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Review Article

Hyperammonemia in Patients with Non-Hepatic Causes in the ICU

Braden Schipp* and Raghav Gupta

Department of Pulmonary and Critical Care, Deaconess Health System, United States of America

***Corresponding Author:** Braden Schipp, Department of Pulmonary and Critical Care, Deaconess Health System, United States of America.

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Abstract

Within the ICU, nonhepatic hyperammonemia is a severe condition that consists of elevated ammonia within the blood, originating from etiologies not connected to liver complications. This can lead to a plethora of critical conditions for the patients such as coma, seizures, and cerebral edema, so quick action with treatment is a necessity. Nonhepatic hyperammonemia can stem from preexisting conditions such as inborn errors of metabolism or it can be inflicted through prior treatments or the use of certain medications, such as anticonvulsants and corticosteroids. With this being said, the etiology of this condition is often complicated to identify and leads to life-threatening effects, hereby solidifying the importance within urgency to make the correct diagnosis and treatment for nonhepatic hyperammonemia.

Keywords: *Nonhepatic Hyperammonemia (NHH); ICU; Anticonvulsants; Corticosteroids*

Introduction

Nonhepatic hyperammonemia (NHH) is a life-threatening condition consisting of elevated ammonia levels in the blood in those without liver complications. NHH is caused by either an overproduction of ammonia or the lack of ammonia elimination from the body. Elevated ammonia can then lead to encephalopathy and cerebral edema, intracranial hypertension, seizures, coma, and death [2,7].

The overproduction of ammonia from non-hepatic causes or the lack of ammonia elimination can be caused by vascular malformation or metabolic disorder, prominently affecting the urea cycle [1,10]. Other causes outside of genetic etiologies include infection of urease-producing organisms such as *Ureaplasma* and *Mycoplasma hominis*, obesity, epilepsy, recent orthopedic surgery, and drugs such as corticosteroids, valproic acid, and carbamazepine [2,3,12].

NHH is a common occurrence within the ICU, affecting roughly 39.8% of patients without hepatic complications [6]. Swift action is essential in both the diagnostic and treatment of NHH to prevent the fatal effects of excess ammonia [1].

Mechanism of ammonia formation

Ammonia is produced by nitrogen containing compounds in intestines via metabolites by bacteria and by uptake of glutamine. Additionally, breakdown of skeletal muscles produces ammonia with examples of seizure activity via the mechanism of severe muscle contraction. Skeletal muscles also absorb hyper ammonia and can be stored as glutamate [7].

Glutamine can be converted to ammonia in kidneys and can be either reabsorbed or excreted depending on acid-base balance [8].

Mechanism of neuro toxicity from hyper ammonia

Astrocytes are one of the essential cells of the central nervous system. Hyperammonemia can cause swelling of astrocytes by various mechanisms including mitochondrial permeability transition (MPT). Astrocyte swelling can further cause cerebral edema and brain herniation [9,10].

Willard-Mack., *et al*. postulated clearly about cortical astrocytes change in abnormal morphology in 6 hours after a dose of ammonium acetate that produced marked hyperammonemia in rats [11]. The crucial role that glutamine upholds in causing cellular swelling is an important consideration for the mechanism of brain injury [12]. Glutamine is generated in histiocytes from metabolic pathway of ammonia and further glutamate in reaction by glutamine synthetase [13].

Subsequently glutamate induces oxidative stress along with MPT resulting in osmotic effects and ultimately leading to neuro-cellular swelling [14].

Causes of hyperammonemia in non-hepatic conditions

Increase production

An increased production of ammonia in the body, that causes NHH, can be further divided into three subcategories: bacterial infection, genetic etiology, and some variation of catabolism of the body. Increased ammonia production due to infection is caused by urease producing bacteria, such as *Ureaplasma* and *Mycoplasma hominis*. It should be noted that infection of these particular species of bacteria are not resolved through traditional broad-spectrum antibiotic treatments [2].

Genetic etiologies consisting of genetic disorders and inborn errors of metabolism are likely affecting metabolic pathways such as the urea cycle or amino acid metabolism [15]. If metabolic disruption is involved in the overproduction of ammonia, it is likely the primary or sole etiology.

Catabolism producing ammonia occurs in numerous ways and is difficult to hinder because it is a necessary biological process. Within the ICU, total parenteral nutrition (TPN) is a common occurrence to meet a patient's nutritional needs. However, TPN along with GI hemorrhage, starvation, and trauma, has been shown to increase blood ammonia levels [1,16]. While in the ICU, fasting is another common occurrence among patients. Fasting-induced muscle protein breakdown is another catabolic process that elevates ammonia within the blood [4].

