Hyperammonemia in the ICU

Postgraduate Education Corner

Hyperammonemia in the ICU

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Patients experiencing acute elevations of ammonia present to the ICU with encephalopathy, which may progress quickly to cerebral herniation. Patient survival requires immediate treatment of intracerebral hypertension and the reduction of ammonia levels. When hyperammonemia is not thought to be the result of liver failure, treatment for an occult disorder of metabolism must begin prior to the confirmation of an etiology. This article reviews ammonia metabolism, the effects of ammonia on the brain, the causes of hyperammonemia, and the diagnosis of inborn errors of metabolism in adult patients.

Abbreviations:

ASS
      argininosuccinate synthetase

CPS
      carbamyl phosphate synthetase

HHH
      hyperammonemia-hyperornithinemia-homocitrullinuria

ICH
      intracranial hypertension

IEM
      inborn error of metabolism

IHA
      idiopathic hyperammonemia

NAGS
      N-acetyl glutamine synthetase

OTC
      ornithine transcarbamylase

TPN
      total parenteral nutrition

UCD
      urea cycle disorder

Patients with acute hyperammonemia have significant morbidity and mortality and are frequently cared for in the ICU. As with many other patients with ailments who seek treatment in the ICU, initial stabilization must focus on treatment, not on diagnosis. Brain edema and intracerebral hypertension must be treated emergently, and ammonia elimination must be facilitated. If acute liver failure is not the cause of hyperammonemia, more unusual causes of acute hyperammonemia must be investigated, such as side effects of certain drugs, infections, or occult disorders of metabolism. Diagnosis, particularly the inborn errors of metabolism (IEMs), often cannot be confirmed until days, or sometimes months, after the initial presentation.

Metabolism and Metabolic Effects of Ammonia

To understand the consequences of, treatments for, and diagnosis of acute hyperammonemia, it is important to review the pathways for the production, metabolism, and excretion of ammonia.

Ammonia Production

Ammonia metabolism involves primarily five organs—the gut, kidney, muscle, liver, and brain (Fig 1) . Ammonia is produced mostly in the gut, but also in the kidney and muscle. Within the GI tract, ammonia is a byproduct of protein digestion[1] and bacterial metabolism.[2] Within the kidney, ammonia is essential for the renal handling of acid. Ammonium is synthesized from glutamine in the proximal tubule and ultimately is concentrated in the medullary interstitium,[3] where it is either released into the systemic circulation or used to facilitate the excretion of protons. Renal ammonia production is dynamic and increases with alterations in renal acid-base status changes and with GI bleeding.[4] [5] Finally, skeletal muscle can also produce ammonia, usually during seizures or with intense exercise.[1]
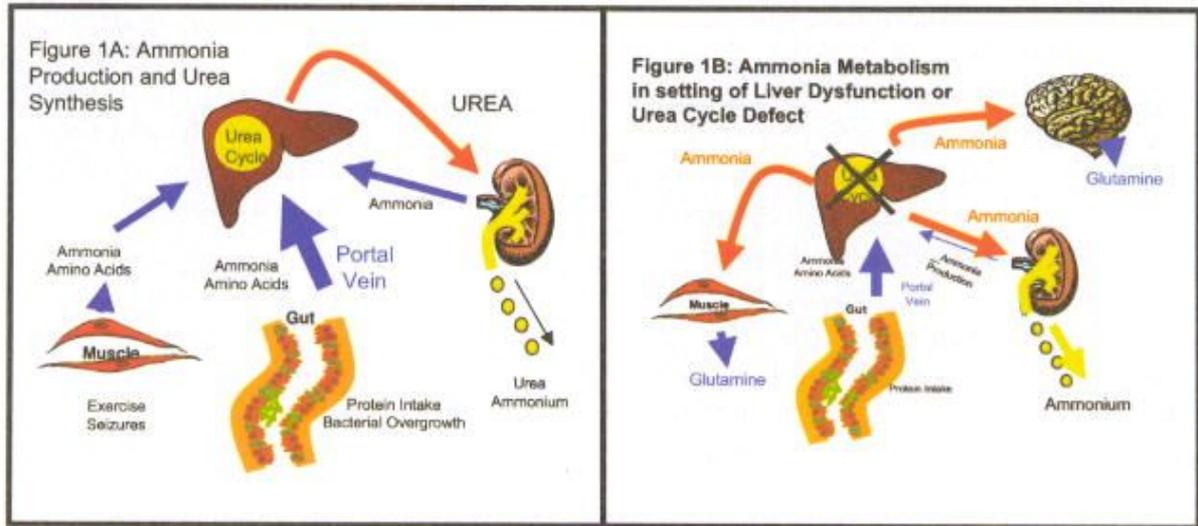
Figure 1. Organs responsible for ammonia metabolism.

