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What the intensivist should know about hyperammonemia without liver failure

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1. Introduction

Hyperammonemia without liver failure can be particularly challenging to diagnose in adult critical care settings, where they are at high risk of being overlooked [1–5]

The state of severe hyperammonemia defined by the simultaneous presence of two criteria: (1) a laboratory finding of elevated plasma ammonia concentrations and (2) a clinical presentation characterized by progressive neurological imparement.

Severe hyperammonemia, with plasma ammonia concentrations exceeding 150 μmol/L, can rapidly progress to a clinical state resembling acute liver failure. This condition is typically associated with deep coma requiring intubation and, if left untreated, may lead to cerebral herniation and death [6–8].Acute severe hyperammonemia plays a central role in this meurological deterioration.

Clinicians should be vigilant for nonspecific clinical signs suggestive of metabolic encephalopathy. These include asterixis (flapping tremor), disorientation, somnolence, and motor abnormalities such as hyperreflexia, a positive Babinski sign, and the presence of primitive reflexes. Pupillary abnormalities should also be carefully assessed and monitored over time. The presence of these findings reinforces the importance of systematically including plasma ammonia measurement in the diagnostic work-up of any unexplained neurological impairment. [7] (See Table 1.)

2. Etiologies of non-hepatic hyperammonemia

Non-hepatic hyperammonemia results from a variety of mechanisms, including inherited metabolic defects (i), drug-induced urea cycle disruption (ii), infections with urease-producing organisms (iii), and complications following transplantation (iiii).

(i) Urea cycle disorders (UCDs) are rare inherited metabolic diseases caused by deficiencies in one of six enzymes or two transporters involved in ammonia detoxification [8]. While severe forms typically manifest in infancy with critical illness and death, partial UCDs may remain latent until adulthood, triggered by acute illness, metabolic stress, or excessive protein intake [5–8].

A triad of neurological, gastrointestinal, and psychiatric symptoms should raise suspicion for UCD decompensation [9].

(ii) Several medications impair ammonia clearance. Valproic acid, a widely used anticonvulsant, is the most common iatrogenic cause [10], readily identified through blood level monitoring. Other implicated agents include carbamazepine, sulfadiazine,

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Table 1
Symptoms suggestive of hyperammonemia secondary to Urea Cycle Disorders.

Gastrointestinal	Psychiatric	Neurological
Nausea, vomiting	Delirium	Coma
Anorexia	Puerperal psychosis	Lethargy or drowsiness
Abdominal pain	Catatonic depression	Confusion
	Behavioral disturbance	Agitation
	Visual hallucination	Seizure
		Ataxia
		Slurred speech
		Increased or decreased muscle tone
		Headache
		Brain oedema
		Pseudo stroke
		Acute loss of vision

cyclophosphamide, ribavirin, salicylates, glycine, and numerous anticancer therapies [11].

(iii) Obstructive urinary tract infections with urease-producing bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, and certain Staphylococcus and Streptococcus species, can lead to secondary hyperammonemia [9]. These pathogens can hydrolyze urea and alkalinize the urine leading to significant ammonia production [2,9].

(iv) Hyperammonemia has been reported following solid organ and hematopoietic stem cell transplantation, with lung transplantation particularly implicated [12]. Incidence rates after lung transplant may reach 4 % [7]. Disseminated infections with Ureaplasma or Mycoplasma species are increasingly recognized as underlying causes in this transplantation setting [7].

2.1. Pathophysiology

Hyperammonemia involves a complex interplay between multiple organ systems, primarily the liver, kidneys, brain, and skeletal muscle.

2.2. Liver (UCDs)

The liver is the principal site of ammonia detoxification via the urea cycle, an energy-intensive process occurring in both the mitochondria and cytoplasmic compartments. Dysfunction of this system, as seen in UCDs, leads to systemic accumulation of ammonia. Clinically, this manifests as lethargy, slurred speech, asterixis, cerebral edema, and in severe cases, cerebral herniation and death.

2.3. Kidneys (Urease-producing Bacteria in Urinary Tract Infections)

Infections caused by urease-producing bacteria within the urinary tract can hydrolyze urea to ammonia [9]. In the setting of alkaline urine, ammonia levels rise substantially [2,9]. Due to its lipid solubility and neutral charge, ammonia (NH_3) diffuses across the urothelium and is subsequently protonated to ammonium (NH_4^+), which then enters the systemic circulation — a phenomenon referred to as "diffusion trapping." This process bypasses hepatic detoxification pathways, contributing to systemic hyperammonemia. Management includes targeted antibiotic therapy, neuroprotective strategies, and the administration of ammonia-scavenging agents [2–9].

