.

Materials and methods

The Russian Scientific Liver Society (RSLS) selected a panel of experts in LC research and management of patients with this disease to make reasoned statements and recommendations on the issue of diagnostic and prognostic value of hyperammonemia in patients with liver cirrhosis and its complications.

A Delphi panel consisted of seven specialists, including six hepatologists/gastroenterologists who specifically treated patients with LC (including those in the liver transplant waiting list and during the post-transplantation period) and one clinical pharmacologist. Of the six hepatologists/gastroenterologists, three specialists are involved in research on the role of hyperammonemia in liver diseases, one specialist has extensive experience in comparing the diagnostic accuracy of blood ammonia measurement using different methods. All experts have academic degrees, extensive practical experience in the management of patients with LC and its various complications.

All participants in the presented agreement took part in the discussion of all questions about the diagnostic and prognostic value of hyperammonemia in patients with LC. The first meeting of experts was held in-person in order to identify the most relevant for clinical practice topics, in the form of PICO questions.

The purpose of the question according to the PICO method is to highlight the problems of a patient or population (patient or population), any intervention or method (intervention), to carry out comparison, if applicable (comparison) and to discuss the result (outcome).

Once the questions were formulated, the Delphi panel discussed them online. Some of these questions were modified and finally they were agreed upon. The answers to the questions were prepared in the form of recommendations and statements and substantiated by the experts as part of evidence-based medicine.

The experts used the simplified Delphi method. The following rules were applied by the experts for approval of the statements: if the statement had been approved by less than 50 % of experts, it was rewrite and resubmitted for discussion and voting; if the statement had been approved by 50–75 % of experts, it was improved and rewrite, discussed and adopted without a second vote; if the statement had been approved by 75–90 % of experts, it was not rewritten, comments were taken into account; if the statement had been approved by more than 90 % of experts, it was adopted with small corrections.

All statements were discussed in three rounds of voting and during two online meetings, resulting in consensus among the experts, meaning that all statements were discussed, modified, and unanimously approved.

An advanced literature search was performed in the English language using the following keywords: hyperammonemia or hepatic encephalopathy or cognitive disorders and liver cirrhosis or liver disease; ammonia level measurement and liver cirrhosis; ammonia level measurement and cognitive disorders or psychiatric disorders or encephalopathy; ammonia-lowering therapy and hepatic encephalopathy and outcome or improvement or clinical course and liver cirrhosis; ammonia level measurement and sarcopenia; hepatic encephalopathy and sarcopenia; ammonia-lowering therapy and sarcopenia and outcome or improvement or clinical course and liver cirrhosis; prognostic role of ammonia and liver cirrhosis. The search was conducted in the following international databases: PubMed, Google Scholar, Web of Science, Embase, Cochrane Database, the relevant studies were also searched for at ClinicalTrials.gov.

An advanced literature search was performed in the Russian language using the same keywords. The search was conducted in the following databases: the electronic resource "The Rubricator of Clinical Guidelines of the Ministry of Health of the Russian Federation", eLibrary, RusMed.

The work of the experts was to formulate questions using the PICO method, make statements on each of the questions and substantiate them using the principles of evidence-based medicine, and reach the consensus using the simplified Delphi method.

The level of evidence was determined based on the criteria of the Oxford Center for Evidence-Based Medicine [33] (Tables 1 and 2).

This document discusses only ammonia-lowering medicinal products that are authorized in the Russian Federation and are mentioned in the clinical guidelines of the Ministry of Health of the

Russian Federation "Liver cirrhosis and fibrosis" (ID 715; approved in 2021)[1].

Questions and statements, recommendations

Should blood ammonia levels be measured in patients with LC and HE before the initiation of ammonia-lowering therapy?

Recommendation. It is not recommended to measure blood ammonia levels in patients with LC or any form of HE (covert or overt) before the start of ammonia-lowering therapy since hyperammonemia is the main factor of pathogenesis of this complication.
(LoE — 3, strong recommendation, 100 % consensus)

The pathophysiology of HE is based on necrosis or functional failure of hepatocytes, leading to decreased detoxification function of the liver and accumulation of toxic substances in the systemic circulation, which cross the blood-brain barrier to the brain and cause dysfunction of the central nervous system [34]. Another pathophysiologic mechanism of HE development in patients with LC and clinically significant portal hypertension is spontaneous or surgical portosystemic shunts, through which toxins formed in the gastrointestinal tract bypass the liver and enter the systemic circulation. Other factors such as neuroinflammation, aberrant neurotransmission, bile acid signalling or microbiome; manganese excess and some others are also considered to be involved in the pathophysiology of HE, however, hyperammonemia is believed to be the key factor in the HE pathogenesis so far [35].