Ammonia Degradation

The liver is primarily responsible for ammonia degradation. Ammonia in the venous system (which is produced by the digestion of protein in the splanchnic circulation and by muscle peripherally) is metabolized to urea through the urea cycle (Fig 2) . Several enzymes are required for the urea cycle, including the rate-limiting enzyme carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinic acid lyase, and arginase. Arginine is necessary for urea cycle function and is a quasi-essential amino acid when dietary nitrogen intake is insufficient or when a defect in the urea cycle is present. Because venous ammonia levels vary locally and because the liver is so adept at the metabolism of ammonia, arterial ammonia levels usually do not correlate with venous ammonia levels.[6] [7] [8] [9]
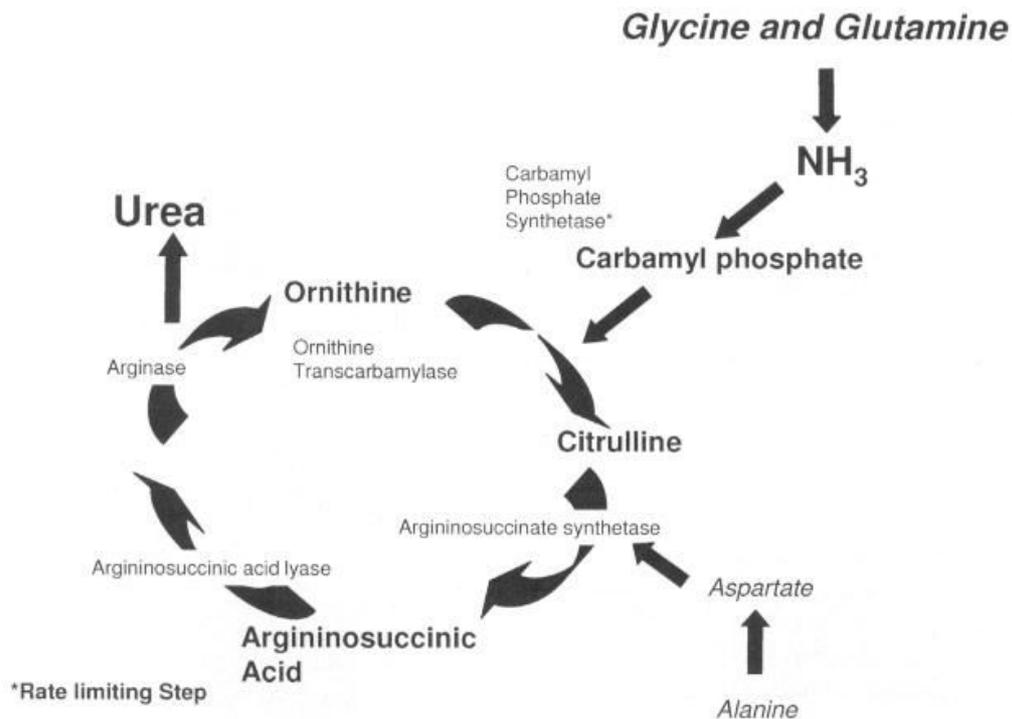

Figure 2. The urea cycle.

When the capacity of the liver to metabolize ammonia is overcome, either because ammonia production exceeds the metabolic capacity of the liver or because the liver is unable to metabolize ammonia, elimination is dependent on the kidney, muscle, and brain. In the setting of hyperammonemia, the kidney decreases ammonia production and increases urinary excretion of ammonia.[4] [10] The muscle[4] [5] [6] [11] [12] and brain metabolize excess ammonia to glutamine.[1] [11] [12] [13] The process of metabolizing ammonia to glutamine is physiologically costly, particularly in the brain where the symbiotic relationship between neurons and astrocytes is disrupted by excess glutamine production.

Under normal physiologic conditions, astrocytes support adjacent neurons with adenosine 5'-triphosphate, glutamine, and cholesterol. The neuron metabolizes glutamine to glutamate, which is a neurotransmitter that activates N-methyl D-aspartic acid receptors. After release into the synapse, glutamate is recycled by the astrocyte to glutamine, resulting in the functional compartmentalization of glutamate and glutamine. When ammonia levels rise acutely within the brain, astrocyte and neuron function are affected. Astrocytes rapidly metabolize ammonia to glutamine, but the subsequent rise in intracellular osmolarity causes astrocyte swelling and loss.[1] [11] [12] [13] Inflammatory cytokines, including tumor necrosis factor-α, interleukin-1, interleukin-6 and interferon, are released by the astrocyte.[13] Ongoing oxidative and nitrosative stress cause additional astrocyte loss through apoptosis.[12] In the remaining astrocytes, ammonia-mediated inhibition of alpha-ketoglutarate dehydrogenase and the depletion of carboxylic acids for glutamine synthesis paralyzes the Krebs cycle.[1] [11] [13] [14] Adenosine 5'-triphosphate and nicotinamide adenine dinucleotide (reduced form) production fall,[1] [11] [13] [14] and rising nicotinamide adenine dinucleotide (oxidized form) favors the metabolism of pyruvate to lactate.[15] Lactate levels in the astrocyte and brain increase.[13] Decreased expression of glutamate receptors in astrocytes cause increased concentrations of glutamate,[1] [11] [12] [13] [14] and seizures may result. Cerebral blood flow increases,[1] [12] effective cerebral autoregulation is lost, [12] [13] and cerebral edema and intracranial hypertension (ICH) may develop.[1]

