Pathophysiology and Management of Hyperammonemia in Organ Transplant Patients

Harish Seethapathy and Andrew Z. Fenves

Introduction

Solid-organ transplantation has been increasingly used in the United States for many clinical indications. Neurologic complications are common after transplantation, occurring in one-third of patients. Immunosuppression-related neurotoxicity (involving calcineurin inhibitors and corticosteroids), opportunistic central nervous system infections, seizures, and delirium are some of the causes of neurologic symptoms following solid-organ transplantation. An uncommon often missed complication posttransplantation involves buildup of ammonia levels that can lead to rapid clinical deterioration even when treated. Ammonia levels are not routinely checked due to the myriad of other explanations for encephalopathy in a transplant recipient. A treatment of choice for severe hyperammonemia involves renal replacement therapy (RRT), but there are no guidelines on the mode or parameters of RRT for reducing ammonia levels. Hyperammonemia in a transplant recipient poses specific challenges beyond the actual condition because the treatment (RRT) involves significant hemodynamic fluctuations that may affect the graft. In this review, we describe a patient with posttransplantation hyperammonemia and discuss the pathways of ammonia metabolism, potential factors underlying the development of hyperammonemia posttransplantation, and choice of appropriate therapeutic options in these patients.

Clinical Vignette: A 65-year-old white man with a medical history significant for hypothyroidism and atrial fibrillation underwent bilateral sequential lung transplantation for severe interstitial lung disease. He was receiving tacrolimus, azathioprine, and prednisone for immunosuppression. 28 days posttransplantation, he was admitted with hyponatremia (serum sodium, 116 mEq/L) secondary to syndrome of inappropriate antidiuretic hormone secretion. He was treated with fluid restriction and hypertonic saline solution. He was on treatment with the antidepressant venlafaxine, which was stopped. His serum sodium level normalized over the next few days. On hospital day 5, he experienced an acute episode of shortness of breath, and his mental status was altered. An arterial blood gas while using a high-flow nonrebreather showed pH of 7.52, PO2 of 31 mm Hg, and PCO2 of 67 mm Hg. His mental status deteriorated, and he was intubated and placed on mechanical ventilation. Serum ammonia level was 506 μmol/L. Liver function test results and serum creatinine, electrolyte, and lactate levels were normal. Thyroid-stimulating hormone level was very low (0.03 mIU/L) and he was started on treatment with high-dose levothyroxine. Continuous venovenous hemodiafiltration was initiated for clearance of ammonia. He also received sodium benzoate, sodium phenylacetate, rifaximin, and lactulose. His ammonia levels gradually decreased to 144 μmol/L after 18 hours and to 75 μmol/L after 36 hours on continuous renal replacement therapy (CRRT). Continuous venovenous hemodiafiltration was stopped and his ammonia levels remained stable. His mental status returned to baseline over the course of the next few days and he was extubated.

Hyperammonemia After Transplantation

In the last 3 decades, hyperammonemia has been increasingly recognized as a serious posttransplantation complication. In 1997, Lichtenstein et al described a patient with normal liver function and severe hyperammonemia 4 days after orthotopic lung transplantation. In the 2 decades since then, multiple case reports and case series have been published, with hyperammonemia being recognized as an important complication post–lung transplantation (Table 1). The incidence of hyperammonemia has been reported to be as high as 4% in lung transplant recipients. While extremely rare (<0.1%),
hyperammonemia has been reported after other transplantations, including liver, bone marrow, kidney, and combined heart-lung. There has also been a case of delayed hyperammonemia after an islet cell transplantation.

In liver transplant recipients, hyperammonemia is unusual and has mostly been described in cases in which there is graft failure or residual portosystemic shunting. Hyperammonemia has been described without graft failure in patients who receive a liver from a donor with ornithine transcarbamylase deficiency. Ornithine transcarbamylase deficiency, the most common congenital urea cycle defect, is an X-linked disorder and hence predominantly affects males. Heterozygous enzyme mutations may be undetected in adult females until the liver is donated and exposed to a stressful environment, such as during transplantation. It has also been described in a pediatric liver transplant recipient with disseminated Serratia marcescens infection.