The role of ammonia in the pathogenesis of encephalopathy after portosystemic shunting was first demonstrated 130 years ago by a group of physiologists led by I.P. Pavlov and M.V. Nencki in the Imperial Institute of Experimental Medicine in Russia. Dogs with an Eck's fistula (a shunt between the portal vein and inferior vena cava) had behavioural changes and developed neurological symptoms that increased after meat intake, while the concentration of ammonium salts in the urine increased [36, 37]. The results of these experiments suggested that ammonia may play a central role in the development of a complex of neuropsychiatric symptoms later named HE.

Studies conducted in the following years confirmed this assumption: increased blood ammonia levels were found in patients with LC and HE [38, 39]. Although some patients with overt HE may have normal ammonia levels [40, 41] the ranges of ammonia concentrations overlap

Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine

LoE	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (with homogeneity) of randomized controlled trials	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomized controlled trials or observational studies with dramatic effects; systematic reviews of lower quality studies (i.e. non-randomized, retrospective)	
3	Non-randomized controlled cohort / follow-up study / control arm of randomized trial (systematic review is generally better than individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Note: LoE — level of evidence.

[1] Liver cirrhosis and fibrosis: Clinical guidelines. Approved by the Research and Practical Council of the Ministry of Health of the Russian Federation. URL: https://cr.minzdrav.gov.ru/schema/715_1 (date of access: August 14, 2023).

Table 2. Grades of recommendation

Grade	Wording	Criteria
Strong	Must, shall, should, is recommended Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient
Weak or open	Can, may, is suggested May not, is not suggested	Preferences, ethical obligations, feasibility

at different stages of HE [42]; a direct correlation between the degree of hyperammonemia and the severity of HE has been established [31, 43, 44], and ammonia level reduction has been shown to be associated with clinical improvement [39, 45, 46]

The main causes of hyperammonemia in patients with LC include loss of functioning periportal hepatocytes in which ammonia is neutralized to its final product, urea, which is excreted via the kidneys [47], and decreased ability of perivenous hepatocytes to bind ammonia to form glutamine [48].

The role of hyperammonemia in the central nervous system disorders has been proven in experimental studies and shown in histological examinations: the main damage develops in astrocytes, which play a crucial role in many aspects of brain physiology, including ammonia metabolism, neurotransmitter uptake, free radical removal, release of neurotrophic factors, and maintenance of synapse function [44].

In recent years, there have been studies that suggest measuring blood ammonia concentration in patients with HE to confirm the diagnosis, predict the development of complications, and develop new therapeutic options [34, 49]. However, there is currently insufficient evidence to support the efficacy of measuring ammonia in all patients with LC and signs of encephalopathy in routine clinical practice to improve clinical outcomes.

When is it should to measure blood ammonia levels in patients with LC and signs of encephalopathy?

Recommendation. It is recommended to measure blood ammonia levels as part of differential diagnosis of altered consciousness in patients with LC and diagnostically unclear encephalopathy.
(LoE — 3, strong recommendation, 100 % consensus)

If a patient with LC has signs of altered consciousness, a standardized diagnostic evaluation by a multidisciplinary team should be conducted [33, 50]. Altered consciousness can be caused by extrahepatic conditions that cause or exacerbate HE symptoms, these are so-called precipitating factors. Among them are well-known factors: infections (pneumonia, urinary infection, spontaneous bacterial peritonitis, sepsis, acute gastroenteritis and others) [51], gastrointestinal bleeding [52], constipation, excessive breakdown of glutamine by small intestinal glutaminases [53], dehydration, hyponatremia [54], hypokalemia [55, 56], uncontrolled use of diuretics, alcohol consumption [57], use of benzodiazepines, excessive protein intake [58, 59] and factors whose role in the development of HE has been actively discussed in recent years: loss of skeletal muscle mass (sarcopenia) [29, 60] and transjugular intrahepatic portosystemic shunt placement [61–63].