Cerebral edema and herniation (as well as seizures) are unique to acute hyperammonemia and usually occur only when arterial ammonia levels are > 200 µmol/L. [12] [13] The rise in ammonia levels, the elevations of glutamine, and the effect of glutamine on the brain are proposed to account for the different effects of acute (vs chronic) hyperammonemia on the brain. In patients with chronic hyperammonemia, ammonia is metabolized more efficiently by muscles and the hepatic-splanchnic beds.[2] Ammonia also has a less pronounced chronic effect on the brain as follows: osmolarity does not rise as an acutely; down-regulation of N-methyl D-aspartic acid receptors results in less neuroexcitation from glutamate[11] [14] ; and ammonia has more of an effect on neuroinhibitory gamma aminobutyric acid receptors.[13]

Although venous, arterial, and brain ammonia levels do not usually correlate, acute hyperammonemia may be an exception. In patients with fulminant hepatic failure, venous ammonia levels correlate with arterial ammonia levels.[2] In addition, arterial ammonia levels may be predictive of what is happening in the brain, as follows: arterial ammonia levels in patients with fulminant hepatic failure correlate with glutamine levels, which correlate with the development of ICH.[2] [9] [16] [17]

Management of Hyperammonemia

Several treatments are appropriate for all patients with hyperammonemia, while some treatments are reserved for those with hyperammonemia that is thought to be related to an IEM (Table 1) . Often, therapy must be given empirically, as the diagnosis of IEM can take weeks to months.

TABLE 1 -- *Evaluation and Treatment of Hyperammonemia[*]

Medical history	Social history
Recent drug changes (antibiotics, anti-TB medications)	Travel (hepatitis A/anti-TB medications)
Recent surgeries (TURP, anesthetics)	Illicit drug use (hepatitis B/C)/tattoos
Addition of TPN	Eating/gathering mushrooms
GI bleeding	Protein avoidance and learning disability
Urinary tract infection	Family history
Diagnostic evaluation	
Ammonia level	Coagulation studies
Hepatitis A antibody	CBC with differential count
Hepatitis B surface antigen and antibody	Blood cultures
	CMV titer and EBV titers
Hepatitis B core antibody	Ultrasound with Doppler
Hepatitis C antibody	Liver biopsy
Hepatitis C polymerase chain reaction	Urine and blood amino acids (see Fig 4)
Acetaminophen level	
Treatment while awaiting test results	If ammonia levels remain at > 100 μmol/L or if IEM is suspected: consider (see Fig 3)
Management of elevated ICP	
Hypothermia, sedatives	Decrease cerebral lactate production with carnitine infusion
Mannitol if ICP > 20 or encephalopathy stage	
III–IV	Methods to facilitate elimination of ammonia
Antiinflammatory drugs:	
N-acetylcysteine	Renal replacement therapy

Treatment for SIRS/coexisting infection with antibiotics	Ammonia trapping agents + arginine
	Branched chain amino acids
Reduce ammonia production/absorption	
Lactulose	
Protein restriction	
Provide calories (D10)	

*TURP = transurethral resection of the prostate; SIRS = systemic inflammatory response syndrome; EBV = Epstein-Barr virus; TB = tuberculosis; CMV = cytomegalovirus.

For both types of patients, initial treatment must focus on the management of ICH, which is a condition that is associated with increased morbidity and mortality.[18] Usually, hyperammonemia in adults is associated with cerebral edema, decreased cerebral metabolism, and increases in cerebral blood flow. The management of these patients entails the reduction of cerebral edema and cerebral blood flow.[18] However, in some patients cerebral blood flow may be reduced; in these patients, drugs that lower cerebral blood flow and cerebral perfusion pressure must be avoided.[18] Unfortunately, placement of intracranial pressure monitoring is associated with complications,[19] and management may need to be performed empirically. Given the dynamic changes in cerebral blood flow, there is controversy about which management strategy is most appropriate.

Hypothermia[12] [18] [20] abrogates many of the metabolic effects of ammonia, as follows: decreasing free radical production,[13] astrocyte swelling, and inflammation; while improving cerebral blood flow and autoregulation. Hypothermia also slows protein catabolism and the production of ammonia by bacteria and the kidney.[20] Hypothermia is the least controversial of treatments. N-acetylcysteine may reduce cerebral edema and cerebral metabolism; as a result, N-acetylcysteine may be beneficial even in the absence of acetaminophen toxicity.[18] Although mannitol may increase the influx of ammonia across the blood-brain barrier in canines,[21] mannitol administration in humans has been shown to reduce cerebral edema and improve mortality.[18] [22] Two additional controversial treatments include the following: the use of indomethacin, which reduces inflammation and decreases cerebral blood flow but which may cause renal failure[12] [18] [23] ; and propofol, which successfully sedates patients and decreases cerebral blood flow[24] but which may be harmful in patients without adequate cerebral perfusion pressures.

