





Initial management of acute hyperammonemia in pediatrics

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ABSTRACT

Hyperammonemia is a medical emergency. There are no publications regarding the availability of resources, supplies, and knowledge necessary for the initial management of hyperammonemia by pediatricians in Argentina; however, according to the authors' experience, the necessary resources are not available all year round in a large portion of our territory.

Based on such state of affairs, an international bibliographic review on this topic and the authors' experience, we developed a series of recommendations for the initial pediatric management of this emergency, with the objective of reducing deficiencies, allowing adequate clinical suspicion leading to a timely diagnosis and emergency management and a rational use of pharmacological resources (some of which are costly) to reduce the morbidity and mortality associated with hyperammonemia.

Key words: hyperammonemia, inborn urea cycle disorders, emergency management, ammonia, Argentina.

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INTRODUCTION

Hyperammonemia is a medical emergency. It is caused by an excessive accumulation of ammonium in the blood, which is toxic to the central nervous system and liver. It results in high mortality and neurological sequelae in 80% of survivors, with a direct relationship between the degree of sequelae and the duration of hyperammonemic coma.¹

The catabolism of amino acids produces ammonium, which enters the urea cycle and is excreted in the urine as urea. Hyperammonemia may be caused by an inborn error of metabolism (urea cycle disorders, organic acidurias, beta-oxidation defects, etc.) or be secondary to liver failure, urinary tract infections by ammonium-producing microorganisms or use of valproic acid, among other factors. Primary causes are always diagnosed as a consequence of suspicion by the pediatrician, since they are not included in mandatory neonatal screening programs.

Rapid treatment modifies the prognosis; there is a time window of hours for it to be effective. Therefore, after the initial clinical suspicion, it is critical to have biochemical ammonium determination available *in situ* and to know how to act in case of hyperammonemia in order to reduce morbidity and mortality.

In Argentina, there are no publications or reports about how many centers perform ammonium determinations and whether providers are trained on what to do in case of hyperammonemia. In practice, according to the authors' experience, in more than half of the provinces of the country, the biochemical determination of plasma ammonium is not available at the point of care and, in the centers where it is, it is not always possible to measure it as an on-call determination all year round.

Similarly, in most provinces, there is no dissemination of specific action protocols for this medical emergency. Also, there are no drugs for emergency management and no accessible dialysis methods available in many centers.

Therefore, the objective of this study is to develop recommendations for the initial management of pediatric patients with hyperammonemia.

MATERIAL AND METHODS

A bibliographic review of PubMed was done using the terms "management of hyperammonemia" for the 2010-2021 period. Additional documents were added that were not

identified by the search term, but clearly have a role in the recommendation, such as available hyperammonemia management guidelines (Garrahan, Spanish-Portuguese, European). A preliminary meeting and 3 synchronous virtual meetings were held; we also worked in an asynchronous manner via e-mail exchanges among the Metabolic Diseases Scientific Groups of Argentina regarding each draft of the manuscript.

As of November 30th, 2021, documents were identified and reviewed to determine their updated relevance as guidelines for the management of hyperammonemia in pediatrics²⁻⁸ and, based on the authors' experience, recommendations for the initial management of pediatric patients with hyperammonemia were developed. These recommendations are not based on evidence following the GRADE approach, but are limited to the experts' opinion.

RECOMMENDATIONS FOR THE INITIAL MANAGEMENT OF PEDIATRIC PATIENTS WITH HYPERAMMONEMIA

Required knowledge and minimum tools necessary for pediatric care during the first 24 to 48 hours of hyperammonemia

a) Clinical suspicion of hyperammonemia

The signs and symptoms of hyperammonemia vary according to age. In neonates, lethargy, weak sucking, and vomiting are common. Suspected sepsis without microorganism rescue is seen in the medical records of patients with toxic conditions of intermediate metabolism. It may progress to central hyperventilation (50% of neonates have respiratory alkalosis due to hyperventilation), seizures, coma, and death if untreated.

