Ammonia

Do Ammonia Levels Correlate with Hepatic Encephalopathy? Hepatic encephalopathy in patients with chronic liver dysfunction is believed to be caused by a failure of the liver to clear toxic products from the stomach. The exact toxins that cause hepatic encephalopathy have not been established, but ammonia may be involved. Many physicians determine ammonia levels to diagnose hepatic encephalopathy and as a guide to treatment.

However, studies have shown that the correlation between serum ammonia levels and severity of hepatic encephalopathy is inconsistent. A recent study suggested that the partial pressure of ammonia may correlate more closely with the severity of hepatic encephalopathy than the total plasma ammonia level. Ong and associates evaluated the correlation between plasma ammonia levels and the severity of hepatic encephalopathy. They also determined the best of the four types of ammonia measurements for this correlation by comparing arterial total ammonia, venous total ammonia, arterial partial pressure of ammonia, and venous partial pressure of ammonia.

Consecutive patients who were admitted to a tertiary care center with the diagnosis of cirrhosis between September 1998 and December 1999 were enrolled in the study. The diagnosis of cirrhosis was established by biopsy or by signs of portal hypertension such as gastroesophageal varices, previous variceal bleeding, or ascites. Researchers collected clinical and laboratory data at the time of admission. The mental status of the patients was assessed using the West Haven Criteria for grading of mental status. A diagnosis of hepatic encephalopathy was established when the patients' mental status was altered and other causes of mental status changes had been excluded. After diagnosis, fasting arterial and venous blood samples were obtained, and total ammonia and partial pressure of ammonia were determined.
The 121 patients who were enrolled in the study had the following West Haven Criteria grades: 30 patients (25 percent) had graded zero encephalopathy; 27 patients (22 percent) had grade 1; 23 patients (19 percent) had grade 2; 28 patients (23 percent) had grade 3; and 13 patients (11 percent) had grade 4. All four measurements of ammonia increased with the severity of hepatic encephalopathy. The arterial total ammonia level had the highest correlation, but it was not statistically significant.

Other variables that had a correlation to the severity of hepatic encephalopathy included International Normalized Ratio (INR) values, serum creatinine levels, bilirubin levels, and lactulose use. A multivariable ordered logistic regression analysis revealed that only serum ammonia levels and INR values were independently associated with the severity of hepatic encephalopathy.

The authors conclude that venous total ammonia levels do correlate with severity of hepatic encephalopathy and should be adequate in evaluating patients with this condition. Total arterial ammonia levels and partial pressure of ammonia levels had similar correlation but did not prove to be better markers than venous total ammonia levels.

Treatment of patients with liver cirrhosis with the signs of liver insufficiency is complex and seldom satisfactory. Carnitine, taking part in liver lipid metabolism might be a potentially effective drug.

The aim of the study was to evaluate the influence of L-carnitine on serum ammonia, cholesterol and triglyceride concentrations. Fourteen patients were treated with L-carnitine, 25--with L-ornitine L-aspartate, 11--were not given those medicaments. All patients had proteins reduced down to 0.5 g/kg b.w. per day in their diet. The serum concentrations of ammonia, cholesterol and triglycerides were assessed on inclusion and after 28 days of treatment.

Results: All patients improved clinically. A significant improvement was observed in the group of patients treated with L-ornitine L-
aspartate (p < 0.003), and among those treated with L-isocarnitine (p = 0.005), while evaluating the Child-Pugh score before and after treatment. The serum ammonia concentration decreased in all patients. However, among the individuals treated with L-carnitine an increase of serum cholesterol and triglyceride concentrations was observed as well (p = 0.02).

Conclusions: L-carnitine lowers the serum ammonia concentration and improves lipid metabolism.

Cirrhosis is the late result of any disease that causes scarring of the liver. Patients with cirrhosis are susceptible to a variety of complications that include hepatic encephalopathy, ascites and portal hypertensive bleeding. Quality of life and survival are improved by the prevention and treatment of these complications. This chapter will review the general principles in the diagnosis and treatment of hepatic encephalopathy.

Hepatic encephalopathy (HE), also known as portosystemic encephalopathy or PSE, is defined as mental or neuromotor dysfunction in a patient with acute or chronic liver disease. Several forms of HE have been described. The acute form of HE is often associated with fulminant hepatic failure and may rapidly progress to seizures, coma, decerebrate posturing and death. In patients with cirrhosis, acute encephalopathy is most commonly associated with a precipitating factor such as electrolyte disturbance, medications, gastrointestinal hemorrhage, or infection. Recurrent HE may occur with or without a precipitating factor and is usually easily reversible. Persistent HE is rare, and is defined as the persistence of neuropsychiatric symptoms despite aggressive medical and dietary therapy. The most frequent form of HE is not always clinically apparent: a patient with subclinical HE has only mild cognitive deficits or subtle personality changes. Specific neuropsychological or neurophysiologic testing is required to secure the diagnosis.
By definition, all patients with fulminant hepatic failure have some degree of hepatic encephalopathy. Because there is no definitive test for HE, the prevalence in other patients is difficult to describe. Clinical findings may be apparent in as many as one third of cirrhotic patients; if rigorously tested, up to two thirds have some degree of mild or subclinical HE.