Obesity is another known risk factor for NHH via multiple processes. Obese patients are known to have chronic, low-grade inflammation within their GI tracts and overall reduced efficiency of the urea cycle. In addition to these factors, obese patients can have not only a higher protein intake, but also higher protein catabolism [3].

Epilepsy and seizures also increase risk of developing NHH. While seizing, active skeletal muscle becomes a producer of ammonia, causing blood ammonia levels to rise significantly. Evidence also supports severe lactic acidosis contributing to NHH from elevated lactate [3].

Decrease clearance

The decreased clearance of ammonia from the bloodstream within NHH largely consists of inborn errors of metabolism and metabolic disorders within the urea cycle due to genetic etiologies [17]. The formation of porto-systemic shunts also allows ammonia to bypass the liver, preventing its transformation into urea [5].

Drug-induced

Valproate is an anticonvulsant medication that is used to treat and prevent seizures from occurring, but majorly contributes to the degradation of the urea cycle and ammonia metabolism as a whole. Valproate has been shown to increase ammonia production through increased propionic acid levels, inhibiting carbamoyl phosphate synthetase which is the rate-limiting, mitochondrial enzyme of the urea cycle [3,16].

An additional medication that prevents the clearance of ammonia is carbamazepine. Carbamazepine was found to reduce the activity of the enzyme glutamine synthetase. This enzyme helps detoxify ammonia within the bloodstream by converting glutamate into glutamine. Other drugs such as glycine, ribavirin, and sulfadiazine have also been suspected to negatively impact ammonia levels [16].

Corticosteroids have also been attributed to the elevated ammonia within NHH patients and has shown to be a risk factor. Due to the effects of corticosteroids causing hypernatremia through the mechanism of increased absorption of sodium within the intestine. The elevated sodium within the blood is believed to be responsible for the excess ammonia [3].

Not only can drugs directly affect the metabolic processes necessary for the detoxification of the blood, but they have also been shown to provoke pre existing genetic conditions. Valproate has been shown to trigger partial urea cycle disorders, those of which were inactive prior to treatment. TPN and high protein nutrition have also been shown to activate these effects [15,16].

The effects that these drugs and treatments have on the state of ammonia within the body are compiled in the table below. Along with the significant effects the medications and nutrition therapy have on ammonia, the major processes by which they can occur are also included.

Drug	Effect	Mechanism of effect
Valproate	-Inhibits ammonia removal	Urea cycle impairment, IEM trigger
Carbamazepine (glycine, ribavirin, and sulfadiazine)	-Inhibits ammonia removal	Urea cycle impairment
Corticosteroids	-Increases ammonia production -Inhibits ammonia removal	Increased catabolism, Impaired enzyme activity
TPN and high protein nutrition	-Increases ammonia production	High protein load, IEM trigger

Table: *Effects of administered drugs on ammonia levels.*

IEM: Inborn Errors of Metabolism; TPN: Total Parenteral Nutrition.

Diagnosis of hyperammonemia

The diagnosis of NHH must be made shortly after the signs arise. This quick action is crucial to prevent the rise of the rapid and severe effects that hyperammonemia has on the body. If the patient shows no signs of liver damage or disease and an unexplained altered mental status is presented, one must swiftly test for elevated ammonia levels within the bloodstream [16].

In addition to the scenario above, if the patient is receiving treatment with valproate or other risk factor drugs, they should have routinely monitored serum ammonia levels. This should also be the case for scenarios involving urea cycle disorders or suspected inborn errors of metabolism alongside protein refeeding and nutritional deficiencies [18].

Management of hyperammonemia in non hepatic patients

Hyperammonemia can occur in non-hepatic patients due to various causes, such as urea cycle disorders, renal failure, gastrointestinal bleeding, infections, or certain medications. Managing hyperammonemia involves addressing the underlying cause, reducing ammonia levels, and providing supportive care.

