Russian Consensus on “Hyperammonemia in Adults”: The 2021 Version (in English)

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Summary

Hyperammonemia is an acute or chronic intoxication with ammonia and ammonium associated with elevated ammonia levels in serum due to either its increased production and/or decreased detoxification. Hyperammonemia can result from a variety of causes and clinically presents with unspecific signs and symptoms, including asthenia, encephalopathy, liver steatosis or fibrosis, and sarcopenia. With impaired liver function, hyperammonemia most frequently manifests in (micro)encephalopathy. Thus in case of unexpected change in mental status hyperammonemia must be excluded as fast as possible. An express method of photometric assay is informative enough to determine the ammonia levels. The following hyperammonemia classification is proposed: a) by ammonia levels (normal level: ≤ 60 μmol/L; mild (Grade 1): ≤ 100 μmol/L; and severe (Grade 3): > 200 μmol/L); b) by etiopathogenesis (hereditary (congenital), functional (physiological), acquired (hepatic, extrahepatic, mixed)); c) by clinical presentation (transient, recurrent or persistent, constant (stable, without treatment), covert). Treatment for hyperammonemia is aimed at treating the primary disease and includes a diet that is restricted in animal protein but contains sufficient vegetable protein, limited physical activities, and use of intestinal non-absorbable antibiotics (rifaximin-alpha) as well as pre- and probiotics. L-ornithine-L-aspartate (LOLA) is a baseline therapeutic product administered in a number of scenarios to correct the level of hyperammonemia.

Keywords: Hyperammonemia, Ammonia, Ammonium, Rifaximin-alpha, Probiotics, Prebiotics, Covert hepatic encephalopathy, Liver fibrosis

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Российский консенсус «Гипераммонемии у взрослых» (Версия 2021)

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Гипераммонемия — это острая или хроническая интоксикация аммиаком и аммонием, связанная с повышенным уровнем аммиака в сыворотке крови из-за его повышенной выработки и / или снижения детоксикации. Гипераммонемия может быть результатом множества причин и клинически проявляться неспецифическими признаками и симптомами, включая астению, энцефалопатию, стеатоз или фиброз печени и саркопению. При нарушении функции печени гипераммонемия чаще всего проявляется (микро) энцефалопатией. Таким образом, в случае неожиданного изменения психического статуса необходимо как можно быстрее исключить гипераммонемию. Экспресс-метод фотометрического анализа достаточно информативен для определения уровня аммиака. Предлагается следующая классификация гипераммонемии: a) по уровням аммиака (нормальный уровень: ≤ 60 мкмоль / л; легкая (степень 1): ≤ 100 мкмоль / л; средняя (степень 2): ≤ 200 мкмоль / л; тяжелая (степень 3): > 200 мкмоль / л); b) по этиопатогенезу (наследственный (врожденный), функциональный (физиологический), приобретенный (печеночный, внепеченочный, смешанный)); в) по клинической картине (преходящая, рецидивирующая или стойкая, постоянная (стабильная, без лечения), скрытая). Лечение гипераммонемии направлено на лечение основного заболевания и включает диету, ограниченную животным белком, но содержащую достаточное количество растительного белка, ограниченную физическую активность и использование кишечных невсасывающихся антибиотиков (рифаксимин-альфа), а также пред- и пробиотиков. … L-орнитин-L-аспартат (LOLA) — это базовый терапевтический продукт, применяемый в ряде сценариев для коррекции уровня гипераммонемии.

Ключевые слова: гипераммонемия, азот, аммиак, аммоний, L-орнитин L-аспартат, рифаксимин-альфа, пробиотики, предбиотики, лактитол, лактулоза, минимальная печеночная энцефалопатия, фиброз печени

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Justification

Given the large number of reports on the peculiarities of liver lesions related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1], a team of experts who participated in the 23rd Congress of the Scientific Society of Gastroenterologists of Russia and the 15th National Congress of Therapists on November 19, 2020, decided to make additions to the Russian Consensus, “Hyperammonemia in Adults,” published in early 2020 [2, 3].

1. Provision 1

Interconverted biologically active molecules (gaseous ammonia \( \text{NH}_3 \) and ammonium cation \( \text{NH}_4^+ \)) are end-products of protein catabolism that are produced by biological tissues and urease-producing bacteria.
1.1. Comments:
Ammonia is mainly metabolized in liver cells and muscle tissue via the synthesis of urea and glutamine, which are excreted from the body through urine, feces, and exhaled air.

The main mechanisms of ammonia formation in the human body are as follows:
1. Non-oxidative deamination of certain amino acids (serine, threonine, and histidine) in the liver
2. Oxidative deamination of glutamic acid in all tissues (except muscle), especially in the liver and kidneys
3. Deamination of glutamic and aspartic acid amides in the liver and kidneys
4. Catabolism of biogenic amines in all tissues, but mostly in the nervous tissue
5. Hydrolytic deamination in intensively working muscles
6. Breakdown of glutamine – the main source of energy for the cells of the small intestinal mucosa
7. Degradation of purine and pyrimidine bases in all tissues
8. Urease-producing microorganism activity in the stomach, colon, and urinary tract

A significant amount of ammonia is formed as a by-product of the metabolism of intestinal bacteria in the colon, where ammonia enters the circulation via the portal vein. Customarily, the liver rapidly metabolizes ammonia from the blood of the portal vein and detoxifies it, such that the blood that is exported from the liver is practically free of ammonia [4].

At physiological pH values, up to 99% of ammonia is easily converted into ammonium ions, which are unable to pass through biological membranes and therefore remain inside the cell.

Ammonia is a toxic gas and its blood concentration in healthy individuals is relatively low (25–40 μmol/L). There are only trace amounts of free ammonia in the blood – no more than 1% of the compound circulates in the free form in the liquid component of blood.

There is no internationally standardized normal range for the level of ammonia in the blood; therefore, it depends on the technique and reagents used in the laboratory. The acceptable level of ammonia in the blood (normal ammonemia) is usually no more than 60 μmol/L [5, 6].

