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The problem of hyperammoniemia after orthotopic liver transplantation

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Abstract

Background. *Currently, there is no doubt that orthotopic liver transplantation increases life expectancy compared to standard treatment methods in patients with decompensated liver cirrhosis. In recent years, diagnostics and treatment of hyperammonemia have attracted increasing attention in various liver diseases, including patient after liver transplantation. At the same time, there are few studies with a high level of evidence establishing a relationship between the blood level of ammonia and the severity of patient condition in the early period after liver transplantation.*

Objective. *To summarize current data on the problem of hyperammonemia after liver transplantation, to analyze the mechanisms*

of appearing high ammonia concentrations in blood serum and their pathogenetic role in the development of complications after orthotopic liver transplantation, and also to investigate the methods for monitoring the blood ammonia levels.

Material and methods. *The analysis of data from world experimental and clinical studies on the pathogenesis, diagnostics, and treatment methods of hyperammonemia after orthotopic liver transplantation has been made. The literature search was conducted in international databases (PubMed/MedLine, ResearchGate), as well as in the scientific electronic library of Russia (eLIBRARY.RU) for the period from 2019–2024.*

Conclusion. *In the analyzed publications, the issues on the problem of hyperammonemia after liver transplantation are worthwhile to be addressed to. Despite advances in understanding the pathogenesis of hyperammonemia and its impact on the development of hepatic encephalopathy and disorders on the part of other body organs and systems, many unresolved issues remain both in diagnosis and in choosing the most effective treatment methods.*

Keywords: hyperammonemia, orthotopic liver transplantation, renal replacement therapy

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AKI, acute kidney injury
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ATP, adenosine triphosphate
BBB, blood-brain barrier
BCAA, branched chain amino acids (a group of proteinogenic amino acids with branched side chains)
CRRT, continuous(prolonged) renal replacement therapy

CVVHD, continuous venovenous hemodialysis
CVVHDF, continuous venovenous hemodiafiltration
CVVHF, continuous venovenous hemofiltration
EFR, effluent flow rate
ET-1, endothelin 1
GABA, gamma-aminobutyric acid
GluA1, glutamate A1 (glutamate receptor 1)
GluA2, glutamate A2, (glutamate ionotropic receptor AMPA type subunit 2)
GS, glutamate synthetase
HD, hemodialysis
HD, hemodialysis
HSC, hepatic stellate cell
IFN-γ, interferon γ
IL-1β, interleukin 1β
iNOS, inducible nitric oxide synthase
IRRT, intermittent renal replacement therapy
LOLA, L-ornithine L-aspartate
Na^+/K^+-ATPase, sodium-potassium adenosine triphosphatase
NF-κB, nuclear factor
NMDA, N-methyl-D-aspartate receptors
OLP, orthotopic liver transplantation
OS, oxidative stress
PD, peritoneal dialysis
PGE2, prostaglandin E2
PS-149, recombinant glutamine synthetase
Q/b, blood flow velocity
Q/d, dialysate flow rate
RNA, ribonucleic acid
ROS, reactive oxygen species
RRT, renal replacement therapy
SYNB1020, an engineered strain of Escherichia coli Nissle 1917 developed by Synlogic Inc.
TNF-α, tumor necrosis factor α

Introduction

Orthotopic liver transplantation (OLT) has dramatically changed the prognosis for patients with end-stage liver disease. Increased surgical activity is accompanied by improvements in surgical techniques and donor organ preservation, by the emergence of effective anti-relapse and antiviral therapy, and lifestyle changes, which leads to improved recipient survival rates: currently, overall survival rates at one and five years are 86% and 74%, respectively. There is currently no doubt that OLT increases life expectancy compared to standard treatments in patients with

decompensated liver cirrhosis [1]. In recent years, diagnostics and treatment of hyperammonemia have received increasing attention in various liver diseases, including those after liver transplantation. However, there are insufficient studies with a high level of evidence establishing a relationship between ammonia levels and the severity of the patient's condition in the early period after liver transplantation. Traditionally, hyperammonemia has been considered a problem of diffuse liver diseases and widely discussed in the literature, being one of the factors associated with hepatic encephalopathy and an unfavorable outcome of liver failure. Despite great advances in understanding the pathogenesis of hyperammonemia and its impact on the development of hepatic encephalopathy and disorders of other organs and systems of the body, many unresolved issues still remain, both in diagnosis and in the choice of the most effective treatment methods [2]. A number of researchers have noted the development of hyperammonemia after solid organ transplantation [3–6]. An interesting observation was presented by the authors [7] who noted the hyperammonemia development after successful transplantation due to a genetic defect in the synthesis of ornithine transcarbamylase identified in the donor liver. A recent study has established the effect of high ammonia levels on the activation of hepatic stellate cells (HSCs) and changes in their cellular morphology. It is well known that the HSCs play a crucial role in normal liver function; and structurally HSCs exhibit a characteristic star-like (or stellate) shape, similar to that of astrocytes. Astrocytes, in turn, play a leading role in the pathogenesis of hepatic encephalopathy, which is caused by hyperammonemia [8].

Our objectives were to summarize current data on the problem of hyperammonemia after liver transplantation, to analyze the mechanisms of

its development and pathogenetic role after orthotopic liver transplantation, as well as to study methods for monitoring ammonia levels.