Hyperammonemia typically presents 5 to 14 days after transplantation, although cases have been reported months later. Many patients go unrecognized and present later in the course with very high ammonia levels. Ammonia levels > 1,000 μmol/L have been reported in some patients. The reason why some patients experience more severe hyperammonemia is unknown. About 80% to 90% of patients with hyperammonemia require renal replacement therapy (RRT), typically using frequent and extended sessions of dialysis. Mortality rates of 40% to 75% have been reported in transplant recipients with hyperammonemia.

### Table 1. Retrospective Studies of Hyperammonemia in Posttransplantation Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Incidence</th>
<th>Cause</th>
<th>Median Peak Ammonia Level, μmol/L</th>
<th>Median Time to Diagnosis After Post-Tx, d</th>
<th>Dialytic Treatment</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krutsinger(2017)</td>
<td>Nonliver solid-organ transplants (N = 844)</td>
<td>Overall: 0.7% (n = 6); lung: 3.9% (n = 5)</td>
<td>Idiopathic in all pts</td>
<td>193.5</td>
<td>6</td>
<td>CRRT (3), HD (1), combined (1), none (1)</td>
<td>33%</td>
</tr>
<tr>
<td>Chen(2016)</td>
<td>Lung transplants (N = 807)</td>
<td>0.99% (n = 8)</td>
<td>Idiopathic in all pts</td>
<td>370</td>
<td>9</td>
<td>HD (8)</td>
<td>75%</td>
</tr>
<tr>
<td>Shigemura(2013)</td>
<td>Lung transplants (N = 759)</td>
<td>0.5% (n = 4)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>CRRT (4)</td>
<td>75%</td>
</tr>
<tr>
<td>Lichtenstein(2000)</td>
<td>Lung transplants (N = 145)</td>
<td>4.1% (n = 6)</td>
<td>2 pts: hepatic GS deficiency Others: idiopathic</td>
<td>2,450</td>
<td>14</td>
<td>CRRT (3), none (3)</td>
<td>67%</td>
</tr>
</tbody>
</table>

Abbreviations: CRRT, continuous renal replacement therapy; GS, glutamine synthetase; HD, intermittent hemodialysis. NR, not reported; pt, patient; Tx, transplantation.

### Ammonia Metabolism and Possible Mechanisms of Hyperammonemia

Several organs are involved in the maintenance of ammonia homeostasis. In healthy humans, plasma ammonia levels are maintained within a narrow range (10-50 μmol/L). At physiologic pH, most (98%) of it exists as ammonium ion (NH₄⁺), but diffusion across cell membranes occurs in its gaseous form of ammonia (NH₃). Ammonia is produced in the intestinal tract, detoxified in the liver, and excreted through the kidneys. Skeletal muscle plays an important role in ammonia uptake. The brain, which is the major target of ammonia toxicity, has limited capacity for ammonia detoxification. In this section, we discuss ammonia metabolism and the role of various organ systems in hyperammonemia.

### Role of the Intestinal Tract and Liver

Both the small and large bowel are major ammonia-producing organs. Dietary protein intake produces half the daily production of ammonia through hydrolysis by bacterial urease. The other half is generated in enterocytes from circulating amino acids, chiefly glutamine, which is the most abundant free amino acid in the body. Intestinal ammonia enters the urea cycle in the liver and is converted to urea in a process that involves several key enzymes plus bicarbonate. Changes in acid-base status may affect ammonia detoxification. Most of the hepatic ammonia detoxification occurs through the urea cycle. The

