Hyperammonemia in the Pediatric Emergency Department

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Abstract: Hyperammonemia is a serious clinical condition associated with significant morbidity and mortality. In the pediatric population, this is often caused by urea cycle disorders, acute liver failure, or other less common underlying etiologies. Children and teens with hyperammonemia can have a broad range of clinical findings, including vomiting, respiratory distress, and changes in mental status. As ammonia levels worsen, this presentation can progress to respiratory failure, encephalopathy, cerebral edema, seizures, and death. Given the risk of neurologic damage, timely identification and management of hyperammonemia is critical and includes initial resuscitation, early consultation with subspecialists, and initiation of appropriate therapies. It is important for pediatric emergency medicine providers to understand the clinical findings, causes, diagnosis, and management of hyperammonemia because they play a key role in the provision of effective, multidisciplinary care of these patients.

Key Words: hyperammonemia, metabolism, resuscitation

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TARGET AUDIENCE

This article is intended for physicians, nurse practitioners, physician assistants, nurses, and other personnel who care for pediatric patients in the emergency setting.

LEARNING OBJECTIVES

After completion of this article, the reader should be better able to:

1. Describe the clinical findings of a pediatric patient with hyperammonemia
2. List the common causes of pediatric hyperammonemia
3. Formulate a management plan for a pediatric patient with hyperammonemia

The elevation of serum ammonia levels, known as hyperammonemia, is a serious condition that requires timely diagnosis and intervention. Ammonia is produced in amino acid metabolism and by intestinal bacteria.[1–4] Most ammonia (~90%) is then metabolized in hepatocytes via the urea cycle, converting to urea. The remaining 10% is also processed in the liver: it is condensed with glutamate to form glutamine via glutamine synthetase. Both urea and glutamine are ultimately excreted via the kidneys. When these elimination mechanisms are not functional, or when there is increased production of ammonia, hyperammonemia results. Ammonia is part of several biochemical reactions in the brain that lead to toxicity, though the most prominent is its conversion to glutamine via glutamine synthetase; glutamine is osmotically active and its accumulation is thought to result in cerebral edema and consequent neurologic sequelae.[5]

In the pediatric population, hyperammonemia is most often caused by urea cycle disorders and acute liver failure. Without appropriate treatment, this condition results in cerebral edema, which often leads to irreversible damage to the central nervous system, seizures, cerebral palsy, encephalopathy, and death.[3,4,6] In this review, we discuss the clinical findings, diagnosis, and causes associated with hyperammonemia and provide a detailed summary of management strategies, with a focus on relevance to the pediatric emergency medicine provider.

CLINICAL FINDINGS

Case 1: A 3-day-old infant, born full-term with no known medical conditions, presents to the emergency department with poor feeding. The parents report that the birth was uneventful. However, in the past day, the patient has been difficult to wake up, has only breastfed once, and has had decreased wet diapers.

This vignette provides insight into how a neonate with hyperammonemia may present to the emergency department. These infants are often well-appearing at birth; however, after initiating feeding—and thus ingesting protein—they become ill-appearing and lethargic, with poor intake and possible vomiting. Typically, this occurs when an infant has a urea cycle disorder or an organic acidemia disorder. Importantly, the differential diagnosis for an ill-appearing infant is broad; the pediatric emergency medicine provider should consider a wide variety of causes including sepsis, congenital cardiac disease, and nonaccidental trauma, as well as hyperammonemia. To further complicate the diagnostic process, small elevations in ammonia are observed in stressed neonates with immature livers or any severe illness, which can lead to mitochondrial stress.

As ammonia levels increase, neonates may develop hyperventilation leading to a respiratory alkalosis. The mechanism behind this is secondary to the metabolism of ammonia in the brain; glutamine synthetase combines ammonia with glutamate to form glutamine, which is osmotically active, leading to cerebral edema. In response to cerebral edema, the patient hyperventilates in an effort to decrease intracranial pressure by inducing cerebral vasoconstriction.[7,8] As ammonia levels continue to rise, precipitating worsening neurologic damage, patients can develop hypoventilation and respiratory failure.