**PATHOPHYSIOLOGY**

HE remains a complex clinical problem, the precise mechanism of which is unknown. The premise of most pathophysiologic theories is that ammonia accumulates in the central nervous system producing alterations of neurotransmission that affect consciousness and behavior. These "ammonia toxicity" theories have been supported by studies demonstrating increased ammonia levels in patients with both fulminant hepatic failure and chronic liver disease. The lack of strong correlation between serum ammonia levels and stage or degree of encephalopathy has been used in the argument that hyperammonemia may not be the sole factor in HE pathogenesis. Most ammonia is produced in the intestine by both colonic breakdown of nitrogenous compounds and enterocytic catabolism of amino acids. Other sources of ammonia are the kidneys and skeletal muscle. Normally ammonia is metabolized in the liver (by its conversion to urea) and is excreted through the kidneys or colon. Another means of detoxifying ammonia is through the formation of glutamine from glutamate in the liver and brain. Impaired liver
function, the shunting of blood around the liver and increased muscle wasting all lead to increased serum ammonia levels in cirrhotic patients. Ammonia interferes with brain function at many sites. Ammonia crosses the blood-brain barrier and directly depresses central nervous system functioning by inhibiting postsynaptic potentials. There is also evidence that hyperammonemia may facilitate the brain's uptake of tryptophan, a substance with neuro-active metabolites such as serotonin. Excess ammonia may reduce levels of brain adenosine triphosphate resulting in impaired cerebral energy. Lastly, the metabolism of ammonia to glutamine in the brain increases the intracellular osmolality of astrocytes, inducing both astrocyte swelling and vasodilation. Increased astrocyte hydration without overt increased intracranial pressure is currently considered a major factor in the development of HE in patients with chronic liver disease.

Toxins other than ammonia have also been implicated in the pathogenesis of HE. Excesses of neuro-toxic short-chain fatty acids and mercaptans have received attention in the past. Patients with cirrhosis have also been shown to have decreased branched-chain amino acid-to-aromatic amino acid ratios. It has been postulated that the increased aromatic amino acid in the cirrhotic patient's brain may competitively inhibit normal neurotransmitters such as dopamine and norepinephrine. Cirrhotic patients with HE have greatly increased serum manganese levels. Manganese may deposit directly in the basal ganglia and induce extra-pyramidal symptoms. Manganese may also act synergistically with ammonia to activate peripheral-type benzodiazepine receptors and the GABA-ergic neuroinhibitory system.

**SIGNS AND SYMPTOMS**

In patients with progressive HE, there is a gradual decrease in level of consciousness, intellectual capacity, and logical behavior along with development of specific neurologic deficits. Two staging systems have been described. (1) Numerous studies have employed the West Haven criteria of altered mental status in patients with HE. (2) Although the Glasgow Coma Scale has not been rigorously evaluated in this specific patient population, its widespread use in various other disorders of brain function makes it applicable in patients with acute
or chronic liver disease.

**DIAGNOSIS**

HE is a diagnosis of exclusion. Similar neuropsychiatric symptoms are seen in a variety of metabolic disorders, toxic ingestions, or intracranial processes. In certain patients, brain imaging or electroencephalography may be indicated to exclude an intracranial abnormality. Lumbar puncture with cerebrospinal fluid analysis may also be required in patients with unexplained fever, leukocytosis, or symptoms suggestive of meningeal irritation. Knowledge of the existence of acute or chronic liver disease and/or the history of HE are often helpful in heightening clinical suspicion and/or securing the diagnosis.

<table>
<thead>
<tr>
<th>Differential Diagnostic Considerations In Hepatic Encephalopathy</th>
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<tr>
<td><strong>Metabolic</strong></td>
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<tr>
<td>Hypo- or hyperglycemia</td>
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<td>Hypo- or hypercalcemia</td>
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<td>Hypokalemia</td>
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<td>Hypoxia</td>
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<td>Uremia</td>
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The most commonly used laboratory test in HE is the venous ammonia level. Because of inconsistent elevation and lack of correlation with the stage of encephalopathy, the ammonia level is not considered a good screening tool. Measurement of serum ammonia can be helpful when, for example, the level is elevated and there is doubt regarding the presence of significant liver disease. The arterial ammonia concentration provides a more accurate assessment.
of the amount of ammonia at the blood-brain barrier, but is also of limited clinical utility.

