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# Nonhepatic Hyperammonemia With Septic Shock: Case and Review of Literature

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**Abstract**

Elevated ammonia levels lead to cerebral edema, encephalopathy, seizures, coma, and death. Hyperammonemia is primarily associated with liver disease; however, there are rare cases without liver disease. Noncirrhotic hyperammonemia is primarily due to increased production and/or decreased elimination of ammonia. We present a rare case of a 35-year-old female with severe acute noncirrhotic hyperammonemia associated with gram-negative septic shock and a suspected undiagnosed partial urea cycle enzyme deficiency. She had elevated blood and urine amino acid levels speculated to be due to an underlying urea cycle defect, which was unmasked in the setting of septic shock with urea splitting bacteria leading to severely elevated ammonia levels. Ammonia levels were rapidly corrected with hemodialysis, as other conventional treatments failed. We highlight the importance of considering noncirrhotic causes of hyperammonemia in patients with elevated ammonia levels and intact liver function. Prompt treatment should begin with reducing the catabolic state, nitrogen scavenging, replacing urea cycle substrates, decreasing intestinal absorption, and augmented removal of ammonia with renal replacement therapy.

**Keywords**

hyperammonemia, septic shock, pulmonary critical care, urea cycle disorder, encephalopathy, cirrhosis, neurology, nephrology

## Introduction

Hyperammonemia is generally associated with severe liver disease, and 50% to 70% of cirrhotic patients develop encephalopathy.[1] A minority of cases develop without severe liver disease; in these cases of elevated ammonia ($NH_3$) not due to cirrhosis, etiologies such as urea cycle enzyme deficiencies, drugs, infections, ureterosigmoidostomy, increased cellular catabolism, and chemotherapy should be considered.[1] Ammonia is toxic to cells and converted to nontoxic metabolites, such as urea or glutamine. Urea is produced in periportal hepatocytes after uptake from the portal blood and subsequently excreted via the kidneys. If detoxification of ammonia does not occur, it is trapped in perivenous hepatocytes and converted to glutamine by glutamine synthetase.[2,3]

Noncirrhotic hyperammonemia is due to the inability of the liver to meet the metabolic demands during excess ammonia production and/or portal circulation bypass of the toxic metabolites directly into systemic circulation.[1] The exact pathogenesis of hyperammonemic encephalopathy is multifactorial and incompletely understood, but is believed to occur since ammonia can penetrate the blood-brain barrier by passive diffusion or mediated transport leading to neurotransmitter synthesis disruption.[4,5] Ammonia directly affects neuronal electric activity by inhibiting the generation of both excitatory and inhibitory postsynaptic potentials.[4,6] Astrocytes are the only brain cells that can metabolize ammonia due to the presence of glutamine synthetase, which generates glutamine from glutamate and ammonia. Glutamine plays a crucial role in neurotoxicity of ammonia on the brain; astrocytes metabolize glutamine in the mitochondria leading to the production of ammonia and reactive oxygen species (ROS). Under normal physiologic conditions, there are low concentrations of glutamine within the astrocytes; however, when there is elevate systemic ammonia levels, there is increased glutamine hydrolysis and ammonia production within the mitochondria leading to increased ROS. The ROS perpetuates mitochondrial dysfunction and triggers

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inflammatory cascades. Furthermore, glutamine affects the osmoregulatory function of astrocytes; elevated ammonia and glutamine levels causes movement of water into the astrocytes, leading to an osmotic imbalance, swelling, and cerebral edema.[7] Glutamine and ammonia leading to astrocyte swelling and generation of ROS is thought to trigger inflammatory cascades, apoptosis, and metabolic pathways that lead to elevated lactate, cerebral edema, and loss of cerebral auto regulation.[8]

Although hyperammonemia-related encephalopathy is mainly associated with cirrhotic dysfunction in majority of the cases, it is important to consider noncirrhotic causes of elevated ammonia. We present a case of severe acute noncirrhotic hyperammonemia and related encephalopathy associated with gram-negative septic shock in the setting of a prior undiagnosed underlying urea cycle enzyme deficiency.

