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Refining the Ammonia Hypothesis: A Physiology-Driven Approach to the Treatment of Hepatic Encephalopathy

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Abstract

Hepatic encephalopathy (HE) is one of the most important complications of cirrhosis and portal hypertension. Although the etiology is incompletely understood, it has been linked to ammonia directly and indirectly. Our goal is to review for the clinician the mechanisms behind hyperammonemia and the pathogenesis of HE to explain the rationale for its therapy. We reviewed articles collected through a search of MEDLINE/PubMed, Cochrane Database of Systematic Reviews, and Google Scholar between October 1, 1948, and December 8, 2014, and by a manual search of citations within retrieved articles. Search terms included *hepatic encephalopathy, ammonia hypothesis, brain and ammonia, liver failure and ammonia, acute-on-chronic liver failure and ammonia, cirrhosis and ammonia*, *portosytemic shunt*, *ammonia and lactulose, rifaximin, zinc,* and *nutrition*. Ammonia homeostatsis is a multiorgan process involving the liver, brain, kidneys, and muscle as well as the gastrointestinal tract. Indeed, hyperammonemia may be the first clue to poor functional reserves, malnutrition, and impending multiorgan dysfunction. Furthermore, the neuropathology of ammonia is critically linked to states of systemic inflammation and endotoxemia. Given the complex interplay among ammonia, inflammation, and other factors, ammonia levels have questionable utility in the staging of HE. The use of nonabsorbable disaccharides, antibiotics, and probiotics reduces gut ammoniagenesis and, in the case of antibiotics and probiotics, systemic inflammation. Nutritional support preserves urea cycle function and prevents wasting of skeletal muscle, a significant site of ammonia metabolism. Correction of hypokalemia, hypovolemia, and acidosis further assists in the reduction of ammonia production in the kidney. Finally, early and aggressive treatment of infection, avoidance of sedatives, and modification of portosystemic shunts are also helpful in reducing the neurocognitive effects of hyperammonemia. Refining the ammonia hypothesis to account for these other factors instructs a solid foundation for the effective treatment and prevention of hepatic encephalopathy.

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Hepatic encephalopathy (HE) is a morbid and costly complication of cirrhosis that presents as a spectrum from mild inattention to coma.[1,2] It is independently associated with increased mortality and reduced quality of life.[3,4] The etiology of HE is multifactorial and incompletely understood, but it has often been tied to ammonia.

In patients with inborn defects of ammonia metabolism, hyperammonemia is directly linked to a spectrum of neuropathology inclusive of neuropsychiatric disorders, severe brain injury, coma, and death.[5,6] For these patients, interventions to prevent hyperammonemia have proved lifesaving.[6] Patients with cirrhosis can develop similar neurocognitive phenomena in the context of measurably elevated blood ammonia levels, and therapies that demonstrably lower ammonia levels improve symptoms. These correlations underpin the ammonia hypothesis.

This concept of ammonia in the pathogenesis of HE, however, is incomplete. Indeed, the ammonia hypothesis presents a clinical conundrum. On the one hand, although frequently assessed, the clinical utility of ammonia levels is unclear because they rarely correlate with symptoms, let alone outcomes.[7-10] On the other hand, the ammonia hypothesis is a widely accepted premise that leads to frequent assessment of ammonia concentrations in general clinical practice.[11] By refining the ammonia hypothesis to include the substantial contributions of

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inflammation, endotoxin, and interorgan ammonia trafficking involving the brain, kidney, and muscle, the true importance of ammonia may be clarified and the clinical power of the hypothesis may increase significantly.

Ammonia is traditionally considered a gut-derived nitrogenous toxin produced by bacterial metabolism of amino acids, primarily glutamine.[1,12,13] Normally, ammonia from the gut is efficiently handled by the liver through 2 main metabolic avenues: the urea cycle (also known as the ornithine cycle) and glutamine synthetase (which converts glutamate to glutamine). Cirrhosis, with its associated hepatocellular dysfunction and portosystemic shunting, reduces the efficiency of these "detoxification" mechanisms. The result is greater systemic distribution of ammonia.[10,14-17] However, although the liver is a critical player in the ammonia story, it is far from the only one.

Herein, we highlight the clinical importance of the multiple organs responsible for ammonia metabolism and the modifying effect of inflammation. We show how a refined ammonia hypothesis informs a complete approach to the patient with HE. This review examines the pathogenesis of HE with a focus on existing and evolving therapeutic targets.