Because of implications for diagnosis and treatment, a precipitating factor should be sought in all cirrhotic patients hospitalized for HE. Serum determination of the complete blood cell count, electrolyte levels, and renal function is indicated in almost all cases. Recent use of psychoactive medications, such as narcotics or sedatives, should also be investigated. In a confused patient who cannot give a reliable history, the examination of stool or placement of a nasogastric tube may be of help in detecting gastrointestinal bleeding. Since infection is a common precipitating factor in HE, the culture of body fluids (urine, blood and ascites, if present) should be routinely performed. Lastly, constipation and the consumption of excessive dietary protein can precipitate HE. This is thought to be due to the increased nitrogen load in the gastrointestinal tract. Rare precipitants, such as hepatoma or vascular occlusion, need be investigated only if no other factors are thought to be contributing, or with clinical suspicion.

<table>
<thead>
<tr>
<th>Precipitating Factors In Hepatic Encephalopathy</th>
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<tr>
<td>• Anemia</td>
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<td>• Azotemia/uremia</td>
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<td>• Constipation</td>
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<tr>
<td>• Dehydration</td>
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<td>• Excessive dietary protein</td>
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<td>• Gastrointestinal bleeding</td>
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<td>• Hepatoma</td>
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<tr>
<td>• Hypokalemia, metabolic alkalosis</td>
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<tr>
<td>• Hypoglycemia</td>
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<td>• Hypothyroidism</td>
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<tr>
<td>• Hypoxia</td>
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<tr>
<td>• Infection (urinary tract, ascites, etc.)</td>
</tr>
<tr>
<td>• Medications (narcotics, sedatives, etc.)</td>
</tr>
<tr>
<td>• Vascular occlusion</td>
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</table>
TREATMENT

The main objectives in the treatment of HE are fourfold: (1) provide supportive care, (2) correct any precipitating factors, (3) reduce the nitrogen load in the gastrointestinal tract, and (4) assess the need for long-term therapy. Each of these objectives will be discussed separately here.

Standard supportive care is required for all hospitalized patients with HE. Patient safety and frequent monitoring of mental status is crucial. This may require additional personnel. In the case of comatose patients, admission to the intensive care unit and/or endotracheal intubation may be necessary. Patients with HE should also avoid prolonged periods of fasting. Although the restriction of dietary protein at the time of acute HE is often a cornerstone of therapy, protracted nitrogen restriction can lead to malnutrition. Therefore, appropriate enteral nutrition, either by mouth or nasogastric feeding tube, should be administered as soon as feasible.

A methodical search to identify and treat any precipitating factors is crucial in reversing the signs and symptoms of HE (see Diagnosis section above).

Because the toxins thought to be responsible for HE arise in the gastrointestinal tract, removal of the nitrogenous load is the mainstay of therapy. Various pharmacologic agents may be used, but the nondigestable disaccharide known as lactulose (Enulose or Kristalose) is currently the first-line therapy. The exact mode of action of lactulose is uncertain, but it is thought to involve both bacteriostatic and cathartic effects in the large intestine. After consumption, lactulose passes through the small bowel completely undigested. Once in the colon, lactulose is metabolized by colonic bacteria and the pH is lowered. This acidification of the bowel is thought to underlie the cathartic effect: ammonia can then pass from the bloodstream into the colonic lumen to be excreted. As a result, peripheral ammonia levels are reduced. Because lactulose is completely nonabsorbed, it does not alter serum glucose levels in diabetic patients, a concern of many patients and primary caregivers.

For acute encephalopathy, lactulose can be administered either orally, by mouth or through a nasogastric tube, or via retention enemas. The usual oral dose is 45 mL
followed by dosing every 1 to 2 hours until evacuation occurs. At that point, dosing is adjusted to attain two or three soft bowel movements daily. This usually requires 15 to 45 mL every 6 to 12 hours. Lactulose by enema is administered as 300 mL in 1 L of water, and should be retained for 1 hour. Due to the difficulty of administration, lactulose by enema is not generally used for chronic therapy. Common side effects include flatulence, bloating, and diarrhea. Lactitol, which is generally easier to tolerate, is used only in Europe and is not currently available in the United States.