## Case

A 35-year-old female with past medical history acute lymphocytic leukemia (in remission since 1997), diabetes mellitus, bipolar disorder, recurrent urinary tract infections, and obesity status post gastric bypass surgery, who presented with altered mental status for 1 day. Per mother, there is no significant family history, and she had been bedbound for 3 months, withdrawn, with decreased appetite and poor nutrition. In the emergency department she was afebrile, tachycardic to 150 bpm, tachypneic to 30-40 bpm, and hypotensive to 72/52 mm Hg. On physical examination, she was found to have severe cachexia, mottled bilateral upper extremities, necrotic sacral decubitus ulcer, sluggish bilateral pupils with right-sided downward gaze preference, and roving eye movements. Laboratory was significant for pH 7.564, $PCO_2$ 23 mm Hg, PO2 67 mm Hg, and lactic acid of 5.3 mmol/L on admission, leukocytosis of 19.2 K/UL, neutrophilic predominance, sodium 137 mmol/L, potassium 3.8 mmol/L, blood urea nitrogen (BUN) 10 mg/dL, creatinine 0.6 mg/dL, albumin 1.5 g/dL, total bilirubin 1.4 mg/dL, direct bilirubin 0.6 mg/dL, aspartate transaminase (AST) 26 IU/L, alkaline phosphatase 109 IU/L, alanine transaminase (ALT) 18 IU/L, total protein 3.4 g/dL, ammonia levels were elevated to 261umol/L, negative urine toxicology, and unremarkable noncontract head computed tomography (CT). Urine, stool, blood, and cerebrospinal fluid (CSF) cultures were sent and she was treated for septic shock with empiric broad-spectrum antibiotics, intravenous fluids, vasopressors, and stress-dose hydrocortisone. Subsequently, she was placed on continuous video electroencephalogram (EEG). No seizures were identified, but generalized delta-range background slowing, excess beta activity, and generalized sharply contoured waveforms with triphasic morphology were identified. This pattern is indicative of moderate-to-severe diffuse cerebral dysfunction in the context of toxic-metabolic encephalopathies and/or due to a medication effect. Patient's home medications included Duloxetine XR 30 mg OD, Gabapentin 800 mg BID, Quetiapine XR 800 mg OD, Alprazolam 1 mg OD, Glargine 40 units OD, and Lispro 9 units TID before meals.

Forty-eight hours postadmission, the patient developed acute hypoxemic respiratory failure requiring intubation. Urine cultures and respiratory cultures grew 2 separate varieties of extended-spectrum beta-lactamase (ESBL) *Escherichia coli* (*E coli*), blood cultures were positive for *Morganella morganii (M morganii)*, and stool cultures were positive for *Proteus mirabilis (P mirablis)*. Patient was on high-dose dextrose intravenous solution, lactulose, rifaximin, and L-carnitine; along with continued broad-spectrum antibiotics covering all culture results.

Despite initial therapy, ammonia levels continued to rise. Urine and plasma amino acids were sent as workup for a possible urea cycle deficiency. New seizure activity was suspected when the patient was seen to have rhythmic jerking movements of her head, jaw, and tongue with right downward gaze, which subsided with IV benzodiazepines and levetiracetam. She underwent a second continuous video EEG, which showed the development of near-continuous approximately 0.5 to 1.5 Hz left hemispheric posteriorly predominant blunted lateralized periodic discharges, intermittently occurring as posteriorly maximal generalized periodic discharges more prominent over the left hemisphere with fluctuation in amplitude and sharp contour but no evolution over time. Findings were concerning for focal epilepsy, though there was no electrographic seizures, and evidence of severe diffuse cerebral dysfunction, typically seen in the context of toxic-metabolic encephalopathies and/or due to a medication effect. Brain magnetic resonance imaging (MRI) showed diffuse gyriform restricted diffusion throughout the cerebral hemispheres and insula bilaterally, which is seen typically with elevated ammonia levels (Figure 1). Given elevated ammonia levels of 551 μmol/L refractory to medical therapy, she was placed on continuous veno-venous hemodialysis (CVVHD). Urine and plasma amino acids were abnormal with severely elevated glutamine (plasma level 1926.8 μM 205-756 μM; urine level 1575 nmol/mg Cr 93-686 nmol/mg), glutamic acid (plasma level 147.3 μM 10-131 μM; urine level 89 nmol/mg Cr $<$34 nmol/mg), asparagine (plasma level 171.7 μM 35-74 μM), urinary ornithine (plasma level 140.3 μM 48-195 μM; urine level 33 nmol/mg Cr $<$25 nmol/mg) and normal arginine (plasma level 72.6 μM 15-128 μM) and citrulline (plasma level 37.5 μM 12-55 μM; urine level 3 nmol/mg Cr $<$12 nmol/mg) suggestive for a possible underlying urea cycle enzyme deficiency. Zinc levels were not measured since she received zinc supplementation on admission to the intensive care unit (ICU). Carnitine levels were normal; however, acylcarnitine/carnitine ratio levels were elevated.

