Journal of Critical Care 70 (2022) 154042

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Undifferentiated non-hepatic hyperammonemia in the ICU: Diagnosis and management

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ARTICLE INFO

Keywords:
Ammonia
Non-hepatic hyperammonemia
Critical illness
Metabolism
Cerebral edema
Status epilepticus
Urea cycle defect

ABSTRACT

Hyperammonemia occurs frequently in the critically ill but is largely confined to patients with hepatic dysfunction or failure. Non-hepatic hyperammonemia (NHHA) is far less common but can be a harbinger of life-threatening diagnoses that warrant timely identification and, sometimes, empiric therapy to prevent seizures, status epilepticus, cerebral edema, coma and death; in children, permanent cognitive impairment can result. Subsets of patients are at particular risk for developing NHHA, including the organ transplant recipient. Unique etiologies include rare infections, such as with *Ureaplasma* species, and unmasked inborn errors of metabolism, like urea cycle disorders, must be considered in the critically ill. Early recognition and empiric therapy, including directed therapies towards these rare etiologies, is crucial to prevent catastrophic demise.

We review the etiologies of NHHA and highlight the first presentation of it associated with a concurrent *Ureaplasma urealyticum* and *Mycoplasma hominis* infection in a previously healthy individual with polytrauma. Based on this clinical review, a diagnostic and treatment algorithm to identify and manage NHHA is proposed.

1. Introduction

Hyperammonemia is a unique cause of altered mental status and encephalopathy in the critically ill patient. When severe, it can cause cerebral edema with intracranial hypertension, seizures, coma and death. Hyperammonemia in the critically ill occurs frequently [1] and is largely related to liver disease, with non-hepatic etiologies accounting for ≤5% of cases [2,3].

Hyperammonemia develops from a diverse set of pathologies, grouped broadly into diseases where the production of ammonia is escalated, and those in which clearance is decreased. Production can be increased due to etiologies localized to the intestine, muscles or due to certain infections. Clearance of ammonia is largely hepatic via the urea cycle with the production of urea (Fig. 1). In the patient without hepatic dysfunction, ammonia clearance is impaired in an assortment of inborn errors of metabolism and metabolic disorders, most notably with the urea cycle [4]. Anatomic bypass of the liver with any porto-systemic shunt will also decrease clearance of ammonia. More complex and multifactorial mechanisms of hyperammonemia also exist.

Non-hepatic hyperammonemia (NHHA) is likely under-recognized and some subtypes are associated with significant morbidity and mortality [1]. Timely identification of the underlying etiology combined with expedited therapy may be lifesaving [5,6]. A basic understanding of ammonia production and metabolism provides a foundation for the evaluation and management of hyperammonemia (Fig. 2).

2. Ammonia homeostasis

2.1. Ammonia production

Ammonia is produced via the metabolism of nitrogen-containing compounds, largely in the intestine, and cleared via the formation and subsequent excretion of urea. In the intestine, enteral protein is degraded and metabolized by urease-producing bacteria and microbial proteolysis, producing glutamine and ammonia, which are absorbed via the portal circulation. Ammonia is also produced in the intestine after uptake of glutamine from the systemic circulation by glutamine deamination by glutaminase, which produces glutamate and ammonia [7-10].

The kidney and muscle contribute to ammonia production to a lesser extent. Skeletal muscle typically serves as a buffer for hyperammonemia, where excess ammonia can be stored as glutamate at a reasonably high capacity [7]. At baseline, muscle protein metabolism creates ammonia, which can increase in severe catabolic states. Intense exercise or tonic-

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https://doi.org/10.1016/j.jcrc.2022.154042
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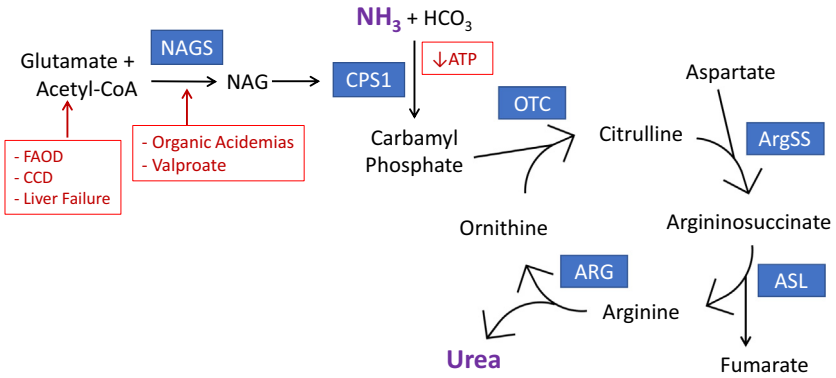

Fig. 1. The urea cycle. defects in necessary enzymatic steps in the urea cycle (blue boxes), or in necessary transport channels between the three enzymatic reactions occurring in the mitochondria (CPS1, OTC & NAGS) and the three in the cytosol (ArgSS, ASL & ARG) result in hyperammonemia. Toxic molecule accumulation in these and other inborn errors of metabolism further impair the urea cycle, frequently by impairing NAG synthesis, necessary for activation of CPS1, or by limiting urea cycle substrates. Red boxes delineate the location of inhibition related to the noted disorder. Patterns in elevation or deficiency of citrulline, arginine, argininosuccinate, ornithine, lysine, aspartate and other pathological urine orotic and serum organic acids, or acylcarnitines, are then used to determine the underlying etiology of hyperammonemia. In OTC deficiency, for example, the citrulline and arginine are low, whereas the urine orotic acids are high [9]. *CCD, carnitine cycle defect; OTC, ornithine transcarbamylase; NAG/NAGS, N-acetylglutamate synthase; CPS1, carbamoylphosphate synthetase 1; OTC, ornithine transcarbamylase; ARG, arginase 1; ArgSS, argininosuccinate synthetase; ASL, argininosuccinate lyase; FAOD, fatty acid oxidation defect.*

clonic seizure activity, on the other hand, can create a substantial acute load of ammonia via intense muscle contraction with deamination of adenosine monophosphate [7,9-16]. In the kidney, glutamine is catabolized to ammonium (NH_4^+) and bicarbonate in the proximal tubule. Ammonium is then reabsorbed by the ascending limb of the loop of Henle, concentrating it in the renal medulla. At the collecting duct, NH_4^+ is secreted in order to facilitate acid secretion. If not secreted in the urine to rid acid, ammonia is released into the systemic circulation [17]. Renal production of ammonia is dependent on renal acid-base and potassium status: acidosis yields a net excretion of ammonia (to rid protons), hyperkalemia inhibits reabsorption, and alkalosis yields net reabsorption [7,11,17-21]. Renal ammoniagenesis has additional modulators including growth hormone, angiotensin II and metabolic intermediaries [21].