The precipitating factors of HE development in patients with LC may be observed in isolation or in various combinations and are accompanied by hyperammonemia. In patients demonstrating signs of HE, they should be ruled out based on the results of standard clinical examination and laboratory tests. Interventions aimed at eliminating/correcting these factors, in combination with ammonia-lowering therapy, are accompanied by clinical improvement of HE [64–67].

If this approach is ineffective, it is advisable to measure the ammonia concentration: high concentration requires the modification of ammonia-lowering therapy (dose increase, use of combination regimens) and active search for precipitating factors that have not been eliminated yet, while normal concentrations require search for alternative causes of altered consciousness.

There is a separate group of causes of altered consciousness in patients with LC that produce their potent independent effect on the central nervous system (without the involvement of hepatic failure and portosystemic shunts). These causes include intracranial lesions (subdural hematoma, intracranial hemorrhage, tumor, stroke, abscess), inflammatory diseases of the central nervous system (meningitis, encephalitis), metabolic encephalopathy (diabetes mellitus, severe anemia), Wernicke encephalopathy, the use of

psychoactive substances (antipsychotics, sedatives, antidepressants) [64, 68–70].

In such cases, measurement of ammonia concentration may be useful: ammonia levels within the reference ranges require active search for other causes of altered consciousness (not associated with HE) as part of differential diagnosis.

It is necessary to remember about extrahepatic causes of hyperammonemia, which should be ruled out in the absence of precipitating factors or no response to adequate ammonia-lowering therapy [1].

Which method of measuring blood ammonia concentration is the most preferable in routine clinical practice?

Statement. The most preferable method of measuring blood ammonia is its determination in the capillary blood using a rapid test.
(LoE — 3, 100 % consensus)

All methods of blood ammonia measurement can be divided into two groups: conventional and rapid tests.

Conventional laboratory methods for the determination of blood ammonia concentrations are difficult to perform, time-consuming and involve the following steps: isolation of ammonia from the sample, ammonia capture followed by quantification by titration, colorimetry/fluorimetry, electrode or enzymatic assays [71].

The first factor limiting the use of these methods in routine clinical practice is the need to standardize a large number of complex technical conditions: the need to draw blood into a cooled vacuum tube with anticoagulant, immediate placement of the sample on ice, refrigerated centrifugation, and a lot of other factors. Ammonia levels in whole blood plasma maintained at 4 °C remain stable for less than 1 hour. If concentration measurements are not carried out immediately, the samples should be frozen, otherwise the persisting metabolism of red blood cells and platelets *in vitro* will lead to increased ammonia concentrations [72, 73]. Each laboratory adopts a different standard of the testing protocol, resulting in various results, as occurred in a recently published study [74]. Venous blood samples collected from patients with LC and HE were placed in a cooled tube, centrifuged in a refrigerator, then divided into two parts to determine on-site ammonia levels and sent to a central laboratory; for this purpose, the samples were frozen at –70 °C and stored at the same or lower temperature in a freezer. The study was conducted at multiple centers, and each of the local laboratories followed a different testing protocol. As a result, the ammonia concentrations measured in the local laboratories and in the centralized laboratory differed, which caused misrepresentation of the testing results [74].

In the Russian Federation, there is currently a rapid test for the determination of blood ammonia concentrations using a portable device PocketChem BA PA-4140 (ARKRAY Factory, Inc., Japan)[2]. This method was developed in 1992 as an alternative to conventional tests. The rapid test is a dry chemistry test that requires a disposable reagent test strip AMMONIA TEST KIT II (ARKRAY Factory, Inc., Japan)[3], on which one drop of whole blood is applied (a microcapillary is attached for taking the required volume, i.e. 20 uL), ammonium ion in the blood sample turns into ammonia gas in the test strip and diffuses onto the indicator layer, which intensity of colour change is used to calculate the ammonia concentration using reflectance photometry. The device is very easy to use, fast (measurement takes about 3 min), accurate and reproducible [75], which makes it most suitable for bedside use. The method is comparable to values obtained by conventional methods: the intra-assay coefficient of variation does not exceed 6.5 % [76].

