Ammonia and nutritional therapy in the critically ill: when to worry, when to test and how to treat?

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Purpose of review
Hyperammonaemia is almost always develops in patients with severe liver failure and this remains the commonest cause of elevated ammonia concentrations in the ICU. Nonhepatic hyperammonaemia in ICU presents diagnostic and management challenges for treating clinicians. Nutritional and metabolic factors play an important role in the cause and management of these complex disorders.

Recent findings
Nonhepatic hyperammonaemia causes such as drugs, infection and inborn errors of metabolism may be unfamiliar to clinicians and risk being overlooked. Although cirrhotic patients may tolerate marked elevations in ammonia, other causes of acute severe hyperammonaemia may result in fatal cerebral oedema. Any coma of unclear cause should prompt urgent measurement of ammonia and severe elevations warrant immediate protective measures as well as treatments such as renal replacement therapy to avoid life-threatening neurological injury.

Summary
The current review explores important clinical considerations, the approach to testing and key treatment principles that may prevent progressive neurological damage and improve outcomes for patients with hyperammonaemia, especially from nonhepatic causes.

Keywords
haemodialysis, scavenging therapy, urea cycle disorders

INTRODUCTION

Ammonia is a toxic metabolite largely resulting from protein catabolism. It is rapidly detoxified via the urea cycle so thus permitting nitrogenous waste products to be more safely transported and eliminated. Severe hyperammonaemia (plasma ammonia concentration of more than 150 μmol/l) is associated with progressive neurological injury and death [1]. Ammonia impacts multiple essential metabolic processes within astrocytes, leading to cytotoxic cerebral oedema, while it simultaneously impedes autoregulation of cerebral blood flow and integrity of the blood–brain barrier resulting in vasogenic oedema [2]. Intracranial hypertension subsequently develops and may proceed to uncal herniation and death unless the process can be halted and reversed [3,4].

Severe liver failure is the commonest cause of urea cycle dysfunction and commonly causes dangerous hyperammonaemia, especially if it is of new-onset and rapidly progressive. The causes and management principles of acute liver failure have been extensively described elsewhere [2]. Nonhepatic causes of hyperammonaemia are much less common [5] but include medications (especially valproate toxicity), urinary tract infection with urea-splitting organisms, and inborn errors of metabolism such as urea cycle disorders. Although these latter causes are responsible for less than 5% of hyperammonemia in the ICU, failure to recognize and treat can be fatal [6,7].

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KEY POINTS

- Hyperammonaemia must be considered in any ICU patient who is unconscious without a clear cause.
- Although severe liver failure is the commonest cause of hyperammonaemia, drugs, infection and urea cycle disorders (UCDs) are important rare causes that may be overlooked and often require specific therapies.
- Treatment of nonhepatic hyperammonaemia includes urgent initiation of neuroprotective measures, therapies to reduce plasma ammonia concentrations and appropriate treatment of the underlying cause.

BACKGROUND

Hyperammonemia may sometimes result from disruption of the urea cycle by various drugs or medication-triggered release of ammonia from the renal tract in the setting of infection with urea-splitting organisms. Valproic acid overdose is the most well-known drug cause of hyperammonaemia [8], but others include carbamazepine, sulfadiazine, cyclophosphamide, ribavirin, salicylate, glycine and various anticancer therapies [9]. A thorough drug history and measurement of blood valproate concentration will readily identify drug-related hyperammonaemia in many instances. Several case reports identify that hyperammonaemia can occur following both solid organ and haematopoietic stem cell transplantation, with lung transplantation being the most recognized [10,11]. The specific underlying contributing factors to all urea cycle disorders are unclear, but likely include a combination of drugs affecting the urea cycle, steroid-induced catabolism, nutritional deficits and infections with urea-splitting organisms [12].