2.2. Ammonia clearance

Periportal hepatocytes receive systemic and portal blood flow and clear >90% of ammonia through urea formation via the urea cycle (Fig. 1). Urea is subsequently excreted by the kidneys. This system is efficient, adaptive to protein intake or increased proteolysis [9], and has remarkable reserve, where in general, even large liver resections infrequently impact systemic ammonia levels [7,18].

When this system is overwhelmed or dysfunctional, other pathways exist for ammonia clearance. In addition to previously discussed renal secretion of ammonia related to acid-base status, systemic hyperammonemia results in increased renal ammonia uptake from the circulation, enabling subsequent urinary secretion [7,22]. Skeletal muscles can also increase uptake and storage of ammonia as glutamine

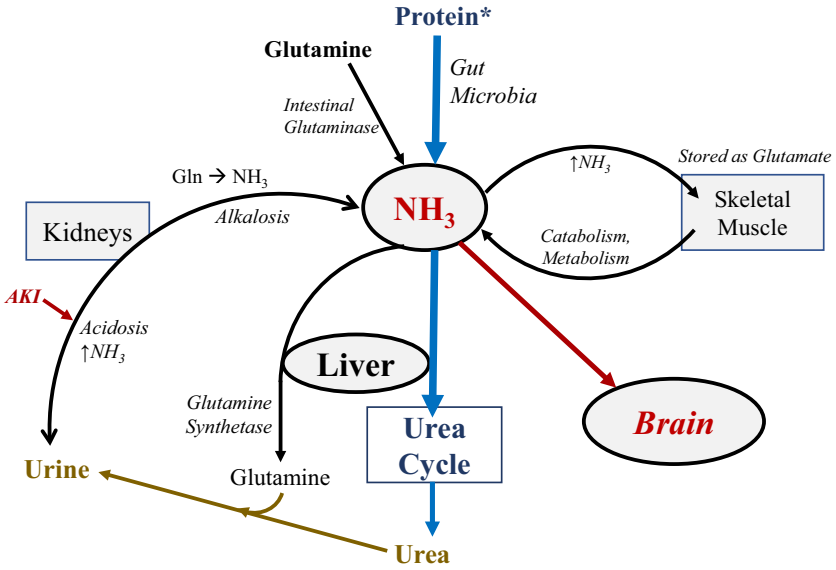

Fig. 2. Ammonia Production and Clearance. Ammonia is largely produced via protein breakdown by intestinal organisms. Glutaminase in intestinal epithelium also converts circulating glutamine to ammonia. The kidneys also convert glutamine to ammonia, and in alkalotic states a net reabsorption of ammonia occurs at the kidney. Clearance of ammonia is largely (>90%) localized to the urea cycle in the liver. In addition, perivenous hepatocytes synthesize glutamine from ammonia, which is renally cleared, and the kidney secretes ammonia directly in states of metabolic acidosis as a means to rid protons. Finally, the brain also metabolizes ammonia to glutamine, but this comes at the cost of neurotoxicity. Skeletal muscle serves as a storage reservoir for ammonia, where it is stored as glutamate. Metabolism of protein and deamination of adenosine monophosphate during intense contractions (e.g. tonic-clonic seizures) can result in hyperammonemia. *AKI, acute kidney injury; NH_3, Ammonia.*

in response to significantly elevated levels [7,9,23]. This is decreased in muscle wasting and significant catabolism [7,8,24]. Glutamine synthetase in the perivenous hepatocytes is an additional low-capacity system for nitrogen detoxification, via the production of glutamine which can be excreted in the urine or used as an energy source [7-9,25]. Finally, the brain is also able to metabolize excess ammonia to glutamine, but this can result in neurotoxicity [9-11,26,27].

3. Neurotoxicity of ammonia

Ammonia is most damaging to the brain, where astrocytes regulate ammonia concentrations by converting ammonia to glutamine via glutamine synthetase (Fig. 3). This can result in progressive elevations of glutamine [28]. Astrocytes deliver glutamine and energy to neurons in the form of ATP. Neurons deaminate glutamine to glutamate, which is then used as a neurotransmitter that activates NMDA receptors. After its action, residual glutamate is reabsorbed by astrocytes and recycled back to glutamine, for re-delivery to neurons [11,28].

When hyperammonemia is severe, astrocytic ammonia detoxification yields osmotic stress [29]. Resultant astrocyte swelling can progress to cerebral edema and brain herniation [9,10,26,27]. Cellular edema causes a release of inflammatory cytokines which induce further glutamine deamination and glutamate production by neurons, fostering increased activation of NMDA receptors [10,11,28]. This causes alterations in metabolism and cellular membrane potentials and results in neuronal mitochondrial dysfunction, reactive oxygen species production and oxidative stress [10,28,30]. Mitochondrial dysfunction and loss also results from ammonia accumulation in the astrocyte [10], while glutamine elevations contribute to organelle dysfunction and injury [10,28,30]. Finally, phosphorylation of protein kinase C is decreased, over-activating the sodium-potassium ATPase pump, changing the cellular membrane potential and further depleting ATP [31]. Energy production is also compromised at the level of the tricarboxylic acid cycle, where ammonia depletes substrates like alpha-ketoglutarate and inhibits enzymes including alpha-ketoglutarate dehydrogenase, isocitrate and pyruvate dehydrogenase [10]. Ammonia additionally inhibits pyruvate oxidation and stimulates glycolysis, elevating brain lactate [10].

