The Role of RRT in Hyperammonemic Patients

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Abstract

Hyperammonemia is an important cause of cerebral edema in both adults with liver failure and children with inborn errors of metabolism. There are few studies that have analyzed the role of extracorporeal dialysis in reducing blood ammonia levels in the adult population. Furthermore, there are no firm guidelines about when to implement RRT, because many of the conditions that are characterized by hyperammonemia are extremely rare. In this review of existing literature on RRT, we present the body’s own mechanisms for clearing ammonia as well as the dialytic properties of ammonia. We review the available literature on the use of continuous venovenous hemofiltration, peritoneal dialysis, and hemodialysis in neonates and adults with conditions characterized by hyperammonemia and discuss some of the controversies that exist over selecting one modality over another.


Introduction

Hyperammonemia can be an important cause of brain edema in adults with acute liver failure and children with inborn errors of metabolism (IEM), which are characterized by decreased hepatic clearance of protein by-products and amino acid breakdown. Although abnormal blood levels of ammonia do not always correlate with neurologic signs and symptoms, blood concentrations >150–200 μmol/L have been correlated with increased intracranial pressure and brain herniation (1). Because only a small number of patients with severe acute liver failure or other conditions associated with hyperammonemia actually present with cerebral edema, there are few published studies that clarify the role of extracorporeal dialysis treatment in reducing blood ammonia levels and thereby, potentially treating the cerebral edema.

The use of RRT to reduce blood ammonia levels in the treatment of cerebral edema has been reported but poorly characterized, with no one definitive dialysis technique shown to be the most appropriate. In neonates with IEM or urea cycle disorders, there are a few small studies that showed that peritoneal dialysis, intermittent hemodialysis (HD), or continuous RRT (CRRT) are effective in lowering blood ammonia levels (2–6). In adults, however, there are no established guidelines about the appropriate threshold to initiate dialysis in patients who present with hyperammonemia accompanied by cerebral edema (2–6).

In the following review, we will summarize the existing literature on the utility of extracorporeal therapies (ECTs) in treating hyperammonemia. Additionally, we will review the body’s intrinsic mechanisms of clearing ammonia from the blood and the properties of ammonia that make it amenable to clearance by dialysis. We also present the available literature on the use of RRT in both neonates and adults with hyperammonemia. Finally, we discuss clinical conditions when dialysis may be warranted and suggest which dialytic modality may be most appropriate to implement.

Metabolism of Ammonia and Hyperammonemia

The metabolism of ammonia depends on the enzymatic activity of multiple different organs, including the kidney, liver, muscle, intestine, and brain. Its metabolic elimination occurs through the conversion of ammonia to urea in the liver and ammonia to glutamine by the brain and skeletal muscle. The intestine is a major site of ammonia production. Urea synthesized in the liver is hydrolyzed in the gut, generating ammonia, which is then returned to the liver for conversion back to urea. The intestinal mucosa produces ammonia from the metabolism of intraluminal amino acids, like glutamine, and within the colon, bacterial degradation of urea and other nitrogenous substances leads to ammonia formation (7). The ammonia from the intestine then enters the portal circulation, where it undergoes detoxification in the liver. The liver processes ammonia through glutamine synthesis as well as via the urea cycle, whereby carbon dioxide and ammonia are converted to urea and water. In cirrhotic patients, there is decreased intrinsic hepatic function as well as some portosystemic shunting, both contributing to the development of hyperammonemia. Deficiencies in enzymes in the urea cycle can also lead to hyperammonemia. Although urea cycle disorders most commonly present within the first 24–48 hours of life, they can manifest in adulthood; partial or milder deficiencies can allow individuals to function relatively normally until they are confronted by a stressor (8). There are case reports, for instance, of late-onset ornithine carbamoyltransferase presenting later in life (9).