Background

At a meeting of the St. Petersburg Society of Naturalists in St. Petersburg on March 8, 1878, M. Hahn presented a report on behalf of the Institute of Experimental Medicine, in which the toxicity of ammonia was first noted in a joint experimental study with I.P. Pavlov where portocaval shunting in dogs caused hyperammonemia and encephalopathy [9]. The pathway for the utilization of ammonia, or ureagenesis, in the body of mammals was described only 50 years later, in 1932, as a metabolic cycle in a publication by two German researchers. The first author, Dr. Hans Krebs (1900–1981), was then working as a physician and researcher in Freiburg, Germany. The second author was his research associate and colleague Kurt Henseleit (1907–1973). Later (in 1953), Hans Krebs was awarded the Nobel Prize in Physiology and Medicine for identifying and first describing the tricarboxylic acid cycle (also called the “Krebs cycle”). The year before this major achievement, Hans Krebs and Kurt Henseleit had conducted research that laid the foundation for the description of the “Krebs–Henseleit cycle,” which we now call the Urea Cycle. Since then, defects in all enzymes and transporters of the Urea Cycle have been described called primary urea cycle disorders, causing primary hyperammonemia. In addition, there is a still growing list of conditions that affect the function of the Urea Cycle through various cascades of mechanisms, thereby leading to secondary hyperammonemia [2].

Ammonia

Several organs are involved in maintaining ammonia homeostasis [10]. In healthy individuals, plasma ammonia levels are maintained

within a narrow range (reference interval) (10–50 μmol/L). At physiological pH, most (98%) ammonium is present as ammonium ion (NH_4^+), but diffusion across cell membranes occurs in the gaseous form of ammonia (NH_3). Ammonia is produced in the intestinal tract, detoxified in the liver and excreted by the kidneys. Deamination of biological amines and catabolism of nitrogen-containing macro- and micromolecules are sources of ammonia in the human body. The intestine is the key site of ammonia genesis in the body, most of it coming from the small intestine; and the metabolism of dietary nitrogen-containing molecules produces ammonia. Glutamine is the main source of energy for enterocytes where glutaminase enzymes deaminate it, forming glutamate and ammonia. Intestinal bacteria metabolize urea and generate ammonia, which is absorbed through the intestinal epithelium and is another source of ammonia. Ammonia exists in two molecular forms, NH_3 and NH_4^+. The relative amounts of each are regulated by a buffer reaction: $NH_3 + H^+ \leftrightarrow NH_4^+$. Under physiological conditions, ammonia has an acid dissociation constant of approximately 9.15. It is therefore almost instantly converted to its ionic form, ammonium (NH_4^+). Subsequently, most of the ammonia in the body exists as ammonium, with only about 1.7% as free ammonia. In muscle tissue, ammonia combines with pyruvate to enter the Cahill cycle (glucose-alanine cycle) to synthesize alanine, which is transported to the liver where it is metabolized again to release pyruvate and ammonia. More than 90% of the ammonia is then converted in urea via Krebs–Henseleit cycle by periportal hepatocytes and is eliminated from the circulatory bed by kidneys by means of glomerular filtration [11–13].

Renal ammonia entering the bloodstream, as well as the ammonia produced by the intestine, is metabolized in the periportal hepatocytes in the liver with the formation of urea, which is excreted in the urine (Fig. 1).

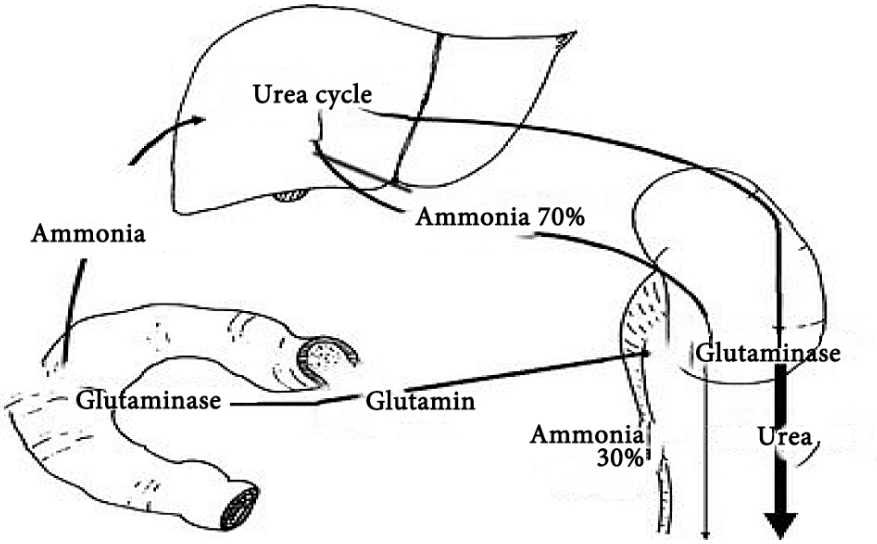

Fig. 1. The role of the kidneys in the interorgan metabolism of glutamine in physiological conditions [11]