Urease-producing bacteria include *Proteus mirabilis*, *Escherichia coli* and *Morganella morganii* as well as some species of Klebsiella, Providencia, Pseudomonas, Staphylococcus, Helicobacter and Mycobacterium. These bacteria hydrolyse urea, leading to increased production of ammonia. Alkalisation of the urine occurs with uropathogenic strains of these organisms, promoting increased concentrations of ammonia of up to 50% compared with neutral pH [13▪,14]. As an electrically neutral and lipid-soluble molecule, the increased urinary ammonia (NH_3) concentration leads to a gradient that results in the diffusion of ammonia into urothelial cells. Within the uroepithelium ammonia is converted to the less permeable ammonium (NH_4^+) in the setting of a neutral pH 7.4, preventing diffusion back into the urine, a phenomenon termed 'diffusion trapping.' Trapped ammonium subsequently enters the systemic circulation via the venous drainage of the bladder, and thus escapes detoxification within the liver, causing hyperammonaemia, encephalopathy and cerebral oedema. Rapid treatment with appropriate antibiotics, neuroprotective measures and therapies targeting hyperammonaemia is essential.

Urea cycle disorders may be challenging to identify, especially for clinicians based in adult critical care practice where they especially risk being undiagnosed and untreated [15]. Although *ammoniotelic* organisms such as fish can excrete their nitrogenous waste products of protein catabolism directly into their aquatic environment in the form of ammonia, most land-dwelling organisms have evolved processes of excretion that involve either uric acid (birds, insects and reptiles) or urea (mammals and many amphibians). This latter group of ureotelic organisms utilize the urea cycle to process highly toxic ammonia into less toxic urea that is subsequently transported to the kidney and excreted in urine (Fig. 1). Inherited or acquired insufficiencies of the urea cycle result in hyperammonaemia due to failure of this detoxification process. The urea cycle disorders are a group of inherited metabolic diseases caused by a deficiency in one or more of the six enzymes or two transporters involved in this process [16,17]. Severe inborn errors of metabolism affecting the urea cycle tend to cause critical illness and death in infancy, while partial urea cycle disorders abnormalities may manifest only in adulthood during periods of illness, metabolic stress or high dietary protein intake. Some patients report self-selection of vegetarian diets to avoid feeling sick even prior to diagnosis. Three of the urea cycle enzymes are mitochondrial: *N*-acetylglutamate synthase, carbamoyl phosphate synthetase I and ornithine transcarbamylase (OTC). A further three are cytoplasmic: argininosuccinate synthetase, argininosuccinate lyase and arginase 1. Finally, two are transporters involved in linking mitochondrial and cytoplasmic compartments: mitochondrial ornithine transporter 1 which transports ornithine into the mitochondria, and the mitochondrial aspartate/glutamate transporter. Like the majority of inborn errors of metabolism, most urea cycle disorders are autosomal recessive disorders, except for OTC deficiency which is X-linked [18]. The overall incidence of urea cycle disorders has been reported as 1 per 35 000 [19] and OTC deficiency accounts for 60% of cases [20].

The possibility of a urea cycle disorder is suggested by the triad of neurological, gastrointestinal and psychiatric symptoms (Table 1) [16]. Triggers may include surgery, extreme exercise, parturition, infection, enteral protein loads (including ingested