Ammonia concentrations in patients with LC can be measured in arterial, venous, and capillary blood samples [39, 43, 77]. The brain ammonia utilization rate has been shown to directly correlate with arterial ammonia concentration [78]. Current studies show an arteriovenous difference of blood ammonia in patients with LC due to the uptake of ammonia by muscles and its binding to form glutamine [78, 79]. Moreover, a wide variability of serum ammonia levels in healthy volunteers has been established when using conventional test methods [80]. In addition to this limitation, possible tourniquet-induced ischemia, which may affect the ammonia concentration in the venous sample, has been discussed [81]. Therefore, it is preferable to measure the levels of ammonia in arterial blood, but this method requires a good practical skill in performing arterial punctures.

Ammonia levels in capillary blood most closely match those in arterial blood, so capillary blood sampling may be a good alternative to more invasive arterial blood sampling [82]. When performing capillary blood testing, it is crucial to

[2] Marketing authorization certificate for the medical device No. RZN No. 2014/1901 issued on September 16, 2014.
[3] Marketing authorization certificate for the medical device No. RZN No. 2014/1845 issued on August 11, 2014.

properly choose the sampling site. For example, artificially elevated ammonia levels can be obtained when blood sampling is performed from a finger as a result of contamination of the sample with sweat [83]. The ammonia concentration in capillary blood obtained from the earlobe, which does not contain sweat glands, more accurately reflects the true ammonia concentration [71, 84].

In the first published studies, the reference ranges for the rapid test for measuring fasting ammonia in arterial blood and in capillary blood taken from the earlobe in healthy volunteers ranged from 8 to 35 μmol/L [71, 84, 85]. When evaluating the measured capillary blood ammonia concentration using the PocketChem BA PA-4140, the units of measurement must be taken into account. The device has the option to change the units of measurement ammonia level: in μg/dL or μmol/L. The upper limit of normal specified for the test strips is 76 μg/dL (measuring range — 10–400 μg/dL) and 54 μmol/L (measuring range — 8–285 μmol/L).

What is the effect of ammonia-lowering therapy on HE outcomes in patients with LC?

Statement. The use of ammonia-lowering therapy in patients with LC improves outcomes of all types of HE (covert or overt).
(LoE — 1, 100 % consensus)

Two groups of medicinal products with an ammonia-lowering effect are authorized in the Russian Federation: medicinal products that stimulate ammonia detoxification and medicinal products that reduce ammonia production in the intestine. Both groups are recommended for use in adult patients with LC in the treatment of covert or overt HE[4].

The most commonly used medicinal product from the first group: L-ornithine-L-aspartate (LOLA) is a stable salt of L-ornithine and L-aspartate, which readily dissociates into its constituent amino acids [86]. L-ornithine is a substrate of the urea cycle and an activator of its key enzyme, carbamoyl phosphate synthetase, in periportal hepatocytes. L-aspartate is converted by transamination to glutamate, which is capable of binding ammonia in perivenous hepatocytes, skeletal muscle, and brain. Through these metabolic pathways, both amino acids participate in reactions in which the ammonia molecule is incorporated into urea and glutamine, resulting in a decrease in blood ammonia concentrations [86]. The presence of reserve ammonia detoxification systems in patients with LC was first shown almost 50 years ago in the clinical settings: administration of LOLA reduced hyperammonemia induced by ammonium chloride intake [87]. LOLA is available in two dosage forms: intravenous and oral.

The agents that reduce the ammonia production in the intestine include nonabsorbable disaccharides (lactulose) and antibiotics, and among them, the most preferable product is currently the one with minimal systemic absorption, namely rifaximin (rifaximin-alpha). Lactulose reduces the ammonia production due to its laxative effect, acidification of colon contents and prebiotic properties [88, 89]. Rifaximin produces an ammonia-lowering effect by modifying the gut microbiome [90, 91]. Both medicinal products are available in the oral dosage form.

There is no gold standard for ammonia-lowering therapy in patients with LC and HE. The Cochrane systematic review on HE (2019) presents a conclusion that there is insufficient evidence to determine the effect of all used ammonia-lowering agents for the prevention and treatment of HE in adult patients with LC, and a suggestion that more evidence is needed to assess their efficacy and safety [92]. However, it is very difficult to conduct international multicenter, double-blind, randomized placebo-controlled trials, which serve as the basis for systematic reviews and meta-analyses, in patients with HE for the following reasons: the variety of HE forms (episodic, persistent, recurrent), ethical considerations (use of placebo in patients with overt HE), multiple effects of precipitating factors, lack of standardized methods of covert HE assessment, impossibility to remain blind in trials involving lactulose due to the need to achieve its main laxative effect for the treatment of HE, as well as limited availability of ornithine and rifaximin in some countries.