The kidneys are one of the key organs that control and maintain normal systemic acid-base status through three mechanisms: reabsorption of filtered bicarbonate, generation of de novo ammonium (NH_4^+) and bicarbonate, and acid excretion, primarily as ammonium. To replace bicarbonate in the body, the proximal tubule produces ammonium, which is secreted by the collecting duct as ammonia and protons to form ammonium in the urine. Dysfunction at either of these two steps results in proximal and distal renal tubular acidosis, respectively. The ammonia excreted in the urine as ammonium ions leads to the formation of new equimolar bicarbonate, while the ammonia returning to the systemic circulation via the renal vein is metabolized by the liver to urea and glutamine. The damaged kidney responds to decreased urinary ammonium excretion by increasing ammonia production in the remaining functional nephrons. However, this compensatory reaction may lead to high local intrarenal ammonia concentrations, which in the long term may trigger pathogenic mechanisms in the remaining healthy renal tissue. The stimulation of the complement system, recruitment of inflammatory cells

and oxidative stress may be associated with high renal ammonia concentrations and contribute to a cascade of events that may ultimately lead to tubulointerstitial fibrosis. The resulting acidosis promotes systemic and renal production of endocrine factors such as aldosterone, angiotensin II or endothelin 1 (ET-1). ET-1 is known to belong to a family of vasoconstrictor peptides, the ETA receptors mediating vasoconstriction and the ETB receptors directly influencing both vasoconstriction and vasodilation. At low concentrations that do not exert a direct vasoconstrictor effect, ET-1 potentiates the effect of other vasoconstrictor agonists, playing a role in the development of renal ischemia. The mechanisms involved in balancing these two antagonistic actions remain to be determined [14, 15].

Etiology of hyperammonemia development after transplantation

There are many potential causes of hyperammonemia in patients after liver transplantation (Fig. 2). These include: a primary graft dysfunction, graft rejection, an acquired or congenital pathology of donor liver metabolism, the remained open portosystemic shunt, intake of certain medications (immunosuppressants), the deficiency of macro- and microelements after gastric bypass, and infectious process [16].

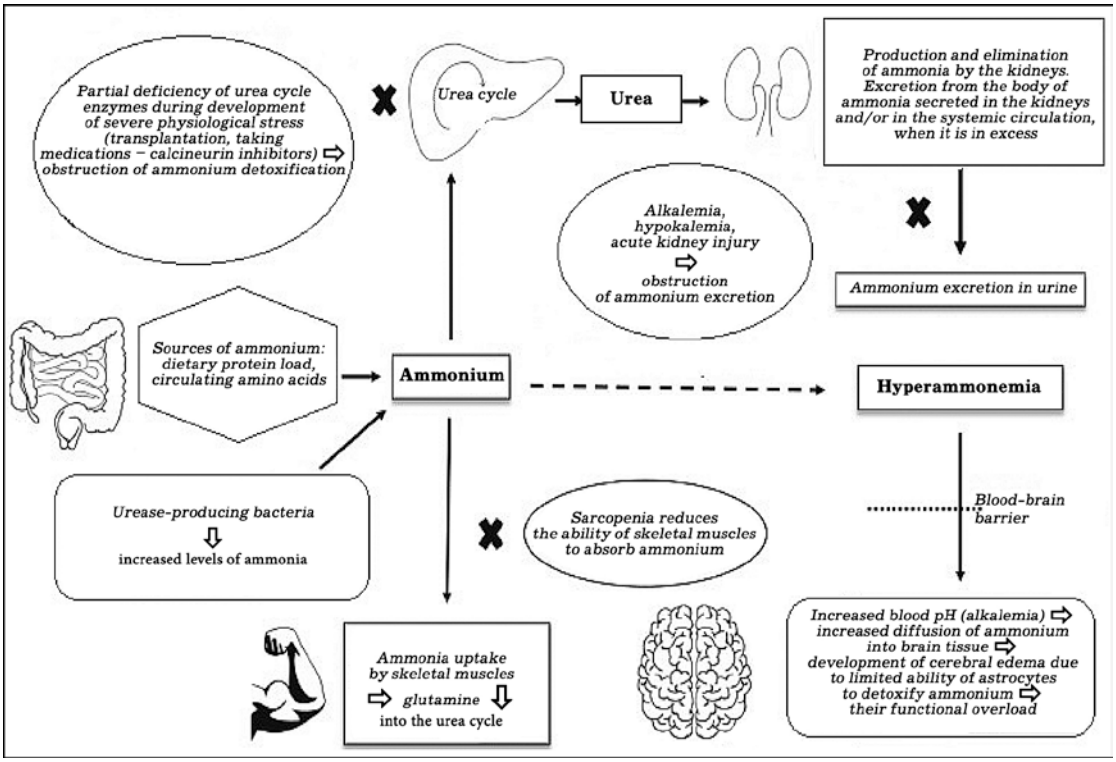

Fig. 2. Mechanisms underlying the development of hyperammonemia in transplant recipients [6]

The role of the gastrointestinal tract. The intestine is the main organ producing ammonia: bacterial metabolism of protein and urea occurs in the large intestine, bacterial decomposition of glutamate occurs in the small intestine. Ammonia production in the intestinal tract can increase significantly in the presence of bacteria that produce urease. Urease is an enzyme that performs the hydrolytic breakdown of urea to form ammonia and carbon dioxide. Detoxification and excretion of ammonia occur in the liver and kidneys; and the skeletal muscles provide significant buffering capacity in relation to ammonia. Urea cycle disorders (hereditary-genetic or caused by immunosuppression), the acid-base balance of the recipient and muscle mass affect the ability of the graft to cope with the increase in the blood level of ammonia, which leads

to an increased perfusion through the blood-brain barrier (BBB) with subsequent damage to astrocytes [6, 17].