Symptoms of chronic intoxication are observed when the ammonia level is 2- to 3-fold higher than the acceptable level; however, even a slight increase (by 30–50%) has an adverse effect on the body, mostly on the central nervous system in the form of headache, fatigue, and drowsiness (everyday fatigue, occupational fatigue, nervous or physical overexertion, etc.).

Nearly all ammonia is excreted from the body via the kidneys through urine in the form of urea, which is synthesized in the liver, while ammonium ion salts are formed in the tubular epithelial cells. Ammonia enters the hepatic and renal cells via the transport processes of non-toxic compounds (glutamine, asparagine, glutamic acid, and alanine) formed during the neutralization (binding) of ammonia [7]. Urease synthesis is the main method of neutralizing ammonia. Urea accounts for 80–85% of all nitrogen excreted from the body.

The amount of excreted urea depends on the protein intake from food. If the daily protein intake is 80–100 g, 25–30 g of urea is produced and excreted per day. Urea production occurs via the ornithine cycle (Krebs–Henseleit cycle) in the liver. This cycle has two functions: (1) the conversion of amino acid nitrogen into urea, which prevents the accumulation of toxic products, mainly ammonia, and (2) the synthesis of arginine and its replenishment in the body. The cycle involves two amino acids that are not protein constituents – ornithine and citrulline – and two proteinogenic amino acids – arginine and aspartic acid. The process includes five reactions: the first two occur in the mitochondria while the rest occur in the cytosol of hepatocytes.

Glutamate dehydrogenase and glutamine synthetase enzymes have regulatory functions and determine the speed of ammonia formation and neutralization. Some enzymes involved in urea production are present in the brain, red blood cells, and cardiac muscle; however, the whole set of enzymes is only present in the liver.

To synthesize 1 mole of urea via the ornithine cycle in the liver, 1 mole of ammonia and 1 mole of aspartic acid are required; thus, 6.3 g of ammonia and 50 g of aspartic acid are required for the daily synthesis of 25 g of urea.

1.2. Excreted urea consists of “ammonia” nitrogen and aspartic acid nitrogen in equal parts
If the detoxifying function of the liver is reduced, the conversion of ammonia into urea is hindered and alternative metabolic pathways for this purpose are activated in the muscular system, astrocytes of the central nervous system, and kidneys [8–10]. Skeletal muscle tissue and nervous tissue are the main ammonia detoxifiers [11].

The conversion of glutamate into glutamine begins in the astrocytes of the brain, where it is catalyzed by glutamine synthetase. In persistent hyperammonemia, in addition to elevated glutamine synthetase, the activity of other enzymes – in particular the glutamate transport protein [12] – is changed. This results in an increased glutamate concentration in the extracellular space, which in turn leads to cytotoxicity through the activation of excitatory neurotransmitters (excitotoxicity) [13].

A stable elevated level of nitrogen compounds leads to the excessive formation of free radicals and further dysfunction of astrocytes. Prolonged hyperammonemia may be accompanied by the production of defective neurotransmitters, leading to a change in the activity of the serotonin and glutamatergic systems, with an increase in the activity of the GABAergic system [14].

The hypothalamic center is the most sensitive area to hyperammonemia in the brain [13], which manifests as persistent anorexia and protein–energy deficiency, aggravating catabolic processes.

Myostatin, produced by myocytes, not only largely inhibits the growth of muscle mass, but also leads to its decrease [15], which in hyperammonemia in patients with liver cirrhosis clinically manifests as sarcopenia [15, 16]. Moreover, a correlation between
2. Provision 2

There are various methods for determining the normal concentration of ammonia (NH₃) and ammonium (NH₄⁺) in the body, the most common of which are the enzymelinked immunosassay (ELISA) and express methods.

2.1. Comments:
Ammonia (NH₃) is a gas; however, at a physiological pH, 97% of the ammonia that is present in the blood is in the form of NH₄⁺.

Historically, the direct enzymatic method has been the most commonly used method for determining ammonia levels (ammonemia). It involves the reaction of ammonium in the sample with a-oxoglutarate in the presence of glutamate dehydrogenase, which reduces nicotinamide adenine dinucleotide phosphate (NADPH) to form glutamate, NADP⁺, and water. Ammonia levels vary in venous, capillary, and arterial blood, although it normally occurs in the range of 11–50 μmol/L[20, 21]. Although arterial blood ammonia is considered a more reliable indicator of systemic ammonia levels, venous blood ammonia is usually analyzed, which somewhat differs from arterial ammonia[22, 23].

It is important to note that the ammonia level in a collected blood sample may spontaneously increase due to a needlestick injury of the vein, hemolysis of red blood cells, or other causes[24, 25]. Stress, exercise, psychological fatigue, smoking, malnutrition, and alcohol abuse may also affect systemic ammonia levels.

The measurement of ammonia levels in the blood is mainly limited by the requirement to strictly ensure proper collection, processing, and delivery of a blood sample. The sample obtained for transportation to the laboratory should be stored at a temperature below 0°C, and the plasma should be separated from the red blood cells within 15 min after collection. After separation of the plasma, ammonia remains stable for 4 h at 4°C. These stringent conditions for analysis require the same conditions to confirm the result. There are different methods for determining ammonia in red blood cells, exhaled air, saliva, sweat, and urine[27].

The measurement of ammonia levels in exhaled air is a non-invasive, easy-to-use, and comfortable diagnostic method suitable for all patient groups. No processing of exhaled air is required, as opposed to many tests performed using serum or urine samples; however, there is no reliable evidence that ammonia levels in exhaled air correlate with those in arterial blood[28–30].

Ammonia levels may be determined using liver tissue in cases where a patient requires a diagnostic liver biopsy. It should be considered that the colorimetric kits for the determination of ammonia in tissue samples are rather expensive and sensitive to other sources of ammonia in the environment; additionally, these samples require work in a special cabinet or negative air pressure area, which is not always available at all laboratories. Moreover, long-term storage of a tissue sample, even at a temperature of –80°C, may affect its stability and lead to false results that are lower than expected.