In older children, symptoms include unexplained changes in consciousness, neurological or psychiatric disease, and acute liver failure. If chronic, hyperammonemia may present as frequent vomiting, headache, ataxia, and protein aversion.

b) Access to plasma ammonium determination 24/7

Knowing the ammonium level is necessary for the diagnosis and follow-up of this medical emergency. It is not appropriate to initiate an empirical treatment. Ammonium increases in blood and plasma after collection, due to the release of ammonium from erythrocytes and the deamination

of plasma amino acids. A difficult sample collection or a delayed sample processing often leads to falsely high levels, being the most frequent causes of hyperammonemia.³

Recommendations for ammonium determination: collect free-flowing venous (or arterial) blood without using a tourniquet in a tube with anticoagulant (EDTA). The tube should be immediately placed on ice and transferred, and the plasma should be separated from the cells within 15 minutes. The use of a tourniquet may alter the sample results. It is worth emphasizing that the sample for detection of ammonium in plasma cannot be preserved without the risk that the detected value is false because it has increased in the pre-analytical stage.

To obtain the sample and check for alterations in preservation and transport, it is suggested that another control sample be sent simultaneously under the same conditions, preferably from a person who is not a relative of the patient and whose sample that has been drawn and processed in the same conditions.

c) Knowledge of normal plasma ammonium values and actionable values

Normal plasma ammonium values vary according to the patient's age. They are usually expressed as $\mu\text{mol/L}$ or $\mu\text{g/dL}$. For the conversion from $\mu\text{mol/L}$ to $\mu\text{g/dL}$, the value is divided by the constant 0.5872. There is no consensus on the upper limit for each age group. A plasma ammonium level $< 50 \mu\text{mol/L}$ ($85 \mu\text{g/dL}$) in infants and children and $< 100 \mu\text{mol/L}$ ($170 \mu\text{g/dL}$) in neonates is considered normal and requires immediate action at levels above the upper limit. With elevated ammonium values without clinical signs, sampling should be repeated to ensure an adequate pre-analytical stage.

d) Initial management of suspected hyperammonemia

While awaiting the result of the ammonium determination (it should not take more than 2 hours), stabilization with basic life support is indicated (as for any critical patient), and the following is recommended:

1. Place vascular accesses, if possible, central venous access.
2. Secure the airway: intubate and ventilate, if necessary.
3. Provide adequate hydration using dextrose $> 10\%$ and high calorie intake; maintain normal blood pressure, with vasopressors, if

necessary.

4. Collect blood and urine samples for ammonium, lactate, blood glucose, acid-base status and electrolytes, chlorine and calcium, creatinine, urea, liver function tests, blood count, acylcarnitines(*), plasma amino acids(*), ketones (test strips), and urine organic acids(*)

(*) Although these tests are not performed on site, the sample should be taken during the event (critical sample) (blood drops on filter paper, 2 mL of plasma and 10 mL of urine minimum) and may be deferred to confirm the etiological diagnosis.

e) What to do if hyperammonemia is confirmed

The patient should receive care in a facility with access to metabolic tests (see * in item d, point 4), access to drugs for treatment, dialysis, and specialists in metabolic diseases. If any of these elements are not available, the patient should be transferred without delay to a specialized facility after these initial measures.

Increased protein catabolism results in an overload of the urea cycle. Therefore, stopping catabolism and inducing anabolism is the rationale behind therapies, in addition to administering drugs that metabolize ammonium into molecules that can be excreted in urine. For this purpose, the following is recommended:

1. Temporarily interrupt sources of protein intake (maximum for 24–48 hours). After this period, progressively reintroduce proteins to avoid deficiency of essential amino acids and secondary catabolism.
2. Contact the pharmacy to prepare the medications (see doses in *Table 1*).

If ammonium $> 85 \mu\text{g/dL}$ (or $> 170 \mu\text{g/dL}$ for neonates), the following is recommended:

- Up to $250 \mu\text{g/dL}$, oral drug treatment if tolerated by the patient.
- Between $250 \mu\text{g/dL}$ and $800 \mu\text{g/dL}$, intravenous drug treatment.
- Above $800 \mu\text{g/dL}$, initiate hemodialysis/hemodiafiltration together with intravenous treatment.