The role of skeletal muscle. An increasing number of research papers are published that demonstrate a significant relationship between sarcopenia and prognosis in patients with liver cirrhosis. It is currently believed that the predictor-to-sarcopenia relationship significantly affects the life expectancy and the quality of life, the onset and course of cirrhotic complications, as well as the liver transplantation outcomes. It has been confirmed that elevated blood ammonia levels increase myostatin expression, which leads to a decrease in muscle mass. Hyperammonemia activates IκB kinase, causing nuclear factor NF-κB nuclear translocation. By binding to specific sites within the myostatin promoter, the NF- κB p65 subunit stimulates myostatin transcription, thereby suppressing muscle protein synthesis. In addition, hyperammonemia promotes muscle autophagy, reduces muscle contractility, initiates the mitochondrial dysfunction, increased production of reactive oxygen species (ROS), in turn initiating the oxidative stress (OS), which leads to damage to muscle proteins, lipids, and ultimately leads to muscle atrophy [18]. Surgical stress, the effects of corticosteroids and calcineurin inhibitors lead to further progression of sarcopenia for several days or weeks after transplantation before muscle mass begins to recover, since low ammonia excretion may play a significant role in exacerbating hyperammonemia. This is especially important for patients who have developed acute kidney injury (AKI) [6].

The role of the kidneys. In the kidneys, the proximal tubules are the main source of ammoniagenesis, with glutamine being the main substrate. The kidneys can be either the final producers or excretors of ammonia. Metabolic acidosis results in increased urinary ammonia excretion with a negative ammonia balance, while alkalosis leads to the

opposite result. In hyperammonemia, the kidneys increase the uptake of ammonia from the blood and its excretion, explained by the influence of the acid-base balance in the blood, thereby playing a critical role in maintaining a stable level of ammonia in its detoxification [6].

When urea synthesis is reduced, ammonia from the intestines or kidneys does not reach the hepatic acinus hepatocytes of the periportal zone. This ammonia is subsequently taken up by pericentral zone hepatocytes via the glutamate synthetase (GS) pathway to form glutamine. Glutamine, in turn, is released back into the circulation and subsequently broken down by glutaminase in the intestine and kidney. In hyperammonemia, most of the ammonia nitrogen produced in the kidneys is excreted in the urine, which modulates the kidneys into an organ that detoxifies the body from ammonia (Fig. 3) [11]. In turn, the recipient is particularly vulnerable because of a high risk of developing AKI, which is common in the early postoperative period after OLT, which is a critical problem [19]. AKI is associated with a graft dysfunction, as evidenced by numerous studies that have demonstrated an association between postoperative AKI and poor transplant outcomes [20]. There is little information in the literature about the development of hyperammonemia after OLT, but it has been described in cases where the graft dysfunction occurred or portosystemic shunting persisted [21].

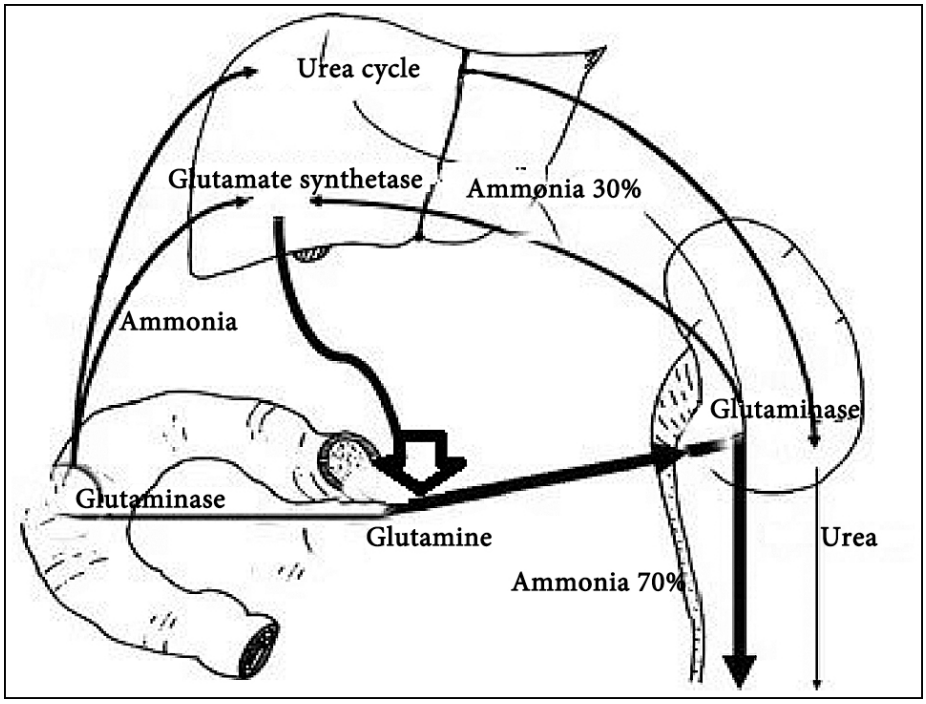

Fig. 3. The role of the kidneys in interorgan glutamine metabolism in hyperammonemia [11]

The role of the brain. Activation of the inflammatory response is directly related to an increased cerebral blood flow, increased intracranial pressure, and disruption of the BBB. Endogenous inflammatory mediators are activated in the transplanted organ during ischemia-reperfusion injury [22]. Several cytokines are involved in neuroinflammation, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ. Activation of microglia releases inflammatory cytokines such as IL-1β, inducible nitric oxide synthase (iNOS), and prostaglandin E2 (PGE 2). Elevated IL-1β levels activate IL-1 receptors. Neuroinflammation alters glutamatergic neurotransmission in the hippocampus, affecting the decrease in membrane expression of GluA1 (a subunit of the amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptor) and the increase in membrane expression of GluA2 (a subunit of AMPA), initiating cognitive impairment, including altered spatial memory in patients with hepatic encephalopathy [23, 24]. In their