### Box 1. Nonhepatic Causes of Hyperammonemia

- Urea cycle defects
- Drugs
  - Antiepileptics: valproic acid, carbamazepine, topiramate, lamotrigine
  - Chemotherapeutic agents: 5-fluorouracil, asparaginase
  - Anesthetics: enflurane, halothane
  - Salicylates
  - Other: ribavirin, glycine, acetazolamide, haloperidol
- Hematologic malignancies: multiple myeloma, leukemia
- Urease-producing bacteria: *Ureaplasma, Proteus, Klebsiella, Pseudomonas*
- Hyperalimentation
- Roux-en-Y gastric bypass surgery
- Urinary diversion: ureterosigmoidostomy, ileal conduit
- Reye syndrome
remarkable functional hepatic reserve in healthy people explains why even a three-fourths liver resection is often well tolerated and ammonia metabolism is unaffected. Complete deficiencies of urea cycle enzymes usually present at birth with devastating neurologic complications. For unclear reasons, partial deficiencies may not manifest until later in life and are usually associated with episodes of severe physiologic stress, such as pregnancy or severe illness. No formal testing was done in the patient described in the clinical vignette, and it is conceivable that he had a partial enzyme deficiency that manifested when he was exposed to a stressful state such as severe hypothyroidism and acute illness.

**Role of the Kidney**

In the kidney, the proximal tubule is the chief source of ammoniagenesis, with glutamine being the major substrate. The kidneys can be net producers or excretors of ammonia. Metabolic acidosis results in increased ammonia excretion in urine with a net negative ammonia balance, whereas alkalosis does the opposite. The patient in the clinical vignette was alkalemic, with pH of 7.52, which affected ammonia excretion. Ammonia production and excretion are also affected by other factors such as ion transporters, potassium levels, hormones (such as angiotensin II), and urine flow. Potassium depletion can lead to enhanced proximal tubular ammonia production.

In hyperammonemia, the kidneys increase uptake of ammonia from the blood and increase excretion, hence playing a crucial role in keeping ammonia levels at a steady state. Acute kidney injury (AKI) is common in transplant recipients in the immediate postoperative period. Around 60% to 70% of lung transplant recipients, 10% to 15% of heart transplant recipients, and 50% to 70% of bone marrow transplant recipients develop AKI. Delayed graft function affects 20% of transplanted kidneys. Hence, the kidneys play an important role in ammonia detoxification. The acid-base status of a patient may explain why some patients have ammonia extraction versus excretion. Transplant recipients are particularly vulnerable due to the high risk for AKI.

**Role of Skeletal Muscle**

Skeletal muscle can adapt to changes in ammonia level and can take up or release ammonia. Intravenous administration of ammonium salts has been shown to increase muscle uptake in healthy humans. High arterial ammonia concentrations have been shown to increase ammonia uptake in skeletal muscle in patients with hepatic coma. This can increase to such an extent that venous ammonia levels may be normal in such patients. This extraction of ammonia by skeletal muscle is reduced in patients with muscle wasting, suggesting that muscle mass plays an important role in controlling ammonia levels. The extracted ammonia is converted to glutamine through glutamine synthetase (GS). The glutamine released from muscle enters the urea cycle in the liver, contributing to urea formation. Hence, skeletal muscle plays a key role in reducing ammonia toxicity without net nitrogen removal.

Most patients needing a transplant have some degree of sarcopenia. Surgical stress, corticosteroids, calcineurin inhibitors, and mammalian target of rapamycin (mTOR) inhibitors lead to further worsening of sarcopenia in the days to weeks after transplantation before muscle mass begins to pick up with improved activity, nutrition, and organ health. The patient in the clinical vignette had low muscle mass to begin with, a consequence of low exercise tolerance and severe interstitial lung disease for years. He also spent considerable time in the hospital and in rehabilitation (22 days posttransplantation). In transplant recipients, the low muscle ammonia extraction may play a critical role in exacerbating hyperammonemia. This may especially be significant in patients with coexisting AKI.