In 2018, a portable express blood ammonia analyzer, the PocketChem BA PA-4140 (Arkray Global Business, Inc., Kyoto, Japan), was registered in Russia. Its method of determination is photometric – based on microdiffusion – that is, indirect; it takes approximately 200 s to determine the ammonia concentration using this device. Capillary blood from a finger is used for the analysis; however, blood collection should be performed under the conditions described in the instructions. Fresh blood samples should be used. In this device, ammonium is converted to ammonia after passing through a semi-permeable membrane; this changes the color of the indicator, the wavelength of which is spectroscopically analyzed. The resulting concentration is automatically indicated. Calibration of the device and correction of the results are also carried out automatically.

3. Provision 3

Hyperammonemia can be classified as follows:

• Level of ammonia (in capillary blood detected using the express method):
  ➢ Normal (physiological) level: ≤ 60 μmol/L
  ➢ Hyperammonemia:
    ➢ Mild (Grade 1): ≤ 100 μmol/L
    ➢ Moderate (Grade 2): ≤ 200 μmol/L
    ➢ Severe (Grade 3): > 200 μmol/L

• Etiopathogenesis:
  ➢ Hereditary (congenital)
  ➢ Functional (physiological)
  ➢ Acquired (hepatic, extrahepatic, mixed)

• Clinical presentation:
  ➢ Transient
  ➢ Recurrent or persistent
  ➢ Constant (stable, without treatment)
  ➢ Covert

The express method is a photometric assay of ammonia in capillary blood using a PocketChem BA PA-4140 portable analyzer (Arkray Global Business, Inc., Kyoto, Japan). It is informative and easy to use.
3.1. Comments:
1. The team of experts believes that with an increase in the number of observations, it will be possible to clarify the presented classification of hyperammonemia.
2. Traditionally, there are two main types of hyperammonemia in clinical practice [31]:
   - Hereditary hyperammonemia, as a result of various genetic defects in the urea cycle enzymes.
   - Acquired hyperammonemia, due to a decrease in the activity of the ornithine cycle and glutamine synthetase reaction; most often hepatic – in liver cell failure, as well as after portosystemic shunt surgery with the development and progression of portal hypertension – or extrahepatic (non-cirrhotic).

To date, the following causes of non-cirrhotic hyperammonemia have been identified [32, 33]:
A. Conditions associated with increased ammonia production
   - Infections with urease producers: *Proteus mirabilis, Klebsiella* species, *Escherichia coli, Morganella morganii, Providencia rettgeri, Corynebacterium* (causative agents of diphtheria), *Mycobacterium genavense, Herpes simplex* [34], and *Helicobacter pylori* (a greater incidence of non-alcoholic fatty liver disease [NAFLD] has been reported in patients with helicobacteriosis [35, 36].
   - Hemato-oncological disorders and their treatment: multiple myeloma, chemotherapy for acute leukemia, bone marrow transplantation, and 5-fluorouracil [37].
   - Organ transplantation [37].
   - Protein load and increased catabolism: intensive physical exercise, seizures, long-term malnutrition or severe injury, parenteral nutrition, gastrointestinal bleeding, steroid use, and bariatric surgery.
   - Overexertion, circadian rhythm disorders, and nightshift work without sufficient rest, i.e., sleep deprivation [38].
   - Hyperammonemic encephalopathy cases have been reported after Roux-en-Y gastric bypass (RYGB) surgery, the most common weight loss procedure performed in the USA [39–41]; a mortality rate approximating 50% has been reported in women aged 34–69 years without a history of liver disease [40–52]. The risk of a fatal outcome may be owing to the bariatric surgery–related hyperammonemia not being accompanied by any biochemical changes in hepatic metabolism.
   - Hyperammonemia may also occur in women during pregnancy and childbirth; it is associated with impaired hydrolytic deamination in intensely working muscles and with eclampsia.
   - In adults, partial enzyme deficiency may manifest as stress-associated diseases – such as postpartum stress, acute intestinal infection, short bowel syndrome, and gastrointestinal bleeding – or occur with heart and lung transplantation or parenteral nutrition with high nitrogen intake [43, 53, 54].
B. Conditions associated with decreased ammonia production
   - Ureterosigmoidostomy.
   - Portal systemic shunts, including congenital.
   - Use of the following medicines: valproic acid, glycine, carbamazepine, ribavirin, sulfadiazine, pyrimethamine, and salicylates.
   - Congenital metabolic defects: ornithine cycle disorders, defects in the β-oxidation of fatty acids and organic acids, and impaired metabolism of pyruvate.

4. Provision 4

The determination of ammonia and ammonium levels in the liver has following purposes:
1. To identify the level of hyperammonemia and monitor the efficacy of therapy in patients with any adjudicated acute or chronic liver disease.
2. To identify hyperammonemia in patients with chronic exo- or endogenous intoxication as part of the diagnosis.
3. To identify hyperammonemia in patients with symptoms of encephalopathy of various grades, asthenia, chronic fatigue, and neuroses as part of the diagnosis.
4. To identify congenital defects of nitrogen metabolism in the pediatric population with psychological defects in personality development.
5. To evaluate the rate of recovery of metabolism in stressful situations, such as physical and psychological stress, surgical interventions, and nutritional distress.
6. For the purpose of other situations, as per a physician’s recommendation.

5. Provision 5

Physiological (functional) hyperammonemia may occur in the following cases: postprandial (high-protein diet), after physical exertion (sports), after psychogenic overload (post-stress), fatigue (long-term sleep deprivation), and in other situations (e.g., pregnancy).

5.1. Comments:
Physiological hyperammonemia is a sign of metabolic disorders in the muscle tissue and often manifests as fatigue due to impaired adenosine triphosphate (ATP) synthesis. Increased adenylyl cyclase activity in the case of impaired ATP resynthesis increases the production of ammonium ions, shifting metabolism towards excessive lactate formation, the development of acidosis, and hyperventilation, that is, hyperpnea [55, 56].
A high-protein diet, malnutrition, overeating, intense physical exertion (mainly in men and bodybuilders),...
total parenteral nutrition, and childbirth also causes an increase in ammonium in the body. Ammonia levels increase especially in cases when a high-protein diet is followed after malnutrition [57]. During anaerobic exercise, ammonia metabolizes to urea in the hepatocytes and skeletal muscles; muscle fatigue occurs as a result of exercise and leads to a noticeable decrease in performance. The main factors in the development of physical and psychological fatigue are decreased muscle contractions, the accumulation of metabolic products of energy sources, and an imbalance of the internal environment.