If ammonia levels are critically elevated, neonates can experience seizures, acute encephalopathy, and ultimately, death. Of note, seizures in neonates may be subclinical and nonconvulsive, and thus the clinician must be aware of this potential finding.[8] Figure 1 illustrates many of the clinical manifestations of hyperammonemia.

Case 2: An 8-year-old child presents to the emergency department with altered mental status. The parents report that the patient has had vomiting and abdominal pain for several days, and today has seemed to be confused and hallucinating. The child is also slurring his words and unable to walk independently.

This case illustrates how an older child may present with hyperammonemia. Clinical findings in older children and teenagers are similar to those in neonates and include gastrointestinal

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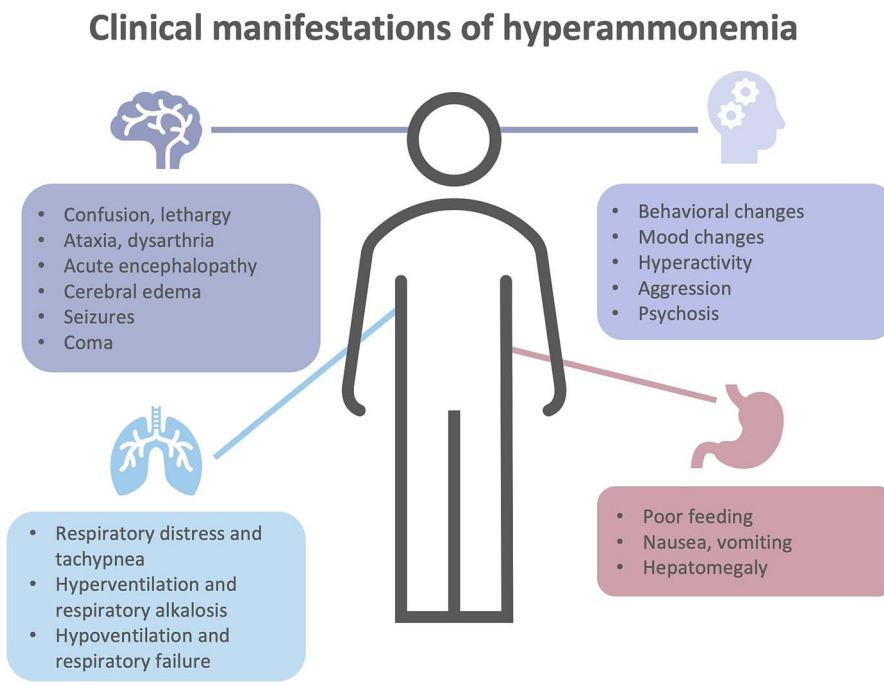

FIGURE 1. Clinical manifestations of hyperammonemia.

manifestations (eg, poor intake and vomiting) and respiratory symptoms (eg, hyperventilation). Neurologic findings may differ in the older child, and can include features such as dysarthria, ataxia, and confusion. As the patient worsens, seizures, acute encephalopathy, and death can result.

Importantly, in the older patient, psychiatric manifestations may also occur, including aggression, hyperactivity, and psychosis. Medications can unmask underlying disorders of ammonia metabolism in this age group. Most notable is the hyperammonemia resulting as an adverse effect of valproic acid.[9] The various clinical manifestations of hyperammonemia are depicted in Figure 1. As in the neonate, the older child or teenager presenting with altered mental status and the aforementioned symptoms also has a broad differential diagnosis that includes sepsis, stroke, toxic ingestion, and intracranial trauma, among others.

DIAGNOSIS

If there is any suspicion for hyperammonemia, the clinician should obtain a serum ammonia level. Although simple in theory, in practice this can often be logistically difficult because blood samples for ammonia need to be free-flowing (ie, obtained without the use of a tourniquet), transported on ice, and analyzed within 1 hour. The purpose of these prerequisites is to decrease the likelihood of falsely elevated ammonia values and relates to how the test is performed as well as how ammonia is naturally produced. First, a sample obtained with use of a tourniquet can lead to release of ammonia from skeletal muscle, resulting in a falsely elevated level, hence the need for a free-flowing sample.[10] Second, ammonia levels increase spontaneously in blood after sample collection, primarily because ammonia is released in the deamination of plasma and cellular proteins.[10–12] Placing the sample on ice slows this process; similarly, analyzing the sample within 1 hour limits the amount of time in which this spontaneous increase can occur.[10–12] Of note, hemolysis can also falsely elevate results. It is important to recognize that meeting all these sample requirements—particularly in an infant or ill patient—can be difficult and requires phlebotomy expertise as well as collaboration with the local laboratory.