current concept of the hyperammonemia impact on the brain function, the authors have noted that high ammonia concentrations lead to pathological changes in neurotransmitters, which is the cause of neuronal damage. Animal studies have shown that acute ammonia intoxication *in vitro* results in increased glutamate levels in the extracellular fluid of the brain. This leads to the activation of N-methyl-D-aspartate (NMDA) receptors, which causes a decrease in the activity of protein kinase C phosphorylation; and the activation of Na/K-ATPase occurs. The depletion of adenosine triphosphate (ATP) reserves results in the occurrence of ammonia intoxication, which is the most likely cause of seizures in acute hyperammonemia. Another consequence of acute hyperammonemia is cerebral edema. This occurs primarily due to swelling of astrocytes, which are the only cells involved in the detoxification of ammonia in the medulla. Supposed mechanisms include the disruption of water and potassium metabolism in astrocytes, activation of the tumor suppressor protein p53, an increased uptake of compounds including pyruvate, lactate, and glutamine, and a decreased uptake of ketone bodies, glutamate, and free glucose. Cerebral edema leads to increased intracranial hypertension and subsequently to the structural dislocation [17]. In a cell culture study, nicotinamide adenine dinucleotide phosphate oxidase was shown to be activated in response to hyperammonemia in astrocytes, leading to increased oxidative stress. Subsequently, various ROS and nitrogen species form modifications of ribonucleic acid (RNA**)** and cause changes in gene expression and downstream signaling pathways. Tyrosine nitration in proteins, especially in glutamate synthase, is enhanced by the formation of 8-hydroxyguanosine [25].

The role of immunosuppression. Recent studies in genetically modified animals have confirmed the importance of the Urea Cycle, but

also suggest that the GS reaction is more important than it was previously thought. While the liver removes about two-thirds of the body's ammonia through the combined action of the Urea Cycle and GS, the extrahepatic tissues do not produce all the components required for the complete Urea Cycle and therefore rely on the glutamate synthetase reaction for ammonia excretion. The brain is particularly vulnerable to the consequences of hyperammonemia, which include the impaired extracellular potassium buffering and cerebral edema. Furthermore, the glutamate synthetase reaction is closely linked to the metabolism of excitatory and inhibitory neurotransmitters of glutamate and gamma-aminobutyric acid (GABA), indicating a key role of this in neurotransmission [9]. It has been noted by researchers that immunosuppressive regimens based on cyclosporine and tacrolimus are associated with hyperammonemia. Although there is no clear explanation for these effects, immunosuppressive drugs can influence ammonia levels in several ways. They can alter the expression of genes responsible for the activity of GS or other enzymes of the Urea Cycle. It is not known whether tacrolimus has a different effect on Urea Cycle enzymes compared to cyclosporine or other immunosuppressive regimens. Measuring GS activity in the liver of patients with hyperammonemia receiving various immunosuppressive drugs is likely one of the tasks of future studies [6].

The role of an infectious agent. *Mycoplasma* and *ureaplasma* infections have been described as causes of the hyperammonemia syndrome leading to a severe neurological impairment in the post-transplant period, most often in lung transplant recipients. The development of clinically significant hyperammonemia caused by other urease-producing organisms remains unclear. It is known that decompensated liver cirrhosis is most often associated with

hyperammonemia. Normal ammonia values are obtained in case of a well-functioning organ after liver transplantation and, in this regard, there is no need to monitor the blood ammonia level. A clinical case after liver transplantation has been described, which revealed a probable association between hyperammonemia and disseminated cryptococcosis [26]. The mechanism of hyperammonemia involves the production of urease by *Cryptococcus neoformans and cryptococcus gattii* [27]. Urease is an enzyme produced by various types of bacteria, including normal flora, non-pathogenic and pathogenic, such as *Proteus mirabilis, Staphylococcus saprophyticus, Klebsiella pneumonia, Citrobacter freundii, enterobacter cloacae Helicobacter spp* and *Helicobacter pylori* [28]. Dissemination of *Serratia marcescens* bacterial infection was the cause of hyperammonemia in a clinical case of pediatric liver transplantation [29]. Hyperammonemia may contribute to an immune dysfunction and infection, which is a common trigger for multiple organ dysfunction in patients (Fig. 4).