6. Provision 6

Congenital hyperammonemia is caused by a deficiency or defect in Krebs cycle enzymes – carbamoyl phosphate synthetase (hyperammonemia type 1), ornithine carbamoyltransferase (hyperammonemia type 2), citrullinase (citrullinemia), argininosuccinate lyase deficiency (argininosuccinaturia), or arginase (hyperargininemia)—and is observed, as a rule, in early childhood.

6.1. Comments:

There are several types of genetic diseases caused by a deficiency or defect in an enzyme:

- Hyperammonemia type 1: based on a defect in carboxyl phosphate synthetase I
- Hyperammonemia type 2: based on a defect in ornithine carbamoyltransferase
- Citrullinemia: based on a defect in argininosuccinate synthetase
- Argininosuccinaturia: based on a defect in argininosuccinate lyase
- Hyperargininemia: based on an arginase deficiency

Some orphan diseases have also been reported in recent years. The rare clinical syndrome of hyperornithinemia–hyperammonemia–homocitrullinuria (HHH), ORPHA:415, Online Mendelian Inheritance in Man (OMIM) number 238970, have been described, which is a genetic disorder of the urea cycle caused by mutations in the LC25A15 gene (MIM 603861, alternatively named ORNT1) encoding mitochondrial ornithine carrier ORC1. HHH syndrome is a heterogeneous disease with various symptoms ranging from mild to severe, regardless of the age of the child. Symptoms include learning difficulties, mild neurogenic disorders to coma, lethargy, liver failure, and seizures [58].

Hyperinsulinism/hypoglycemia (HI/HA) syndrome has also been described; it has the second highest incidence after congenital hyperinsulinism, and is caused by mutations in the mitochondrial enzyme – glutamate dehydrogenase – which regulates the GLUT1 glucose transporter. Clinically, HI/HA syndrome manifests as episodes of postprandial protein- and leucine-sensitive hypoglycemia with persistent hyperammonemia [59].

Furthermore, there are reported cases of hyperammonemia associated with genetic lysinuric protein intolerance caused by mutations in the SLC7A7 gene, which determines the membrane transport of dibasic amino acids (ornithine, arginine, and lysine). In the absence of protein intake through food, the ammonia level is within the normal range; however, it increases significantly after the consumption of proteins, which can lead to coma [60].

7. Provision 7

Acquired hyperammonemia can be divided into the following types according to the pathogenesis:

- Hepatogenic: infectious, toxic, infectious-toxic, and metabolic
- Gastroenterogenic
- Urogenic
- Vascular: for example, in portal hypertension
- Postoperative, including post-transplant
- Toxic: medicinal, including cytostatic, as well as post-radiation, oncological, oncohematological, associated with burns, smoking, and alcohol
- Catabolic: high-protein diet, deficient diets, anaerobic exercise, age-related sarcopenia
- Acidosis, bacterial overgrowth syndrome, and long-term constipation

Hyperammonemia may be observed in any pathologies with increased protein catabolism, such as massive blood loss, severe burns, tissue compression or crush syndrome, extensive purulent necrosis, gangrene of the extremities, hyperthermia of various origins, and sepsis. These disorders cause loss of muscle mass, lack of antioxidation protection, and significantly suppressed immunity. An increase in ammonia, or imbalance in the ionized and non-ionized forms, is registered in autism; its role in the development of Alzheimer’s disease is also not excluded. Viruses causing acute respiratory infections have been shown to decrease the activity of carbamoyl phosphate synthetase – the main
The binding of ammonia during glutamate synthesis causes difficulty in urine outflow complicated by infections caused by urease-producing bacteria (Proteus species, Corynebacterium species, Klebsiella species, Morganella morganii, etc.). In this case, the resulting free ammonia diffuses into the blood [63]. A correlation between small intestinal bacterial overgrowth (SIBO), capillary blood ammonia levels, and cognitive impairment has been established [64]. Hyperammonemia after transurethral resection of the prostate has been described [65].

Cases of hyperammonemia have also been registered after lung transplantation [66], with ureaplasma among the causes [67], as well as after kidney transplantation [68, 69].

8. Provision 8

The most researched clinical manifestations of hyperammonemia are hepatic encephalopathy (HE) including minimal and so-called “covert” encephalopathy, without observed clinical symptoms, subclinical hepatic failure due to endothelial dysfunction, and activation of hepatic stellate cells leading to aggravation of hepatic fibrogenesis.

8.1. Comments:

The Number Connection Test (NCT) may be used as a screening method for encephalopathy. HE is the most common manifestation of hyperammonemia.

There are several proposed theories and stages of HE pathogenesis:

- The binding of ammonia during glutamate synthesis causes depletion of α-ketoglutarate in the tricarboxylic acid cycle, with a decrease in ATP production and impaired cell activity.
- NH₄⁺ ions cause alkalization of blood plasma. Simultaneously, the affinity of hemoglobin for oxygen (the Bohr effect) increases; consequently, hemoglobin does not release oxygen in the capillaries, resulting in cellular hypoxia.
- The accumulation of free NH₄⁺ ions in the cytosol affects the membrane potential and activity of intracellular enzymes as it competes with Na⁺ and K⁺ pumps.
- Glutamine, the product resulting from the binding of ammonia to glutamic acid, is an osmotically active substance. This leads to water retention in and subsequent swelling of the cells, which causes tissue swelling. In the case of nervous tissue, this may cause cerebral edema, coma, and death.
- Glutamine is removed from the central nervous system via a transport system, by means of exchange; therefore, an increase in the rate of ammonia release is accompanied by an increase in the transport of aromatic amino acids from the blood. This causes inhibition of the enzymatic system, which normally converts tyrosine into dopamine and noradrenaline. Consequently, the initial compounds are metabolized by the formation of false neurotransmitters – similar in structure to true adrenergic neurotransmitters – which replace the latter at neuromuscular synapses, but with a 50-fold lower efficiency in transmitting nerve impulses.