The upper limit of serum ammonia levels differs based on age and should be considered in the context of sample processing.[13–15] For any elevations outside the expected range, consultation with a metabolic center should be initiated for support in determining the timeline for management and treatment steps.

CAUSES

In pediatrics, hyperammonemia is often caused by urea cycle disorders and acute liver failure, though there are various causes, including drugs and other inborn errors of metabolism.[4]

Urea Cycle Disorders

The urea cycle is a biochemical process that converts ammonia, which is toxic to the body, to urea, which can be safely excreted. Though an in-depth examination of the urea cycle is beyond the scope of this review, it is important to note that there are 6 enzymes and 2 amino acid transporters that comprise this pathway (Fig. 2).[16] The 6 enzymes are carbamoyl phosphate synthetase I (CPS1), ornithine transcarbamylase (OTC), argininosuccinic acid synthetase (ASS1), argininosuccinic acid lyase (ASL), arginase (ARG1), and N-acetyl glutamate synthetase (NAGS). The 2 amino acid transporters are ornithine translocase (ORNT1) and citrin. A urea cycle disorder is defined as a deficiency in any of these enzymes or transporters. These can lead to hyperammonemia secondary to the body's inability to sufficiently convert ammonia to urea, with varying levels of severity. In severe cases (ie, severe or complete deficiencies), patients present in the newborn period. In milder cases (ie, partial deficiencies), the time of first presentation is variable and can even occur in adulthood, typically triggered by illness or stress.[16] In fact, older children presenting with a urea cycle disorder may report a history of repeated episodes of sepsis-like illnesses without a source.

The prevalence of urea cycle disorders is estimated to be 1 in 35,000, with two thirds of patients presenting in the newborn

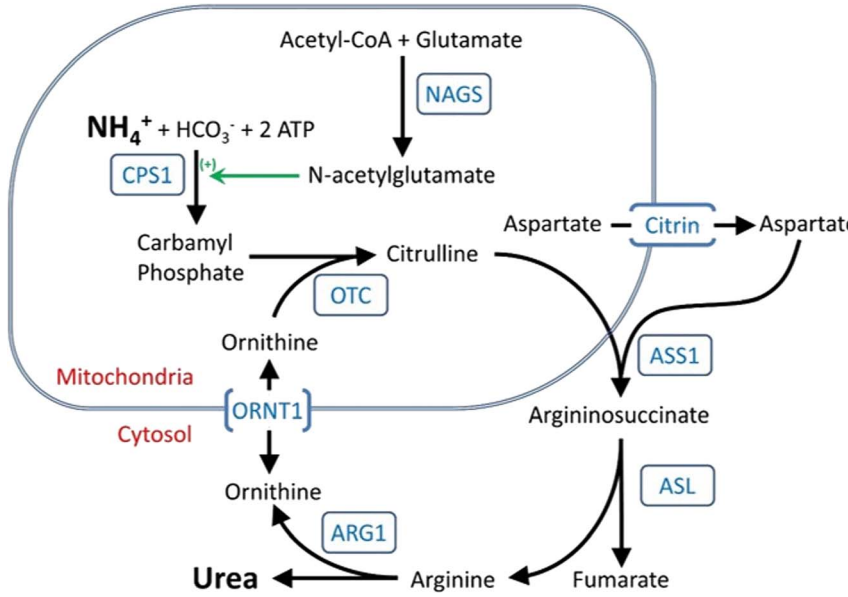

FIGURE 2. The urea cycle. © 1993–2023 University of Washington, http://www.genereviews.org. Reproduced with permission from [16]

period and one third of patients presenting later in life.[17] The mortality rate is considerable: 24% in neonatal onset cases and 11% in later onset cases.[17] Previous studies have found that episodes of hyperammonemia in newborns and children with urea cycle disorders can lead to irreversible damage to the developing central nervous system.[3,16,17] Given the significant mortality and morbidity risks associated with these disorders, prompt identification and management are paramount. Although newborn screening programs test for several types of urea cycle disorders, it is important for the pediatric emergency medicine provider to know that the newborn screen is not reliable to identify a child with a urea cycle disorder because not all types are included in many screens, and screen contents vary by state.[18] Thus, providers should consider this diagnosis in patients of any age presenting with concordant symptoms, even if newborn screen results are reported as normal.