In addition to therapies that treat ICH, additional supportive therapy is recommended. Because up to 40% of patients with hyperammonemia and elevated intracranial pressure have subclinical seizures,[12] [25] therapy with dilantin or phenobarbital should be considered.[18] [25] Lactulose, a main stay of treatment in patients with chronic hyperammonemia,[26] has not been shown to affect mortality in patients with acute hyperammonemia, but it is unlikely to be harmful.[18] Antibiotics and antifungal agents can treat underlying infection and may prevent superinfection in these immunocompromised patients.[27] [28] Nutritional support must be provided to prevent protein catabolism. Protein intake must be stopped; normal or supranormal caloric intake may be provided with dextrose and lipids. Once the patient is sufficiently stable to be fed enterally, a protein-free enteral formula (*eg*, Pro-Phree; Abbott Nutrition; Columbus, OH; or PFD 1 or 2 [formerly known as 80056]; Mead Johnson; Evansville, IN) should be provided.

If ammonia levels remain at > 100 μmol/L and/or the etiology of hyperammonemia remains elusive, an IEM may be present. For these patients, additional therapies are useful to reduce ammonia levels, by actively removing ammonia, facilitating its metabolism, and by decreasing its production (Fig 3) . A multifaceted approach can have a dramatic effect on serum ammonia levels (Fig 4) .
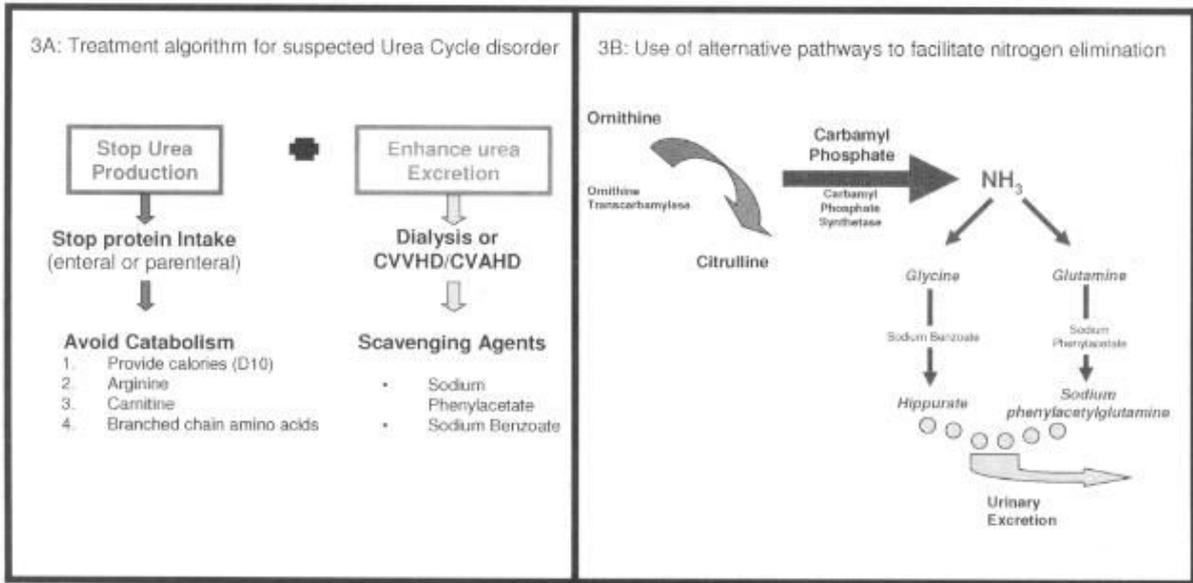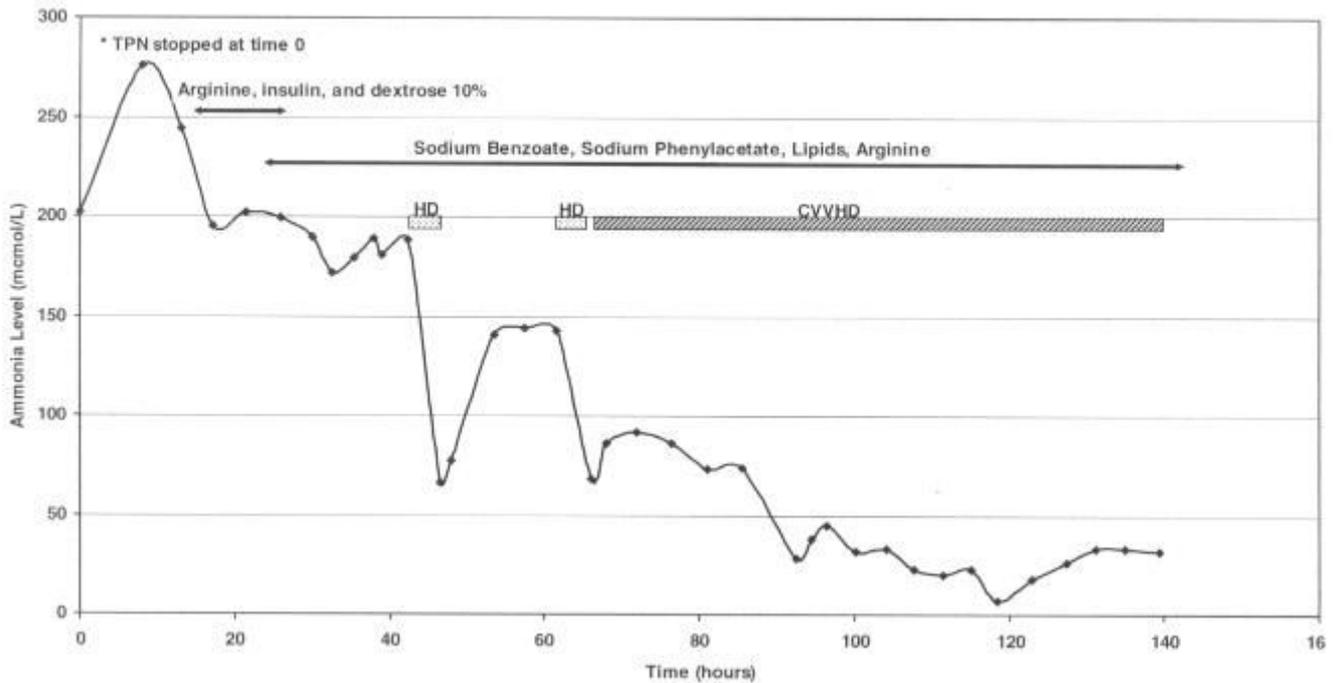
Figure 3. Treatment of UCDs.