The patient was removed from CVVHD after maximal decrease in ammonia level to 55 μmol/L. On day 22, she had

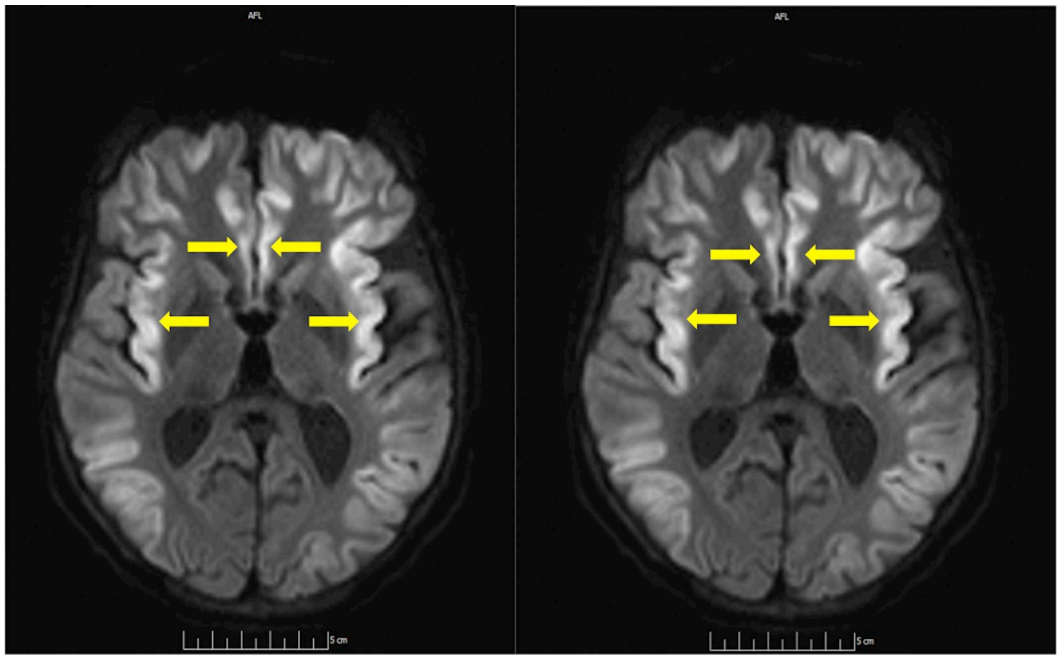

**Figure 1.** Diffusion-weighted imaging (DWI), with extensive restricted diffusion in cortex, including cingulate and insular cortices (yellow arrows) typically seen with elevate ammonia levels.

a tracheostomy placed and was able to track motion with her eyes with minimal responsiveness to painful stimuli.