2.4. Brain (Implicated In All Etiologies)

The central nervous system is particularly vulnerable to elevated ammonia levels. Hyperammonemia impairs cerebral autoregulation, compromises blood-brain barrier integrity, and promotes both vasogenic and cytotoxic edema [13]. Although the precise mechanisms of ammonia-induced neurotoxicity remain incompletely understood, it is hypothesized that alterations in neurotransmitter systems underlie the neuronal damage observed in both acute and chronic hyperammonemia [5–7]. Animal studies have shown that ammonia toxicity is associated with elevated extracellular glutamate, activation of *N*-methyl-D-aspartate (NMDA) receptors, and overactivation of Na^+/K^+-ATPase, ultimately resulting in ATP depletion — a likely contributor to seizure activity in acute settings [5–7].

Astrocytes, the main site of cerebral ammonia detoxification, undergo swelling in response to ammonia accumulation, contributing to cerebral edema, elevated intracranial pressure, and the risk of herniation. Proposed mechanisms of astrocyte swelling include disruptions in water and potassium homeostasis, activation of tumor suppressor protein p53, increased uptake of pyruvate, lactate, and glutamine, and decreased uptake of ketone bodies, glutamate, and glucose [5–7].

2.5. Skeletal Muscle (Aggravating Factor Across Etiologies)

Under physiological conditions, skeletal muscle functions as an auxiliary site for ammonia clearance [1]. However, in catabolic states or in the presence of sarcopenia, muscle may shift from ammonia consumption to production, thereby exacerbating hyperammonemia [2]. Loss of muscle mass therefore contributes to a self-perpetuating cycle of reduced ammonia detoxification capacity.

2.6. Diagnostic considerations and when to investigate

While hepatic encephalopathy is a common complication in patients with chronic liver disease and may progress to coma, these individuals typically exhibit long-term adaptation to low-grade hyperammonemia and rarely develop cerebral edema [13]. In contrast, hyperammonemia unrelated to liver failure can rapidly precipitate life-threatening cerebral edema and must be recognized as a medical emergency. Consequently, serum ammonia levels should be urgently assessed in any comatose patient without an identifiable cause.

Accurate measurement of plasma ammonia requires strict procedural adherence: a fresh, non-hemolyzed sample must be collected in a plasma (EDTA or heparin) tube and transported on ice for immediate laboratory analysis to prevent false elevation.

A history of recurrent gastrointestinal symptoms, fluctuating somnolence, and neuropsychiatric disturbances—particularly when precipitated by high protein intake or intercurrent illness—should raise suspicion for an UCD, especially in individuals with a history of habitual meat avoidance or selective protein restriction.

3. Clinical management

Management of severe acute hyperammonemia requires a combination of urgent neuroprotective strategies, ammonia-lowering interventions, and the correction of underlying etiologies (See Fig. 1).

3.1. Urgent general measures

Immediate neuroprotective measures and interventions aimed at reducing plasma ammonia concentrations form the cornerstone of treatment across all etiologies of severe hyperammonemia. Addressing the underlying cause is equally critical. For instance, antimicrobial therapy should be promptly initiated in the case of infections due to urea-splitting organisms, and any ammonia-promoting drugs should be discontinued.

3.2. Urgent ammonia-lowering techniques

3.2.1. Renal Replacement and Blood purification therapies

3.2.1.1. Rationale. Ammonia is a small, water-soluble molecule with clearance properties similar to those of urea, making it amenable to