Acute Liver Failure

Acute liver failure is relatively rare in children, though the exact incidence is unknown.[19] Most often, the cause cannot be determined and is termed idiopathic.[19] Infection is a known cause, including viruses such as herpes simplex virus; hepatitis A, B, C, D, and E; adenovirus; and enterovirus. Other causes include drug toxicity (eg, acetaminophen), metabolic disorders (eg, galactosemia, mitochondrial disorder), hemochromatosis, and autoimmune conditions.[19,20]

When acute liver failure occurs, patients are at risk for developing hepatic encephalopathy—a constellation of neuropsychiatric symptoms that result from the liver's inability to effectively clear toxins, including ammonia.[21] Symptoms include altered mental status, dysarthria, ataxia, and behavioral changes, progressing to cerebral edema and seizures. Hyperammonemia plays a central role in the development and manifestations of hepatic encephalopathy, explaining why the 2 diagnoses have overlapping clinical findings.

Other Causes of Hyperammonemia

Additional causes of hyperammonemia include drugs such as valproic acid, carbamazepine, topiramate, and chemotherapy. Hyperammonemia also occurs with Reye syndrome, a condition characterized by encephalopathy and liver damage, and often triggered by the use of salicylates in children with viral infections.[22]

In neonates, hyperammonemia may follow and parallel perinatal asphyxia; these patients typically have poor neurologic outcomes.[23] It is posited that hypoxic stress increases catabolism and decreases urea cycle activity, a combination that leads to hyperammonemia.[23] In contrast, transient hyperammonemia of the newborn can occur in infants, likely secondary to a transient deficiency of one of the enzymes in the urea cycle or a renal amino acid transport defect.[24] These patients can be either symptomatic or asymptomatic, though their neurologic outcomes tend to be favorable.[24]

Finally, other inborn errors of metabolism can result in hyperammonemia. Organic acidemias such as propionic acidemia, methylmalonic acidemia, and isovaleric acidemia are leading causes of hyperammonemia in newborns.[25,26] Organic acidemias are caused by a deficiency of the enzymes needed to break down amino acids. This results in a buildup of substrates that interact with the urea cycle and decrease its ability to effectively metabolize ammonia, leading to hyperammonemia.[25,26] Various other metabolic disorders can also lead to hyperammonemia by impairing the normal function of the urea cycle, including fatty acid oxidation defects and mitochondrial disorders.[26]

MANAGEMENT

Management of hyperammonemia is critically time-sensitive, given the risk of neurologic impairment and death. Key priorities include initial resuscitation, early consultations with subspecialists, and timely initiation of relevant pharmacologic therapies and/or dialysis, as indicated (Fig. 3).

Initial Resuscitation and Evaluation

True hyperammonemia requires timely evaluation and management at a center with an intensive care unit and relevant subspecialists. Consultation with pediatric specialists in metabolism, nephrology, gastroenterology, and/or toxicology (depending on the etiology and severity of the hyperammonemia) is critical. As