In addition to detoxification within the urea cycle, there are other important pathways for ammonia clearance. For instance, ammonia undergoes peripheral conversion to glutamine in muscle tissue. Glutamine is then taken up by organs, including the small intestine and kidney, and split by the intramitochondrial phosphate–dependent enzyme glutaminase into glutamate and ammonia, and it is subsequently
excreted into the urine (3). Renal ammoniagenesis, which occurs predominantly in the proximal tubule, plays an important role in acid-base homeostasis. Glutamine is metabolized into ammonia and bicarbonate; ammonia is then either excreted into the urine or returned to the systemic circulation and metabolized by the liver (10). Ammonia production and transport are highly regulated by extracellular pH and potassium levels as well as mineralocorticoids and glucocorticoids (10).

AKI can be both a cause and an effect of pathologic processes that increase blood ammonia levels. AKI can present in conjunction with acute liver failure from either the first insult affecting both organs (e.g., acetaminophen toxicity) or a systemic response affecting both organs (e.g., systemic inflammatory response syndrome) (4). With the development of kidney injury in patients with existing liver failure, blood ammonia levels may increase. In healthy patients, as much as 20% of the daily generated ammonia load is excreted by normally functioning kidneys (3). In the setting of renal dysfunction, a progressive rise in the blood ammonia level overwheels the renal tubules’ excretory capabilities, resulting in hyperammonemia (Table 1).

Encephalopathy

Hepatic encephalopathy is, in part, driven by the effects of glutamate on the brain. Extracellular glutamate activates N-methyl-D-aspartate receptors and leads to alterations in nitric oxide metabolism and a shortage of ATP (11). In the presence of hyperammonemia, concentrations of tryptophan and its oxidation product quinolonic acid both increase in the brain and stimulate N-methyl-D-aspartate receptors as well (11). Hyperactivation of neuronal NMDA receptors leads to sodium, potassium, and calcium influx; excitotoxicity; and an increase in intracellular glutamine. Glutamine is also generated in the cytosol of astrocytes and metabolized by mitochondria, leading to additional ammonia production as well as the creation of reactive oxygen species, which ultimately trigger inflammatory cascades (5). These cascades ultimately lead to free radical accumulation and the formation of nitric oxide, which further inhibits glutamine synthetase activity, leading to a decrease in ammonia elimination from the brain. Furthermore, glutamine is osmotically active, and increased levels in the brain lead to increased intracellular osmolarity with subsequent oxidative stress and eventually, alterations in glucose metabolism. This cascade of events leads to astrocyte swelling and disruption of the blood-brain barrier. This, in part, is thought to be mediated by increased nitric oxide production as well as prostaglandins, which cause cerebral vasodilation, leading to a loss of autoregulatory control in cerebral blood flow and vasogenic edema (6). Recently, another theory behind cerebral edema has been postulated. Within the astrocytes of hyperammonemic animals, there are fewer proteins that regulate potassium and water transport at the blood-brain barrier; as a result, ammonia is able to permeate through aquaporin channels, altering the excretion of water and contributing to brain edema formation (12).

At physiologic blood pH, there is an equilibrium between the ammonia species NH₃ and NH₄⁺. Changes in blood pH affect this dynamic equilibrium between NH₃ and NH₄⁺ and influence brain uptake of ammonia, because it is only the nonionized form (NH₃) that readily crosses the blood-brain barrier. A direct correlation has been reported between changes in blood pH and tissue ammonia concentrations. In fact, in both metabolic and respiratory alkalosis (the latter of which commonly occurs in liver failure), brain and muscle ammonia concentrations can increase two- to three-fold (13). After this occurs, there is a lower threshold for blood ammonia levels to reach clinically relevant (symptomatic) levels.