Figure 4. Response to treatment. CVVHD = continuous venovenous hemodiafiltration; HD = hemodiafiltration.

Peritoneal dialysis,[29] [30] hemodialysis,[29] [30] [31] [32] continuous venovenous hemofiltration,[29] [33] [34] continuous venovenous hemodiafiltration,[35] and continuous arteriovenous hemodiafiltration[36] are effective ways to remove ammonia and have been helpful in treating hyperammonemia associated with urea cycle disorders in children and adults. These interventions could serve as a potential bridge for adults with fulminant hepatic failure who are awaiting transplantation.

Nitrogen elimination may also be accomplished through pharmacologic manipulation[31] [37] [38] [39] [40] [41] (Fig 3) . Sodium phenylacetate and sodium benzoate promote the degradation of ammonia through "alternate" metabolic pathways. The side effects of these medications, which are administered IV, include nausea, vomiting, and hypokalemia.[39] In some cases of acute hyperammonemia, the use of these agents has prevented the need for

dialysis.[40] [41] When dialysis is used in conjugation with these medications, the drugs should be dosed after dialysis.[34] Treatment with these agents must often begin before a diagnosis is confirmed. Although these drugs have a hypothetical benefit for all patients with hyperammonemia, they have been approved by the US Food and Drug Administration only for the treatment of hyperammonemic crisis in patients with IEMs. IV arginine administration may also promote nitrogen excretion by preventing protein catabolism, especially in patients with diseases in which *in vivo* synthesis of arginine is limited by enzyme deficiencies.[41] L-carnitine facilitates lipid metabolism, and may reduce cerebral lactate levels by indirectly stimulating pyruvate dehydrogenase.[42]

Liver transplantation has been used successfully for cirrhosis and fulminant hepatic failure (whether from drug induced, viral, autoimmune, or cryptogenic)[43] [44] as well as for disorders of the metabolism, including citrullinemia,[45] [46] [47] [48] OTC deficiency,[31] [45] [49] and CPS deficiency.[31] [48]

Causes of Hyperammonemia

After instituting measures to stabilize the patient and to reduce the risk of herniation, a diagnostic evaluation should begin. The causes of hyperammonemia can be divided into processes that increase ammonia production or decrease ammonia elimination (Table 2) .

TABLE 2 -- *Causes of Hyperammonemia in Adults*[*]	
Increased Ammonia Production	**Decreased Ammonia Elimination**
Infection	Liver failure
Urease producing bacteria (Proteus, Klebsiella)	Fulminant hepatic failure
	Trans-hepatic, intrajugular
Herpes infection	Shunt
Protein load and increased catabolism	Portosystemic shunt (TIPSS)
Severe exercise	Drugs (see Table 2)
Seizures	Glycine
Trauma or burns	Valproate
Steroid administration	Carbamazepine
Chemotherapy	Rifabutin
Starvation	IEM

TABLE 2 -- *Causes of Hyperammonemia in Adults**	
Increased Ammonia Production	**Decreased Ammonia Elimination**
Gastric bypass	Ornithine transcarbamylase deficiency
GI hemorrhage	
Increased renal ammonia production	Carbamyl synthetase deficiency
Increased splanchnic ammonia production	NAGS deficiency
	Arginosuccinate lyase deficiency
Increased peripheral catabolism due to deficiency of essential amino acids	Hyperomithinemia, hyperammonemia, homocitrillinuria
TPN	Lysinuric protein intolerance
Other	
Cancers (multiple myeloma)	Organic acidurias
	Fatty acid oxidation defects
	Other:
	IHA

*TIPSS = transjugular intrahepatic portosystemic shunt.