Overt HE

The efficacy of LOLA in patients with overt HE (episodic or persistent type) grades 2–4 of the West Haven classification has been demonstrated in three meta-analyses [93–95]. LOLA (daily oral dose of 9–18 g or intravenous dose of 20 g, treatment duration of 3 to 14 days) was more effective in reducing HE symptoms, mortality rate, rate, and extent of a decrease in both fasting and postprandial hyperammonemia compared

[4] Liver cirrhosis and fibrosis. Approved by the Research and Practical Council of the Ministry of Health of the Russian Federation. Approved in 2021. URL: https://cr.minzdrav.gov.ru/recomend/715_1 (date of access: October 14, 2023).

with placebo/no intervention. However, the tolerance ratio and incidence of adverse events were similar in the LOLA group and placebo/no intervention groups.

Comparison of LOLA with other ammonia-lowering agents for the treatment of overt HE has shown either the similar effect [6] or superiority of LOLA with respect to clinical improvement, reduction in ammonia concentration, and tolerability [6, 96].

Lactulose is effective in improving symptoms of overt HE and improving survival rates compared to placebo/no intervention [97]. The product may be administered through a gastric/nasogastric tube or as enemas. During use, the development of adverse events (diarrhea, bloating, abdominal pain), hyponatremia is possible. The latter should be monitored: hyponatremia itself may be a precipitating factor for the HE development.

The clinical efficacy of rifaximin is equivalent to lactulose, however, the former has a better safety profile [98]. Rifaximin and lactulose have demonstrated similar efficacy in the treatment of overt HE grades 2–3 [99].

Combination therapy with rifaximin and lactulose improves clinical efficacy, reduces hospital length of stay, and mortality in patients with HE compared to lactulose monotherapy [100, 101].

Combination of three ammonia-lowering agents can be used in patients with severe overt HE (grades 3–4). The addition of LOLA for 5 days to the combination of lactulose and rifaximin compared to the addition of placebo improved grades of HE, recovery time from encephalopathy, with lower 28-day mortality [102].

After acute bleeding from esophageal/gastric varices, patients with LC are likely to develop an episode of overt HE. In such cases, LOLA (oral or intravenous dosage form) [103] or lactulose [104] may be used for primary prophylaxis of overt HE.

At present, there is no evidence to recommend any of the ammonia-lowering agents as monotherapy for primary prevention of overt HE after transjugular intrahepatic portosystemic shunt placement, perhaps combination therapy may produce a more significant effect [105, 106].

Secondary prophylaxis of HE usually includes the combination therapy, in particular, a combination of lactulose and rifaximin has demonstrated the reduction in the HE recurrence and HE-related hospitalization in patients with decompensated LC in one-year follow-up [107].

Covert HE

LOLA (daily oral dose of 9–18 g) and lactulose (daily dose of 30 mL) have been shown to have similar efficacy in the treatment of covert HE (grade 1 of the West Haven classification) for 14 days [6, 7].

In patients with minimal HE treated for 3 months, the efficacy of primary prophylaxis of overt HE, improvement in the results of psychometric tests, and improvement of the quality of life were similar in patients receiving LOLA and lactulose, while LOLA was better tolerated [95, 103].

A meta-analysis of studies in patients with minimal HE comparing the use of LOLA with placebo/no-treatment has shown the improvement of the psychometric test results in patients receiving LOLA, lactulose and rifaximin. Also, improvement has been demonstrated in patients who received LOLA or lactulose for the prevention of overt HE. The mean duration of treatment was 2–3 months; LOLA was used at a dose of 9–18 g/day; rifaximin – at a dose of 1,100–1,200 mg/day, and lactulose – at a dose of 30–60 mL/day [108].

In patients with HE, therapy with LOLA, lactulose or rifaximin improves health-related quality of life and social functioning [109, 110].

Is it should to measure blood ammonia levels in patients with LC and sarcopenia?