METHODS

A search of the representative literature was performed. Articles were collected through a search of MEDLINE/PubMed, Cochrane Database of Systematic Reviews, and Google Scholar and by a manual search of citations within retrieved articles. Search dates spanned October 1, 1948, to December 8, 2014. Search terms included *hepatic encephalopathy* [MeSH], *ammonia hypothesis, brain and ammonia, liver failure and ammonia, acute-on-chronic liver failure and ammonia, cirrhosis and ammonia*, *portosytemic shunt*, transjugular intrahepatic portosystemic shunt, *portocaval shunt*, *ammonia and lactulose, rifaximin, zinc,* and *nutrition.*

The terminology used to describe HE has changed over time. We use the term *overt HE* to describe an episode of acute disorientation or coma. *Controlled* or *resolved* refers to patients who have recovered from overt HE. *Secondary prophylaxis* describes the use of therapies to prevent another episode of HE. *Covert HE* includes patients who have abnormal psychometric testing without overt confusion.[18]

ARTICLE HIGHLIGHTS

- Ammonia is an important cause of hepatic encephalopathy (HE), but its levels do not correlate with symptoms, partly because of the additive effect of inflammation.
- The kidney, muscle, brain, and gut all play critical roles in ammonia metabolism.
- Muscle wasting (sarcopenia) is associated with HE.
- Renal injury, hypokalemia, and acidosis can each precipitate HE.
- Standard treatment for HE includes reducing ammonia and bacterial translocation from the gut, nutritional supplementation, and sedative or narcotic avoidance.
- Second-line treatments for HE include probiotics, zinc, closure of portosystemic shunts, and ammonia scavengers, such as glycerol phenylbutyrate.

The Ammonia Hypothesis: The Brain

Multiple organs contribute to absolute ammonia concentrations in the blood, but the symptoms of HE are driven mainly by ammonia's effect on the brain. These effects are mediated by the three critical determinants of HE neuropathology: ammonia, glutamine, and inflammation (Figure 1).[14,19,20]

Astrocytes are the principle brain cells affected in states of hyperammonemia.[20] They are the primary carrier of glutamine synthetase in the brain, which converts ammonia and glutamate to glutamine.[12,21-25] Glutamine plays a significant role in the neurotoxicity of ammonia in HE, contributing to the brain dysfunction associated with hyperammonemia in 2 ways. First, glutamine, generated in the cytosol, is, in turn, actively metabolized by astrocyte mitochondria via glutamine hydrolysis (by the mitochondrial protein phosphate-activated glutaminase), leading to the production of ammonia and the accumulation of reactive oxygen species (ROS). Under physiologic conditions, low intra-astrocyte concentrations of glutamine trigger very low levels of hydrolysis. However, with elevated systemic ammonia concentrations, increased glutamine leads to increased hydrolysis and ammonia production in mitochondria, generating increased ROS.[25] In turn, ROS leads to mitochondrial dysfunction and triggers inflammatory cascades.[12,23,25]

Second, cytosolic glutamine is osmotically active. In the presence of hyperammonemia and

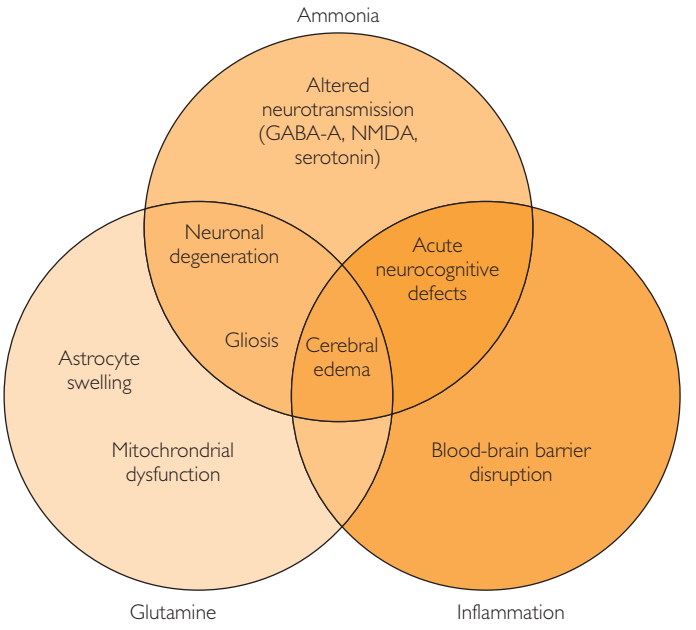

FIGURE 1. The neuropathology of hepatic encephalopathy reflects the interplay of ammonia, glutamine, and inflammation. GABA-A = γ-aminobutyric acid type A; NMDA = *N*-methyl-D-aspartate receptor.

elevated glutamine concentrations, astrocyte osmoregulatory mechanisms, including the degradation of cytosolic myo-inositol to maintain water balance, do not seem to suffice.[26] Astrocyte swelling and, therefore, cerebral edema ensue, leading to reactive transcriptional changes that result in gliosis and cellular dysfunction.[20,24] Glutamine, therefore, causes cerebral dysfunction indirectly (through ROS generation) and directly (through astrocyte swelling).[22,24,27]

In addition to astrocyte injury via glutamine, ammonia is directly neurotoxic. In brief, ammonia enhances inhibitory signaling by modifying neurotransmission through multiple mechanisms, including γ-aminobutyric acid, glutamate, and monoaminergic signal modulation.[12,22,27-29] There is strong evidence for many pathologic changes involving signaling molecules, although their precise impact remains unclear. These changes include stimulation of the peripheral-type benzodiazepine receptor, which leads to enhanced neurosteroid production and increased γ-aminobutyric acid type A expression; an increased synaptic glutamate concentration with resultant *N*-methyl-D-aspartate receptor stimulation; and increased serotonin signaling and metabolism.[30] The net effect of these alterations in neurotransmission is a combination of overstimulation and transcriptional deregulation, leading to neuronal degeneration and cell death.[31] Progressive brain damage manifests in the long-term, which may persist after liver transplantation.[22,27,32]