Several processes result in increased ammonia production. The metabolism of protein increases blood ammonia levels and can be seen with total parenteral nutrition (TPN),[50] [51] GI hemorrhage,[52] steroid use,[21] trauma,[21] and GI hemorrhage.[5] Other conditions can also increase ammonia production, such as infection with urease-splitting organisms,[53] [54] [55] [56] [57] herpes infection,[58] urinary diversion,[54] [59] [60] [61] or multiple myeloma.[31] [62] [63] [64] [65] [66] [67]

Decreased ammonia elimination is seen in the setting of fulminant hepatic failure, portosystemic shunting, drug administration, or IEM. Fulminant hepatic failure is the most common cause of acute hyperammonemia in adult ICUs, with about 2,000 cases annually.[44] In a prospective study[68] of acute liver failure at 17 US tertiary care centers, acetaminophen toxicity accounted for 39% of cases, drug reactions for 13% of cases, viral hepatitis (A or B) for 12% of cases, and idiopathic causes for 17% of cases. Additional causes of fulminant hepatic failure include the following: infections (*eg*, the hepatitides, varicella, Epstein-Barr virus, and cytomegalovirus); drugs (Table 2) ; autoimmune diseases; vascular diseases (*eg*, Budd-Chiari and venoocclusive disease); pregnancy-related conditions (*eg*, acute fatty liver of pregnancy, and eclampsia); and toxins (*eg*, mushrooms and herbs).[43] [44]

Several drugs cause hyperammonemia by disrupting the urea cycle. Glycine, which is used during transurethral resection of the prostate, stimulates ammonia production.[69] Salicylates can reduce mitochondrial function in the liver as is suggested to occur with Reye syndrome.[70] [71] Valproate increases propionic acid levels, which inhibit CPS. As a result, an overdose with valproate may cause marked hyperammonemia in healthy patients,[31] [72] while therapeutic doses of valproate may cause hyperammonemic coma in patients with underlying urea cycle disorder (UCD).[31] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] Although the mechanisms are not known, case reports have also described hyperammonemia after the use of carbamazepine,[83] [84] ribavirin,[85] and sulfadiazine with pyrimethamine.[86]

IEMs may also cause hyperammonemia,[31] [87] including defects in the β-oxidation of fatty acids causing carnitine deficiency, organic acidurias, and UCDs. Most severe IEMs present early in childhood. However, UCDs may present in adulthood when they are unmasked by precipitants such as increased protein intake, drugs, or infection. The prevalence if UCDs is estimated at 1 in 25,000 cases to 1 in 30,000 cases.[31] [37] [88] The most common UCDs diagnosed in adults are OTC deficiency, ASS deficiency, and carbamyl phosphate deficiency.

OTC deficiency is the most common UCD discovered in adults. OTC deficiency is a X-linked disease usually presenting in male infants,[37] [89] or rarely in adolescents.[89] [90] [91] [92] However, the carrier ratio in women is approximately 1:70. In female heterozygotes, random inactivation (lyonization) of the X chromosome within each hepatocyte results in phenotypic variation. As a result, clinical manifestations of OTC do not develop in many female patients until they are adults.[50] [77] [78] [89] [93] [94] [95] [96] [97] [98] [99] [100]

TABLE 3 -- *Drugs Associated With Hyperammonemia*[*]	
Drugs Associated With Fulminant Hepatic Failure	**Drugs Associated With UCDs**
Acetaminophen	Glycine
Lipid-lowering agents: atorvastatin	Salicylates
Antiinflammatories: ibuprofen, celecoxib, diclofenac	Valproate
	Carbamazepine
Anesthetics: halothane	Sulfadiazine
Antibiotics: amoxicillin, amoxicillin clavulonate, flucloxacillin, telithromycin, moxifloxacin, levofloxacin, trovafloxacin, minocycline, sulfamethoxazole, trimethoprim	Pyrimethamine
	TPN
HIV medications: indinavir, nevirapine	
Antifungals: fluconazole, terbinafine	
Anti-tuberculous medications: isoniazid, rifampin, rifabutin, pyrizinamide	
Antiparasitic: dapsone	
Anti-epileptics: carbamazepine, valproate, phenytoin, phenobarbital	
Anti-depressants: nefazadone, sertraline, duloxetine, buproprion	
Other psychoactive: lamotrigine, donepezil, disulfiram	

TABLE 3 -- *Drugs Associated With Hyperammonemia*[*]	
Drugs Associated With Fulminant Hepatic Failure	**Drugs Associated With UCDs**
Illegal drugs: MDMA (ecstasy)	

*MDMA = 3,4 methylenedioxymethamphetamine.