Furthermore, an increase in blood ammonia level is associated with the administration of a number of medicinal products, including salicylates, tetracycline, glucocorticoids, asparaginase, 6-azauridin, allopurinol, thiazide diuretics, ethacrynic acid, isoniazid, and carbamazepine. [61] Valproate-induced hyperammonemic encephalopathy in patients with epilepsy is not a rare complication and sometimes has a fatal outcome. In these cases, the increase in neurotoxin level is caused by the depletion of N-carbamylglutamate; it may develop rapidly and with long-term use of the medication [70]. The mechanism of drug-related hyperammonemia is not always clear. Secondary infections, hypovolemia, and a history of constipation are some of the risk factors involved in its development.

Hyperammonemia may also develop due to alcohol or substance abuse. One cigarette increases the level of ammonia in the blood by 10 μmol/L.

Table 1

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>minimal clinical symptoms</td>
</tr>
</tbody>
</table>

The pathogenesis of HE is based on an imbalance in amino acids in the brain, leading to astrogial swelling and dysfunction, namely, altered postsynaptic receptors and neurotransmission, impaired permeability of the blood–brain barrier, and decreased energy supply to neurons. The severity of clinical manifestations often correlates with the level of ammonia in the blood serum. Depending on the severity of the brain disorder, four grades of HE are distinguished (Table 1).

In recent years, progress in diagnostic techniques has enabled distinguishing symptomatic HE stages (disorientation, ataxia, and coma) from the stage presenting with minimal clinical symptoms (covert HE).

Covert HE can be diagnosed using special questionnaires or the method of evoked potential. Often, patients and their relatives do not perceive observed cognitive and psychomotor disturbances, such as difficulties with decision-making or a reduction in psychomotor speed, as symptoms of the disease. It should be taken into account that clinical symptoms of covert HE include increased fatigue, weakness, irritability, sleep inversion (drowsiness during the day and insomnia at night), speech disorders, impaired handwriting, difficulty focusing while driving and performing work that requires increased focus, tremor, and hypoactive...
Table 1. West Haven criteria for grading hepatic encephalopathy

<table>
<thead>
<tr>
<th>HE grade</th>
<th>Level of Consciousness</th>
<th>Flapping tremor (asterixis)</th>
<th>NCT time (s)</th>
<th>EEG, alpha rhythm frequency (waves/s)</th>
<th>Arterial ammonia level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No changes</td>
<td>No</td>
<td>15–30</td>
<td>8.5–12</td>
<td>Normal (11–55 μmol/L)</td>
</tr>
<tr>
<td>1</td>
<td>Sleep pattern disturbance, confusion, euphoria or anxiety, shortened attention span, difficulty performing arithmetic addition</td>
<td>Rare flapping tremor (1–2 movements/30 s) (asterixis)</td>
<td>31–50</td>
<td>7–8</td>
<td>Increased, up to 1.33-fold higher than the upper limit of normal</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy or apathy, minimal disorientation of time and place, personality change, inappropriate behavior, difficulty performing arithmetic subtraction</td>
<td>Irregular tremor (3–4 movements/30 s) (asterixis)</td>
<td>51–80</td>
<td>5–7</td>
<td>Increased, 1.33–1.67-fold higher than the upper limit of normal</td>
</tr>
<tr>
<td>3</td>
<td>Somnolence but responsive to verbal stimuli, gross disorientation</td>
<td>Frequent tremor (5–10 movements/30 s) (asterixis)</td>
<td>&gt; 120</td>
<td>3–5</td>
<td>Increased, 1.67–2-fold higher than the upper limit of normal</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>Almost constant flapping tremor (inability to finish the test)</td>
<td>&lt; 3</td>
<td></td>
<td>Increased, &gt; 2-fold higher than the upper limit of normal</td>
</tr>
</tbody>
</table>

Table 2. Differential diagnosis of hepatic encephalopathy and conditions accompanied by cognitive impairment

<table>
<thead>
<tr>
<th>Diseases and syndromes</th>
<th>Causes</th>
<th>Clinical signs and neurovisualization data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wernicke–Korsakoff syndrome</td>
<td>Thiamine deficiency–related encephalopathy. The main cause is alcohol abuse, as well as uncontrollable vomiting, malnutrition, and bariatric surgeries.</td>
<td>Acute or subacute onset, possible progression to coma, characteristic regress of symptoms with appropriately timed thiamine-replacement therapy. Classic triad (16–38% of cases): ocular disturbances (nystagmus, ocular disorders, abnormal papillary responses), ataxia, changes in consciousness/behavior. MRI findings: symmetric hyperintense lesions in mamillary bodies, thalami, or periaqueductal grey matter. Specificity of changes, 93% [74].</td>
</tr>
<tr>
<td>Marchiafava–Bignami disease</td>
<td>Corpus callosum primary degeneration (demyelination) in adults and older patients. Rare syndrome associated with abuse of poor-quality red wine.</td>
<td>Typical gradual onset with steady progression. Clinical signs are associated with cortical disorders: overt memory derangement, apathia, apraxia, episodes of agitation followed by depression, propensity to violence, auditory and visual hallucinations. Subcortical disorders (athetosis, chorea, tic disorders), gait disturbances (irregular step length, absence of anteropulsion, shuffling “skier’s” gait). MRI findings: hyperintense lesions in the corpus callosum on T2-weighted MRI in the acute phase, with cysts in necrotic areas [75, 76].</td>
</tr>
<tr>
<td>Alcoholic dementia*</td>
<td>Long-term alcohol abuse</td>
<td>Gradual onset and slow progression: impaired attention span, impaired short-term memory, thinned flattening, primitive sense of humor, personality changes (anger, aggression). It differs from vascular dementia in having more pronounced delayed recall and recognition, and from Alzheimer’s disease due to the absence of severe memory deficit. MRI findings: diffuse cerebral atrophy with more pronounced atrophy of the frontal cortex and cerebellum, characteristic dilatation of the third ventricle [75, 77].</td>
</tr>
<tr>
<td>Alcohol withdrawal syndrome</td>
<td>Complete withdrawal from alcohol use or its reduction in individuals with physical addiction</td>
<td>Characteristic generalized mild or moderate tremor, tachycardia, skin hyperemia, hypertension. Behavioral disturbances: overt anxiety, sleep disturbances (nightmares). In the worst-case scenario, development of acute psychosis (delirium tremens) with auditory, visual, and olfactory hallucinations. A specific pattern in neurovisualization has not been described [75].</td>
</tr>
<tr>
<td>Diseases and syndromes</td>
<td>Causes</td>
<td>Clinical signs and neurovisualization data</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pellagra</td>
<td>Lack of niacin (vitamin B3) in patients with chronic alcoholism or malnutrition (homeless people, patients with anorexia). Cases have been reported in HIV, Crohn’s disease, carcinoid syndrome, patients undergoing dialysis, and during the administration of certain medicines (isoniazid, ethionamide, 6-mercaptopurine).</td>
<td>Classic pellagra triad: dermatitis, diarrhea, dementia. Dermatitis: symmetric erythema, pruritus, vesicular rash on non-covered parts of the body – extremities, face, around the neck (Casal collar). Neuropsychiatric signs vary from headaches and irritability to memory loss and psychosis. A specific pattern in neurovisualization has not been described [78].</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Underactive thyroid gland</td>
<td>Clinical signs: memory and concentration disturbances, general lack of interest, hyponnia, tiredness and somnolence. Possible development of seizures, vestibular ataxia (abnormal gait, nystagmus). Rare neurological signs: psychosis and severe impairment of consciousness. Based on several clinical observations, hypothyroidism may be considered a factor, aggravating the development of HE and possibly inducing hyperammonemia [79]. A specific pattern in neurovisualization has not been described. Diagnosis is based on TSH, T3, and T4 levels, and etiology of the disease.</td>
</tr>
</tbody>
</table>