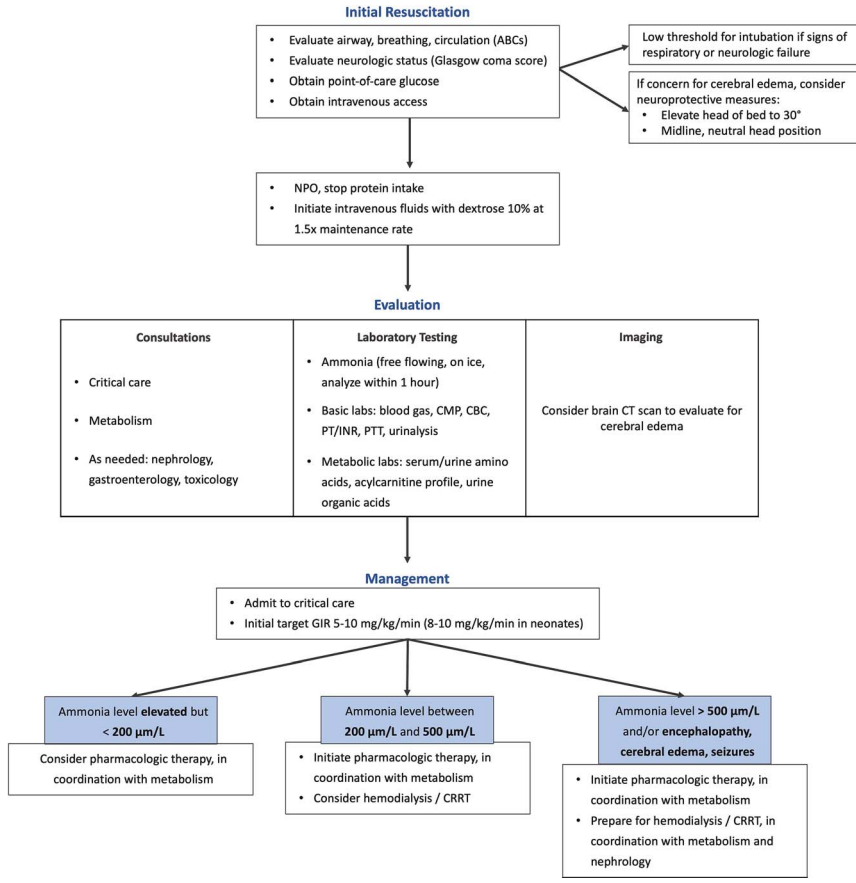

FIGURE 3. Management of hyperammonemia. CBC indicates complete blood count; CMP, comprehensive metabolic panel; CRRT, continuous renal replacement therapy; CT scan, computerized tomography scan; NPO, nil per os; PT/INR, prothrombin time/international normalized ratio; PTT, partial prothrombin time.

such, early initiation of facility transfers, if warranted, should be considered for patients with concerns for hyperammonemia.

Initial management focuses on resuscitation and stabilization, with attention to the patient's airway, breathing, and circulation. Hyperammonemia may present with respiratory compromise, specifically hyperventilation and respiratory alkalosis as a result of cerebral edema, which can then progress to hypoventilation and respiratory failure as neurologic damage worsens. Supportive respiratory care, including a low threshold for intubation, should be prioritized. Neurologic status should be evaluated because hyperammonemia can result in significant alterations in mental status. Again, if the patient is determined to be markedly altered or obtunded, intubation for airway protection is indicated. Given the risk of cerebral edema with hyperammonemia, implementation of neuroprotective measures, such as head bed elevation and midline neck positioning, can be considered.

In parallel with initial stabilization, the patient needs intravenous access for laboratories and fluids. Checking a point-of-care glucose level is also important because many of the causes of hyperammonemia are due to inborn errors of metabolism, which can also present with hypoglycemia. The patient should be made nil per os (NPO), with particular focus on stopping all protein intake. Fluids with a high glucose content (10% dextrose with appropriate electrolytes) should be initiated at 1.5 times the patient's maintenance rate to achieve a glucose infusion rate of 5 to 10 mg/kg/min; in neonates, this target should be on the higher end at 8 to 10 mg/kg/min. This is critical because providing sufficient dextrose promotes anabolism and decreases catabolism, or the ongoing breakdown of proteins that further increase ammonia levels.[4] If the patient is clinically hypovolemic—as may be the case in patients who have had vomiting and poor feeding—it is appropriate to give a 20 mL/kg normal saline bolus while simultaneously providing dextrose-containing fluids. Sodium levels in the upper limit of normal (140–145) should be targeted.

Initial laboratory testing should include an ammonia level, a blood gas, a comprehensive metabolic panel (including liver function tests), a complete blood count, and coagulation studies. Specific studies to evaluate for inborn errors of metabolism should be obtained if possible and include serum amino acids and an acylcarnitine profile, as well as urine testing for ketones, amino acids, and organic acids.[1,4,27] If there is clinical concern for increased intracranial pressure, an emergent brain computerized tomography (CT) scan should be completed.