The effect of inflammation and gut-derived endotoxemia on blood-brain barrier integrity and cerebral blood flow are of paramount importance in modulating the effects of systemic ammonia on cerebral dysfunction. Gut-derived endotoxemia and infection frequently occur in the setting of cirrhosis and have been independently associated with increased mortality and morbidity.[9,22,33,34] Inflammatory cytokines, primarily interleukins 1-β and 6 and tumor necrosis factor-α, and endotoxins potentiate ammonia neurotoxicity. This effect is exerted by enhancing diffusion of ammonia across the blood-brain barrier and by independently contributing to neuronal dysfunction.[22,28,33-35] Acute liver failure is accompanied by particularly high levels of inflammatory cytokines, much higher relative to patients with cirrhosis. These cytokines disrupt the natural function of the blood-brain barrier and may explain why acute liver failure with hyperammonemia and HE is associated with a higher prevalence of clinically apparent cerebral edema and brain herniation compared with the HE that accompanies decompensated cirrhosis.[9,33,35,36]

Targeted neurospecific therapies are not yet available for HE. However, glutamate uptake by mitochondria may prove a valid target.[37] The focus then is aimed at reducing the passage of ammonia across the blood-brain barrier by reducing systemic inflammation, preventing and treating infections,[38] scavenging of ROS during albumin dialysis,[39] and enhancing ammonia clearance and metabolism by other organs.[40-42] To prevent the exacerbation of inhibitory signaling, benzodiazepines should be avoided if possible.[43,44] Last, systemic inflammation and endotoxemia, powerful determinants of ammonia-induced neuropathology, can be reduced by prevention and treatment of infection and modulation of the gut microbiome, as discussed later.

The Pathogenesis of Hyperammonemia

The Gut. Without question, the gut is a critical component in the pathogenesis of HE. Dietary

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nitrogen (particularly glutamine) is converted to ammonia by gut enzymes and urease-containing bacteria. Glutamine is metabolized by intestinal epithelial glutaminase, converting more than one-third of its nitrogen to ammonia, which diffuses into the portal circulation.[13] For unclear reasons, patients with cirrhosis and portosystemic shunting have highly active phosphate-activated glutaminase, which leads to greater ammonia production from glutamine.[45,46] Ammonia is then freely absorbed across the gut epithelial membrane. The gut is also the principle source of bacterial endotoxin, which contributes to HE.[9,33,34] In the 1960s, McDermott and Sherlock evaluated total colectomy for refractory HE. This approach is effective as a proof of principle but is ill-advised.[47,48] Inhibitors of intestinal glutaminase have been shown to reduce portal ammonia levels even after treatment with lactulose and antibiotics.[49] However, these have never been studied in humans. Accordingly, direct elimination of ammonia from the gut via purgatory treatments and reduction of proteolytic bacterial flora, as well as reduction of inflammation secondary to gut translocation of bacterial by-products, form the mainstay of HE therapy.

Nonabsorbable synthetic disaccharides, such as lactulose and lactitol, were first introduced in 1966[50] and constitute first-line therapy for HE.[1] Their mechanism of action is likely multifactorial. First, they decrease colonic transit time, reducing the opportunity for absorption of gut-derived ammonia, ie, the purgatory effect. The purgatory effect was recently reinforced in a trial of high-dose polyethylene glycol and in a study of high-volume lactulose for the treatment of overt HE.[51,52] Second, nonabsorbable disaccharides lower colonic pH. This effect converts ammonia to a nonabsorbable ammonium ion (preventing the production of ammonia by gut urealysis and inhibiting ammonia absorption).[53-55]

Lactulose is the first-line therapy for patients with overt HE, where the focus is on rapid laxation. However, beyond the readily apparent efficacy of lactulose in the acute setting, it has been difficult to prove its value for secondary prophylaxis of overt HE in rigorous trials.[56-62] As noted by Leise and colleagues,[18] these studies were old and included mixed study populations of patients with covert, chronic, and overt HE. The most recent trial from a leading group of HE investigators, however, did show significant benefit for lactulose in the secondary prevention of overt HE.[62] Conventional therapy with lactulose involves administration 2 to 3 times daily, with the absolute amount titrated to 3 to 4 daily soft bowel movements. When patients are admitted to the hospital with overt encephalopathy, however, a rapid bowel purge by high-dose, high-frequency lactulose therapy may rapidly improve symptoms.[52] Further study is required to determine the relative benefits of strictly osmotic laxatives compared with agents such as lactulose that also alter gut pH.

Efficacy aside, the overarching problem with nonabsorbable disaccharides has always been patient tolerability vis-à-vis taste and displeasure with the inconvenience of its purgatory effects. Accordingly, there is substantial interest in therapies directed at the bacterial species responsible for ammonia generation and the reduction of proinflammatory mediators.