Energy failure, cellular edema, oxidative stress and inflammatory cytokine production cause astrocyte apoptosis, which amplifies these processes by decreasing glutamate uptake and energy delivery to the neurons. Other cell types are also injured and contribute to inflammatory activation and alterations in the blood brain barrier [10,32-35]. The combination of hyperactivation and neuronal irritability from NMDA activity, cerebral edema and oxidative stress, and energy production dysfunction causes an energy mismatch that results in rapid cellular injury [10,11,25,36-38].

4. Acute versus chronic hyperammonemia

Patients with chronic liver disease frequently suffer from mild chronic hyperammonemia. These patients exhibit alterations that decrease hyperammonemic neurotoxicity. First, chronic elevations in glutamate lead to a downregulation of glutamate receptors, which impairs signal transduction for NMDA receptors [31]. While this has important consequences towards hepatic encephalopathy and cognitive dysfunction, it may decrease injury from acute hyperammonemia [31]. Second, chronically elevated glutamine in astrocytes impairs GABA clearance from the nerve terminal and subsequent astrocytic re-synthesis to glutamine. As a result, GABAergic tone is increased [10,30]. Other factors, including altered glutamine handling, may also play a role [11].

5. Etiologies of nonhepatic hyperammonemia

The etiologies of NHHA can be broadly grouped into escalated production, or impaired clearance (Table 1). In the patient without hepatic disease, etiologies of NHHA are diverse. Some are associated with high mortality [2-4,6,7]. Clinical outcomes depend on timely identification and therapy initiation prior to the development of irreversible injury. Meanwhile, ammonia clearance – even with typically-utilized renal replacement therapy – is slow.

5.1. Increased production

Production of ammonia is increased in highly catabolic patients. Muscle turnover is increased in states of sarcopenia, and hyperammonemia

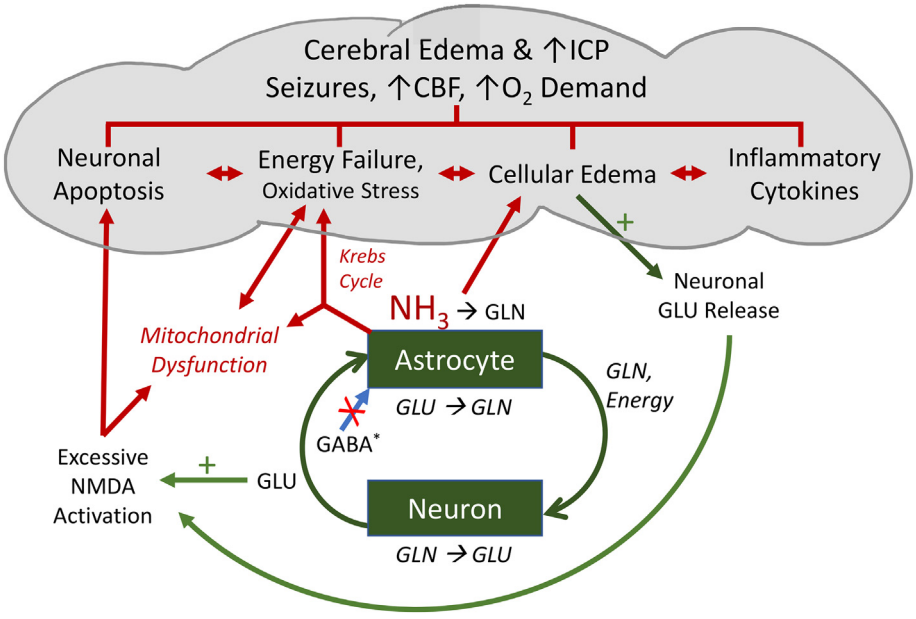

Fig. 3. The Neurotoxicity of Hyperammonemia. Multiple overlapping and synergistic pathways of neuronal injury occur in patients with hyperammonemia; the mechanisms are still being elucidated. In short, excess ammonia is metabolized into glutamine; the reaction yields osmotic strain on the astrocytes, causing edema, inflammation and increased neuronal glutamate release. *GABA, γ-aminobutyric acid; GLN, glutamine; GLU, glutamate; NMDA, N-methyl-D-aspartate. * Chronically elevated glutamine in astrocytes impairs GABA clearance from the nerve terminal and subsequent astrocyte re-synthesis to glutamine. As a result, GABAergic tone is increased* [10,30].

Table 1
Etiologies of Nonhepatic Hyperammonemia.