If ammonium levels do not go down after 2–3 hours, depending on the clinical status of the patient, the next step should be carried out immediately. A coma secondary to hyperammonemia for more than 72 hours is associated with irreversible neurological damage.

3. Monitor blood glucose regularly.
4. Regardless of the initial glycemia level, initiate calorie intake to cover 110% of the daily

TABLE 1. Drugs used for the emergency management of hyperammonemia

Drug	Dosage form	Dosage	Route	Administration	Observations
Sodium benzoate	Injection: V. × 10 mL (imported product): 20% (200 mg/mL) Amp. × 30 mL (compounded preparation): 20% (200 mg/mL) p.o./catheter Syrup × 150 mL (compounded preparation) 20% (200 mg/mL).	Loading dose: i.v.: ≤ 20 kg: 250 mg/kg > 20 kg: 5.5 g/m ² to be administered over 90 minutes. Maintenance: ≤ 20 kg: 250 mg/kg/day > 20 kg: 5.5 g/m ² /day in spite of division into "n" postprandial doses.	i.v. or p.o.	i.v.: Dilute at 20 mg/mL in D10%. Maximum strength: 50 mg/mL p.o.: administer with food. Compatible with milk, enteral formula or juice i.v.: compatible at Y-site with arginine, carnitine, and phenylbutyrate.	Cautions in neonates with hyperbilirubinemia. Control natremia and kalemia. Dosage and infusion times may be adjusted as per course and type of condition.
Sodium benzoate – Sodium phenylacetate (Ammonul®)	Injection × 50 mL (imported product): sodium benzoate 10% (100 mg/mL) sodium - phenylacetate 10%.	Loading dose: ≤ 20 kg: 250 mg/kg > 20 kg: 5.5 g/m ² of benzoate to be administered over 90 minutes. Maintenance: ≤ 20 kg: 250 mg/kg/day > 20 kg: 5.5 g/m ² /day every 6 hours, to be administered continuously or over 90 minutes.	i.v.	Dilute at 10 mg/mL in D10%.	The dose is calculated based on benzoate. Strength: 100 mg/mL of benzoate. Phenylacetate is the active form of phenylbutyrate. Administer via a central line. Extravasation may cause necrosis. Use with caution in patients with liver failure and kidney failure. Control natremia, pH, and PCO ₂ frequently. Dosage may be adjusted as per course and type of condition.
Sodium phenylbutyrate i.v.	V. × 10 mL (imported product): 20% (200 mg/mL).	Loading dose: ≤ 20 kg: 250 mg/kg > 20 kg: 5.5 g/m ² to be administered over 90 minutes. Maintenance: ≤ 20 kg: 250 mg/kg/day > 20 kg: 5.5 g/m ² /day every 8 hours, to be administered continuously or over 90 minutes.		Dilute at 20 mg/mL in D10%. Maximum strength: 50 mg/mL.	
Phenylbutyrate p.o. (imported product)	Powder: cachet or syrup at 20% (200 mg/mL).	≤ 20 kg: 250 mg/kg/day > 20 kg: 5.5 g/m ² /day every 8 hours.	p.o.	With food. Avoid acidic beverages.	
L-Arginine, hydrochloride	Amp. × 250 mL: 10% (100 mg/mL).	Loading dose: ≤ 20 kg: 250 mg/kg > 20 kg: 5.5 g/m ² to be administered over 90 minutes.	i.v.	Undiluted or diluted in D10% - normal saline solution.	Arginine 10% hypertonic saline solution (950 mOsm/L): caution with peripheral lines Control potassium, phosphate, and chloride. Caution with kidney failure. Avoid arginine aspartate.