Antibiotic drugs are a conventional and effective treatment. Many have been studied—neomycin, vancomycin, and metronidazole—but none are as proven as rifaximin.[56,63-65] A rifamycin derivative with poor bioavailability (ie, nonabsorbable), rifaximin acts by disrupting bacterial ribonucleic acid polymerase function. These 2 traits lend rifaximin a truly broad spectrum of action without the toxicities of previously evaluated antimicrobial agents.[66]

The precise mechanism of rifaximin's efficacy for the treatment of HE is unclear. It is likely multimodal and involves the modulation (not the reduction) of the small intestinal and colonic microbiome with a shift toward less pathogenic bacterial composition and metabolism.[41,67-69] The result is decreased ammonia production and systemic endotoxemia. Both effects likely play important roles.[33,70-72] Although rifaximin monotherapy may be effective, it has not been rigorously studied.[73] Rifaximin is best studied in conjunction with lactulose, and the combination seems superior to lactulose alone for the prevention of overt HE.[63,64] Further study is needed to determine the role of rifaximin in the treatment of overt HE.

Similarly, probiotics have been assessed in the treatment of HE, albeit with mixed results.[67,68,71,74] The beneficial effects observed have been obtained from small trials of adherent patients. One such trial examining the primary prevention of overt HE in patients taking a probiotic yogurt was remarkably successful.[67,68] A

recent randomized trial showed that in patients taking neither lactulose nor rifaximin, a commercially available probiotic reduced the risk of HE hospitalization and the severity of liver disease.[74] The mechanism of probiotic effect is not entirely clear, although there is evidence that at least some strains of bacteria (eg, *Lactobacillus* GG) modulate the gut microbiome, with a shift away from proteolytic and pathogenic bacteria. As with rifaximin, the result is a reduction in peripheral ammonia, endotoxin, and inflammatory cytokine levels.[40,74] Beyond probiotics, it is conceivable that well-selected stool transplantation may play a role for this indication by this mechanism.

In summary, the gut is a major source of ammonia and inflammation related to bacterial endotoxin. Effective therapy for HE, therefore, should address both aspects. Finally, agents that slow bowel motility, such as opiates, facilitate ammonia absorption and may precipitate overt HE and preclude recovery despite adequate therapy during overt HE episodes.[44]

The Liver. The liver processes ammonia and gut-derived bacterial products that are received from the systemic and portal circulation. Hepatic contributions to the hyperammonemia of cirrhosis are a function of decreased intrinsic hepatic function and portosystemic shunting.

Intrinsic Liver Function. The liver handles ammonia through 2 principle mechanisms. The first is the urea cycle, whereby carbon dioxide and ammonia are ultimately converted to urea and water. This process occurs primarily in the periportal hepatocytes. Beyond being affected by hepatocyte volume, urea cycle efficiency is reduced by 2 factors common in cirrhosis. First, portosystemic shunting bypasses periportal hepatocytes. Second, as a function of increased catabolism and inflammation, malnutrition is a hallmark of advanced liver disease.[75] The urea cycle requires the presence of specific amino acids (eg, ornithine, alanine, and arginine) and zinc-dependent enzymes, all of which are less available in the setting of malnutrition.

Patients with cirrhosis and particularly those with HE should receive a nutritional assessment and nutritional supplementation if they cannot achieve adequate protein intake.[76] Protein restriction is not recommended because it may exacerbate sarcopenia, which has deleterious effects on ammonia metabolism (see later). On the contrary, patients with cirrhosis and HE benefit from nutritional supplementation and can tolerate high-protein diets.[76,77] Based on a randomized controlled trial, 1.2 g/kg of daily protein did not exacerbate HE and prevented muscle breakdown.[78] In general, patients with decompensated cirrhosis are recommended to receive a daily intake of 1.5 g of protein and 35 to 40 kilocalories per kilogram.[79]

Beyond protein and calories, it is unclear whether specific nutrients should be supplemented. The European Society for Clinical Nutrition and Metabolism recommends that nutritional supplements include branched-chain amino acids (BCAA) for patients with HE.[79] Supplementation with BCAA (the rationale for which is discussed later) seems to support the cirrhotic patient's nutritional status and may be associated with lower rates of clinical deterioration, albeit with generally mixed results and without reducing the risk of overt HE.[80,81] To specifically combat HE, investigators have assessed diets enriched with BCAA, also with mixed results.[76,82-85]

Similarly, zinc supplementation has been studied. Zinc is an important cofactor for urea cycle enzymes. It is also frequently deficient in cirrhotic patients, particularly those with alcoholic liver disease.[86] Controlled, if small, trials have examined zinc supplementation, with largely positive results. However, the generalizability of these results is uncertain because no trial has evaluated zinc supplementation with the current standard of care for HE.[87-91]

In summary, adequate nutritional intake is paramount to maintain liver function. Beyond that, supplementation with BCAA or zinc is a safe, viable option but requires further study in patients receiving the current standard of care.