Increased Production of Ammonia		
Nutritional and Enteral	Protein Catabolism due to burns, trauma or glucocorticoid use	Protein catabolism causes increased release of amino acids and ammonia. Catabolism also decreases the ability of skeletal muscle to buffer ammonia elevations [7,9,11].
	Increased ammonia absorption from the intestines	This can be due to enteral microbial ammonia production due to bacterial overgrowth, or GI bleeding [3,41].
	High protein intake or Hyperalimentation	Typically related to total parenteral nutrition or *N*-acetylcysteine use, especially in setting of malnutrition and/or nutritional deficiencies.
Infection-Mediated	Infections with urease-producing bacteria, most frequently of the urinary tract.	Causal organisms can include *Ureaplasma, Proteus mirabilis, Morganelli morganii, Klebsiella, Pseudomonas,* diphtheroids, *Escherichia coli*, *herpes simplex* or *Providencia rettgeri.* [26]
	Mycoplasma hominis	This organism depletes arginine, a necessary urea cycle cofactor [7].
Oncologic	Multiple myeloma	Due to plasma cell amino acid metabolism [3,26,42]
Muscular	Generalized tonic-clonic seizures or high-intensity exercise	Intense muscle contractions result in hyperammonemia due to adenosine monophosphate deamination [7,9-16]. This is typically short-lived with cessation of activity and normal liver function; hyperammonemia due to seizures should clear in 3–8 h [15].
Drug-Induced	Chemotherapeutics: 5-Fluorouracil, Cytarabine & L-Asparaginase	May result in increased production of ammonia [26].
Decreased Clearance of Ammonia		
Metabolic Disorders	Primary hyperammonemia due to Urea Cycle Disorders	These include OTC, NAGS, CPS1, ArgSS, ASL and ARG deficiencies, HHH syndrome and type-2 citrullinemia. Complete deficiencies in urea-cycle enzymes are typically detected by newborn screening. X-linked or partial urea cycle defects can be triggered by metabolic stressors, such as sepsis or critical illness [4,26,55,56].
	Disorders that cause urea cycle substrate deficiency (secondary hyperammonemia) [9]	Includes disorders in the carnitine cycle or pyruvate dehydrogenase complex, fatty acid β-oxidation, pyruvate carboxylase deficiency, pyrroline-5-carboxylate synthetase deficiency, HHH syndrome, lysinuric protein intolerance, hyperinsulinemia-hyperammonemia syndrome, and liver failure [9].
	Disorders that inhibit the urea cycle (secondary hyperammonemia) [9]	Includes ATP-deficiency (results in CPS1 deficiency); Valproate metabolism (see below); Propionic or methylmalonic acidemia, or 3-hydroxy-3-methylglutaryl-CoA-lyase deficiency.
Drug-Induced	*Antiepileptics*: Valproate, Carbamazepine, Topirimate & Lamotrigine	A metabolite of valproate inhibits carbamoyl phosphate synthetase. Carnitine deficiency is also caused by valproate and results in urea cycle substrate deficiency [59,60].
	Anesthetics: Halothane & Enflurane	
	Analgesics: Gabapentin & Salicylates	
	Others: Tacrolimus, Cyclosporine, Acetazolamide, Gabapentin, Haloperidol, Primidone, Ribavirin & Methamphetamine	Tacrolimus and cyclosporine may alter expression of genes responsible for urea clearance (urea cycle or glutamine synthetase) [7]. Other agents generally decrease the clearance / elimination of ammonia [26].
Renal	Acute or chronic kidney dysfunction	Renal ammonia secretion is impacted by acid-base status; acidosis and hyperkalemia promote ammonia secretion; alkalosis increases reabsorption [7,8,62]. Decreased urine output can decrease ammonia clearance.
Anatomic	Porto-systemic shunting	Any intra- or extrahepatic shunt decreases clearance of ammonia.
	Urinary Diversion, including ureterosigmoidostomy or ileal conduit	Urine, with ammonia and urea, is secreted directly into the intestine, providing urea to bacteria and increasing ammonia absorption.
Multifactorial Etiologies		
Post-Surgical	Organ Transplantation, most commonly after lung transplantation	Multifactorial etiology including catabolism-induced relative urea cycle deficiency, drug-induced progression of sarcopenia, reduced muscle buffering of hyperammonia and, commonly, infections (as above) [7].
	Bariatric surgery, including gastric bypass via roux-en-Y or blind-loop intestinal bypass.	Multifactorial etiology including systemic catabolism & hyperinsulinemia alongside of down-regulation of hepatic urea cycle enzymes & nutritional deficiencies (e.g. carnitine) that cause a functional OTC deficiency [63].

OTC, ornithine transcarbamylase; NAGS, *N*-acetylglutamate synthase; CPS1, carbamoylphosphate synthetase 1; ArgSS, argininosuccinate synthetase; ASL, argininosuccinate lyase; ARG, arginase 1; HHH, hyperornithinemia-hyperammonemia-homocitrullinuria.

related to muscle catabolism is amplified by decreased protein and glutamine synthesis, which limits muscle storage of ammonia as glutamine, an important buffer for hyperammonemia [7,11]. NHHA has been associated with total parenteral nutrition (TPN)-dependence, which combines catabolism and malnutrition with elevated protein loads [3,7]. In addition to catabolism, generalized tonic-clonic seizure activity or even intense exercise can cause hyperammonemia via deamination of adenosine monophosphate (AMP) and branched chain amino acids in muscle [7,9-16], though other mechanisms may also contribute [39]. Hyperammonemia occurs in up to 67% of patients presenting to the emergency department with seizures, and can be severe (e.g. 537 μmol/L) [15,40]. This usually clears within 3–8 h via hepatic clearance [15].

Though exceedingly rare outside of severe cirrhosis, ammonia production can be increased with hyperalimentation and if a bacterial overgrowth pattern results in increased urea production or proteolysis in the gut. Similarly, upper- or lower-gastrointestinal bleeding can "deliver" more protein to enteric bacteria [3]. Gastrointestinal bleeding may also escalate systemic release of ammonia into the circulation due to elevations in circulating amino acids, glutamine and alanine, though this has only been studied in cirrhosis [41]. Patients with multiple myeloma with a high tumor burden may also suffer from hyperammonemia, due to high levels of plasma cell metabolism of amino acids [3,26,42].