CPS deficiency, an autosomal-recessive disease,[101] may also present in adulthood.[82] [101] [102] [103] [104] [105] [106] [107] [108] At least 14 mutations have been described in the CPS gene.[109] Deficiency of N-acetyl glutamine synthetase (NAGS) mimics CPS deficiency[110] because N-acetyl glutamine is an essential allosteric activator of CPS I. Although complete NAGS deficiency usually presents in children,[111] patients with hypomorphic alleles may present in adulthood if their partially functional enzyme is inhibited by short-chain fatty acids or treatment with valproic acid.[111] [112] [113] [114] Partial NAGS deficiency may be more common than previously thought.[112]

ASS deficiency, also called *citrullinemia* due to the accumulation of citrulline, has an incidence of approximately 1 case per 70,000 to 100,000 cases.[37] [115] [116] There are two types of recessively inherited ASS deficiency, one that presents in infants (type I) and one that presents in adults (type II). Type II citrullinemia, which is characterized by a genetic mutations in the citrin gene, affects the expression of ASS within the liver.[115] Nearly 50% of patients with type II ASS deficiency present in their 20s or early 30s, usually with psychiatric manifestations.[46] [115] [116] [117] [118] [119] In most patients with type II ASS deficiency, the disease progresses to death from cirrhosis within years after the onset of hyperammonemia[47] [115] [116] unless liver transplantation is undertaken.

Other inherited disorders of metabolism that may present with hyperammonemia in adulthood include hyperammonemia-hyperornithinemia- homocitrullinuria (HHH)[37] [120] [121] [122] [123] and lysinuric protein intolerance.[37] [124] [125] [126] [127] Neither of these diseases is a UCD, but both impair the utilization of ornithine, causing functional impairment of the urea cycle.[121] [125] HHH is an autosomal-recessive disease that is characterized by defective ornithine transport across the inner mitochondrial membrane.[121] The disease is characterized by neurologic deficits, including spastic paresis, ataxia, seizures, and mental retardation.[121] [128] Patients with HHH may present with acute liver disease and coagulopathy.[129] Lysinuric protein intolerance is a disease with defective dibasic amino acid transport. Patients have protein intolerance, osteoporosis, interstitial lung disease, and focal segmental glomerulosclerosis,[124] [125] [130] and an autoimmune disease with hemolytic anemia that mimics systemic lupus erythematosus may develop.[130]

Although there are multiple UCDs, their clinical presentations are quite similar. In the fulminant form, patients present with coma and encephalopathy, while in the milder forms of the disease patients often have intermittent periods of confusion or bizarre behavior, presumably from hyperammonemia.[31] [37] [46] [50] [78] [80] [88] [90] [93] [101] [105] [115] [117] [118] [119] Many patients have seizure disorders, including partial complex seizures, which may explain their occasional confusion.[37] [46] [77] [88] [90] [94] A history of repetitive or cyclical vomiting may be present.[29] [31] [34] [38] [46] [77] [80] [81] [88] [90] [93] [101] [102] [105] [125] Patients may have intellectual limitations such as learning disabilities or mild mental retardation.[37] [77] [101] Patients may voluntarily limit their protein intake (called *auto-vegetarianism*) to avoid postprandial headaches or somnolence.[31] [37] [38] [50] [77] [90] [93] [108] [121] [124] [129] [130] Patients with citrullinemia (*ie*, ASS deficiency) often have a history of preferring beans, presumably because beans provide arginine, which is an essential amino acid, in these patients.[37] [46] [115]

Physiologic stressors that provoke hyperammonemia in patients with these metabolic disorders include the following: upper respiratory tract illnesses[102] ; pneumonia[115] ; dietary changes; fever[90] ; pregnancy[36] [78] [96] [108] ; GI bleeding[52] [59] ; and infection with urease-splitting organisms.[54] [55] [56] [57] Insults to the liver, such as alcohol or acetaminophen, can provoke or worsen hyperammonemia in a susceptible patient.[115] TPN, which often provides more protein than the patient usually consumes enterally, has provoked hyperammonemia in many patients with UCDs, most often OTC.[50] [78] The presence of hyperammonemia following TPN should prompt an investigation of a UCD.

One final cause of hyperammonia is idiopathic hyperammonemia (IHA), a clinical condition in which elevated ammonia levels are disproportionate to liver dysfunction in the absence of an inherited metabolic disorder. IHA was first described as a complication of intensive chemotherapy in leukemia patients but has subsequently been described in patients undergoing bone marrow transplantation, in patients with solid tumors treated with

continuous infusions of 5-fluorouracil,[131] [132] [133] [134] [135] [136] and in patients after lung transplantation.[137] The mortality rate exceeds 75% in the reported cases. The incidence is unknown, but in previous retrospective reviews[131] [134] was estimated to range from 0.5 to 2.4%. The etiology of IHA is not known; although some investigators[134] have postulated transient abnormalities in urea synthesis. Others[138] have suggested that the increased production of ammonia present in these patients occurs from tissue breakdown, mucositis, and GI bleeding. Those patients who have survived IHA were identified and treated exceptionally early with ammonia-trapping agents and dialysis.