Muscle reflexes. Such dysfunctions may lead to serious car accidents with severe consequences [71, 72]. In this regard, diagnosing covert HE is of great importance for workers in many fields, such as vehicle drivers and automated equipment operators.

Among all the grades of HE, covert HE is the most difficult to differentially diagnose because, despite satisfactory time and place orientation, there are changes in psychomotor or neuropsychological test results. Clinical examination at this stage may reveal some cognitive dysfunctions and/or behavioral disorders, including mild disorientation, euphoria or anxiety, decreased focusing ability, difficulty performing arithmetic addition or subtraction, and a change in sleep pattern [73]. At this stage, HE should be differentiated from a number of conditions accompanied by cognitive impairment (Table 2).

Given that there is a correlation between the level of hyperammonemia and the grade of HE, which can be determined using the NCT, it is possible to implicitly assume the severity of hyperammonemia using the same NCT. The severity of encephalopathy is calculated based on the speed of the test performance (Table 3).

For the convenience of the physician and the patient, an NCT can be carried out online as well.

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>HE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>0</td>
</tr>
<tr>
<td>40–60</td>
<td>Covert</td>
</tr>
<tr>
<td>61–90</td>
<td>1, 1–2</td>
</tr>
<tr>
<td>91–120</td>
<td>2</td>
</tr>
<tr>
<td>121–150</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 150</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3. Determination of hyperammonemia severity based on the time taken to complete the Number Connection Test

Note: HE: hepatic encephalopathy

9. Provision 9

Persistent and progressive hyperammonemia in NAFLD has a profibrogenic effect, contributing to hepatic hemodynamic disorders, development of portal hypertension, and subsequently sarcopenia.

9.1. Comments:

In a study among patients with chronic liver disease with fibrosis grade 0–1 as per polyhepatography, portal hepatic hemodynamic disorders were reported. In patients with fibrosis grade 0, these changes were dynamic as per functional tests with deep breathing and nitrates. The obtained data demonstrate that intrahepatic microcirculation disorders at various locations already develop in the early stages of chronic liver disease. Endothelial dysfunction was also observed in patients with chronic liver disease, including endothelium-dependent vasodilation impairment, an increase in nitric oxide metabolites in the peripheral blood, and impaired expression of nitric oxide synthases in the liver tissue (a decrease in the expression of endothelial nitric oxide synthase).
10. Provision 10

Physiological (functional) transient, rapidly reversible, hyperammonemia does not require therapy. Pathogenetic therapy for hyperammonemia, regardless of the grade of severity, is aimed at treating the primary disease; this includes a diet that is restricted in animal protein and contains sufficient vegetable protein, limitation of physical exertion, and administration of intestinal non-absorbable antibiotics (rifaximin-alpha), or pre- and probiotics (if indicated).

L-ornithine-L-aspartate (LOLA) is a baseline medicinal product, administered as monotherapy or in combination with other medicines, to help correct the level of hyperammonemia; it may potentiate the specified pharmacodynamic effects of medicines of other pharmacological classes.

10.1. Comments:

Modern treatment methods for hyperammonemia aim to reduce ammoniogenesis, absorb ammonia in the gastrointestinal tract, and activate ammonia removal – through the activation of ureagenesis – by treating the primary disease or supplementing intermediate products of the urea cycle and glutamine synthesis [93, 94].

A very low-protein diet may increase serum ammonia levels owing to the activation of muscle catabolism. In addition, limiting protein intake worsens nutritional status (stimulates protein catabolism in the body), which adversely affects the health of patients with HE [95]. In patients diagnosed with liver cirrhosis, the minimum daily dietary protein intake necessary to maintain a nitrogen balance is 0.8–1.0 g per kg of body weight [96]. Therefore, at present, some physicians recommend a normoprotein diet to patients with HE, while in cases of intolerance of vegetable protein substitution with animal protein is recommended [97–99].

LOLA, a stable salt of ornithine and aspartic acid, is an important substrate for the synthesis of glutamine and urea, the main components of deamination [100]. LOLA promotes the glutamine synthetase reaction in the liver and muscles. It also plays an important role in ensuring that aspartate enters the Krebs cycle; that is, it increases the synthesis of macroergic (high-energy) compounds and reduces the formation of lactic acid which, in turn, reduces the permeability of the blood–brain barrier to toxic substances.