Portosystemic Shunting. Portosystemic shunting exposes the brain to ammonia and bacterial products—the toxins associated with HE neuropathology. The disruption of the hepatic architecture seen in cirrhosis leads to spontaneous portosystemic shunting in 2 ways. First, portal hypertension mechanically forces blood flow from the gut away from the liver through portosystemic collaterals. Second, sinusoidal fibrosis disrupts the normal interaction between hepatocytes and blood contents, leading to intrahepatic portosystemic shunting.

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Shunts that lead to encephalopathy can be spontaneous or postsurgical, selective or unselective.[92] Eck and Pavlov first demonstrated episodic stupor as a function of surgical portosystemic shunts (Eck fistula) in dogs.[22] McDermott later confirmed this pattern in humans and implicated ammonia after he described similar postprandial stupor in a patient without liver disease with a mesenteric vein-inferior vena cava anastamosis made during a pancreaticoduodenectomy.[93,94] Even modern selective shunt procedures, namely, transjugular intrahepatic portosystemic shunts (TIPSs), can precipitate or exacerbate HE.[95,96] Indeed, the familiar risk stratification scoring systems pertinent to cirrhosis, including the Child-Pugh and the Mayo Clinic Model for End-Stage Liver Disease (MELD), were developed to assess patient risks after shunt procedures, and they remain valid today.[96,97] Based on previous study, guidelines recommend that TIPS not be offered to patients with difficult-to-control HE or a MELD score greater than 18.[98]

Symptoms of patients with refractory HE can be improved with closure of portosystemic shunts. Well-selected patients (ie, MELD score < 16) with spontaneous shunts complicated by symptomatic HE refractory to medical therapy can obtain relief from embolization procedures that reduce portosystemic shunting.[99,100] Similarly, patients with TIPS can undergo shunt revisions to reduce flow.[95,96]

The Kidney. Recognizing the kidney's role in ammonia metabolism is critical for clinicians caring for patients with HE. Even in healthy patients, sharp increases in ammonia concentrations are handled in large part by renal processes.[101] The principle mechanism by which the kidney disposes of ammonia is through the formation of glutamine by renal tubular enzymes.[15,101-103] Although renal insufficiency clearly limits these processes, there is still a limit to the functional kidney's ability to eliminate ammonia. Indeed, the kidney requires glutamine to perform 2 of its essential functions, potassium and acid homeostasis, both of which lead to ammonia production.[102,104,105] As a result, renal contributions to the levels of ammonia and glutamine, 2 key neurotoxins, depend on the patient's clinical status.[15,106,107]

In the service of acid-base balance and eukalemia, the kidney takes up approximately half of all glutamine in the bloodstream as a substrate for tubular enzymes. In the setting of metabolic acidosis or hypokalemia, the production of renal glutaminase is increased, and glutamine is used to facilitate the disposal of acid into or recovery of potassium from the glomerular filtrate. Each glutamine used for either purpose generates 2 ammonium ions, some of which result in ammonia that then diffuses into circulation.[13,29,108-110]

Through this mechanism, potassium depletion enhances renal ammoniagenesis and increases arterial ammonia levels.[103,106] In the setting of hypokalemia, the proximal tubule conserves potassium via a proton-potassium antiporter that facilitates potassium recovery from glomerular filtrate. To support this process, renal glutaminase generates an ammonium ion from glutamine that donates a proton to be exchanged across the membrane for the potassium ion. The end result is recovered potassium, acidified urine, and ammonia, a by-product that diffuses into the serum. Acidosis, similar to hypokalemia, can occur in patients with cirrhosis presenting with overdiuresis, alcohol excess, or infections. Here, again, the renal tubule uses glutamine to maintain homeostasis through the disposal of acid (protons) in the urine using glutamine.[110-112] Fortunately, acidosis and hypokalemia are often correctable.[109,113,114] Furthermore, patients with HE and high normokalemia (potassium level, 5.4-5.5 mEq/L [to convert to mmol/L, multiply by 1]) show an earlier improvement in mental status and longer event-free survival than those with low normokalemia (potassium level, 3.5-3.6 mEq/L).[109,114]

Gastrointestinal bleeding is a major trigger for hyperammonemia, also through a renal mechanism. During hemorrhage, hemoglobin and albumin are digested in the gut. As pointed out in elegant studies by Olde Damink and colleagues,[107] these proteins contain glutamine but lack isoleucine, an essential amino acid. In the absence of isoleucine, glutamine is absorbed from the gut but cannot be used for protein synthesis.[107] It, therefore, persists in the circulation, where it leads to ammonia production by renal glutaminase. Indeed, during gastrointestinal bleeding, ammonia production by the kidney swells to rival that of the gut.[15,107]