**Hyperammonemia and the Brain**

Transport of ammonia across the blood-brain barrier depends on arterial pH. Ammonia enters the brain primarily through diffusion. Ammonia crosses more readily than ammonium ion, but a substantial portion of ammonia enters the brain as ammonium ion. Alkalemia, as seen in the patient in the clinical vignette, alters the balance in favor of ammonia and is associated with a higher rate of diffusion of ammonia into the brain. Astrocytes are the seat of GS, the major enzyme involved in ammonia degradation in the brain. The enzyme functions at maximal capacity under normal physiologic conditions and is easily overwhelmed when faced with a high ammonia load. Glutamine is normally transported out of the brain by active transport, and elevation in glutamine levels causes saturation of the transporter, leading to glutamine accumulation. Both glutamine and ammonia lead to deleterious effects on the brain.

Neurotransmitter interference causing astrocyte injury, a glutamine-mediated osmotic effect, disruption of oxidative brain metabolism, and elevated cerebrospinal fluid lactate levels have all been proposed as mechanisms for brain swelling and edema in hyperammonemic states. In patients with hepatic encephalopathy, a systemic inflammatory response with or without infection has been shown to be a prognostic marker for mortality. Inflammation is directly associated with increased cerebral blood flow and hence intracranial pressure and may also play a role in disrupting the blood-brain barrier. This may be important in transplant recipients because there is increased inflammation within the transplant organ at the time of the donor’s brain death, during the ischemic periprocurement, and during implantation in the form of ischemia-reperfusion injury. Lungs, being highly vascular organs, are particularly susceptible to ischemia-reperfusion injury. Bone marrow transplants also elicit a robust inflammatory response. It is not known if these patients have more severe effects of hyperammonemia.

Ammonia metabolism is complex and involves multiple organs, as discussed. There have been several proposed...
mechanisms for the development of hyperammonemia. To date, there is not one mechanism that is accepted as the main driving force for this condition, and it is likely that multiple factors play a role. In addition, when hyperammonemia develops, there are multiple adaptations to this pathophysiologic condition, which when overwhelmed can lead to elevated serum ammonia levels (Fig 1).

**Association of Hyperammonemia With Immunosuppression**

Both cyclosporine- and tacrolimus-based immunosuppressive regimens have been associated with hyperammonemia. Tuchman et al measured hepatic GS activity from autopsy samples in 2 lung transplant recipients with hyperammonemia. They found that both patients had normal activity of carbamoyl phosphate synthetase I and ornithine carbamoyltransferase, major enzymes in the urea cycle. However, GS activity in the liver was markedly reduced in both patients.

Hepatic GS plays a key role in the removal of excess ammonia not metabolized through the urea cycle. Hepatic GS knockout mice were found to develop elevated ammonia levels in the blood. In the case series by Krutsinger et al, hyperammonemia in lung transplant recipients improved when immunosuppression was switched from tacrolimus- to cyclosporine-based regimens. Interestingly, they also noted that ammonia levels increased when tacrolimus was reintroduced. Although there is no clear explanation for these effects, immunosuppressive medications may affect ammonia levels in a few ways. They may change the expression of genes responsible for the activity of GS or other enzymes of the urea cycle. It is not established whether tacrolimus has a differential effect on urea cycle enzymes compared to cyclosporine or other immunosuppression regimens. Immunocompromised patients are more at risk for developing infections such as with *Ureaplasma spp*, which has been associated with the development of hyperammonemia. Measurement of changes in hepatic GS activity in hyperammonemic patients with different immunosuppressive regimens may provide some answers.