## Discussion

Hyperammonemia is a metabolic disturbance typically due to intrinsic liver disease with elevated ammonia levels in the blood. Extreme elevations of blood ammonia levels can be life-threatening and cause severe neurologic dysfunction. Treatment should be rapidly instated and ammonia levels should be quickly reduced. Elevated ammonia levels that are not related to intrinsic liver disease may be a result of increased ammonia production or decreased elimination of ammonia.[9]

Increased ammonia production may be related to infections by urease-producing bacteria, hematological-oncological disorders, organ transplant, and increased protein catabolism. We will focus on increased production of ammonia due to infections by urease-producing bacteria, which include *Proteus mirablis*, *Klebsiella* sp., *E coli*, *Morganella morganii*, *Providencia* sp., *Pseudomonas sp*., Anaerobic species, *Staphylococcus* sp., *Helicobacter* sp., and *Mycobacterium* sp.[4,10] These bacteria hydrolyze urea, leading to the increased production of $NH_3$. In uropathogenic strains, the urine becomes alkalinized, thus allowing for increasing concentrations of ammonia and ammonium by up to 50% compared with approximately 5% to 10% in neutral pH.[10] Ammonia is electrically neutral and lipid soluble. Therefore, increased urinary ammonia concentration produces a gradient leading to diffusion of $NH_3$ into urothelial cells. Within the urothelial cells, it is converted to the less permeable ammonium ($NH_4^+$) in the setting of a neutral pH 7.4, preventing diffusion back into the urine, this is known as "diffusion trapping."[11,12] Trapped ammonium enters the systemic circulation via the venous drainage of the bladder escaping detoxification by the liver and contributing to hyperammonia and hyperammonemic encephalopathy.[11-13]

Decreased elimination may be related to ureterosigmoidostomy, portosystemic shunts, and drug-induced and inborn errors of metabolism (eg. urea cycle disorders or mitochondrial cycle disorders).[1,9] We will focus on decreased elimination of ammonia related to urea cycle disorders (UCDs). Figure 2 highlights the role of urea cycle in the excretion of ammonia,[14] deficiencies in any of the enzymes will lead to disruption of urea synthesis, leading to accumulation of ammonia and other metabolites depending on where the pathway is blocked.[15] A portion of the urea cycle takes place in the mitochondria; the conversion of carbamoyl phosphate to citrulline with ornithine transcarbamylase (OTC) and ornithine. Therefore, deficiency of OTC would potentiate hyperammonemia, and any other disturbances within the mitochondria could lead to dysfunction in cellular energy metabolism and ammonium accumulation.[16] In patients with partial deficiency, enzyme activities may vary, and symptoms may occur during times of physiological stress such as infective illness, childbirth,