Consultations

Discussion with relevant subspecialists is recommended early in the resuscitation of a child with hyperammonemia. Critical care colleagues should be notified because patients with hyperammonemia will require close monitoring in the intensive care unit. Next, a metabolism expert will guide management after the initial resuscitation. This consultation is important because the

treatment of hyperammonemia can include pharmacologic therapies (eg, arginine, sodium phenylacetate-sodium benzoate, see next section) that many institutions may not have access to or may not use frequently. A metabolism specialist will assist with recommendations for dosing of these medications and often can liaise with a pharmacist to expedite administration. If the hyperammonemia is severe, more aggressive measures to reduce the ammonia level with dialysis may be indicated. If this is suspected, an early conversation with nephrology is needed. Finally, conversations with gastroenterology (if there is concern for acute liver failure and/or hepatic encephalopathy) or toxicology (if there is concern for toxic ingestion) may be warranted.

Hyperammonemia Therapies

If the ammonia level is more than 200 μmol/L and/or the patient has symptoms of hyperammonemia, pharmacologic therapy should be initiated in consultation with a metabolism specialist. Note that pharmacologic therapy may be advised at lower ammonia levels, depending on the patient's presentation. Intravenous fluids with a high glucose infusion rate should be initiated, as noted previously, while awaiting repeat ammonia levels and preparing pharmacologic therapies. The 2 intravenous medications used most often are sodium phenylacetate-sodium benzoate (Ammonul, Ucyclyd Pharma, Inc., Scottsdale, AZ) and arginine hydrochloride. Ammonul is comprised of 2 nitrogen scavengers that serve to lower ammonia levels by binding with amino acids and facilitating their excretion in urine. Specifically, sodium phenylacetate binds with glutamine whereas sodium benzoate binds with glycine.[27,28] Due to the mechanism, initiation in some patients may not be effective or could worsen liver function; thus this is considered both a lifesaving and high-risk medication and should be administered in coordination with a subspecialist with experience in its administration. In addition, the sodium load of Ammonul requires close monitoring and adjustment of fluids run with this medication. Arginine hydrochloride is particularly useful when the suspected cause is a urea cycle disorder; when there is an enzyme deficiency in the urea cycle, arginine is not produced, thus rendering it an essential amino acid. Lack of arginine in the body results in a catabolic state, which worsens hyperammonemia.[27] Administration of arginine intravenously does have the adverse effect of vasodilation and can lead to blood pressure instability, so it should be done with careful monitoring. Importantly, these 2 medications are most often used when the cause of hyperammonemia is thought to be secondary to an inborn error of metabolism, specifically urea cycle disorders; discussion with relevant specialists should guide potential usage of these medications if other underlying causes are suspected.

In the case of hyperammonemia secondary to acute liver failure and/or hepatic encephalopathy, the aforementioned medications are not used; however, lactulose can be administered.[29] Lactulose is converted to lactic acid in the intestine, promoting an acidic environment that converts ammonia (NH_3) to ammonium (NH_4+), an ionized form that cannot be absorbed.[29] Lactulose also promotes the diffusion of ammonia from the blood to the intestine.[29] Via both of these mechanisms, elevated ammonia levels are reduced. Lactulose is not used in cases of hyperammonemia secondary to inborn errors of metabolism due to its long time to response.

Finally, dialysis should be initiated in cases of severe hyperammonemia, which we define as ammonia level more than 500 μmol/L, lack of improvement in ammonia level within 2 hours after initiating medical management, or persistent/worsening encephalopathy, cerebral edema, or seizures.[27,30–32] Transfer to a center experienced in continuous renal replacement therapy (CRRT) for hyperammonemia is often required for this treatment and should be expedited.

CONCLUSIONS

Hyperammonemia is a medical emergency that requires timely evaluation and management due to the significant risk of morbidity and mortality associated with this clinical condition. Pediatric emergency medicine providers must be aware of the common causes, presenting clinical findings, and diagnosis of hyperammonemia, as well as important steps in management, which include initial resuscitation, early consultation with subspecialists, and initiation of appropriate therapies. Ultimately, the provision of effective care for the patient with hyperammonemia requires an emergent, multidisciplinary approach, in which pediatric emergency medicine providers play a key role.

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