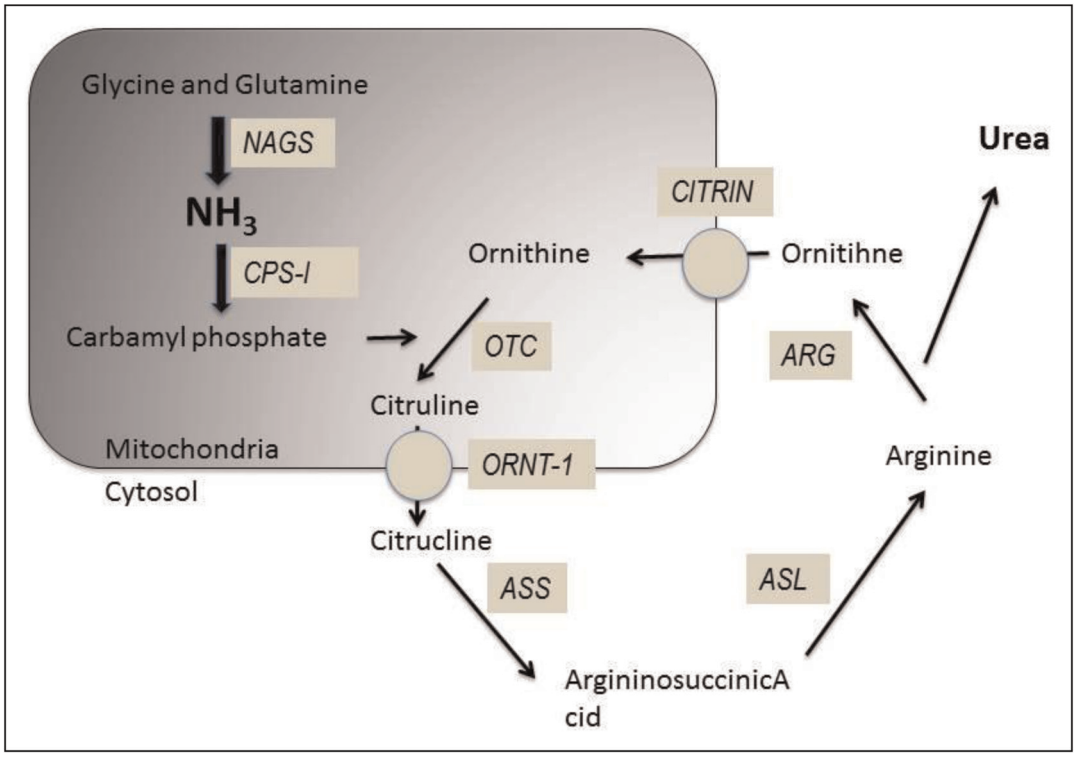

FIGURE 1. Diagram showing the urea cycle and the detoxification of ammonia into urea. Arginase, mitochondrial ornithine transporter 1, and mitochondrial aspartate/glutamate carrier; ASL, arginosuccinate lysase; ASS, arginosuccinate synthetase; CPS-1, carbamoyl phosphate synthetase I; NAGS, *N*-acetylglutamate synthase; OTC, ornithine transcarbamylase.

or upper gastrointestinal bleeding), parenteral nutrition and therapeutic use of valproate [21▪]. The diagnosis is made on the basis of highly elevated plasma ammonia (e.g. >100 μmol/l, and specialized investigations that include plasma and urinary amino acids and the measurement of urinary orotic acid [20].

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
	Behavioural disturbance	Agitation
	Visual hallucination	Seizure
		Ataxia
		Slurred speech
		Increased or decreased muscle tone
		Headache
		Brain oedema
		Pseudo stroke
		Acute loss of vision

WHEN TO WORRY AND WHEN TO TEST

Patients with decompensated chronic liver disease and hyperammonaemia will often experience hepatic encephalopathy that may result in coma but rarely do they develop serious cerebral oedema. This is probably because of long-term adaptation to low-grade elevations in ammonia concentration [5]. Any other cause of extreme hyperammonaemia may cause life-threatening cerebral oedema and must be treated as a medical emergency. The inexplicably comatose patient should be urgently tested for hyperammonaemia followed by a thorough assessment for possible causes if the ammonia concentration is elevated. Testing for hyperammonaemia requires a fresh, nonhaemolysed blood sample in a plasma tube to be rapidly transported to the laboratory on ice for prompt analysis. A history of recurrent gastrointestinal symptoms, somnolence and neuropsychiatric symptoms coinciding with high protein intake or intercurrent illness suggests the possibility of a urea cycle disorder (UCD), especially if associated with a habitual avoidance of meat.

MANAGEMENT

Urgent neuroprotective measures and treatments to lower ammonia concentrations are the mainstays for all causes of severe acute hyperammonaemia. Specific treatments for underlying causes are determined by the aetiology and include *n*-acetyl cysteine for paracetamol overdose-related acute liver failure, antibiotics for infection with urea-splitting organisms and avoidance of drugs such as valproate.

Neuroprotection

Quadruple-H therapy delivers a suite of interventions that may mitigate the impact of hyperammonaemia-induced cerebral oedema in rapidly progressive conditions (Table 2) [22,23]. Gentle hyperventilation, mild hypothermia, infusion of hypertonic saline and haemodiafiltration (or other related forms of continuous renal replacement therapy) are neuroprotective measures that can be readily applied in the ICU and target key pathophysiological processes [2]. All four therapies can be provided in a continuous manner for the duration of the high-risk period of severe hyperammonaemia and then weaned over subsequent days.