For patients who do not tolerate lactulose or have continued symptoms, antibiotics are a second-line alternative for therapy. Antibiotics are thought to reverse HE by alteration of colonic bacteria. Metronidazole (Flagyl) and neomycin sulfate (Neo-Fradin) are most commonly used. Metronidazole is generally administered at 250 mg every 8 to 12 hours (500 to 750 mg daily). Dose and duration of metronidazole should be minimized as much as possible to avoid peripheral neuropathy, a side effect associated with its long-term use. Neomycin is as effective as metronidazole and is administered at 1000 mg orally every 4 to 8 hours (3 to 6 grams daily) in acute encephalopathy and 500 to 1000 mg orally every 6 to 12 hours (1 to 2 grams daily) when used chronically. Neomycin use should also be limited, if possible, since long-term use can lead to rare ototoxicity and/or renal failure. If administered chronically (with or without lactulose) to control HE symptoms, periodic renal and annual auditory monitoring should be performed. If a patient is already receiving antibiotics for prophylaxis of spontaneous bacterial peritonitis-usually norfloxacin (Noroxin) or trimethoprim-sulfamethoxazole (Bactrim or Septra)-the use of additional antibiotics for treatment of HE is discouraged. There are currently no data to suggest that multiple antibiotics provide additional therapeutic benefit, and may contribute to the development of drug-resistant infection.

Several other HE therapies have been investigated but are not
routinely used. These include use of ornithine aspartate, flumazenil (Romazicon), and bromocriptine (Parlodel). Early studies using ornithine aspartate are encouraging, but the drug is not currently available in the United States. Flumazenil may also be helpful, but is currently indicated only for patients with acute HE and suspected benzodiazepine intake. No oral or long-acting preparations are currently available which would make flumazenil very cumbersome to use long-term. Improvement of extra-pyramidal symptoms has also been reported when bromocriptine was added to more conventional therapies. Bromocriptine at 30 mg orally twice daily can be considered in patients refractory to other therapies.

Occasionally, a portosystemic shunt (spontaneous, surgical or from placement of a transhepatic portosystemic shunt), is thought to be the primary cause of recurrent or chronic HE. In these rare cases, the shunt can be occluded. This is generally accomplished by the placing of occlusive coils by an interventional radiologist. This advanced procedure should be undertaken only at experienced medical centers and after all other measures have failed.

Before discharge from the hospital, all cirrhotic patients with HE should be assessed for the need for long-term therapy. Patients should be counseled on avoiding precipitating factors such as constipation and psychoactive medications. Compliance with chronic medications, including lactulose and/or antibiotics, should be emphasized. Prophylaxis for spontaneous bacterial peritonitis and gastroesophageal varices should be implemented when indicated. Lastly, appropriate candidates should be referred to a liver transplantation center after the first episode of overt encephalopathy. The ultimate therapy for cirrhosis and HE is orthotopic liver transplantation.

OUTCOMES

Some forms of HE are reversible, but the development of overt HE carries a poor prognosis. Recovery and recurrence rates vary, but without liver transplantation
the 1-year survival is only 40%. Both acute and chronic HE, once advanced to stage 4 (coma), are associated with 80% overall mortality.

**Hyperammonemia**

Hyperammonemia is not a true disease; it is a sign that specific abnormalities that cause blood ammonia levels to become elevated may be present. Elevated blood ammonia levels cause a constellation of signs and symptoms that may appear to be a single disease. Normal blood ammonia levels range from 10-40 µmol/L, compared with a BUN level of 6-20 mg/dL. The total soluble ammonia level in a healthy adult with 5 L of circulating blood is only 150 mcg, in contrast to approximately 1000 mg of urea nitrogen present. Because urea is the end product of ammonia metabolism, the disparity in blood quantities of the substrate and product illustrates the following 2 principles:

- The CNS is protected from the toxic effects of free ammonia.
- The metabolic conversion system that leads to production of urea is highly efficient.

An individual is unlikely to become hyperammonemic unless the conversion system is impaired in some way. In newborns, this impairment is often the result of genetic defects, whereas, in older individuals, the impairment is more often the consequence of a diseased liver. However, a growing number of reports address adult-onset genetic disorders of the urea cycle in previously healthy individuals.

**Pathophysiology**

The true mechanism of neurotoxicity in hyperammonemia is not yet fully determined. Irrespective of the underlying cause, the clinical picture is relatively constant. This implies that the pathophysiologic mechanism, focusing on the CNS, is common to all individuals with hyperammonemia.
The normal process of removing the amino group present on all amino acids produces ammonia. The α-amino group is a catabolic key that protects amino acids from oxidative breakdown. Removing the α-amino group is essential for producing energy from any amino acid. Under normal circumstances, both the liver and the brain generate ammonia in this removal process, substantially contributing to total body ammonia production. The urea cycle is completed in the liver, where urea is generated from free ammonia.