**Treatment**

**Nondialytic Management**

Nondialytic therapeutic strategies in hyperammononemia treatment involve decreasing ammonia synthesis,
preventing endogenous catabolic ammonia generation, and using drugs that facilitate alternate pathways of ammonia excretion (Table 2). After the recognition of high ammonia levels, protein intake should be temporarily restricted in these patients to minimize the nitrogen load. Caloric intake should be maintained through adequate intake of lipids and carbohydrate to decrease catabolic stress. Lactulose is a nonabsorbable disaccharide that inhibits the growth of urease-producing bacteria through colonic acidification. The acidic pH favors the formation of ammonium ions, which are not as easily absorbed as ammonia. Lactulose is also a cathartic and thus increases ammonia excretion in the stool. Ammonia production can be decreased by using antibiotics targeting urease-producing organisms in the gut. Rifaximin, a rifampin derivative, is a broad-spectrum antibiotic with minimal bioavailability. It alters the gut microbiome and has been shown to reduce ammonia levels in clinical trials of hepatic encephalopathy. Treatment effect can take days to weeks and hence it is an adjunctive treatment. Lactulose and rifaximin are well tolerated and not associated with major adverse effects in transplant recipients.

Sodium phenylacetate and sodium benzoate are nitrogen scavengers that bind with the amonagenic amino acids glutamine and glycine to form water-soluble products that are easily excreted in urine, thereby reducing total-body ammonia load. Arginine, citrulline, carginic acid, ornithine aspartate, and ornithine phenylacetate are compounds that enable ammonia removal through the urea cycle or provide alternate pathways for excretion of the daily nitrogen load.

Novel approaches for hyperammonemia treatment, which include albumin dialysis, bioartificial liver support systems, and probiotic-induced gut microbiome manipulation, are not well studied and their utility in acute hyperammonemia management is not clear. Induced hypothermia (to 32°C-33°C) has been shown to reduce cerebral blood flow, intracranial pressure, and ammonia uptake across the blood-brain barrier in patients with liver failure. The complexities of maintaining a patient on hypothermia make it an adjunctive treatment at best. In centers that have the capability, it should be considered as an add-on treatment in patients with demonstrable cerebral edema and severe hyperammonemia while instituting aggressive ammonia removal through RRT.

Dialytic Management
The goal of hyperammonemia treatment is to reduce ammonia levels quickly and safely. Cognitive outcomes are worse for patients with longer exposure to hyperammonemia. It is now well recognized that hemodialysis (HD) is the modality that best accomplishes rapid ammonia removal. Although peritoneal dialysis has been successfully used to reduce ammonia levels, it is not efficient when starting ammonia levels are high or there is ongoing excessive production. Acute peritoneal dialysis is rarely used in adult nephrology in the United States, and it is an unlikely choice in the post-transplantation setting.

Rapid ammonia removal in the absence of azotemia carries no risk for dialysis disequilibrium syndrome because ammonia is not an effective osmole. With the advent of CRRT, there has been much interest in its use as a preferred therapy in patients with hyperammonemia.

Hemodialysis
In 1958, Kiley et al were the first to describe ammonia removal using HD with a Kolff rotating drum artificial kidney in 5 patients with hepatic encephalopathy. Using blood flow (Qb) of 100 to 150 mL/min, they found that ammonia was efficiently removed during 4- to 6-hour dialysis sessions.

Ammonia is a small molecule, similar in size to urea without significant protein binding. The ionized form of ammonia is not freely permeable across a dialyzer membrane. Cordoba et al looked at determinants of ammonia clearance at different dialytic parameters using an in vitro model. They found that ammonia clearance is dependent on Qb, dialysate rate (Qd), and surface area of the dialyzer membrane. In this study, Qb and Qd were capped at 300 mL/min and 800 mL/min, respectively. Being similar in size, clearances of ammonia and urea mirror each other. Hence, extrapolating from urea clearance studies, it is unlikely there would be much benefit with Qb rates > 400 mL/min and Qd rates > 800 mL/min. Dialysis access may also limit Qb rates. Dialytic duration should be extended in the first few sessions, especially with ammonia levels > 500 μmol/L. Although dialytic urea clearance can be used as a surrogate marker for ammonia clearance in patients with end-stage kidney disease, this may not be applicable in solid-organ transplant recipients who have normal kidney function.