1. Cause of hyperammonemia

- **Urea cycle defects:** IEM affecting the enzymes that make up the urea cycle, such as carbamoyl-phosphate synthetase I deficiency or ornithine transcarbamylase deficiency [19,20].
- **Renal failure:** The buildup of ammonia within the blood due to impaired secretion from acute or chronic kidney disease [21].
- **Gastrointestinal bleeding:** Bacteria within the gut produce ammonia by breaking down blood found within the gastrointestinal tract [22].
- **Infections:** Ammonia levels can rise due to sepsis or other infections, especially from urea-splitting organisms [22].
- **Medications:** Ammonia levels can increase due to corticosteroids, valproic acid, certain diuretics, and other drugs [3,16].
- **Inborn errors of metabolism:** Phenylketonuria, maple syrup urine disease, or other genetic conditions [24].
- **Other causes:** Dehydration, hypovolemia, or metabolic alkalosis [23].

2. Supportive measures

- **Airway protection:** Airway protection should be considered if neurological symptoms such as coma, confusion, or lethargy are caused by high enough ammonia levels [25].
- **Monitoring:** Regular monitoring of ammonia levels, electrolytes, acid-base status, and renal function is essential. Continuous monitoring may be needed in severe cases.

3. Reduction of ammonia levels

- **Dietary management:** Ammonia intake can be decreased through a reduction in protein consumption, especially in those with renal failure or urea cycle defects [26,27].
- **Intravenous fluids:** Ammonia secretion can be supported via electrolyte correction and rehydration, reinforcing renal function [23].

4. Pharmacological treatments

- **Lactulose:** Lactulose helps to decrease ammonia levels by acting as a laxative and increasing excretion through the feces. Lactulose acidifies the colon and prevents the absorption of ammonia by trapping it as ammonium (NH_4^+) [28].
- **Rifaximin:** Rifaximin is an antibiotic that decreases the production of ammonia from bacteria from the gut. Rifaximin is effective in cases with gut-related ammonia accumulation or gastrointestinal bleeding [28].
- **Sodium benzoate, phenylbutyrate:** These drugs act as nitrogen scavengers and can be used in cases with IEM and urea cycle defects to help eliminate excess ammonia [29].
- **Arginine:** Arginine supplementation promotes the production of urea and can be used to treat specific urea cycle disorders by facilitating ammonia removal as urea [30].

5. **Correct underlying metabolic disturbances**

- **Hemodialysis or continuous renal replacement therapy (CRRT):** Dialysis can help to remove ammonia and other toxins that have accumulated due to renal failure [21].
- **Treat infection:** Ammonia production can increase from infections and should be counteracted with antibiotics [22].
- **Correct hypovolemia/acidosis:** Ammonia elimination can be promoted by treating dehydration, metabolic acidosis, or other metabolic disorders [23].

6. **Specific treatments for urea cycle disorders**

- **Supplementation with missing enzymes:** Enzyme replacement therapies or gene therapy should be considered for some cases, such as ornithine transcarbamylase deficiency [29,30].
- **Ammonia scavengers:** Ammonia excretion can be promoted by medication such as sodium benzoate or sodium phenylbutyrate through binding to excess nitrogen [29].

7. **Neurological support**

- **Sedation or anticonvulsants:** If the patient exhibits seizures, confusion, or agitation due to hyperammonemia, sedation with benzodiazepines or anticonvulsants may be required.

8. **Liver transplantation (In certain cases)**

- Liver transplantation may be considered for patients with urea cycle disorders that cannot be controlled through medical treatment. Transplantation should especially be considered if the disorder is severe enough and life-threatening [31].

9. **Long-term management**

- **Dietary modifications:** A low-protein diet should be considered for the long-term management of urea cycle disorders or other IEM [27].
- **Regular monitoring:** Lifelong monitoring of ammonia levels and metabolic status is required in patients with chronic conditions like urea cycle defects.

Summary

The management of hyperammonemia in non-hepatic patients involves a multi-pronged approach focused on quickly identifying and addressing the underlying cause, using pharmacologic agents to reduce ammonia levels, providing supportive care, and closely monitoring the patient's response to treatment.

Bibliography

1. Clay AS and Hainline BE. "Hyperammonemia in the ICU". *Chest* 132.4 (2007): 1368-1378.
2. Long MT and Coursin DB. "Undifferentiated non-hepatic hyperammonemia in the ICU: Diagnosis and management". *Journal of Critical Care* 70 (2022): 154042.

3. Zhao L., *et al*. "Prognostic role of ammonia in critical care patients without known hepatic disease". *Frontiers in Medicine* 7 (2020): 589825.

4. Prado FA., *et al*. "Hyperammonemia in ICU patients: A frequent finding associated with high mortality". *Journal of Hepatology* 62.5 (2015): 1216-1218.