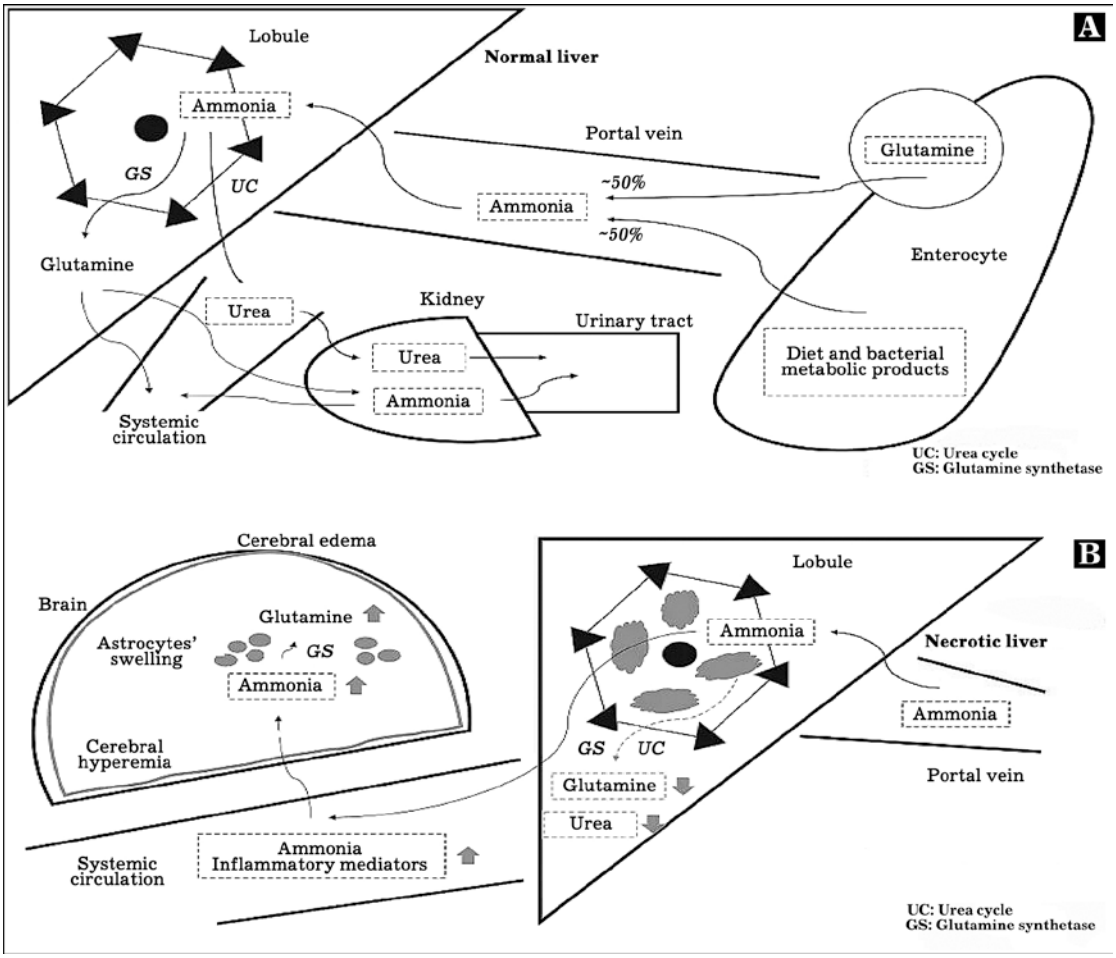

Fig. 4. Panel A: Ammonia metabolism under normal homeostasis [30]. Panel B: Ammonia metabolism following liver necrosis [30]

Problems in laboratory analysis of ammonemia level. Collection of serum samples for ammonia analysis and laboratory testing involves logistical challenges that can result in significant variability and instability in laboratory values, requiring careful sample handling and rapid measurement using a reliable analyzer to obtain accurate results. For example, the use of a tourniquet can significantly increase ammonia levels. After sample collection, the red blood cells and platelets continue to metabolize in the laboratory, and ammonia concentrations increase when stored at room temperature. Therefore, it is recommended to store samples on ice or to process them immediately after collection. It should also be taken into account that the ammonia level in venous blood may be

less accurate due to the peripheral absorption of ammonia by muscle and brain tissue, which may lead to an underestimation of the ammonia level. In turn, the BBB is permeable to arterial blood, therefore, when assessing the BBB, it is preferable to use the level of ammonia in arterial blood. Currently, there are no generally accepted cutoff values for defining normal and abnormal ammonia levels. The mean ammonia level in healthy volunteers can vary significantly between centers, and laboratories often set different upper limits of normal, for example, in some laboratories, the upper limit of normal for serum ammonia is from 32-72 μmol/L [31, 32]. In 2018, an express analyzer device for quantitative determination of ammonia in blood was certified in Russia. It uses a photometric method based on microdiffusion, i.e. an indirect method; the time to determine the ammonia concentration is about 200 seconds. For the assay, the capillary blood is taken from the finger, however, the collection technology requires the compliance with certain conditions set out in the instructions. Only fresh blood samples are used. In the device, the converted from ammonium ammonia that has passed through the semipermeable membrane changes the color of the indicator, which wavelength is subjected to spectroscopic analysis and automatically indicates its quantitative contents. The device calibration and the adjustment of results are preformed automatically. Reference values are from 11–54 μmol/L [33]. Serial measurements of arterial ammonia levels may be more informative than single measurements at specific points in time. A normal serum ammonia level has a high negative predictive value for hepatic encephalopathy (HE), meaning that if the ammonia level is normal, it's unlikely the patient has HE. However, it's important to remember that an elevated ammonia level doesn't automatically confirm HE, as other factors can contribute to elevated ammonia [30].

Strategies to reduce hyperammonemia

Therapeutic methods include reducing ammonia synthesis, preventing endogenous catabolic ammonia formation, and using drugs that promote alternative pathways for ammonia excretion [6]. The protein intake should be temporarily limited but not stopped. Attention should be paid to monitoring blood electrolyte levels, especially those of calcium and potassium. Patients should be closely monitored for hypoglycemia; and the use of hypotonic solutions should be avoided, as they can provoke hyponatremia and cerebral edema [34]. Sodium levels should be maintained at the upper limit of normal, in the range of 145–150 mmol/L after the development of severe encephalopathy [35].

Table 1 presents the main therapeutic methods for reducing hyperammonemia.