The hepatic urea cycle is the major route for disposal of waste nitrogen chiefly generated from protein and amino acid metabolism. In the same context, low-level synthesis of certain cycle intermediates in extra-hepatic tissues also makes a small contribution to waste nitrogen disposal. Two moles of waste nitrogen are eliminated with each mole of urea excreted. A portion of the cycle is mitochondrial in nature; mitochondrial dysfunction may impair urea production and result in hyperammonemia. Overall, activity of the cycle is regulated by the rate of synthesis of N-acetylglutamate (NAG), the enzyme activator that initiates incorporation of ammonia into the cycle. The brain must expend energy to detoxify and to export the ammonia it produces. This is accomplished in the process of producing adenosine diphosphate (ADP) from ATP by the enzyme glutamine synthetase, which is responsible for mediating the formation of glutamine from an amino group. Synthesis of glutamine also reduces the total free ammonia level circulating in the blood; therefore, a significant increase in blood glutamine concentration can signal hyperammonemia.

The biologic requirement for tight regulation is satisfied because the capacity of the hepatic urea cycle exceeds the normal rates of ammonia generation in the periphery and transfer into the blood. Hyperammonemia never results from endogenous production in a state of health.

An elevated blood ammonia level, although it may be secondary, must never be ignored. Moreover, since the normal ureagenic
capacity of the liver is so great in relation to physiologic load, such a finding points directly to an impairment of the urea cycle in the liver. The CNS is most sensitive to the toxic effects of ammonia. Many metabolic derangements occur as a consequence of high ammonia levels, including alteration of the metabolism of important compounds, such as pyruvate, lactate, glycogen, and glucose. High ammonia levels also induce changes in N-methyl D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) receptors and causes down regulation in astroglial glutamate transporter molecules.

As ammonia exceeds normal concentration, an increased disturbance of neurotransmission and synthesis of both GABA and glutamine occurs in the CNS. A correlation between arterial ammonia concentration and brain glutamine content in humans has been described. Moreover, brain content of glutamine is correlated with intracranial pressure. In vitro data also suggest that direct glutamine application to astrocytes in culture causes free radical production and induces the membrane permeability transition phenomenon, which leads to ionic gradient dissipation and consequent mitochondrial dysfunction. However, the true mechanism for neuro-toxicity of ammonia is not yet completely defined. The pathophysiology of hyperammonemia is that of a CNS toxin that causes irritability, somnolence, vomiting, cerebral edema, and coma that leads to death.

The frequency of each genetic cause of hyperammonemia is undetermined because of the absence of an organized newborn screening program. The combined incidence of urea cycle disorders has been estimated at approximately 1 per 20,000-25,000 live births (U.S.). Providing incidence figures for secondary causes of hyperammonemia is not possible. Any severe impairment of liver function, whether temporary or permanent, can initiate the onset of hepatic encephalopathy.

**Mortality/Morbidity**
• Progressive hyperammonemia, whether treated or not, eventually causes cerebral edema, coma, and death.
• A rapid diagnostic evaluation and alleviation of the cause must be accompanied by treatment.
• Although the vast majority of morbidity associated with hyperammonemia derives from the primary cause, such as chronic liver disease, repeated hyperammonemic episodes can also cause morbidity. The result, given the direct toxicity of ammonia on the CNS, is a progressive decrease in intellectual function. Animal studies suggest actual cell death as the cause.

Sex
• In the genetic forms of hyperammonemia, men and women are affected equally because almost all types are autosomal recessive traits.

• The only exception to equal sex distribution is X-linked ornithine transcarbamylase (OTC) deficiency, the most common of the urea cycle disorders. OTC deficiency predominantly affects males, although female carriers have been clinically affected.

• Acquired causes are distributed randomly between the sexes. However, some acquired causes, such as alcoholic cirrhosis, show a population distribution skewed by societal phenomena.

Age
• Genetic causes of hyperammonemia manifest as a wide variety of conditions. The different presentations are categorized as catastrophic newborn, late-infantile, and adult. Each inherited disorder is reported in various clinical presentations. In some patients with adult-onset disease, no precedent sign of intellectual dysfunction was present, leading to the assumption that the disorder was truly latent until the first acute presentation.
• Age of onset depends on the age and rate of progression of the underlying disease process. Impairments that must be considered range from hepatic necrosis with hepatocellular damage to inborn genetic disorders of the urea cycle. Although history and age of the patient are helpful to diagnosis, genetic causes must never be disregarded, irrespective of the stage of life.

**CLINICAL**

**History**

The multiple primary causes of hyperammonemia, specifically those due to urea cycle enzyme deficiencies, vary in presentation, diagnostic features, and treatment. For these reasons, the members of the family of urea cycle defects are individually considered in this article. However, the common denominator, hyperammonemia, can be clinically manifested by some or all of the following: anorexia, irritability, heavy or rapid breathing, lethargy, vomiting, disorientation, somnolence, asterixis (rarely), combativeness, obtundation, coma, cerebral edema, and death, if treatment is not forthcoming or effective. As a consequence, the most striking clinical findings of each individual urea cycle disorder relate to this constellation and roughly temporal sequence of events.