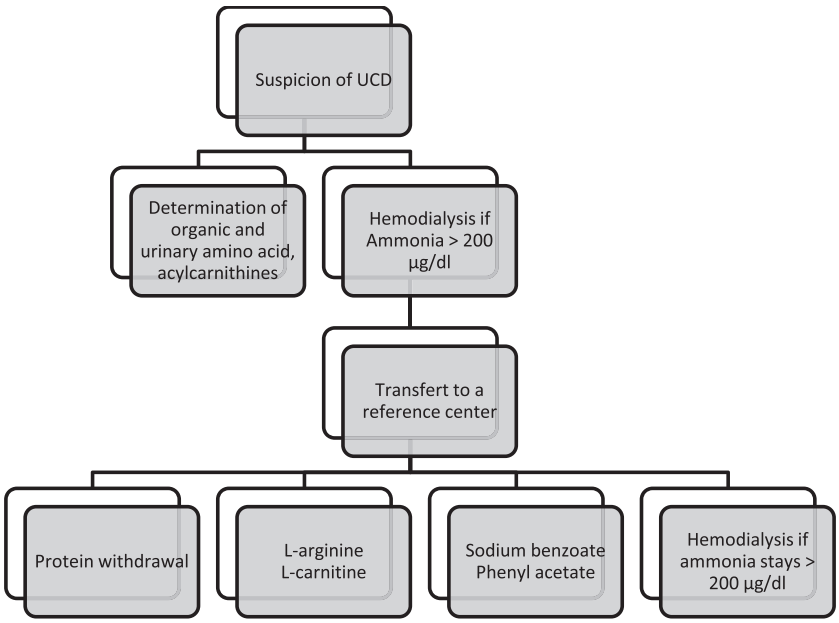

Fig. 1. Summarizes the ways to handle the UCDs.

clearance via kidney replacement therapies (KRT) [14]. While diffusive modalities such as intermittent hemodialysis (IHD) may offer theoretical advantages, no single dialysis modality has proven definitively superior for ammonia removal [14].

The clinical impact of plasma ammonia concentration varies with etiology. In hepatic failure, levels exceeding 100 µmol/L are typically associated with encephalopathy, often without cerebral edema. Conversely, in non-hepatic hyperammonemia, concentrations above 150 µmol/L are strongly linked to intracranial hypertension and an increased risk of brainstem herniation [5–7].

3.2.1.2. Techniques.

- *Peritoneal dialysis and exchange transfusion* are generally insufficient for managing severe hyperammonemia and should be avoided [14].

- *IHD* is effective for rapid reduction of plasma ammonia levels. However, it should be followed by early transition to continuous kidney replacement therapy (CKRT) to maintain biochemical stability and minimize fluctuations in ammonia levels.

- *CKRT* is the preferred modality in critically ill patients. It offers superior hemodynamic tolerance, reduces the risk of rebound hyperammonemia, and allows for continuous control of intracranial pressure. CKRT also enables the management of fluid balance, acid-base status, electrolyte disturbances, and temperature regulation — all essential components in the prevention of cerebral edema and intracranial hypertension [5–7].

3.2.2. Less urgent metabolic measures

3.2.2.1. Dietary and metabolic management. All patients with hyperammonemia should avoid excessive caloric intake and large quantities of exogenous protein [15]. In suspected UCDs, protein intake should be completely halted for the first 24–48 h. While prolonged protein restriction may pose nutritional risks, short-term restriction is generally well tolerated and effective in the acute setting [7].

To meet caloric demands and suppress proteolysis, intravenous nutritional support is recommended, typically consisting of a 20 % lipid emulsion and a 10–30 % dextrose solution [15].

3.3. Specific nutritional supplements

Several metabolic cofactors and supplements may be beneficial in both acute and long-term management of UCDs. L-carnitine has shown efficacy in reducing ammonia levels by enhancing mitochondrial energy metabolism and promoting the activity of glutamate dehydrogenase. Due to its ability to cross the blood-brain barrier, L-carnitine may also mitigate the neurotoxic effects of ammonia and improve cerebral energy balance [5–7].

3.4. Key takeaways and clinical implications

Hyperammonemia should be systematically considered in any ICU patient with unexplained altered consciousness, even in the absence of liver failure. Non-hepatic causes—such as urea cycle disorders, infections, drug toxicity, and post-transplant complications—are often underrecognized. Management involves urgent neuroprotective measures, temporary protein restriction, metabolic support, and rapid ammonia clearance, ideally with high-dose continuous renal replacement therapy. Early intervention is critical to prevent cerebral edema and improve neurological outcomes.

Availability of data and materials

Not applicable.

CRediT authorship contribution statement

Aurelien Gonze: Writing – review & editing, Writing – original draft, Conceptualization. **Thibault Gennart:** Writing – review & editing, Writing – original draft. **Reda Ghazali:** Writing – review & editing, Writing – original draft. **Sami Ghazali:** Writing – review & editing, Writing – original draft. **Emily Perriens:** Writing – review & editing, Writing – original draft. **Sydney Blackman:** Writing – review & editing, Writing – original draft, Conceptualization. **Patrick M. Honore:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare to have no competing interests.

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