Table 1. Non-dialysis methods of ammonia removal. Categories and characteristics of actual clinical use of some drugs for hyperammonemia in transplantology [6, 30, 36, 37]

Metabolic nitrogen scavengers
Sodium benzoate (ineffective for hyperammonemia after transplantation), sodium phenylbutyrate, phenylacetylglutamine, sodium phenylacetate, glyceryl phenylbutyrate, ornithine phenylacetate. Essential and non-essential amino acid mixtures, L-ornithine, L-aspartate (LOLA): mechanism of action is related to activation of the urea cycle, no side effects reported; L-ornithine phenylacetate: low efficacy after transplantation; L-arginine, L-citrulline (no randomized clinical trials have been conducted on these drugs, have been used as adjunctive therapy in many institutions due to their low cost, and safety). Branched-chain amino acids (BCAAs): leucine, isoleucine, and valine are essential amino acids with a carbon chain.
A group of agents capable of reducing the ammonia absorption from the bowel
Indigestible disaccharides: lactulose (often used in many centers as first-line non-dialysis therapy), lactitol.

Aminoglycosides (neomycin), rifaximin (produces a synergistic effect with lactulose in reducing ammonia levels, minimal systemic absorption and better tolerability, compared to lactulose, make it a low-risk drug), metronidazole (not used routinely due to concerns about side effects and low additional benefit).
Systemic antibiotics
Azithromycin (effective in a series of cases in which systemic Ureaplasma urealiticum infection is associated with a potential risk of developing hyperammonemia; quinolones are also effective against other urease-producing microorganisms, can be used as adjunctive therapy)
Probiotics
(*Lactobacillus* sp) (reduce bacterial urease activity, change intestinal pH to the acidic side, neutralizes inflammatory reaction. Unproven efficacy in patients without liver failure. No regular use)
Laxatives
Polyethyleneglycol 3350 and electrolyte solutions, AST-120 carbon microsphere preparation, no data on use in transplantation

Note: Lactulose and rifaximin are well tolerated and do not cause serious side effects in liver transplant recipients. But the use of laxatives or rifaximin may be difficult due to intestinal insufficiency syndrome. New approaches that involve manipulating the gut microbiome with probiotics have been poorly studied and their efficacy in treating acute hyperammonemia is questionable

When using artificial hypothermia (up to 32–33°C), the cerebral blood flow, intracranial pressure, and ammonia absorption through the BBB are reduced. No side effects have been observed. In centers where this method can be used, it should be considered as an additional treatment method in patients with severe cerebral edema and severe hyperammonemia with highly effective ammonia removal using renal replacement therapy (RRT) methods [38]. Other new strategies for reducing ammonia levels are still being explored in preclinical studies, including: the use of AST-120 activated carbon microspheres, being an oral adsorbent of activated carbon microspheres with a surface area of over 1600 m^2/g that acts as a scavenger for neurotoxins and hepatotoxins present in the intestine; intracorporeal "DIALIVE" albumin dialysis device (a new one for peritoneal dialysis); modified bacteria (a modified orally administered form of the probiotic

Escherichia coli Nissle 1917, into strain SYNB1020, which converts NH3 to L-arginine with the enhancement of arginine biosynthesis in SYNB1020 by removing the negative regulator of L-arginine biosynthesis and inserting a feedback-resistant enzyme synthesizing L-arginine and a glutamine synthetase (PS-149-recombinant glutamine synthetase) replacement [39–42].

Methods of renal replacement therapy provide rapid and safe reduction of ammonia levels in critical conditions. It is currently generally recognized that hemodialysis is the method that is best suited for effective elimination of ammonia (Table 2). Ammonia does not bind to proteins and is amenable to elimination, since it is a small molecule with a molecular weight of 17 g/mol, a molecular size of 0.326 nm. Peritoneal dialysis (PD) is successfully used to reduce the level of hyperammonemia, but it is ineffective with high initial ammonia levels and is not used in transplant patients due to the risk of infectious complications. Hemodialysis (HD) is used in hemodynamically stable patients with severe hyperammonemia and concomitant intracranial hypertension. After HD, an increase in the ammonia level is observed, which is explained by a delay in its movement from secondary depots: from cells to plasma. In recipients with lower ammonia concentrations who do not require a rapid reduction in ammonia, and/or in patients with unstable hemodynamics, it is preferable to use prolonged RRT methods for graft protection; this is explained by the fact that with hemofiltration and hemodiafiltration, the incidence of intradialytic hypotension is observed less frequently [6, 43].

Table 2. Dialysis methods for the treatment of hyperammonemia [6]

Intermittent renal replacement therapy (IRRT)	Continuous renal replacement therapy (CRRT)
Hemodialysis (HD)	Continuous venovenous hemofiltration (CVVHF)
• accessible method • highly effective in eliminating ammonium	• Hemodynamic stability • Continuous ammonia elimination with minimal intervals
• Q/blood (blood flow velocity) 400–450 mL per minute • Q/dialysate (dialysis solution flow rate) 800 mL per minute	• Q/blood (blood flow velocity) 250–300 mL per minute • Bicarbonate-based substrate, 50–80 mL/kg/h
4-6 hours, daily sessions	Continuous
Q/b, 250 mL/min; Q/d, 500–600 mL/min; 6–8 hours in patients with initial cerebral edema and/or unstable hemodynamics	Switching to HD when ammonia levels rise