The most helpful diagnostic information of history in a patient with suspected hyperammonemia is inter-current illnesses with exaggerated lethargy and vomiting.

**Physical**

• General
  o Poor growth may be evident.
  o Hypothermia is occasionally seen.
• Head, ears, eyes, nose, and throat (HEENT): Papilledema may be present if cerebral edema and increased intracranial pressure have ensued.

• Pulmonary
  o Tachypnea or hyperpnoea may be present.
  o Apnea and respiratory failure may occur in latter stages.

• Abdominal: Hepatomegaly is usually mild, if present.

• Neurologic
  o Poor coordination
  o Dysdiadochokinesia
  o Hypotonia or hypertonia
  o Ataxia
  o Tremor
  o Seizures
  o Lethargy that progresses to combativeness to obtundation to coma
  o Decorticate or decerebrate posturing

Causes

• Urea cycle defects with resulting hyperammonemia are due to deficiencies of the enzymes involved in the metabolism of waste nitrogen. The enzyme deficiencies lead to disorders with nearly identical clinical presentations. The exception is arginase, the last enzyme of the cycle. Arginase deficiency causes a somewhat different set of signs and symptoms.

• Genetic defects of the urea cycle include the following:
  o NAG synthetase deficiency
  o Carbamyl phosphate synthetase (CPS) deficiency
  o OTC deficiency
  o Citrullinemia (argininosuccinic acid synthase deficiency, citrullinuria)
  o Argininosuccinate (ASA) lyase deficiency (argininosuccinic aciduria, argininosuccinase deficiency)
Arginase deficiency (hyperargininemia, familial argininemia, argininemia).

**Lab Studies**

- **Plasma ammonia level**
  - Obtain this measurement when clinical signs and symptoms are suggestive of hyperammonemia.
  - No other laboratory test can substitute for this measurement, nor does any other test indicate need for it.
  - Only clinical suspicion indicates need.

- **Liver function studies** (ie, serum transaminases, prothrombin time [PT]/activated partial thromboplastin time [aPTT], alkaline phosphatase levels, bilirubin levels): Severe liver disease can cause hyperammonemia; therefore, evaluating the function of the liver is always appropriate as a first approximation to etiology.

- **Plasma amino acid level quantitation**
  - Certain primary genetic causes can be suspected based on specific increases in amino acid levels, such as increased citrulline or argininosuccinic acid levels.
  - By contrast, severe liver disease tends to cause a generalized increase in plasma amino acid levels.

- **Urinary organic acid profile**
  - Disorders that involve metabolic intermediates of amino acid catabolism can cause mild-to-moderate inhibition of the urea cycle, resulting in hyperammonemia as a secondary phenomenon.
  - This test can help to identify level increases in such intermediates as propionic acid, methylmalonic acid, isovaleric acid, or other organic acids and aid in diagnosis.
• Urine amino acid levels: These are helpful in confirming argininosuccinic aciduria; lysinuric protein intolerance; or hyperornithinemia, hyperammonemia, and homocitrullinuria (HHH) syndrome.
• Blood lactate levels: This is useful in ruling out mitochondrial diseases.
• Blood gas levels
  o Patients with urea cycle disorders may have alkalosis due to stimulation of the respiratory drive by ammonia.
  o Patients with urea cycle disorders are rarely acidotic. Severe refractory acidosis suggests organic acid disorder or mitochondrial disorder.

BUN level: This is often very low (<3 mg of urea/100 mL) in persons with urea cycle disorders.

• N-carbamoyl-L-glutamic acid: In infants with confirmed hyperammonemia, oral loading with N-carbamoyl-L-glutamic acid has been advocated as both diagnostic and therapeutic for patients with NAG synthetase deficiency.

Imaging Studies

• Some authors advocate baseline MRI studies in patients with confirmed genetic causes of hyperammonemia; this is because some suggestive data indicate an elevated risk for stroke in these patients.

TREATMENT

Medical Care
• Hyperammonemia is a medical emergency because of the neuro-toxicity, which is a direct effect of ammonia on the CNS.

• Initial management should consist of protein intake cessation with the provision of as many non-protein calories as is practical via intravenous routes, oral routes, or both (if possible). More specific therapy depends on the etiology of the hyperammonemia. Hemodialysis, intravenous sodium phenylacetate/benzoate (Ammonul), or both may be needed.

Consultations:

Geneticist
  - The role of the biochemical geneticist is to assist in interpretation of available laboratory tests toward a diagnosis of a specific genetic entity. Treatment must be guided by a professional experienced in the treatment of urea cycle disorders. This professional may be a biochemical geneticist, clinical geneticist, endocrinologist, or pediatrician, depending on the expertise available at a specific institution.
  - If such a diagnosis is confirmed, the patient requires long-term follow-up with a geneticist.