Comparison of dialytic modalities for hyperammonemia treatment has been described in infants with urea cycle defects and inborn errors of metabolism. Lai et al showed that the 50% reduction time for ammonia was less in HD compared to predilution continuous venovenous hemofiltration (mean of 1.7 vs 7.5 hours). They had just the 1 patient treated with HD; other reports indicate similar timelines of 2 to 3 hours for significant reduction in ammonia levels. However, CRRT is considered the treatment of choice in infants due to the high risk for hemodynamic instability with HD.

Continuous RRT
There have been no head-to-head trials comparing HD with CRRT for hyperammonemia in adult patients. HD induces an initial significant decrease in plasma ammonia levels, followed by a rebound effect within a few hours after treatment termination. CRRT enables continuous removal of ammonia. The optimal CRRT dose in adults with hyperammonemia is not established. In patients who are critically ill, the standard dialytic dose is 25 mL/kg/h.
Table 2. Nondiagnostic Treatments for Hyperammonemia Management

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Evidence and Clinical Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nitrogen Scavengers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sodium benzoate (oral and IV)</td>
<td>• Sodium benzoate: glycine conjugation → eliminated as hippurate</td>
<td>• Sodium benzoate: nausea, vomiting, unpleasant taste</td>
<td>• Similar efficacy to lactulose in lowering ammonia levels in RCT in pts with acute hepatic encephalopathy61</td>
</tr>
<tr>
<td>• Sodium phenylbutyrate (oral and IV)</td>
<td>• Sodium phenylbutyrate: binds to glutamine → excreted as phenylacetylglutamine</td>
<td>• Sodium phenylbutyrate: decreased appetite, disagreeable body odor, unpleasant taste, neurotoxicity (somnolence, fatigue, lightheadedness)</td>
<td>• Combination (with sodium phenylacetate) efficacious in significant ammonia reduction in open-label uncontrolled study in neonates with urea cycle defects62</td>
</tr>
<tr>
<td>• L-Ornithine L-Aspartate</td>
<td>Activation of urea cycle</td>
<td>• No adverse drug reaction reported with either drug</td>
<td>• Unproven in transplantation hyperammonemia, used as adjunctive treatment in many institutions</td>
</tr>
<tr>
<td>• L-Ornithine Phenylacetate</td>
<td>(oral and IV)</td>
<td>• Rare GI symptoms reported in practice</td>
<td>• IV formulation (combination of sodium benzoate and sodium phenylacetate) very expensive</td>
</tr>
<tr>
<td>• L-Arginine</td>
<td>Activation of the urea cycle</td>
<td>Side effects such as abdominal pain and diarrhea are rare but more often reported with L-arginine</td>
<td>• No RCTs have been conducted with these drugs</td>
</tr>
<tr>
<td>• L-Citrulline</td>
<td></td>
<td></td>
<td>• Used as adjunctive treatments in many institutions due to their low cost and safety profile</td>
</tr>
<tr>
<td><strong>Bowel Decontamination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td>Colonic acidification, catharsis, colonic flora modification</td>
<td>Cramping, flatulence, electrolyte imbalances</td>
<td>• In RCTs and small studies, lowered ammonia levels in pts with cirrhosis65</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Alteration of gut flora, decreasing systemic inflammation</td>
<td>Rare; nausea, flatulence, and diarrhea have been reported</td>
<td>• Frequently used in many centers as first-line nondiagnostic management</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Alteration of gut flora</td>
<td>Neomycin: ototoxicity, nephrotoxicity</td>
<td>• In RCTs and small studies, similar in efficacy to lactulose and has synergistic effect with lactulose in lowering ammonia levels in pts with hepatic encephalopathy65,66</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td>Metronidazole: neurotoxicity</td>
<td>• Frequently used in many centers along with lactulose</td>
</tr>
<tr>
<td><strong>Systemic Antibiotics</strong></td>
<td></td>
<td></td>
<td>• Minimal systemic absorption and better tolerability compared to lactulose makes it a low-risk medication</td>
</tr>
<tr>
<td>• Azithromycin</td>
<td>Activity against urease-producing organisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotics (Lactobacillus sp)</td>
<td>Decrease bacterial urease activity, gut acidification, decrease inflammation</td>
<td>Bloating, constipation</td>
<td>• Unproven in patients without liver failure</td>
</tr>
<tr>
<td>Artificial liver support systems</td>
<td>Removal of albumin-bound substances such as ammonia</td>
<td>Thrombocytopenia, access complications</td>
<td>• Not used routinely</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Abbreviations: GI, gastrointestinal; IV, intravenous; LOLA, L-Ornithine L-Aspartate; LOPA, L-Ornithine Phenylacetate; pt, patient; RCT, randomized controlled trial.</td>
<td></td>
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</table>
High-volume hemofiltration rates (60–90 mL/kg/h) have been used in severely ill patients such as those in refractory septic shock, for which beneficial effects such as improved hemodynamics have been attributed to blunting of the peak pro- and anti-inflammatory effects of cytokines. In transplant recipients, this blunting of the inflammatory response may be beneficial.