There is currently no consensus on when to initiate dialysis in clinically significant hyperammonemia. Generally, the main goals of RRT are to reduce blood ammonia concentrations and to relieve clinical symptoms associated with hyperammonemia. It has been suggested that if blood ammonia levels are 3 times the upper limit of normal or if the patient has severe encephalopathy, it is worth considering the RRT initiation. In addition, there is insufficient data on whether extracorporeal therapy can provide adequate ammonia clearance. This is because most studies only report the time required to reduce blood ammonia levels by mean of 50%, rather than directly to change clearance by using an extracorporeal circuit. However, such a reduction is influenced by such factors as the dependence on concentration gradients, heterogeneity in measurement methods, calculation formulas, and other concomitant interventions, the adequacy of caloric intake with protein restriction, and a pharmacological therapy [13, 44]. Renal dysfunction may not be

adequately displayed by standard serum creatinine or urea levels. In patients with an acute renal failure, the role of the kidney in ammonia elimination becomes increasingly important, and arterial ammonia levels should be closely monitored. An early initiation of RRT regulates the biochemical and temperature control, fluid and electrolyte balance, and blood ammonia levels [35]. Ammonia clearance increases with higher dialysis solution flow rates or ultrafiltration rates, higher blood flow rates, and longer procedure times. Thus, a moderate correlation has been found between ammonia clearance and effluent flow rate (EFR), when comparing two ammonia clearance formulas: Cordoba formula: (ammonia concentration in the filtrate × filtrate volume)/ammonia concentration in plasma × time, and Wiegand formula based on the ammonia level in the blood sampled pre- and post-filter (pre-filter ammonia level − post-filter ammonia level) × blood flow rate/pre-filter ammonia level [45]. Theoretically, postdilution should result in high clearance due to a higher concentration of dissolved substances in the filter. However, postdilution may lead to clot formation and reduce the filter life. It should be noted that the effect of predilution and postdilution on daily ammonia clearance during CRRT is unknown [46]. HD provides the most efficient ammonia clearance, which depends on high dialysate flow rates, ultrafiltration rates, and higher blood flow rates. CRRT can provide significant ammonia clearance, which increases with higher replacement flow rates [44]. Clinically significant ammonia reduction can be achieved in hyperammonemia patients by means of continuous high-flow ultrafiltration [30, 45]. According to other authors, in critically ill patients with hyperammonemia secondary to liver failure who were treated with CRRT, no significant differences were found between the methods in terms of ammonia clearance using CRRT: continuous venovenous hemofiltration (CVVHF), continuous venovenous

hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). Ammonia clearance was approximately half that of urea and creatinine clearance for all methods. The key aspect of ammonia clearance was the delivered dose of effluent flow. These results inform clinicians in their choice of the CRRT method and on the need to investigate the cause of low transfilter ammonia movement [47]. It should be noted that there are currently two categories of extracorporeal liver support (ECLS): artificial and bioartificial. Artificial ECLSs do not include active hepatocytes and are based on the principles of filtration and adsorption, Prometheus® (Fractionated Plasma Separation and Adsorption), albumin dialysis, MARS® (Molecular Adsorbent Recirculating System) and SPAD (Single Pass Albumin Dialysis). Bioartificial ECLSs use active hepatocytes (of human or porcine origin) to improve the liver's detoxifying capacity and support liver synthetic function, and include ELAD® (Extracorporeal Liver Assist) and HepatAssist ® (bioartificial liver assist) [48]. The best studied in clinical practice are Prometheus® (plasma fractionation plus adsorption) and MARS® (albumin dialysis plus adsorption), however, their impact on treatment results in general, the efficacy in terms of ammonia concentration dynamics and cost-effectiveness remain controversial [49]. The SPAD technique combines a conventional hemofiltration circuit and dialysis with 5% albumin through a high-flux, high-permeability filter and, according to some authors; it probably has the potential for use in the development of acute liver failure [48]. Bioartificial ECLSs are aimed at achieving detoxification through stimulation of cytochrome P450 activity, ureagenesis and protein synthesis, gluconeogenesis; but their use in clinical practice is limited by their complexity, the need for specific cells, critical bioactive mass, the risk of contamination with animal viruses when using porcine hepatocytes, and a high final cost [50]. A recent study

by R. Maiwall et al. is worthwhile to note, they conducted a randomized controlled trial in patients with clinical signs of cerebral edema, comparing the results of standard therapy according to clinical guidelines and those of exchange plasmapheresis (EP). In the EP group, the authors obtained better results in reducing lactate and ammonia [51]. The combination of CRRT and plasmapheresis also improved survival in patients with acute liver failure [52].

Discussion

Thus, in the development of acute liver failure, two most significant pathophysiological events can be identified that precede the development of the clinical signs of deterioration. The first event is the development of hyperammonemia due to the loss of such liver function as the urea synthesis. As a result, the entire splanchnic system (abdominal organs) becomes a source of ammonia, progression of hepatic encephalopathy (HE), and cerebral edema. Hyperammonemia in the intensive care is associated with a high mortality rate, so an effective therapy is required to solve a critical and life-threatening problem. The choice of the method involves a multifactorial and personalized approach of the multidisciplinary team.

The second complication is caused by liver cell necrosis, which results in the release of large biologically active molecules as the products of protein degradation, which were termed damage-associated molecular patterns (DAMPs). They, in turn, cause an inflammatory activation of intrahepatic macrophages and saturation of the systemic bloodstream with large-molecular compounds, which leads to a clinical pattern resembling a septic shock. In this regard, the combined use of continuous RRT (CRRT) and plasmapheresis are rational and the simplest ways to eliminate ammonia and DAMP molecules.

More in-depth research in this area may help in developing effective treatments to reduce the incidence of complications in the early post-transplant period, as well as in making differential diagnosis of conditions associated with varying degrees of impaired consciousness.

Conclusion

Studies of the dynamics of ammonia levels after liver transplantation are promising for the purpose of determining early indications for the use of methods of renal replacement therapy of ammonia clearance, making a differential diagnosis between the causes of impaired consciousness, and identifying correlations between the severity of the condition and hyperammonemia.

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