Recommendation. It is not suggested to measure blood ammonia levels in patients with LC and sarcopenia since hyperammonemia is the main factor of pathogenesis of this complication. **(LoE – 4, weak recommendation, 100 % consensus)**

The course of LC is often accompanied by muscle disorders: atrophy, sarcopenia and myosteatosis. These disorders are caused by several factors: increased catabolism in cirrhosis (when essential amino acids necessary for muscle protein production are used for albumin synthesis or gluconeogenesis due to the depletion of glycogen stores); malnutrition; decreased levels of testosterone and growth hormone; sedentary lifestyle, etc. [111].

The association between hyperammonemia and sarcopenia has been established. In patients with LC, the mechanism of ammonia detoxification changes: due to decreased activity of the ornithine cycle enzymes and glutamine synthesis

in the liver (as well as the presence of portosystemic shunts), skeletal muscle takes up more ammonia and plays a major role in (temporarily) detoxifying ammonia to glutamine.

Therefore, the development of sarcopenia in patients with LC is associated with hyperammonemia and an increased risk of developing both covert and overt HE [60, 112].

Ammonia detoxification in muscles occurs via glutamine synthesis: an ammonia molecule combines with a glutamate molecule, and the reaction requires ATP energy. Alpha-ketoglutarate (an intermediate product of the tricarboxylic acid cycle) and branched-chain amino acids (BCAAs) are required to produce sufficient amounts of glutamate. In patients with hyperammonemia, ammonia detoxification in muscles leads to depletion of α-ketoglutarate, BCAA, and ATP stores, resulting in a decreased protein synthesis, oxidative stress, and uncontrolled autophagy [113–116].

Other mechanisms contributing to the decrease of skeletal muscle protein synthesis in patients with hyperammonemia are also being considered, particularly, myostatin activation via NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) [117]. In an experimental model, a reduce in myotube diameter, impaired protein synthesis, and increased autophagy were observed in response to hyperammonemia and partially reversed following 24-hour and 48-hour withdrawal of ammonium acetate. [118].

All the mechanisms described above contribute to the loss of muscle mass with even greater accumulation of ammonia, forming a *circulus vitiosus* [119]. Currently, there is no evidence to support the need to measure ammonia levels in patients with LC and sarcopenia in routine clinical practice to improve clinical outcomes.

What ammonia-lowering agents are effective in combination therapy for sarcopenia in patients with LC?

Statement. In patients receiving combination therapy for LC and sarcopenia, the following ammonia-lowering agents may be potentially effective: ornithine (LOLA) and rifaximin; their use can improve the clinical outcome.
(LoE — 4, 100 % consensus)

Patients with LC and sarcopenia may be prescribed both pharmaceutical and non-pharmaceutical therapies. Modern non-pharmaceutical therapy is based on the combination of physical activity (moderate strength workouts) and balanced diet. The latter includes the consumption of a sufficient amount of protein (1.2–1.5 g/kg body weight) to prevent protein catabolism in muscles and a high-calorie daily diet (30–35 kcal/kg body weight per day for non-obese patients) [120–122].

The European Society for Clinical Nutrition and Metabolism (ESPEN) [120] and the Indian National Association for Study of the Liver [122], the RSLS and the Russian Gastroenterology Association [17] recommend long-term oral supplementation with BCAA (0.25 g/kg/day) in patients with advanced stages of LC in order to reduce the risk of cirrhosis decompensation and to improve the quality of life. Recently published meta-analyses have demonstrated the efficacy of BCAAs in terms of increased muscle mass; however, the effect on muscle strength has not been established [123, 124].

Several studies conducted in Japan have shown the effect of L-carnitine in combination with BCAAs on preventing muscle mass loss, reducing the incidence of muscle cramps, and treating hyperammonemia that is refractory to lactulose, non-absorbable antibiotics, and low-protein diets [125–129]. The primary function of L-carnitine is to transport long-chain fatty acids into the mitochondria for subsequent beta-oxidation, potentially reducing energy deficits in patients with hyperammonemia. The ESPEN guidelines do not specify L-carnitine [120].

Among patients with cirrhosis, there is a subgroup of patients who develop HE when having normal protein consumption. This phenomenon, considered to be historical by the ESPEN, is called protein intolerance [120]. A significant increase in the ammonia concentration in patients with LC after protein intake is considered to be the major mechanism for the development of protein intolerance. Intravenous administration of LOLA at a dose of 20–40 g resulted in a decrease in the postprandial ammonia concentration after the intake of oral protein loads: 0.25 g/kg in the morning and 0.5 g/kg at lunch [130], which can be considered as a therapeutic option in such patients.