However, unselective removal of mediators during high-dose hemofiltration may mean that some of the beneficial molecules may be removed as well. The effects of such removal are unknown. Slack et al compared ammonia clearances between high-dose (90 mL/kg/h) versus low-dose (35 mL/kg/h) hemofiltration volumes in patients with liver failure. Mean ammonia clearance was 39 mL/min in the low-dose group compared to 85 mL/min in the high-dose group. High-dose hemofiltration was safe for the most part, and no immediate ill effects were observed. Higher ammonia clearance was observed in the higher dialysis rate group.

Hemodynamic changes during dialysis in transplant recipients are more akin to changes in patients with AKI than those with end-stage kidney disease because the burden of vascular disease is lower. Intradialytic hypotension, which is a frequent occurrence in outpatient dialysis, has been shown to be frequent in patients with AKI, complicating around 20% to 30% of dialysis treatments. A newly transplanted organ is very sensitive to blood pressure changes. Convective therapies such as hemofiltration and hemodiafiltration have a lower incidence of intradialytic hypotension and may be less harmful in transplant recipients.

We suggest that HD be considered as the initial modality of choice in most hemodynamically stable patients with severe hyperammonemia and imminent cerebral herniation. After 1 to 2 HD sessions, switching to CRRT is appropriate in such patients to prevent rebound of ammonia levels. In patients with lower ammonia levels (<500 μmol/L) in whom rapid reduction in ammonia level is not needed and/or those with hemodynamic instability, CRRT may be preferred and, in those with hemodynamic instability, may be better tolerated and graft-protective. The advantages and recommended prescriptions for each modality are listed in Box 2.

**Conclusion**

Hyperammonemia after solid-organ transplantation occurs with some frequency in lung transplant recipients and rarely in other solid-organ transplant recipients. The key to diagnosis is a high index of suspicion, particularly if mental status changes occur soon after surgery. There are several proposed mechanisms that may act alone or in concert to result in this severe clinical entity. Mortality rates are high, and accordingly, prompt and aggressive therapy is essential. Nondiagnostic interventions are often ineffective, and RRT is required in most patients. The RRT modality chosen is influenced by many factors, and different choices may be effective in individual patients.

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**Support:** This article was written without specific funding support.

**Financial Disclosure:** The authors declare that they have no relevant financial interests.

**Acknowledgements:** We thank Michael Emmett, MD, for providing us with a case from Baylor University Medical Center that served as the inspiration for the clinical vignette.

**Peer Review:** Received October 9, 2018, in response to an invitation from the journal. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form March 4, 2019.

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