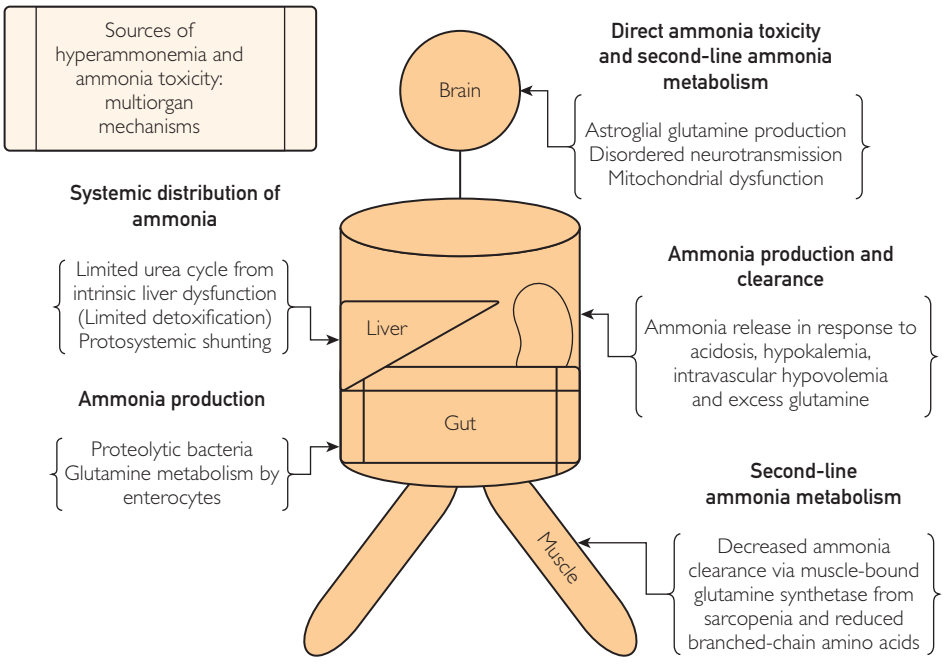

FIGURE 2. Sources of hyperammonemia and ammonia toxicity: multiorgan mechanisms.

Intravascular volume status is also an important determinant of systemic ammonia concentrations. The renin-angiotensin system, which responds to intravascular volume changes, is linked to ammonia hemostasis. The interactions are complex and incompletely characterized but are most likely related to angiotensin II levels. Angiotensin II increases ammonia production, whereas angiotensin receptor blockers markedly reduce urinary excretion of ammonia.[115] As such, states of volume depletion, such as gastrointestinal bleeding and diuresis, could enhance renal ammonia production. Conversely, a volume challenge can increase ammonia excretion possibly by lowering angiotensin II levels.[115,116] Similarly, a reduction in the diuretic dose or temporary suspension may aid in the treatment of patients with HE taking diuretics.

Recently, a novel pathway for renal ammonia elimination was tested in clinical trials. Glycerol phenylbutyrate is an orally administered odorless molecule. It can lower arterial ammonia levels in patients without effective urea cycles, namely, those with inborn metabolic defects and cirrhosis.[5] Glycerol phenylbutyrate is metabolized to phenylacetate and is subsequently conjugated with glutamine into a water-soluble molecule that is readily eliminated by the kidney, reducing available glutamine, preventing its metabolism by tissue glutaminases, and thereby reducing the risk of overt HE.[42,117] A similar mechanism was previously leveraged in a trial using sodium benzoate.[118] However, the utility of sodium benzoate is limited given the salt load of its required doses. Finally, there are ongoing trials of intravenous ornithine phenylacetate for the treatment of severe overt HE. The elimination product of ammonia and orthnithine phenylacetate is a water-soluble conjugate (phenylacetylglutamine) that is renally excreted.[119]

Muscle. Muscle is a significant site of ammonia metabolism for patients with cirrhosis, particularly those with portosystemic shunting, gastrointestinal bleeding, and sepsis.[29,79,120-122] Ammonia is taken up by muscle and converted to glutamine via its glutamine synthetase, a process that is upregulated in the setting of portal hypertension.[29,104] Glutamine synthesis demands the availability of glutamate, which is derived in the cytoplasm from α-ketoglutarate that is

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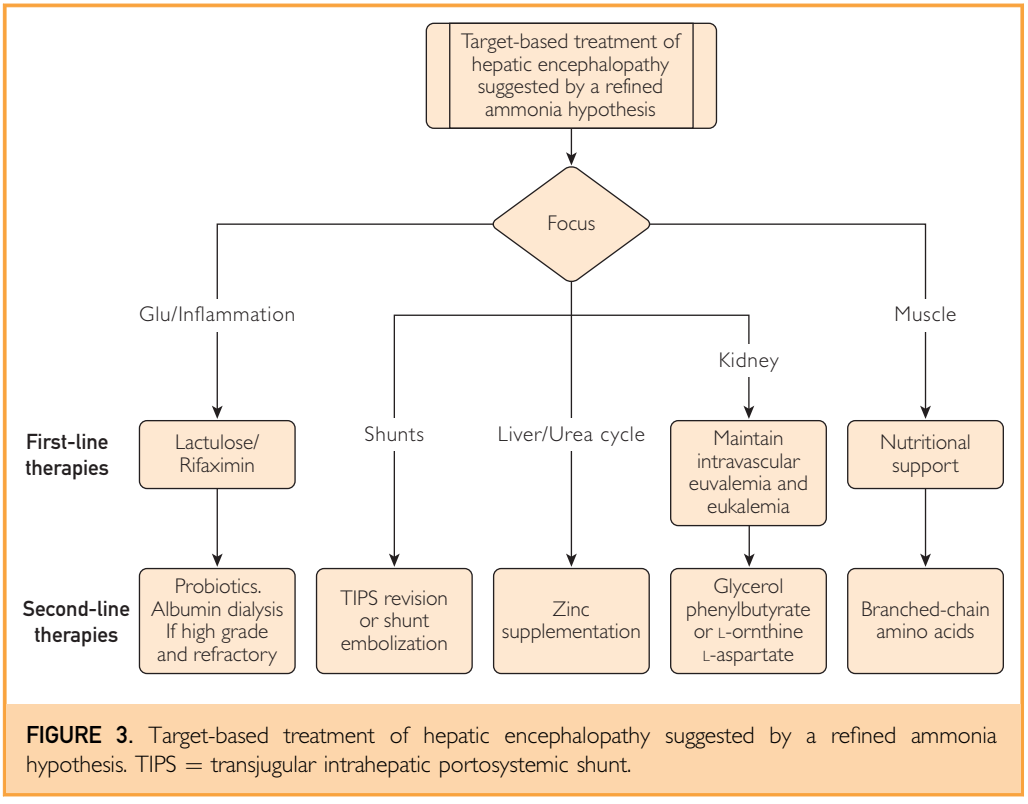