Experimental and clinical data on the effects of LOLA on sarcopenia have been obtained. A randomized clinical study in patients with LC receiving LOLA supplementation in addition to protein intake has shown that the muscle protein synthesis rates measured in percutaneous biopsies

of anterior tibialis muscle improved significantly compared to placebo [131]. Experimental hyperammonemia induced in rats by portosystemic shunt placement resulted in decreased lean body mass and grip strength. Four-week oral administration of LOLA and rifaximin was associated with decreased ammonia concentration, increased protein synthesis in the calf muscle, muscle fiber diameter and skeletal muscle weight, and grip strength [118].

Another positive effect of LOLA in patients with sarcopenia is an increase in the production of L-arginine and consequently nitric oxide, leading to the S-nitrosylation of calpain results in slowing of sarcopenia in aging [119].

Conclusion

The statements in this document have been prepared by the experts in the management of patients with liver cirrhosis and its major complications in clinical practice. The experts are experienced in research on hyperammonemia and its role in the development of complications of liver cirrhosis and are qualified in evaluating the respective diagnostic tests and therapeutic options.

Members of the Expert Group

Bakulin I.G., Bessonova E.N., Bueverov A.O., Zharkova M.S., Maevskaya M.V., Nadinskaia M.Yu., Okovityi S.V.

Work with literature sources and text

Gulyaeva K.A., Ostrovskaya A.S.

Scientific project director

Vladimir T. Ivashkin — Dr. Sci. (Med.), Academician of the Russian Academy of Sciences, Professor, Head of the Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University); Chief Freelance Gastroenterologist of the Ministry of Health of the Russian Federation; President of the Russian Scientific Liver Society.

Состав экспертной группы

Бакулин И.Г., Бессонова Е.Н., Буеверов А.О., Жаркова М.С., Маевская М.В., Надинская М.Ю., Оковитвый С.В.

Работа с литературой и текстом

Гуляева К.А., Островская А.С.

Научный руководитель проекта

Ивашкин Владимир Трофимович — доктор медицинских наук, академик РАН, профессор, заведующий кафедрой пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет); Главный внештатный специалист гастроэнтеролог МЗ РФ; Президент Российского общества по изучению печени (РОПИП).

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Information about the authors

Maria Yu. Nadinskaia* — Cand. Sci. (Med.), Associate Professor at the Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: nadinskaya_m_yu@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0002-1210-2528

Marina V. Maevskaya — Dr. Sci. (Med.), Professor, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: mvmaevskaya@me.com;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0001-8913-140X

Igor G. Bakulin — Dr. Sci. (Med.), Professor, Head of the Department of Propaedeutics of Internal Medicine, Gastroenterology and Dietetics named after S.M. Ryss, North-Western State Medical University named after I.I. Mechnikov.
Contact information: igbakulin@yandex.ru;
191015, St. Petersburg, Kirochnaya str., 41.
ORCID: https://orcid.org/0000-0002-6151-2021

Elena N. Bessonova — Dr. Sci. (Med.), Chief Freelance Gastroenterologist of the Ministry of Health of the Sverdlovsk Region, Head of the Sverdlovsk Regional Hepatological Center, Sverdlovsk Regional Clinical Hospital No. 1.
Contact information: benbessonova@yandex.ru;
620102, Yekaterinburg, Volgogradskaya str., 185.
ORCID: https://orcid.org/0000-0002-4223-3473

Alexey O Bueverov — Dr. Sci. (Med.), Professor at the Department of Medical and Social Expertise, Emergency and Pathogenetic Therapy, I.M. Sechenov First Moscow State Medical University (Sechenov University); Leading Researcher, Department of Hepatology, M.F. Vladimirsky Moscow Regional Research and Clinical Institute.
Contact information: bcl72@yandex.ru;
129110, Moscow, Shchepkina str., 61/2.
ORCID: https://orcid.org/0000-0002-5041-3466

Maria S. Zharkova — Cand. Sci. (Med.), Head of the Hepatology Department, V.Kh. Vasilenko Clinic of Internal Disease Propaedeutics, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: zharkova_m_s@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0001-5939-1032

Сведения об авторах

Надинская Мария Юрьевна* — кандидат медицинских наук, доцент кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: nadinskaya_m_yu@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-1210-2528