Finally, infections with urease-producing bacteria like *Ureaplasma*, *Escherichia coli* and *Proteus mirabilis* can also induce hyperammonemia. These organisms adhere to the mucosal epithelium of the urogenital tract and can cause bacteremia, endocarditis, central nervous system, joint and wound infections, wounds and pneumonia [43]. These organisms hydrolyze urea into ammonia and promote further host ureagenesis, causing a dangerous up-cycling of ammonia levels [44]. In the urine, hydrolysis of urea to NH_4^+, elevates urinary pH, decreasing ammonia secretion and increasing systemic absorption of ammonia [45]. The incidence of hyperammonemia due to these infections is not known, due to infrequent laboratory assessment for hyperammonemia and struggles in bacterial recognition, discussed

below. Nonetheless, non-urinary infection with *Ureaplasma species* and *Mycoplasma hominis* has been increasingly recognized after lung transplantation, in 1–4.1% of patients [6,8,44]. Uniquely, *Mycoplasma* is not a urease producing organism but does use arginine, a necessary urea cycle cofactor, to generate energy, thus creating a urea cycle deficiency [46]. *Mycoplasma* has also been noted to cause hyperammonemia after skin transplantation [47], and can co-infect along with *Ureaplasma* [7,46]. *Ureaplasma* has also been recognized as the cause of NHHA in one adult and two pediatric patients on chemotherapy for leukemia [46,48,49], one patient after renal transplantation [46], one patient after heart transplant [50] and one patient after stem cell transplant [51]. Testing for these microbes requires dedicated assessments with specific polymerase chain reaction (PCR) assays as they frequently go unseen on gram stain and do not culture on standard media [52,53]. Dedicated testing of lung donors for these organisms, with initiation of empiric therapy, can reduce NHHA after lung transplant [54].

5.2. Decreased clearance

Clearance of ammonia can be impaired due to defects in urea production. This occurs with inborn errors of metabolism, including fatty acid oxidation defects and defects of the urea cycle. Urea cycle disorders are typically diagnosed in the newborn period via a newborn screen or in the presence of severe hyperammonemia. Defects in the urea cycle are all inherited in an autosomal recessive manner except for ornithine transcarbamylase (OTC) deficiency, the most common urea cycle defect. OTC deficiency is inherited in an X-linked fashion with variable symptomatology in females due to the mosaicism of X-inactivation patterns [4]. Partial deficiencies in the urea cycle may present later in life during windows of catabolic stress, including critical illness, in the postpartum or perioperative period, with gastrointestinal hemorrhage, or malnutrition (particularly in those receiving TPN or patients with hepatic dysfunction) [4,55-58]. These patients may present with non-specific neurologic symptoms like confusion, lethargy, obtundation, ataxia or hyperammonemia-induced hyperventilation [57]. The blood urea nitrogen (BUN) may be low, reflecting impaired ureagenesis [57]. Case series have also described new, adult-onset urea cycle disorders in the critically ill without a specific clinical or drug exposure, genetic risk or genetic anomaly. All of these patients were critically ill, however, and had severe protein malnourishment while several also had low zinc levels [6].

Several drugs inhibit the urea cycle directly or alter urea cycle gene expression and result in a secondary urea cycle disorder (Table 1). Valproate may cause NHHA by depleting carnitine stores and decreasing carnitine transport resulting in inhibition of the urea cycle. In addition, at high drug levels, metabolism of valproate shifts towards an altered pathway that results in increased production of a metabolite that induces a secondary urea cycle defect (Fig. 1) [59,60].

Anatomic aberrancies may result in decreased clearance of ammonia via liver bypass. Both cirrhotic and noncirrhotic, and intra- and extrahepatic shunts exist [26], with some portocaval shunts persisting post-liver transplantation [52]. In addition, persistent neonatal circulation such as a patent ductus venosus, can also bypass the liver [9]. Urinary diversion such as ureterosigmoidostomy anatomically diverts urine and, thus, urea and ammonia are secreted directly into the intestine. This increases ammonia absorption and urea breakdown by enteric bacteria. Typically, this ammonia is returned to the liver and urea cycle via the portal vein [26], however, the venous drainage of the distal colon and rectum can bypass the portal system [61]. Note that, as above, the kidneys are important in urea clearance as well as ammonia production and excretion; acute kidney injury and renal tubular acidosis, therefore, can contribute to hyperammonemia, though this is rare [62].

5.3. Multifactorial etiologies

More complex, multifactorial mechanisms exist. Patients undergoing bariatric surgery including gastric bypass, for example, can have a combination of catabolism, hormonal alterations such as hyperinsulinemia, and change in urea cycle enzymes alongside of nutritional deficiencies, frequently of carnitine, that results in NHHA [63].

NHHA has been reported after solid organ transplantation [5], most frequently after lung transplantation [8,44], but also after liver [52,64,65], bone marrow [46,66], kidney [46,66-68] and islet cell transplantation [69]. This rare condition generally occurs soon after transplantation and carries a high mortality ranging from 40 to 75% [7]. In lung transplantation, several causal factors contribute, including infections with urease-producing bacteria, a stress-induced catabolic state causing a relative urea cycle deficiency [44,70,71], corticosteroid- and calcineurin-induced progression of sarcopenia and resultant reduced ability of skeletal muscle hyperammonia buffering and even alterations in urea cycle function secondary to tacrolimus or cyclosporine use [7,8].

6. Management of the patient with NHHA

6.1. Laboratory assessment

We support broader assessment for hyperammonia in critically ill patients as described in Table 2 [6-9,11,44,56,72-74]. Unfortunately, laboratory assessment of ammonia is notoriously prone to preanalytic error. Ideally, the lab should be drawn from a central vessel, particularly if peripheral perfusion is compromised. Free flowing blood is necessary; capillary samples are only useful to *exclude* hyperammonemia [75]. Hemolysis must be avoided by using a chilled, anticoagulated tube [9]. Ice-water is preferential to ice-alone as directly contacting ice can freeze cells and result in hemolysis. Plasma should be separated quickly [9]. Given these pre-analytic errors, a slightly elevated ammonia is challenging to interpret and rapid re-testing may be necessary. The team and laboratory should all be aware of the importance of the sampling steps.

Once hepatic dysfunction has been ruled out and hyperammonemia confirmed, the diagnostic evaluation to determine the etiology of NHHA should commence. Laboratory assessment should include measurement of plasma amino acids, plasma carnitines (free & total), a plasma acylcarnitine profile, urine orotic acid, organic & amino acids, creatine kinase, plasma zinc levels, and a complete nutritional assessment. Valproic acid levels should be obtained in case of accidental or intentional ingestion. In addition, infectious workup should include assessment for urease-producing organisms via urinalysis, urine culture, blood culture and PCR testing for *Ureaplasma species* and *Mycoplasma hominis* [6,56-58].