Diagnosis

The search for the source of hyperammonemia should initially focus on fulminant hepatic failure and then progress to a workup for IEM if the hyperammonemia cannot be explained (Table 1) . In addition to liver function and coagulation tests, the measurement of acetaminophen levels, alcohol/drug toxicology, and viral serologies for the hepatitides should be drawn.[43] A careful medication and social history should be obtained to rule out drug-induced acute liver failure.[43] Ultrasound should be performed to rule out portal vein thrombosis and fatty infiltration. Abdominal CT scanning may be helpful.

The presence of infection, increased protein catabolism, or drug administration should be evaluated. If the degree of hyperammonemia is inconsistent with one of these diagnoses or they are ruled out, the physician should also consider an occult UCD. In UCD, routine blood chemistry measurement and liver function test results may be abnormal, including elevations of transaminase levels and mild elevations of indirect bilirubin levels,[31] [38] [47] [78] [115] [118] [129] [139] coagulopathy,[31] [47] [78] [118] respiratory alkalosis,[103] [139] and metabolic acidosis (sometimes with an elevated anion gap).[118]

To evaluate further for a suspected IEM, quantitative plasma and urine amino acids (including citrulline, argininosuccinic acid, and glutamine), urine organic acid analysis, urine orotic acid, and carnitine should be obtained.[31] [37] [140] [141] Specimens used for these analyses should be sent to the laboratory on ice to prevent spurious results.[31] Falsely low glutamine levels can limit the diagnostic evaluation. A diagnostic algorithm is provided to aid the interpretation of these test results (Fig 5) .
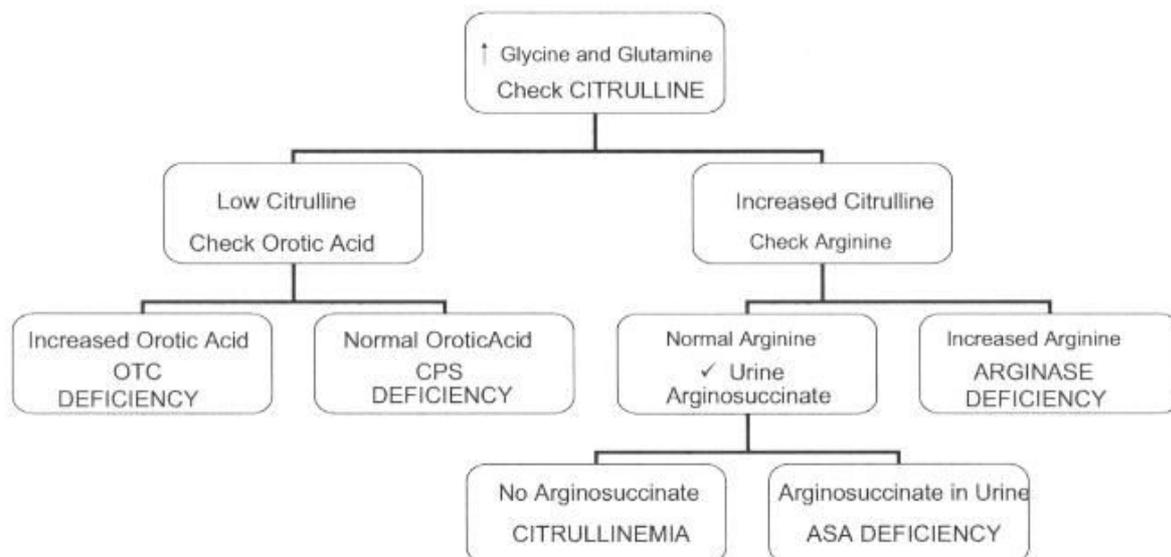

Figure 5. Diagnostic algorithm for UCD. ASA = acetylsalicylic acid.

When an IEM is suspected, liver biopsy should be considered to confirm the diagnosis. A biopsy must be undertaken with caution to prevent a hyperammonemic episode. Mutation analysis may be performed utilizing DNA derived from blood lymphocytes. However, because of the high frequency of genetic polymorphisms in large genes, genetic confirmation of the disease may not be possible until the expression of the presumed

mutations is undertaken *in vitro* or *in vivo* model systems.[142] At present, genetic testing is routinely available only for OTC deficiency.[141]

Although the UCD disorders are rare, diagnosis is important. Reducing ammonia levels quickly and preventing future episodes of hyperammonemia can prevent death and neurologic deterioration.[37] [39] [40] [143] [144] [145] Early recognition of these diseases may also help to prevent consequences for other patients or family members. A liver transplant recipient[146] [147] died from hyperammonemia after receiving an organ from an adult male patient who had died of cerebral edema of unknown etiology. Subsequent studies[146] [147] revealed OTC deficiency in the donor. Incidents such as this are a reminder that the true prevalence of inherited metabolic disorders such as UCDs cannot be known until they are readily identified and diagnosed in adulthood.

Conclusions

Hyperammonemia with altered mental status often requires treatment by an intensivist. The effects of hyperammonemia on the brain are significant and often fatal. Early management of cerebral hypertension is essential. When ammonia levels are disproportionate to the degree of liver function or when no obvious cause for hyperammonemia can be immediately identified, intervention may also require empiric management for IEM.

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