Маевская Марина Викторовна — доктор медицинских наук, профессор ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: mvmaevskaya@me.com;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0001-8913-140X

Бакулин Игорь Геннадьевич — доктор медицинских наук, профессор, заведующий кафедрой пропедевтики внутренних болезней, гастроэнтерологии и диетологии им. С.М. Рысса ФГБОУ ВО «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Министерства здравоохранения Российской Федерации.
Контактная информация: igbakulin@yandex.ru;
191015, г. Санкт-Петербург, ул. Кирочная, 41.
ORCID: https://orcid.org/0000-0002-6151-2021

Бессонова Елена Николаевна — доктор медицинских наук, главный внештатный гастроэнтеролог Министерства здравоохранения Свердловской области; руководитель Свердловского областного гепатологического центра ГАУЗ Свердловской области «Свердловская областная клиническая больница № 1».
Контактная информация: benbessonova@yandex.ru;
620102, г. Екатеринбург, ул. Волгоградская, 185.
ORCID: https://orcid.org/0000-0002-4223-3473

Буеверов Алексей Олегович — доктор медицинских наук, профессор кафедры медико-социальной экспертизы, неотложной и патогенетической терапии ФГАОУ ВО «Первый Московский государственный университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет); ведущий научный сотрудник отделения гепатологии ГБУЗ МО «Московский областной научно-исследовательский клинический институт им. М.Ф. Владимирского».
Контактная информация: bcl72@yandex.ru;
129110, г. Москва, ул. Щепкина, 61/2.
ORCID: https://orcid.org/0000-0002-5041-3466

Жаркова Мария Сергеевна — кандидат медицинских наук, заведующая отделением гепатологии Клиники пропедевтики внутренних болезней, гастроэнтерологии, гепатологии им. В.Х. Василенко ФГАОУ ВО «Первый Московский государственный университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: zharkova_m_s@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0001-5939-1032

* Corresponding author / Автор, ответственный за переписку

Sergey V. Okovityi — Dr. Sci. (Med.), Professor, Head of the Department of Pharmacology and Clinical Pharmacology, Saint Petersburg State Chemical Pharmaceutical University.
Contact information: sergey.okovity@pharminnotech.com;
197376, St. Petersburg, Professor Popov str., 14A.
ORCID: https://orcid.org/0000-0003-4294-5531

Оковитый Сергей Владимирович — доктор медицинских наук, профессор, заведующий кафедрой фармакологии и клинической фармакологии ФГБОУ ВО «Санкт-Петербургский государственный химико-фармацевтический университет» Министерства здравоохранения Российской Федерации.
Контактная информация: sergey.okovity@pharminnotech.com;
197376, г. Санкт-Петербург, ул. Профессора Попова, 14а.
ORCID: https://orcid.org/0000-0003-4294-5531

Anna Sergeevna Ostrovskaya — Physician at the Department of Hepatology, V.Kh. Vasilenko Clinic of Internal Disease Propaedeutics, Gastroenterology and Hepatology. I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: ostrovskaya_a_s@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0002-9152-1279

Островская Анна Сергеевна — врач-специалист отделения гепатологии клиники пропедевтики внутренних болезней, гастроэнтерологии, гепатологии им. В.Х. Василенко ФГАОУ ВО «Первый Московский государственный университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: ostrovskaya_a_s@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-9152-1279

Kseniya A. Gulyaeva — Postgraduate, Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: xen59@mail.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0002-3462-0123

Гуляева Ксения Александровна — аспирант кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: xen59@mail.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-3462-0123

Vladimir T. Ivashkin — Dr. Sci. (Med.), Academician of the Russian Academy of Sciences, Professor, Head of the Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University); Chief Freelance Gastroenterologist of the Ministry of Health of the Russian Federation; President of the Russian Scientific Liver Society.
Contact information: ivashkin_v_t@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0002-6815-6015

Ивашкин Владимир Трофимович — доктор медицинских наук, академик РАН, профессор, заведующий кафедрой пропедевтики внутренних болезней, гастроэнтерологии и гепатологии ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет); Главный внештатный специалист гастроэнтеролог МЗ РФ; Президент Российского общества по изучению печени (РОПИП).
Контактная информация: ivashkin_v_t@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-6815-6015

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