Drug	Dosage form	Dosage	Route	Administration	Observations
L-arginine, hydrochloride or arginine base	Bottle × 500 mL (compounded preparation): 10% (100 mg/mL) cachet.	≤ 20 kg: 250 mg/kg/day > 20 kg: 5.5 g/m ² /day.	p.o.	With food.	Stable for 14 days once reconstituted.
Carbamyl glutamate (carglumic acid)	Tab. 200 mg.	Loading dose: 100 mg/kg Maintenance: 100 mg/kg/day every 6 hours.	p.o.	Before meals, milk or enteral formula.	Administration p.o. or catheter: do not crush tablets. Disperse in 2.5 mL until a final concentration of 80 mg/mL, shake gently for total dispersion. Administer immediately. When using a catheter, flush with water. Tablet storage: before opening the bottle, keep refrigerated (2–8 °C); once open, keep at room temperature (< 30 °C).

i.v.: intravenous; *p.o.*: orally; *amp.*: ampoule; *v.*: vial; *tab.*: tablet; *g*: grams; *mg*: milligrams; *kg*: kilogram; *mL*: milliliter;

D5%: dextrose 5%; *D10%*: dextrose 10%.

Adapted from: Hospital de Pediatría J. P. Garrahan. *Medicación de emergencia para Errores Congénitos del Metabolismo*.

Buenos Aires, 2012. [Accessed on: January 3rd, 2022]. Available at: https://www.garrahan.gov.ar/PDFS/medicamentos/tablas/drogas_emergencia_metabolica.pdf

recommendation according to age to prevent catabolism (daily recommendation: < 1 year: 110–120 kcal/kg/day, 1–3 years: 100 kcal/kg/day, 4–6 years: 90 kcal/kg/day, 7–10 years: 70 kcal/kg/day, 11–14 years: 50–55 kcal/kg/day). Initiate minimum glucose flow: 0–1 year: 8–10 mg/kg/min, 1–12 years: 6–8 mg/kg/min, adolescents and adults: 4–6 mg/kg/min.

Insulin is used as a hormone that suppresses catabolism and induces anabolism, but its use requires experience and caution due to the risk of hypoglycemia. Start with insulin flow at 0.005–0.01 unit/kg/h (regular intravenous insulin) and adjust until glycemia is stabilized between 100 and 180 mg/dL.

5. If beta-oxidation defects are excluded as a cause of hyperammonemia, intravenous lipid infusions can be started at 2–3 g/kg/day to deliver additional calories.

f) Drugs used for emergency management of hyperammonemia

Sodium benzoate and sodium phenylbutyrate

work as ammonium-chelating agents by conjugation of benzoate with glycine to generate hippurate and of phenylacetate with glutamine to generate phenylacetylglutamine, which are excreted in urine.

L-arginine is an amino acid that is synthesized within the urea cycle and can increase the residual activity of the cycle. It is contraindicated in arginase deficiency, but this urea cycle disorder rarely occurs with hyperammonemia.

Carglumic acid can replace N-acetylglutamate as an activator of the enzyme mitochondrial carbamoyl-phosphate synthetase, the first enzyme of the urea cycle.

Table 1 summarizes drug dosages, administration, and other observations.

Sodium benzoate, sodium phenylbutyrate, and arginine hydrochloride should be infused at the same time, in parallel, but without being mixed in the same bag, so it would be necessary to have two 2-channel infusion pumps, which can confluence in a central access, or use 2 peripheral lines.

It is important to remember that these drugs are diluted in dextrose 10% and that it is necessary to calculate the amount of glucose contributed by this infusion to the total glucose flow to complete the total flow target (for example: 8 mg/kg/min in infants) with an additional dextrose hydration plan. The practical aspects regarding the form of administration and drug compatibilities for loading doses, including an example of use in a hypothetical patient, are summarized in *Supplementary material 1*.⁷

g) When to indicate dialysis

Dialysis should be initiated if ammonium levels are greater than 800 µg/dL or with lower levels if the response to treatment failed in the first 4 hours or if the patient is in a coma. It is worth noting that rapid action is required to prevent brain injury and a vascular access for dialysis should be placed immediately.