Strategies targeting hyperammonaemia

The hypothermia and haemodiafiltration components of Quadruple-H therapy are neuroprotective and also reduce plasma ammonia concentrations. Other strategies to promote a reduction in ammonia levels may also be appropriate under specific circumstances.

Nutritional therapies

Avoiding hyperalimentation with large amounts of exogenous protein is appropriate for all hyperammonaemic patients [24]. Situations where a urea cycle disorder is suspected warrant the immediate cessation of *all* exogenous protein for 48 h. Dietary protein should subsequently be slowly reintroduced to avoid endogenous protein catabolism. Protein restriction may have complex long-term consequences for patients, however, the short-term impact appears to be minimal [25▪,26▪]. Intravenous nutritional support with a 20% fat emulsion and a 10–30% dextrose infusion to meet energy requirements and suppress catabolism can be followed by a transition to a normal diet during recovery. Intravenous insulin must be commenced if hyperglycaemia develops while dextrose is administered, and it is essential that the dextrose infusion is not interrupted or ceased during this critical period [27].

Specific nutritional supplements may be used as a long-term management strategy for patients with UCD and might also have a role in treating an acute hyperammonaemia crisis resulting from UCD. L-Arginine stimulates an alternative pathway for waste nitrogen excretion and limits proteolysis [21▪]. Citrulline administration may also be considered to promote an alternative pathway of

Table 2. Quadruple-H therapy

Intervention	Target	Method	Mechanism of benefit
Hyperventilation	The lower of $PaCO_2 = 35$ mmHg, or that achieved by patient prior to intubation	Adjust mechanical ventilation to achieve necessary minute ventilation	Reduction of cerebral hyperaemia and ICP
Haemo(dia)filtration	Blood ammonia <60 μmol/l and even daily fluid balance	High-exchange continuous hemofiltration incorporating dialysis if required	Ammonia clearance Prevention of fever Metabolic, fluid and electrolyte control
Hypernatraemia	Serum sodium 148–152 mmol/l	Continuous infusion of concentrated saline via CVC	Increase serum tonicity causing cerebral dehydration Possible improvements in microcirculatory dynamics Anti-inflammatory effects Expansion of intravascular volume without significant overall positive fluid balance
Hypothermia	Core temperature of 35°C	Usually via CRRT circuit	Reduced ammonia production Reduced ammonia uptake in the CNS Reduced CBF Reduced CMR Reduced neuroexcitation Anti-inflammatory effects

CBF, cerebral blood flow; CMR, cerebral metabolic rate; CRRT, continuous renal replacement therapy; CVC, central venous catheter; ICP, intracranial pressure.

metabolism [21▪,27]. L-Carnitine crosses the blood–brain barrier and restores impaired cellular function by promoting several beneficial metabolic pathways, including glutamate dehydrogenase. This leads to both a reduction in ammonia concentration and associated cytotoxicity [21▪,27]. *N*-carbamoyl-l-glutamic acid is another agent demonstrated to increase ureagenesis by activating the urea cycle [21▪]. It has been approved for the acute and long-term management of *N*-acetyl glutamate and other inborn errors of metabolism as well as drug-induced hyperammonaemia, however, it is extremely expensive and use should be in accordance with local guidelines for potentially life-saving high-cost therapies.

Scavenging agents

Ammonia scavenging agents promote ammonia excretion of nitrogenous waste via alternative pathways through the urinary excretion of hippurate and phenylacetylglutamine. Sodium phenylacetate and sodium benzoate have both been utilized for the long-term management of urea cycle disorders associated with hyperammonaemia. The role of scavenger therapy in the management of a UCD-associated severe hyperammonaemia remains unclear however and these therapies may lead to potentially dangerous acidosis and other serious complications. Animal studies indicate that energy starvation triggers hyperammonemia through enhanced glutaminolysis while dimethyl α-ketoglutarate reduces ammonia accumulation via pleiotropic mechanisms both *in vitro* and *in vivo*. Thus, cell-permeable forms of α-ketoglutarate may be feasible candidates for a novel hyperammonemia treatment [28]. Expert guidance from clinicians with experience in managing complex metabolic disorders is essential prior to initiating therapy. Suggested doses of nutritional and scavenging therapies are outlined in Table 3. The administration of lactulose is an established therapy for hepatic encephalopathy in the setting of decompensated cirrhosis, however, there is less evidence for its use in acute liver failure and nonhepatic hyperammonemia.