6.2. Supportive care

Timely diagnosis and therapy for NHHA is crucial as patients are at risk of refractory status epilepticus, cerebral edema and death [3]. General critical and neurocritical supportive care measures that may be required are outlined in Table 3.

6.3. Ammonia clearance

Endogenous renal ammonia secretion is assisted by avoiding acute kidney injury, correcting hypovolemia, avoiding alkalosis and maintaining urine output. Exogenous clearance of ammonia can be provided by renal replacement therapy or blood purification therapy. In general,

Table 2
Screening for Hyperammonia in the Critically Ill Patient without Hepatic Dysfunction. In these patients, an ammonia level should be strongly considered as part of a complete laboratory assessment.

New-onset moderate-to-severe encephalopathy, without another clear etiology
Unexplained persistent neurologic symptoms including refractory emesis
New-onset seizures without a history of seizure disorder
Altered mental status in the organ transplant recipient or immune-suppressed patient

Table 3
Supportive Critical and Neurocritical Care Measures for the Critically Ill Patient with Undifferentiated Nonhepatic Hyperammonemia (NHHA).

Supportive Care for the Critically Ill Patient with NHHA	
Critical Care	Treat any identified or suspected underlying conditions, including infections. Hemodynamic monitoring & tailored therapy that may include fluids, vasoactives and/or steroids. Intubation and lung-protective mechanical ventilation with targeted carbon dioxide goals. Establish intravenous access and maintain circulating volume and urine output. Monitor blood glucose and electrolyte levels
Neurocritical Care	Maintain appropriate sedation & analgesia goals. Targeted temperature management focused on strict avoidance of fever. Sodium targets should be clearly established. Continuous seizure monitoring (EEG) and, if indicated, antiepileptic medications, excluding valproate [59,60,94,96,109,110]. If cerebral edema develops, the head of the bed should be elevated to 30 degrees and sodium targets escalated with consideration for hypertonic saline and/or mannitol. Arterial carbon dioxide levels should be assessed and goals established; minimally, hypercarbia should be avoided. The neck should not be compressed and large central venous catheters or bilateral lines in the neck may need to be removed. Burst-suppression with barbituates or other agents may be considered. Cerebral perfusion pressure should be maintained; intracranial pressure monitoring may be considered. Although decompressive craniectomy is not typically indicated for intracranial hypertension related to global metabolic-induced cerebral edema, and risks/benefits are not established, a bilateral decompressive craniectomy has been performed with good outcome in this population [111]. Cooling may be considered but has not been assessed in this population. Note that cerebral, versus systemic, ammonia clearance is delayed [58].

intermittent hemodialysis (IHD) may offer the highest initial ammonia clearance rate [76,77]. Crucial to note, however, is that IHD can worsen cerebral edema. In addition, there is high risk of hyperammonemia rebound since IHD clears blood levels while cerebral hyperammonemia persists. Continuous renal replacement therapy (CRRT), on the other hand, while clearing ammonia more slowly, may clear greater total ammonia over a longer duration (e.g. 24 h) and carries fewer risks while enabling closer monitoring of the patient (e.g. temperature & electrolytes) throughout [76]. In acute liver failure, earlier institution of CRRT prevented progression to severe hyperammonemia and was associated with improved outcomes [78]. Similarly, early institution of therapy in severe valproate overdose resulting in hyperammonemia likely improves outcomes [79]. Overall clearance may be improved with higher dialysate flow, blood flow and hemofiltration rates, and duration of therapy [76], ammonia reductions in acute liver failure correlated best with cumulative duration of therapy hours, as opposed to intensity or technique [80,81].

Plasmapheresis is another approach to exogenous ammonia clearance. Limited work has shown utility in hyperammonemia after lung transplantation, both with and without CRRT [82,83], and in acute liver failure [84,85]. Importantly, however, plasmapheresis occurs over a limited time window and exogenous clearance must be continued thereafter [82].

Bowel decontamination with rifaximin, metronidazole or neomycin, or acidification with lactulose may offer benefit in hepatic hyperammonemia [86]. In NHHA, however, the benefit is less clear. Lactulose, for example, acidifies the intestine and can decrease ammonia uptake [9,87], but one retrospective study evaluating its use in NHHA discovered lack of benefit and longer hospital and ICU lengths of stay in the lactulose cohort [88]. It has also not been shown to be beneficial in valproate-induced hyperammonemia [89].

7. Empiric therapy: Infectious etiologies

When the etiology of NHHA is unclear, infection with *Mycoplasma hominis* and/or *Ureaplasma*, and other urease-producing organisms, must be considered. Uniquely, *Ureaplasma* species and *Mycoplasma hominis* are not treated by typical broad-spectrum antibiotic regimens and require "atypical" coverage with doxycycline or other tetracyclines, or the fluoroquinolone levofloxacin [90]. *Ureaplasma* may be susceptible to macrolides [44,54]. Thus, initiation of a tetracycline (e.g. doxycycline), or levofloxacin is indicated [6,8]. Note that empiric therapy should precede diagnostic confirmation, due to typical PCR assay delays [52,53].

8. Empiric therapy: Urea cycle defects

Therapy for a previously known, or newly unmasked, urea cycle defect should also be initiated when the etiology of NHHA is unknown. In the acute phase, catabolism is avoided by delivering a goal energy intake of 110% of estimated energy demands; proteolysis is further avoided with strict avoidance of protein intake. Generally, concentrated dextrose 10% is infused at 1.5-times a maintenance fluid rate, providing approximately 8–10 mg/kg/min of dextrose, with a coincident insulin infusion to further promote anabolism and maintain glycemic control. Intralipid may be utilized for additional caloric intake [9].