Dialysis options include hemodialysis (HD) and continuous renal replacement therapy (CRRT). HD is intermittent and provides higher ammonium clearance, but in neonates it is difficult due to technical challenges and a high risk for complications. CRRT, including continuous venovenous hemofiltration or continuous venovenous hemodiafiltration, is the preferred method.⁴ Exchange transfusions should be avoided. Continuation of ammonium-chelating drug therapy during dialysis is necessary.

Peritoneal dialysis (PD) removes ammonium at a much lower rate compared to the other options: it is not fast enough to avoid irreversible neurological damage.

h) Other aspects to be considered during the initial management of acute hyperammonemia⁸

1. If no etiologic diagnosis has been established, consider additional administration of intravenous carnitine at 100 mg/kg, intramuscular/intravenous hydroxocobalamin 1 mg, and intravenous/oral biotin 10 mg.
2. Avoid steroids, as they increase protein catabolism and nitrogen loading.
3. Avoid valproic acid in patients at risk for hyperammonemia because it decreases the function of urea cycle by inhibiting N-acetylglutamate synthase.
4. Additional loading doses of ammonium-

chelating agents are only indicated in patients with severe decompensation due to hyperammonemia or undergoing dialysis. They should be administered with caution to avoid adverse effects.

5. Constipation should be managed aggressively, as ammonium is also produced from the breakdown of urea by intestinal bacteria.
6. Deoxyribonucleic acid (DNA) sampling is recommended for molecular etiologic confirmation if the patient is critically ill. The EDTA blood sample (blood count tube) should be stored at room temperature, adequately labeled, and sent to a laboratory that can perform DNA extraction.

CONCLUSION

Knowing that delays in diagnosis and treatment are associated with a worse prognosis, we consider that these recommendations could help to reduce the current deficiencies of the health care system by providing a detailed description of necessary resources and how to use them rationally.

Finally, the dissemination of this information to the health care community in our country, complemented with more training on the problem, could have a positive impact on the treatment of this infrequent medical emergency. ■

Supplementary material available at:
https://www.sap.org.ar/docs/publicaciones/archivosarg/2023/2614_AE_Eiroa_Anexo.pdf

REFERENCES

1. Msall M, Batshaw ML, Suss R, Brusilow SW, Mellits ED. Neurologic outcome in children with inborn errors of urea synthesis. Outcome of urea-cycle enzymopathies. *N Engl J Med*. 1984; 310(23):1500-5.
2. Auran A, Brophy PD. Hyperammonemia in review: pathophysiology, diagnosis, and treatment. *Pediatr Nephrol*. 2012; 27(2):207-22.
3. Maranda B, Cousineau J, Allard P, Lambert M. False positives in plasma ammonia measurement and their clinical impact in a pediatric population. *Clin Biochem*. 2007; 40(8):531-5.
4. Raina R, Bedoyan JK, Lichter-Konecki U, Jouvet P, et al. Consensus guidelines for management of hyperammonaemia in paediatric patients receiving continuous kidney replacement therapy. *Nat Rev Nephrol*. 2020; 16(8):471-82.
5. Häberle J, Boddaert N, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis*. 2012; 7:32.

6. Häberle J, Burlina A, Chakrapani A, Dixon M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. *J Inherit Metab Dis*. 2019; 42(6):1192-230.
7. Área de Emergencias, Área de Farmacia, Servicio de Errores Congénitos del Metabolismo. Guía para cálculo de goteos de fármacos en Trastornos del Ciclo del Urea en 7 pasos. Hospital Garrahan. [Accessed on: May 23rd, 2022]. Available at: <https://www.garrahan.gov.ar/PDFS/medicamentos/tablas/Guia%20calculo%20goteos%20mantenimiento%20D10.pdf>
8. Alfadhel M, Mutairi FA, Makhseed N, Jasmi FA, et al. Guidelines for acute management of hyperammonemia in the Middle East region. *Ther Clin Risk Manag*. 2016; 12:479-87.