Neurologist
  - The role of the neurologist is to provide a basic status evaluation for later reference during follow-up care.
  - This evaluation is especially useful in the primary genetic entities, in which recurrence is a virtual certainty and the risk of additional nervous system compromise exists.

Gastroenterologist:
A gastroenterologist may be of assistance in evaluation of liver disease or when hepatic transplant is considered as therapy for a urea cycle defect.

Diet

- Dietary therapy greatly depends on the etiologic diagnosis.
- Protein restriction is helpful in most cases, and restriction of specific amino acids may be imperative in treatment of particular entities.
- Dietary treatment of urea cycle disorders is highly specialized and usually requires consultation with a registered dietitian who works in a metabolic disease clinic.

Treatment of hyperammonemia is somewhat dependent on cause. Emergency treatment of life-threatening severe hyperammonemia is hemodialysis. Recommendations for treatment of urea cycle disorders may be found in the specific articles (ie, Ornithine Transcarbamylase Deficiency). (See Differentials and Other Problems to be Considered.)

Drug Category:

Metabolic agents

The use of benzoate and phenylacetate is based on the need to provide alternate routes for disposition of waste nitrogen. Benzoate is transaminated to form hippuric acid, which is rapidly cleared by the kidney. Phenylacetate is converted to phenylacetyl CoA and then conjugated with glutamine to form phenylacetylglutamine. Each of these 2 pathways results in disposition of 1 and 2 molecules of ammonia, respectively. Phenylbutyrate is more acceptable as a form of oral therapy because of a diminished odor but is not available for intravenous use.

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<th>Drug Name</th>
<th>Sodium phenylacetate and sodium benzoate (Ammonul)</th>
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www.healthoracle.org
<p>| <strong>Description</strong> | Benzoate combines with glycine to form hippurate, which is excreted in urine. One mole of benzoate removes 1 mole of nitrogen. Phenylacetate conjugates (via acetylation) glutamine in the liver and kidneys to form phenylacetylglutamine, which is excreted by the kidneys. The nitrogen content of phenylacetylglutamine per mole is identical to that of urea (2 mol of nitrogen). Ammonul must be administered with arginine for CPS, OTC, ASA synthetase, or ASA lyase deficiencies. Indicated as adjunctive treatment of acute hyperammonemia associated with encephalopathy caused by urea cycle enzyme deficiencies. Serves as an alternative to urea to reduce waste nitrogen levels. |
| <strong>Adult Dose</strong> | Ammonul 10% injection (100 mg/mL): Loading: 55 mL (5.5 g)/m² IV over 90-120 min via central line Maintenance: 55 mL (5.5 g)/m²/d IV over 24 h via central line Dilute IV dose in at least 25 mL/kg of dextrose 10% before administration |
| <strong>Pediatric Dose</strong> | Ammonul 10% injection (100 mg/mL) |</p>
<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Documented hypersensitivity</th>
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<tbody>
<tr>
<td>Interactions</td>
<td>Penicillin may decrease effects of sodium benzoate/sodium phenylacetate; probenecid may inhibit renal excretion of products of sodium benzoate and sodium phenylacetate; valproate may antagonize efficacy of sodium benzoate and sodium phenylacetate; corticosteroids may increase body protein metabolism, thereby increasing plasma ammonia levels; do not use concomitantly with oral sodium phenylbutyrate (Buphenyl) due to additive effects</td>
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<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established</td>
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<tr>
<td>Precautions</td>
<td>Caution when administering to</td>
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patients with neonatal hyperbilirubinemia (competes for bilirubin binding sites on albumin); due to sodium content exercise caution when giving to patients with congestive heart failure, severe renal dysfunction, and sodium retention with edema; common side effects include nausea, vomiting, tinnitus, and visual disturbance; IV must be diluted with dextrose 10% and administered via central line; phenylacetate may cause neurotoxicity; typically administered with antiemetic to prevent common occurrence of nausea and vomiting; caution in severe congestive heart failure or severe renal insufficiency since it contains large amount of sodium (30.5 mg/mL in undiluted IV product)

Transfer

- During initial stabilization, transfer to an academic medical center for further investigation and long-term treatment is mandatory. Transfer is especially necessary for newborns, who may require highly specialized equipment and personnel for hemodialysis, for example.

Complications
• Hyperammonemia can cause irreversible neuro-toxicity and cell death in the CNS.
• Acutely, the effects can conspire to cause cerebral edema, increased intracranial pressure, and death.

Prognosis

• Regardless of the etiology, prognosis depends on both the severity and duration of the ammonia level elevation. The sites of damage are not predictable and require careful neurologic evaluation for documentation.

Medical/Legal Pitfalls

• Failure to recognize symptoms and signs associated with hyperammonemia may cause prolongation of the episode and increased severity of CNS damage.