A combination of sodium phenylacetate and sodium benzoate (Ammonul®) can increase the excretion of the ammoniagenic amino acids glycine and glutamine [91]. This therapy has potential toxicity including worsening of acidosis and ketosis, lactatemia and hyperventilation, and is contraindicated in patients with hypokalemia or hypernatremia. Additionally, this can result in intramitochondrial CoA depletion and cellular injury in secondary urea cycle defects (e.g., valproate toxicity). Thus, medical genetics involvement in this decision is mandatory [9]. However, for patients in whom a urea cycle defect is known or highly likely, and in centers with expertise in its use, it can be administered as a maintenance infusion with or without a loading dose [58,92].

In addition, *L*-arginine is a urea cycle intermediate that can prime the urea cycle and improve residual function. Other urea cycle intermediates can be used in select deficiencies (e.g. carbamylglutamate, used in *N*-acetylglutamate synthetase (NAGS) deficiency, which is exceedingly rare) [9,58,93]. Importantly, *L*-arginine is a precursor to nitric oxide and can therefore cause hypotension requiring reduced doses [92]. Carnitine supplementation can be helpful to prevent deficiency as a result of the disorder or the therapy, or if valproate administration caused hyperammonemia [94-96].

9. Hyperammonemia severity and injury

Normal levels of ammonia vary based on age, with normal levels being <150 μmol/L in preterm neonates, 50–75 μmol/L in term neonates and evolving to <50–60 μmol/L in adults [10,92,97]. In patients with acute hepatic failure, levels >100 μmol/L are predictive of hepatic encephalopathy [98], with levels >144 μmol/L increasing the risk of intracranial hypertension [99] and with intracranial hypertension developing in 55% of patients with an ammonia level > 200 μmol/L. [98] A case series of 44 patients showed that a mean level of 230 μmol/L was associated with cerebral herniation, noting that this occurred in several patients with ammonia levels <200 μmol/L and even one just below 150 μmol/L. [99]

In contrast, NHHA more often results in a rapid, profound rise in ammonia to levels >200 μmol/L. [6] In pediatric urea cycle disorders, the severity of neurologic injury, including cognitive outcomes and brain anatomic changes, are impacted by the ammonia level, the duration of hyperammonemic coma and the presence of intracranial hypertension [10,100-104]. In children, levels >200 μmol/L can cause irreversible injury and coma >3 days is associated with extremely

poor outcomes [10]. Mortality in urea cycle defects rise as ammonia increases above >200 μmol/L, with a marked worsening at >500 μmol/L and again at >1000 μmol/L. [105] In contrast, for NHHA due to generalized tonic-clonic seizures, ammonia elevations, even >500 μmol/L, do not correspond to neurologic outcome, possibly due to rapid ongoing hepatic metabolism [39,40].

Table 4
Evaluation and Therapy for the Critically Ill Patient with Undifferentiated Nonhepatic Hyperammonemia (NHHA). Recommendations are made for the expansive workup and empiric therapy based on ammonia level. Note that patients with generalized tonic-clonic seizure- or intense muscle activity-induced hyperammonemia develop hyperammonemia that clears rapidly and does not warrant treatment.

Diagnostic and Management Recommendations for Undifferentiated NHHA by Ammonia Level	
***Ammonia Level 60–100* μmol/L**	Trend ammonia levels frequently, at least every 3 h. Frequent assessment can rule out false elevations yet enable timely therapy. Ensure lab is drawn and sent correctly. Check blood gases, blood counts, liver enzymes, coagulation metrics and metabolic panels including creatinine, electrolytes and serial glucose levels. Review potential etiologies of NHHA including a close review of recently administered medications and potential for accidental or intentional ingestions including of valproate. Obtain an adequate history focusing on a known or late-onset inborn error of metabolism, or recent tonic/clonic seizure activity. Infectious workup should include a urinalysis and cultures of the urine, blood and lungs, and urine & serum PCR testing for *Ureaplasma species* and *Mycoplasma hominis*. Empiric antimicrobial therapy should be instituted in the immune suppressed and target urease-producing organisms (e.g. *ureaplasma urealyticum, eschericia coli, proteus mirabilis,* and others) and *mycoplasma hominis*. Typical coverage may include piperacillin & tazobactam, cefepime & metronidazole and a third-generation cephalosporin, with coverage for *ureaplasma* and *mycoplasma* provided by either doxycycline or levofloxacin. Early involvement of genetics is beneficial in guiding workup and therapy. Laboratory assessment for an inborn error of metabolism should include: plasma amino acids, plasma carnitines (free & total), a plasma acylcarnitine profile, urine orotic, organic & amino acids, creatine kinase and plasma zinc levels [6,56-58]. Stop protein intake, including parenteral nutrition. Promote anabolism (administer concentrated dextrose at approximately 8–10 mg/kg/min) with concomitant insulin infusion to maintain glycemic control. Consider intralipid for added calories to meet 110% of needs and further avoid catabolism. Strictly avoid any protein intake [6,73,92,106].
≥*100* μmol/L	Consider empiric initiation of therapies targeting inborn errors of metabolism (e.g. *L*-arginine, levocarnitine and/or sodium phenylacetate & sodium benzoate) with close consultation with a genetics team. Sodium phenylacetate & sodium benzoate have potential toxicity including worsening of acidosis and ketosis, lactatemia and hyperventilation. It is contraindicated with hypokalemia or hypernatremia and can worsen injury in secondary urea cycle defects.
***>150* μmol/L or Severe Symptoms**	Exogenous ammonia clearance is typically deployed for levels >200–250 μmol/L, pediatric patients with levels ≥3-fold normal, for hyperammonemic encephalopathy, coma or seizures, intracranial hypertension, or for rising ammonia in the face of other therapy [55,58,68,72,77,92,106-108]. We, however, support earlier institution of these measures for ammonia levels >150 μmol/L or for any of the other criteria above. If early, rapid clearance is necessary (e.g. impending brain herniation), plasmapheresis may be a safer alternative to IHD and, as above, should be immediately followed by CRRT.