FIGURE 3. Target-based treatment of hepatic encephalopathy suggested by a refined ammonia hypothesis. TIPS = transjugular intrahepatic portosystemic shunt.

harvested, in turn, from BCAA.[77,120,123] The paucity of BCAA in cirrhotic patients with malnutrition leads to a reduced ability to convert ammonia to glutamine in skeletal muscle cells.[107,120]

The clinical relevance of skeletal muscle's role in ammonia metabolism is heightened further when one examines the consequences of sarcopenia in patients with cirrhosis. Indeed, muscle wasting has been associated with an increased risk of HE, both covert and overt.[121,124] Accordingly, as described previously above, efforts to maintain nutritional status and forestall the development of clinically significant sarcopenia are crucial for patients with cirrhosis.[1,76] Maintaining the nutritional status by ensuring appropriate dietary intake and supplementation is paramount and is the shared responsibility of all providers involved in the care of cirrhotic patients.

PUTTING IT ALL TOGETHER

By focusing on the determinants of ammonia metabolism and neurotoxicity, clinicians may develop an effective multimodal therapeutic strategy for their patients with HE. In patients with cirrhosis and portosystemic shunting, amino acid bypass of the liver in the postabsorptive state and loss of intrinsic hepatic function significantly raise the importance of alternative sites of ammonia metabolism. Namely, the muscle and kidney are critical for maintaining ammonia homeostasis (Figures 1 and 2). With further potentiation and enhanced diffusion of ammonia across the blood-brain barrier by endotoxemia and systemic inflammation, early and aggressive treatment of infection, preservation of muscle mass and renal function, and maximal elimination of gut-derived ammonia and bacterial products should form the cornerstones of optimal HE treatment.

A refined, multiorgan view of the ammonia hypothesis is instructive for all clinicians interested in the care of patients with cirrhosis. Ammonia levels may not reliably correlate with HE symptoms or outcomes in chronic liver disease.[7,8,10,125] However, as we described, serum ammonia and its ill-effects are a function of not only intrinsic liver disease and portosystemic shunting but also malnutrition, sarcopenia, renal injury, and gastrointestinal bleeding. Each factor requires special attention from the team of clinicians with whom these patients