Urea cycle. Compounds that comprise the urea cycle are numbered sequentially, beginning with carbamyl phosphate. At the first step (1), the first waste nitrogen is incorporated into the cycle; also at this step, N-acetylglutamate exerts its regulatory control on the mediating enzyme, carbamyl phosphate synthetase (CPS). Compound 2 is citrulline, the product of condensation between carbamyl phosphate (1) and ornithine (8); the mediating enzyme is ornithine transcarbamylase. Compound 3 is aspartic acid, which is combined with citrulline to form argininosuccinic acid (4); the reaction is mediated by Argininosuccinate (ASA) synthetase. Compound 5 is fumaric acid generated in the reaction that converts ASA to arginine (6), which is mediated by ASA lyase.

Ammonia

www.healthoracle.org
Increased ammonia indicates hepatic-insufficiency

Increased baseline blood ammonia levels or persistently high blood ammonia levels after oral administration of ammonium chloride (available as a urine acidifier) indicate hepatic insufficiency. This test is helpful in evaluating chronic weight loss, abnormal CNS signs, and a small liver. Abnormalities correlate with serum bile acid assays. Congenital and acquired hepatic shunts, bile duct obstruction, cholangiohepatitis, and cirrhosis increase blood ammonia levels.

An inverse relation is known to link blood potassium with renal synthesis and the release of ammonia. Given the liability of hyperammonemia for precipitating hepatic encephalopathy (HE).

The ammonia test can be used to help investigate the cause of changes in behaviour and consciousness. It may be requested with other tests such as glucose, electrolytes, and kidney and liver function tests to help diagnose the cause of a coma or to help support the diagnosis of Reye’s syndrome or hepatic encephalopathy. An ammonia level may also be requested to help detect and evaluate the severity of a urea cycle defect.

Some doctors use the ammonia test to monitor the effectiveness of treatment of hepatic (liver) encephalopathy, but there is not widespread agreement on how best to use the test clinically. Since hepatic encephalopathy can be caused by the build-up of a variety of other poisonous substances in the blood and brain, blood ammonia levels may not be very good at showing how bad the disease is.

An ammonia test may be requested on a newborn when they are irritable, vomiting, tired, and have seizures during the first few days after birth. It may be performed when a child develops these symptoms about a week after a viral illness such as flu or a cold when the doctor suspects that the child may have Reye’s syndrome. When adults experience mental changes, disorientation, sleepiness, or lapse
into a coma, an ammonia level may be requested to help investigate the cause of the change in consciousness. In patients with stable liver disease, an ammonia level may be requested, with other liver function tests, when a patient suddenly ‘takes a turn for the worse’ and becomes more acutely ill.

NOTE: A standard reference range is not available for this test. Because reference values are dependent on many factors, including patient age, gender, sample population, and test method, numeric test results have different meanings in different labs. Your lab report should include the specific reference range for your test.

Significantly increased concentrations of ammonia in the blood indicate that the body is not effectively breaking down and removing ammonia but do not explain the cause. In infants, extremely high levels can be seen with an inherited urea cycle enzyme deficiency or defect but may also be seen with haemolytic disease of the newborn (where the baby’s red blood cells are destroyed). Short-lived increases in blood ammonia levels are relatively common in newborns, where levels may rise and fall without causing detectable symptoms.

Increased ammonia levels and decreased glucose levels may suggest the presence of Reye’s syndrome in children and adolescents with symptoms. Increased ammonia concentrations in the blood may also suggest a previously undiagnosed enzymatic defect of the urea cycle. In children and adults, elevated ammonia levels may also indicate liver or kidney damage. Frequently, an illness will act as a trigger, increasing ammonia levels to the point that an affected patient has difficulty removing the ammonia.

Normal concentrations of ammonia do not rule out the possibility of hepatic (liver) encephalopathy. Not only do other waste products contribute to the changes in mental function and consciousness, but brain levels of ammonia may be much higher than blood levels. In this situation, patients with severe symptoms do not always have very high blood ammonia levels.
Increased levels of ammonia may also be seen with:

- Gastrointestinal bleeding – blood cells are haemolysed (broken apart) in the intestines, releasing protein which is digested, absorbed and converted into ammonia.
- Muscle exercise – muscles produce ammonia when active and absorb it when resting.
- Tourniquet use – ammonia levels can be increased in blood samples collected using a tourniquet when it has been applied for a long time.
- Drugs that can increase blood ammonia levels include: alcohol, barbiturates, diuretics, Valproic acid and narcotics
- Smoking
- Decreased levels of ammonia may be seen with high blood pressure and the use of some antibiotics (such as neomycin).

Ammonia tests can also be measured on blood taken from arteries, but this is rarely done although some doctors believe that arterial ammonia measurements are more useful.