5. Dams K., *et al*. "Hyperammonemia in the adult critical care setting". Yearbook of Intensive Care and Emergency Medicine (2008): 481-490.

6. Kim JH., *et al*. "Impact of non-hepatic hyperammonemia on mortality in intensive care unit patients: a retrospective cohort study". *The Korean Journal of Internal Medicine* 36.6 (2021): 1347-1355.

7. Häberle J. "Clinical practice". *European Journal of Pediatrics* 170.1 (2010): 21-34.

8. Weiner ID and Verlander JW. "Renal ammonia metabolism and transport". *Comprehensive Physiology* 3.1 (2013): 201-220.

9. Laish I and Ben Ari Z. "Noncirrhotic hyperammonaemic encephalopathy". *Liver International* 31.9 (2011): 1259-1270.

10. Sepehrinezhad A., *et al*. "Astrocyte swelling in hepatic encephalopathy: molecular perspective of cytotoxic edema". *Metabolic Brain Disease* 35.4 (2020): 559-578.

11. Willard-Mack CL., *et al*. "Inhibition of glutamine synthetase reduces ammonia-induced astrocyte swelling in rat". *Neuroscience* 71.2 (1996): 589-599.

12. Braissant O., *et al*. "Ammonia toxicity to the brain". *Journal of Inherited Metabolic Disease* 36.4 (2012): 595-612.

13. Norenberg MD and Martinez-Hernandez A. "Fine structural localization of glutamine synthetase in astrocytes of rat brain". *Brain Research* 161.2 (1979): 303-310.

14. Brusilow SW and Traystman R. "Hepatic encephalopathy". *The New England Journal of Medicine* 314.12 (1986): 786-787 author reply 787.

15. Machado MC and Pinheiro da Silva F. "Hyperammonemia due to urea cycle disorders: a potentially fatal condition in the intensive care setting". *Journal of Intensive Care* 2.1 (2014): 22.

16. Kalra A and Norvell JP. "Cause for confusion: noncirrhotic hyperammonemic encephalopathy". *Clinical Liver Disease* 15.6 (2020): 223-227.

17. Walker V. "Severe hyperammonaemia in adults not explained by liver disease". *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine* 49.3 (2012): 214-228.

18. Amra Sakusic., *et al*. "Features of adult hyperammonemia not due to liver failure in the ICU". *Critical Care Medicine* 46.9 (2018): e897-e903.

19. Summar ML and Mew NA. "Inborn errors of metabolism with hyperammonemia". *Pediatric Clinics of North America* 65.2 (2018): 231-246.

20. Ribas GS., *et al*. "Hyperammonemia in inherited metabolic diseases". *Cellular and Molecular Neurobiology* 42.8 (2021): 2593-610.

21. Gupta S., *et al*. "The role of RRT in hyperammonemic patients". *Clinical Journal of the American Society of Nephrology* 11.10 (2016): 1872-1878.

22. Morillas RM., *et al*. "Profilaxis de la encefalopatía hepatica". *Medicina Clínica* 142.11 (2014): 512-514.

23. Tapper EB., *et al*. "Refining the ammonia hypothesis". *Mayo Clinic Proceedings* 90.5 (2015): 646-658.

24. Wasim M., *et al*. "Aminoacidopathies: Prevalence, etiology, screening, and treatment options". *Biochemical Genetics* 56.1-2 (2018): 7-21.

25. Taneja V and Jasuja H. "Severe hyperammonemia from intense skeletal muscle activity". *Medicine* 98.47 (2019): e17981.

26. Bilsborough S and Mann N. "A review of issues of dietary protein intake in humans". *International Journal of Sport Nutrition and Exercise Metabolism* 16.2 (2006): 129-152.

27. Camacho J and Rioseco-Camacho N. "Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome". Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, *et al*., editors. PubMed. Seattle (WA): University of Washington, Seattle (1993).

28. Wijdicks EFM. "Hepatic encephalopathy". *New England Journal of Medicine* 375.17 (2016): 1660-1670.

29. Phenylbutyrate [Internet]. PubMed. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (2012).

30. Barcelos RP., *et al*. "Creatine and the liver: metabolism and possible interactions". *Mini-Reviews in Medicinal Chemistry* 16.1 (2015): 12-18.

31. García Vega M., *et al*. "Urea cycle disorders and indications for liver transplantation". *Frontiers in Pediatrics* 11 (2023): 1103757.

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