The main pharmacological properties of LOLA include a double mechanism of action, as both amino acids enter the ornithine cycle, increasing protein tolerance and having an anabolic effect, increasing the energy potential of cells, and enhancing the utilization of lactic acid. The membrane-stabilizing effect provides the antioxidant effect of LOLA; this is especially important in chronic liver disease, primarily that with an alcoholic etiology.

Experimental and clinical studies have demonstrated that in NAFLD, hyperammonemia develops at the precirrhotic stage owing to the decreased activity of enzymes of the ornithine cycle [83–88]. In mice with NAFLD that were fed a high-fat diet, a decrease in enzyme levels was observed; it was accompanied by a decrease in urea synthesis and an increase in the level of ammonia in the liver tissue in comparison with the control group. In patients with NAFLD and obesity, a significant decrease in the number and activity of enzymes of the ornithine cycle was observed as compared to healthy individuals, and these changes were much more pronounced at the stage of steatohepatitis than at the stage of steatosis [89–92].

A British study [82] demonstrated in vitro and in vivo that hyperammonemia is the cause of:

- activation of stellate liver cells,
- reduction of cellular metabolism and proliferation of stellate liver cells,
- activation of the profibrogenic/pro-inflammatory profile of stellate cells,
- intrahepatic hemodynamic disorders and an increase in portal venous pressure,
- stimulation of endoplasmic reticulum stress, and
- induction of formation of reactive oxygen species.

In patients diagnosed with liver cirrhosis, the liver fibrosis profile of stellate cells,
- increase in portal venous pressure,
- stimulation of endoplasmic reticulum stress, and
- induction of formation of reactive oxygen species.
10.2. Pharmacological methods of reducing ammonia and ammonium synthesis

The main purpose of treating patients with hyperammonemia and HE is to inhibit the growth of urease-producing intestinal bacteria. The beneficial effect of rifaximin-alpha in the treatment of hyperammonemia has been demonstrated in several clinical studies [111-113]. Rifaximin alpha, a non-absorbable broad-spectrum antibiotic, is effective against most gram-positive and gram-negative aerobic and anaerobic bacteria. This medicinal product remains practically unabsorbed in the gastrointestinal tract; no more than 1% of the dose remains in the blood after oral administration under fasting conditions. Minimal absorption of the active substance into the blood plasma reduces the risk of systemic adverse effects and extraintestinal interactions with other medicinal products, and eliminates the need for dose adjustment in patients with liver disease.

It has been shown that rifaximin-alpha is more effective for the treatment of HE than non-absorbable disaccharides. Good Clinical Practice–compliant studies have confirmed that rifaximin-alpha may be more effective than lactulose in a number of patients with HE grades 1–3 [81, 114, 115]. The recommended total daily dose for adults (1200 mg/day) is usually divided into three doses of 400 mg each per day over 7–10 days; such a treatment course should be repeated monthly over an extended period, if necessary [116].

This medication has demonstrated clinical benefits in terms of lowering the level of ammonium in the blood and improving the clinical manifestations of HE. Several studies have also shown a decrease in the number of hospitalizations in patients with recurrent encephalopathy receiving rifaximin-alpha [117-120].

The use of probiotics enables competitive displacement of urease-producing pathogenic bacteria in the intestine. Studies that assessed the effect of probiotics on HE [121, 122] revealed a reduction in intestinal permeability and secretion of bacterial urease, an increase in the release of ammonia, and an improvement in the metabolic potential of the intestinal epithelium; moreover, probiotics play a role in reducing the concentration of ammonia in the portal blood given that they inhibit bacterial urease activity.

Since most probiotics produce acids that lower the intestinal pH, ammonia absorption decreases [123]. In addition, probiotics help to reduce inflammation and oxidative stress in liver cells, which results in an increase in the hepatic clearance of ammonia and a decrease in the absorption of other toxins.

A meta-analysis of 21 randomized clinical studies including 1420 patients with HE showed that probiotics reduce the clinical manifestations of HE, improve the quality of life of patients, and contribute to a decrease in ammonia concentrations in the portal blood plasma [124]. In another study employing rheohepatography, impaired portal blood flow was conclusively observed in hyperammonemia in patients with chronic liver disease of various etiologies [104–107]. Data from a multicenter, non-randomized, prospective cohort study among 1167 patients with chronic liver disease – including 648 patients with non-alcoholic steatohepatitis – demonstrated the efficacy and good tolerability of LOLA [107]. An increase in the concentration of ammonia is already recorded in patients with chronic liver disease at the precirrhotic stage [104]. In a study among patients with non-alcoholic fatty liver disease, it was shown that with the use of LOLA, the hyperammonemia that was initially present with fibrosis grade 0–1 decreased significantly and was accompanied by an improvement in the overall health status and laboratory test results. In another study employing rheohepatography, impaired portal blood flow was conclusively observed in hyperammonemia in patients with precirrhotic stages of chronic liver disease [108].

The treatment of 289 patients with non-alcoholic steatohepatitis using LOLA for 3 months, with good tolerability and high patient compliance, contributed to a decrease in ammonia levels, correlated with a decrease in vascular disorders, and lead to a significant improvement in clinical and biochemical parameters and quality of life [80]. LOLA improves intrahepatic blood flow in patients with various types of portal hemodynamic disorders. In addition, it reduces ammonia in the blood and, consequently, probably deactivates stellate liver cells, decreases their contractility, and improves hepatic blood flow.