10. Diagnostic and treatment thresholds

No definitive guideline exists for a specific threshold to broaden workup or institute empiric therapy in the critically ill adult with undifferentiated NHHA. Elevations in ammonia (60–100 μmol/L) should be followed closely to rule out false elevations yet enable timely therapy. For immune suppressed patients, particularly organ transplant recipients, empiric antibiotics covering organisms detailed above and infectious testing should be strongly considered for any hyperammonemia. We note the diagnosis of NHHA in an at-risk, but previously immune-competent patient (Appendix 1) and therefore recommend broad application of these antimicrobials in the critically ill with NHHA (limited evidence).

Other etiologies of NHHA should be excluded (Table 1) and, if no alternative diagnosis is likely, laboratory assessment for inborn errors of metabolism should be initiated along with cessation of protein intake and initiation of a dextrose infusion, often paired to insulin (Table 3) [6,73,92,106]. Importantly, with improved hyperammonemia (e.g. <100 μmol/L), protein must be reintroduced by 48-h to prevent catabolism [92,106].

Empiric initiation of therapies targeting inborn errors of metabolism (e.g. *L*-arginine, levocarnitine, sodium phenylacetate & sodium benzoate) should be considered for ammonia >100 μmol/L with close consultation with a genetics team, noting that risks exist. Guidelines vary in initiation recommendations for these therapies: some at levels >100 [106], others at >125 [6,73] or > 150 μmol/L. [92]

Guidance towards exogenous clearance of ammonia focuses on urea cycle disorders, where renal replacement therapy as advised for adults with ammonia levels >200–250 μmol/L, pediatric patients with levels ≥3-fold normal, for hyperammonemic encephalopathy, coma, or seizures, or for rising ammonia in the face of other therapy [55,58,68,72,77,92,106-108]. For undifferentiated NHHA, however, earlier exogenous therapy may be preferential. This is underscored by the slow ammonia clearance of ammonia from CRRT, the risks related to IHD, and the risk of intracranial hypertension and brain herniation with more conservative elevations in ammonia (albeit in liver failure), with little known regarding safe levels for many of the broad categories of NHHA (e.g. infectious). Earlier institution may allow improved clearance and prevention of progression to life-threatening levels [80], with less risk while other evaluative and therapeutic measures are deployed. As above, this has been deemed beneficial in acute liver failure [78] as well as valproate toxicity [79]. We therefore support a more conservative initiation of hemodialysis for levels >150 μmol/L along with other indications listed above (e.g. hyperammonemic coma). If early, rapid clearance is necessary (e.g. impending brain herniation), plasmapheresis may be a safer alternative to IHD and, as above, should be immediately followed by CRRT.

Importantly, the differentiation of hyperammonemia-induced seizure and seizure-induced hyperammonemia is challenging, and for patients presenting with generalized tonic-clonic seizures not thought to be due to hyperammonemia, NHHA treatment should not be initiated. Instead, ammonia should be followed frequently, with expected rapid clearance over 3–8 h. Workup and Treatment for NHHA should commence if hyperammonemia does not quickly decline or if neuroimaging reveals intracranial hypertension without other clear source.

A guide to evaluation and therapy of undifferentiated NHHA is shown in Table 4.

11. Summary

Non-hepatic etiologies of hyperammonemia are uncommon. Screening for hyperammonemia in the absence of hepatic dysfunction should be strongly considered in critically ill patients with new onset moderate-to-severe encephalopathy without another clear etiology, with unexplained neurological symptoms including refractory emesis,

new-onset seizures, and in the immune suppressed patient with unexplained altered mental status.

The treatment of NHHA includes aggressive supportive care and initiating therapies that decrease production and enhance clearance of ammonia. Empiric treatment for two rare diagnoses is often warranted: an unmasked urea cycle defect, and infection with urease-producing organisms such as *Ureaplasma* or *Mycoplasma hominis*.

No consensus exists on diagnostic and treatment thresholds for NHHA. We recommend close follow up of ammonia levels between 60 and 100 μmol/L and diagnostic and treatment pathways initiated once the diagnosis of NHHA is confirmed. For levels >100 μmol/L, therapies directed at inborn errors of metabolism should be considered with consultation with a genetics team. Finally, for levels >150 μmol/L, we support early initiation of exogenous ammonia clearance therapy (e.g. CRRT) while other diagnostic and therapeutic measures are deployed.

Financial disclosures

None.

CRediT authorship contribution statement

Micah T. Long: Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Douglas B. Coursin:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

None.

Appendix 1 Potential Under Recognition: A Case of NHHA in a Previously Immunocompetent Male

It is likely that patients with infection-induced NHHA are unrecognized since ammonia is infrequently measured without suspected or known hepatic disease [6]. With consent obtained from the family to discuss his care, a previously healthy middle-aged man was admitted to the University of Wisconsin Hospital after sustaining severe polytrauma including bladder rupture. He developed acute, severe encephalopathy in the face of a previously normal neurologic examination on post-injury day 10 after having undergone repeated operations to address his multiple orthopedic and abdominal injuries. NHHA was identified after he developed fixed gaze palsy overlying several hours of persistent encephalopathy, with an ammonia of 283 μmol/L. Computerized tomography of the brain revealed signs of intracranial hypertension. Despite attempting to clear ammonia with hemodialysis, empiric therapy for a urea cycle defect and urease-producing organisms, advanced monitoring including continuous electroencephalography (EEG), and supportive care including hypertonic saline, he developed severe intracranial hypertension and then, refractory status epilepticus. Given his poor neurologic prognosis, the family elected to pursue comfort measures. *Ureaplasma urealyticum* and *mycoplasma hominis* infections were identified by PCR which, when combined with critical illness catabolism and TPN use, caused severe NHHA that resulted in the patient's demise.

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