Blood purification therapies

Ammonia is a small water-soluble molecule with similar properties to urea in terms of clearance utilizing renal replacement therapy [29]. Although diffusive therapies may have theoretical advantages, no specific modality has demonstrated superiority. Peritoneal dialysis and exchange transfusion have long been recognized as inferior treatment strategies [30▪▪] and the role of more complex blood purification modalities remains unclear [31,32,33▪]. Conventional haemodialysis can rapidly reduce ammonia concentrations, however continuous modalities may be preferred in the critical care setting because this approach is less likely to result in rebound hyperammonaemia, exacerbation of cerebral oedema and potential haemodynamic instability [34]. Continuous modalities of renal replacement therapy also offer the benefits of preventing fever, optimized management of electrolyte and acid–base status as well as the avoidance of dangerous fluid accumulation that may exacerbate cerebral oedema [35]. In situations where treatment commences with conventional dialysis, it is important to follow on with continuous renal replacement therapy (CRRT) in order to maintain biochemical control. Continuous veno-venous haemodialysis is the approach of choice for children under 3 months of age [30▪▪], while modality and dose may be less crucial considerations in adults, where the total duration of uninterrupted therapy appear to be more important [36▪]. Avoiding delays in the initiation of therapy is important as the onset of permanent neurological injury can occur suddenly in vulnerable patients. Reliable vascular access that permits high blood flow is useful to minimize clotting and prolong filter lifer; a key priority in order to maintain continuity of treatment.

Table 3. Nutritional supplements and scavenging agents for hyperammonemia secondary to urea cycle disorders

Medication for acute primary hyperammonaemia		
Substance	**Acute action**	**Mechanism**
Sodium benzoate	250 mg/kg as bolus in 90–120 min, then continuous infusion 250–500 mg/kg/day	Conjugation with glycine and excretion as nontoxic hippuric acid in urine
Sodium phenylbutyrate/ sodiumphenyl acetate	250 mg/kg as bolus in 90–120 min, then continuous infusion 250–500 mg/kg/day	Conjugation with glutamine and excretion as nontoxic phenylacetylglutamine in urine
L-Arginine hydrochloride	250 mg/kg (1.2 mmol/kg) as bolus in 90–120 min, then continuous infusion 250 mg/kg/day	To improve the residual function of the urea cycle and avoid arginine deficiency
N-Carbamyl-glutamate	100 mg/kg as oral bolus (or via NG tube), then 25–62.5 mg/kg every 6 h	Activation of CPS1

The correlation between plasma ammonia concentration and the severity of encephalopathy and cerebral oedema is somewhat variable, levels of more than 100 μmol/l are highly predictive of encephalopathy in hepatic hyperammonaemia, while ammonia concentrations of more than 150 μmol/l in adults are associated with intracranial hypertension that may be complicated by neurological injury and death from brainstem herniation [1]. CRRT can successfully treat hyperammonemia-associated acute liver failure [37▪] and prevent both cerebral oedema and death in patients with urea cycle disorders [38].

Role of liver transplantation

Liver transplantation has been shown to improve survival outcomes for patients with nonparacetamol-associated acute liver failure and is currently the only known cure for patients with UCDs [39]. The decision to proceed with liver transplantation is complex and requires the involvement of experienced clinicians to guide patient and family decision-making [40]. Considerations include the likelihood of survival and quality of life without transplantation compared with the overall immediate risks as well as the long-term burden and complications of transplantation.

CONCLUSION

Hyperammonaemia must be considered in any ICU patient who is unconscious without a clear cause. Untreated acute hyperammonaemia can lead to fatal cerebral oedema. While hepatic failure is the commonest aetiology, drugs, infection and UCDs are important causes that may be overlooked. Treatment for these latter causes includes urgent initiation of neuroprotective measures and efforts to reduce plasma ammonia concentrations through modification of nutritional protein intake, blood purification with renal replacement therapy aggressive treatment of underlying infection and, under appropriate circumstances, specific nutritional additives in the setting of urea cycle disorders.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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