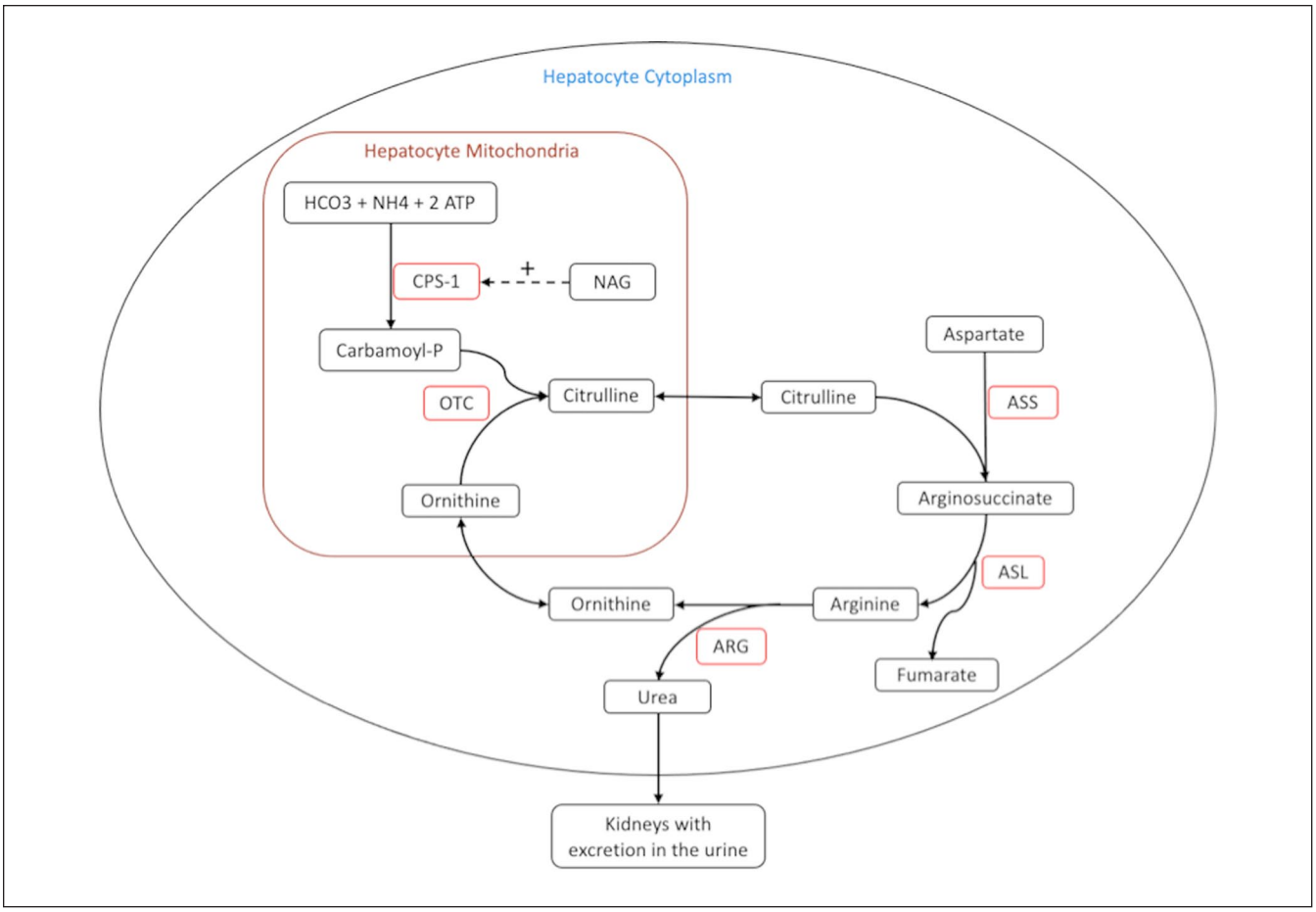


**Figure 2.** The urea cycle and related reactions of ammonia metabolism. Enzymes include CPS-1, OTC, ASS, ASL, and ARG.
Abbreviations: CPS-1, carbamoyl phosphate synthetase-1; OTC, ornithine transcarbamylase; ASS, argininosuccinate synthetase; ASL, argininosuccinate lyase; ARG, arginase.

or postoperatively.[15,17,18] Ornithine transcarbamylase (ODC) deficiency is the most common of the urea cycle disorders, it has an X-linked inheritance pattern and can have extremely varied expression from neonates to adults.[1,15] Males are primarily affected and typically present in the neonatal period. However, there have been case reports in older children and adults including homozygous males and heterozygous females.[19] Another UCD with similar biochemical markers as OTC deficiency is carbamoyl phosphate synthetase-1 (CPS-1) deficiency. It is rare, with an autosomal recessive inheritance pattern and 2 phenotypes: neonates or late form. CPS-1 may lead to lethal hyperammonemia with complete deficiency; however, with partial deficiency or late form presentation, patients may have recurrent bouts of hyperammonemia associated with physiological stresses.[20] OTC is a zinc enzyme, its activity decreases if there is any form zinc deficiency, which occurs in patients with chronic liver disease, with malabsorption disease such as inflammatory bowel disease (IBD) or patients with gastric bypass surgeries like our patient. Zinc deficiency thereby reduces hepatic capacity to metabolize ammonia; in healthy patients, the glutamine-synthesizing system in skeletal muscles compensates for the decrease in ammonia metabolism by the liver and hyperammonemia does not develop.