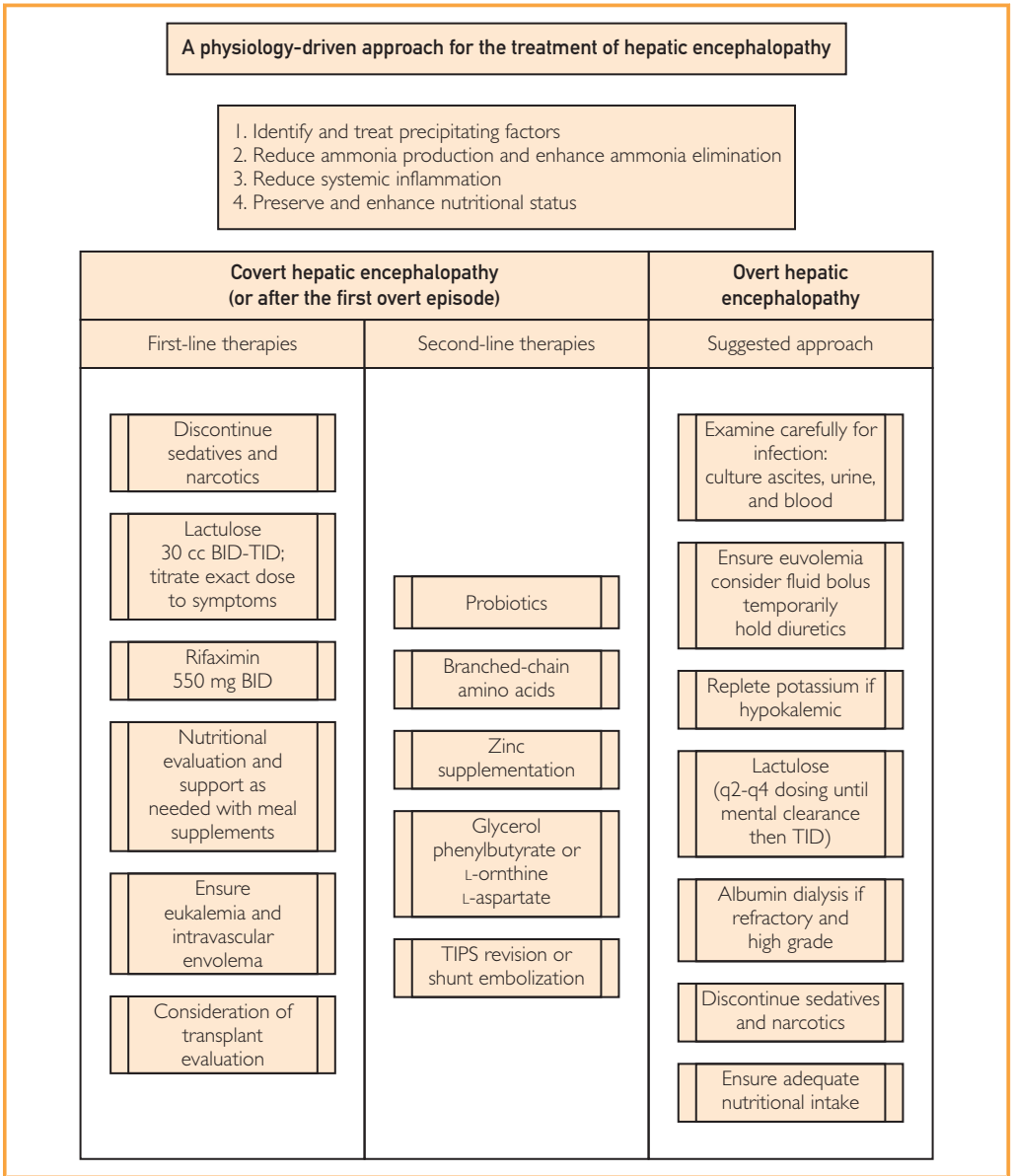

FIGURE 4. A physiology-driven protocol for the treatment of hepatic encephalopathy. BID = twice daily; q2 - q4 = every 2-4 hours; TID = 3 times daily; TIPS = transjugular intrahepatic portosystemic shunt.

follow. To maximize the power of the refined ammonia hypothesis, clinicians should consider the following therapeutic framework (Figures 3 and 4).

Overt HE

On admission, the hospitalized patient with acute HE should be broadly assessed for infection (from the urinary tract to a sampling of the ascites) and be treated for any infections promptly and aggressively. In addition, patients should receive a volume challenge if dehydrated, potentially with albumin (although not necessarily), and should have their diuretics discontinued at least temporarily, as well as any narcotics and benzodiazepines. Deficits in potassium should be repleted. Beyond that, all patients should receive lactulose. Consider albumin dialysis for refractory HE.[18] Ammonia levels do not need to be assessed. Before hospital discharge, a nutrition consultation should be arranged, previous authorization to cover rifaximin for secondary

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prophylaxis should be considered, and the risks of driving should be explained. A referral for transplant evaluation should be pursued if not already undertaken. For a review of the stepwise in-hospital management of HE, please refer to the study by Leise and colleagues.[18]

Covert or Resolved HE After an Acute Episode

Clinicians should maintain patients on lactulose or rifaximin therapy if their symptoms are mild and should consider combination therapy when their symptoms have been overt, required hospitalization, or did not respond to lactulose alone. Routine examinations should include assessments of volume status, especially for patients taking diuretics to guide dosing decisions. Efforts should be undertaken to ensure eukalemia and consider supplementation, especially for those with a history of hypokalemia. Clinicians should carefully track and address the patient's nutritional status, supplementing macronutrients and micronutrients as needed with consideration of BCAAs. For patients who are not candidates for first-line therapies or for those who do not completely respond, consideration of probiotics, zinc supplementation, or, when available, glycerol phenylbutyrate or L-ornithine L-aspartate is reasonable. Hepatic encephalopathy should be viewed as a contraindication for the prescription of sedatives and narcotics. Finally, the risks of driving must be explained.

CONCLUSION

In summary, the ideal therapeutic approach to patients with HE can be guided by a refined ammonia hypothesis. This refined and up-to-date view of the ammonia hypothesis is one that acknowledges the contribution of inflammation to the neurotoxicity of serum ammonia and underscores the importance of multiple organ systems, namely, the gut, kidney, and skeletal muscle, in achieving ammonia homeostasis.

Abbreviations and Acronyms: **BCAA** = branched-chain amino acids; **BID** = twice daily; **GABA-A** = γ-aminobutyric acid type A; **HE** = hepatic encephalopathy; **MELD** = Model for End-Stage Liver Disease; **NMDA** = *N*-methyl-D-aspartate receptor; **q2-q4** = every 2-4 hours; **ROS** = reactive oxygen species; **TID** = 3 times daily; **TIPS** = transjugular intrahepatic portosystemic shunt

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