LOLA also helps to prevent traffic accidents in drivers with chronic hepatitis C and minimal liver fibrosis [109]. Furthermore, hyperammonemia correction using LOLA potentiates the effects of the alpha- and beta-blocker, carvedilol, in patients with circulatory failure related to alcoholic liver disease [110].
11. Provision 11

Liver injuries related to coronavirus disease (COVID-19) have multiple etiologies and require pharmacological treatment. The disease prognosis is worsened by pre-existing chronic diseases, such as non-alcoholic fatty liver disease and alcoholic and toxic liver damage, including drug-induced and chronic viral hepatitis. The severity of the patient’s condition, including: examination of the abdomen, palpation, percussion of the abdominal organs with the definition of areas of hyperactive bowel sounds, tenderness to deep palpation, and the size of the liver and spleen according to Kurlov. It is also necessary to clarify the characteristics of the stool: frequency per day, volume, shape (consistency), color, smell, and pathological impurities

- Laboratory tests: alanine transaminase, alanine aminotransferase, gamma–glutamyl transpeptidase, alkaline phosphatase, and bilirubin
- Measurement of ammonia levels (for correction of hyperammonemia)
- Abdominal ultrasound (in case of clinical signs and laboratory findings suggestive of liver injury)

The disease prognosis is worsened by pre-existing chronic diseases, including:
- non-alcoholic liver disease,
- alcoholic liver disease,
- toxic liver damage,
- drug-induced liver injury, and
- viral hepatitis.

An increase in the level of ammonia in the peripheral blood has been reported in all hospitalized patients with COVID-19. It should be noted that a further increase in this value (above the cut-off point) results in severe disease progression with deterioration of the clinical state, which requires specialized respiratory support and the transfer of the patient to anesthesiology and resuscitation units. Thus, the grade of hyperammonemia may be considered a prognostic marker of disease severity [130].

Medication, LOLA, in these clinical cases is required to manage hyperammonemia while monitoring the levels of ammonia and ammonium in the peripheral blood [131].

11.1. Comments:

Frequent digestive system lesions caused by SARS-CoV-2, as well as its possible combination with gastrointestinal pathology, complicates the set of therapeutic and diagnostic measures for such patients and implies modification of the existing approaches and clinical guidelines.

The COVID-19 spike glycoprotein has a tropism for endothelial cells, hepatocytes, and cholangiocytes containing ACE2 receptors, which cause damage to parenchymal organs, including the liver and mucous membranes. Chronic liver disease aggravates the severity of the patient’s condition.

Diarrhea, nausea, and vomiting may be among the first symptoms of COVID-19, in addition to the clinical signs of acute respiratory viral infection. Studies show rather heterogeneous data on the frequency of symptoms of digestive system lesions from the onset of the disease.

Fifty percent of patients with COVID-19 have a transient increase in transaminase activity, bilirubin levels (up to 2-fold higher than the upper limit of normal) caused by hyperactivation of the immune system, cytokine production, and inflammation (bystander hepatitis), together with viral damage to cholangiocytes and hepatotoxic effects secondary to the medications administered.

Patient examination should include:

- Clarification of digestive system complaints: anorexia, change in bowel habits, flatulence, nausea, vomiting, and abdominal pain
- Physical examination, determining the severity of the patient’s condition, including: examination of the abdomen, palpation, percussion of the abdominal organs with the definition of areas of hyperactive bowel sounds, tenderness to deep palpation, and the

in the concentration of ammonia in the blood plasma; however, they do not affect mortality rate [124].

Oral administration of Lactobacillus strains reduces blood ammonia levels in patients with liver cirrhosis [125]. Studies have shown that Lactobacillus acidophilus strains modify the intestinal flora and improve cognitive function in patients with liver cirrhosis, while the Enterococcus faecium SF68 strain increases protein tolerance, contributes to a decrease in ammonia levels, and improves mental state and psychometric indicators in the long-term treatment of patients with liver cirrhosis and HE grade 1–2 [126, 127]. Combinations of high-concentration probiotic strains (Bifidobacterium sp., Lactobacillus sp., and Streptococcus thermophilus) have a significant effect on the grade of hyperammonemia in patients with cirrhosis and HE [128].

Currently, probiotics are considered second- or third-line therapy for hyperammonemia and HE. Simultaneously, lactitol and lactulose prebiotics may be the treatment of choice in certain cases of HE [127, 129, 35].

Experts note that there are no proven correlations between the level of hyperammonemia and clinical signs of any diseases apart from liver disease. HE and liver fibrosis pathogenesis is widely studied and these conditions require a thoughtful and differential approach to treatment, which therefore should target numerous pathophysiologic factors that contribute to elevated levels of nitrogen metabolism end products.
12. Provision 12

Therapeutic indications for LOLA are:
- acute and chronic liver disease, accompanied by hyperammonemia,
- HE (covert and overt), and
- steatosis and steatohepatitis (of various etiologies).

Depending on the severity of hyperammonemia, the recommended treatment courses are:
- Mild hyperammonemia (grade 1): LOLA 3.0–6.0 g (1–2 sachets) 3 times per day for 4 weeks; after the completion of treatment, performance of the NCT and measurement of the ammonia level in the blood
- Moderate hyperammonemia (grade 2): LOLA 3.0–6.0 g (1–2 sachets) 3 times per day for up to 3 months; during and after completion of treatment, performance of the NCT and measurement of the ammonia level in the blood
- Severe hyperammonemia (grade 3): LOLA 10.0–40.0 g (20.0–80.0 mL) per 400.0 mL of sodium chloride saline solution intravenously by slow drip infusion daily until clinical symptoms are resolved and ammonia levels in the blood are reduced. Thereafter, 3.0–6.0 g (1–2 sachets) 3 times per day for up to 3–6 months (if necessary, for a longer period); during and after completion of treatment, performance of the NCT and measurement of the ammonia level in the blood

If necessary, treatment courses may be repeated. Before using the medication, the patient should carefully read the instructions.

13. Conclusion

Hyperammonemia is a condition characterized by an elevated level of ammonia and ammonium in the blood. It can be physiological (transient, which does not require therapy) or pathological (related to the increased formation or decreased excretion of these toxic entities due to the reduced protective function of the liver). Chronic hyperammonemia manifests in the development of hepatic steatosis or fibrosis, encephalopathy, and sarcopenia. Hyperammonemia treatment involves a combination of therapeutic options to neutralize and excrete toxic products of nitrogen metabolism in order to prevent life-threatening complications. Among the medications to treat hyperammonemia, L-ornithine-L-aspartate (LOLA) should be considered, which is available in a parenteral and oral dosage forms for the treatment of hepatogenic hyperammonemia and hepatic encephalopathy of different stages, and may help to mitigate the risk of liver disorder progression related to hyperammonemia.

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