Clinical features of hyperammonemia vary and include symptoms caused by ammonia toxicity to the brain. They include personality changes, lethargy, vomiting, irritability, confusion, and in severe cases seizures, stupor, coma, and death.[1,4,15] Workup for hyperammonemia includes measuring blood levels of ammonia, with levels >150 µmol/L patients will typically be encephalopathic. In isolated hyperammonemia with no liver dysfunction, acid-base status, serum bicarbonate, sodium, chloride, and urinary ketones should be evaluated. Respiratory alkalosis in the absence of metabolic acidosis may be an indication of urea cycle disorder. As a workup of UCD, both plasma and urine amino acids should be measured.[21] Neuroimaging demonstrates characteristic changes of hyperammonemia encephalopathy, diffusion restriction seen with diffusion weight imaging (DWI) on MRI are predominantly in the cortex—mainly the insular cortex and cingulate gyrus and are diffuse, symmetrical, and

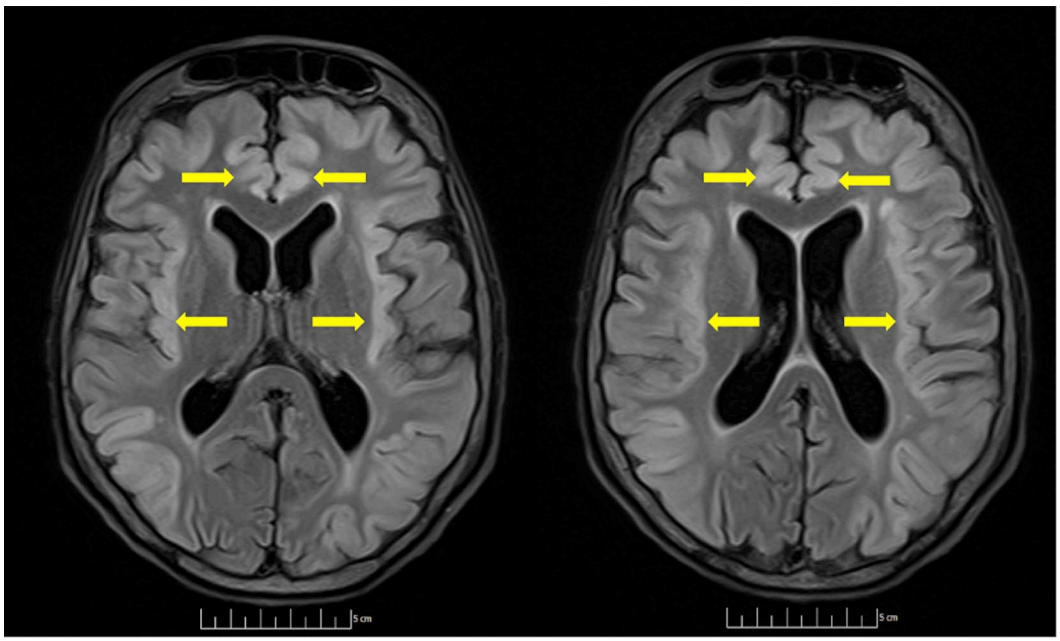

**Figure 3.** T2-Fluid Attenuated Inversion Recovery (FLAIR) images with extensive bilateral hyperintensity in the cortex, including cingulate and insular cortices (yellow arrows) typically seen with elevate ammonia levels.

have corresponding fluid attenuated inversion recovery (FLAIR) hyperintensities (Figures 1 and 3).[22-24] The biochemical abnormalities seen with OTC deficiency and CPS-1 deficiency include hyperammonemia, elevated levels of glutamine, alanine, and asparagine, which serve as storage forms of waste nitrogen, and normal or decreased levels of citrulline. To differentiate between the 2 deficiencies, urine orotic acid is measured and elevated in OTC deficiency.[1,20]

Our patient had culture positive *E coli* in the urine and respiratory cultures, *M morganii* in the blood, and *P mirablis* in the stool. These bacteria are all urease-producing bacteria, leading to diffusion trapping and catastrophic elevation of plasma ammonia levels sufficient to oversaturate hepatic excretory pathways. Her MRI brain findings were characteristic of hyperammonemia. In addition, she was found to have respiratory alkalosis and elevated amino acid levels in the blood and urine: elevations of glutamine, glycine, alanine, and proline suggestive of a urea cycle disorder, with possibly an OTC or CPS-1 deficiency leading to decreased metabolism of ammonia. Concomitantly, our patient may have also had an acquired zinc deficiency from her gastric bypass surgery, which would potentiate impairment of ammonia metabolism. However, our patient was receiving oral zinc supplementation in the intensive care unit, which likely prevented her ammonia levels from rising further.

Treatment was started with antibiotics specific for these infections to help mitigate the burden of ammonia in the body and help restore the initial function of the kidneys and nervous system. Antibiotics would decrease bacterial proliferation and lower urease concentrations, which would subsequently lead to less hydrolysis of urea into ammonia. Further treatment for our patient included lactulose, rifaximin, L-carnitine, along with high-concentration dextrose intravenous fluids, all of which did not lower the ammonia levels sufficiently to nontoxic concentration and she required CVVHD to further facilitate ammonia elimination.

A targeted diagnostic evaluation for urea cycle enzyme deficiency was not done for our patient prior to her passing. However, we can speculate that she had a partial underlying urea cycle deficiency likely, a heterozygous carrier for OTC or carrier of CPS-1 deficiency unmasked by septic shock caused by urea splitting gram-negative bacteria causing such a profound elevation of ammonia.

Early intervention is crucial in severe elevations of ammonia, with the goal to rapidly reduce production of nitrogen waste and blood ammonia levels.[25] Initial therapy should begin with reducing the catabolic state, nitrogen scavenging, replacing urea cycle substrates, and decreasing intestinal absorption; subsequent use of renal replacement therapy is suggested. Restriction of protein intake, high-dose intravenous glucose/fat, and low-dose continuous insulin infusion are needed to reduce the catabolic state. Nitrogen scavenger therapy with sodium phenylacetate and sodium benzoate, sodium phenylbutyrate, or glycerol phenylbutyrate assist by diverting nitrogen from the urea cycle to alternative routes of excretion. Lactulose and rifaximin are conventionally used

to decrease intestinal absorption of ammonia. L-carnitine is frequently used in the setting of hepatic encephalopathy. L-carnitine can augment ureagenesis, along with further decreasing levels through fatty acid oxidation, and stimulation of protein membrane phospholipid synthesis preventing excessive neuronal cell death.[26] Renal replacement therapy (RRT) for the management of hyperammonemia has been used; however, there is a paucity of experience using RRT for hyperammonemia in adults.[25] Consensus recommendations suggest RRT for ammonia concentrations of >150 µmol/L with rapidly deteriorating neurological status, coma, or cerebral edema.[27] A recent review article published in the *Annals of Intensive Care* demonstrated cases of management of hyperammonemia in adulthood and found that RRT should be used for ammonia levels >200 µmol/L since RRT is readily available as compared with other modes of treatment which would be only available at a center specialized in metabolic pathologies.[28] Ammonia readily crosses the blood-brain barrier and has direct toxicity to neurotransmission. Furthermore, glutamine synthetase pathways within astrocytes convert ammonia and glutamate to glutamine, which acts as an osmolyte leading to cerebral edema in hyperammonemic conditions. Rectifying the neurological dysfunction by reducing the ammonia levels to nontoxic concentrations (<60-70 µmol/L) would be paramount over abdominal or renal dysfunction since ever increasing ammonia levels poses a big risk for dangerous levels of cerebral edema, which would lead to herniation and death.[25,27,29,30] Both CVVHD and intermittent hemodialysis should be effective in rapidly removing ammonia from the bloodstream given ammonia is like urea in its diffusive clearance.[25,29]

## Conclusion

Hyperammonemia is most often related to liver cirrhosis. However, noncirrhotic hyperammonemia should be included in the differential diagnosis of patients presenting with encephalopathy, intact synthetic liver function, and elevated ammonia levels. Our case highlights that sepsis with urea splitting bacteria can unmask underlying asymptomatic urea cycle disorders and lead to profound hyperammonemic encephalopathy and death. Prompt intervention should be instituted with intent to quickly reduce ammonia levels by reducing the catabolic state, nitrogen scavenging, replacing urea cycle substrates, decreasing intestinal absorption, and removal with RRT.

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### Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

### Informed Consent

Verbal informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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