There is no consensus on what defines a dangerous ammonia level. Blood ammonia levels are considered normal at levels <35 μmol/L, whereas blood ammonia levels >200–500 μmol/L are generally associated with poor neurologic outcomes and death (14). It is debated about whether arterial or venous sampling of ammonia is necessary for the accurate determination of hyperammonemia, but recent studies suggest that venous blood may be appropriate for ammonia assessment (15). To add more confusion, in clinical laboratories, the total ammonia blood levels are routinely measured. Nevertheless, the partial pressure of ammonia (which is calculated using the pH and total ammonia levels) is thought to more accurately reflect cerebral exposure to ammonia, because it represents the freely diffusible form (16). There is ongoing debate concerning this issue (15,17). The best clinical approach involves judging each situation on the basis of whether the patient has clinical evidence for encephalopathy.

Initial Management of Hyperammonemia and Alternate Modalities of Treatment

Current therapy for hyperammonemia focuses on decreasing the waste products from endogenous protein breakdown, minimizing nitrogen intake, reducing protein catabolism, and replacing deficient urea cycle substrates. Treatment of acute hyperammonemia should be instituted right away, with the goal of rapidly reducing both the production of nitrogen waste and blood ammonia levels.

### Table 1. Causes of hyperammonemia

| Liver failure | Urea cycle disorders (ornithine transcarbamylase deficiency, carbamoyl phosphate synthetase deficiency 1, and citrullinemia) |
| Organic acidemias (propionic acidemia, methylmalonic acidemia, maple syrup urine disease, and dibasic aminoacidurias hyperammonemic-hyperornithinemia-homocitrullinuria) |
| Drugs (salicylates, carbamazepine, valproic acid, topiramate, and certain chemotherapeutic agents) |
| Reye syndrome |
| Pregnancy |
| Distal renal tubular acidosis |

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focusing on rapid rehydration to prevent circulatory collapse and AKI (18). Protein intake should be temporarily discontinued, because it is a source of nitrogen waste (11). In addition to hydration and nutritional status, careful attention must be paid to electrolyte and mineral imbalances, particularly calcium and potassium (11). Patients with liver failure must be monitored closely for hypoglycemia, and infusions of hypotonic fluids should be avoided, because these can precipitate hyponatremia and cerebral edema (19). Patients with liver failure are often administered lactulose and rifaximin. In contrast to patients with IEM, patients with liver failure must be monitored closely for hypoglycemia, and rifaximin. In contrast to patients with IEM, patients with liver failure have high protein catabolism and often require protein supplementation depending on their degree of hyperammonemia (19,20).

Nitrogen scavengers, like sodium benzoate and arginine, are often administered to patients with urea cycle disorders to provide an alternate pathway for ammonia excretion (9). Other pharmacologic therapies that may be administered before initiating RRT include carnitine, hydroxycobalamin, and biotin; however, there is concern that these medications will be at least partially cleared with dialysis (21). McBryde et al. (22) found that HD, when used in patients treated with arginine, cleared both ammonia and arginine. Similarly, although the combination of phenylacetate, benzoate, and sequential HD followed by hemofiltration led to a rapid reduction in ammonia levels in a neonate with IEM, it also resulted in significant clearance of both medications (21). The clinical significance of this is not completely understood, but most argue that dialysis should not be delayed or withheld despite the high clearances of the metabolic cocktail (21,22).

More recently, a number of novel therapies, including hyperthermia, phenytoin, hypertonic saline, and albumin dialysis, have been trialed, with the principal goal of decreasing ammonia levels and therefore, reducing intracranial hypertension (23). There are investigational extracorporeal hepatic support devices that incorporate hemodialfiltration with albumin dialysis to remove water–soluble and protein–bound hepatic toxins, including ammonia (24,25). Albumin dialysis involves circulation of blood through an albumin-loaded hemofilter with simultaneous countercurrent dialysis with an albumin–based replacement solution. Albumin-bound toxins included free fatty acids, endogenous benzodiazepines, and false neurotransmitters, whereas water-soluble ones included ammonia, phenols, and mercuricants. All of these toxins, particularly those that are protein bound, have been implicated in hepatic encephalopathy and cerebral edema (26).

The molecular adsorbent recirculating system is another form of an artificial liver support system that reduces serum levels of ammonia, bilirubin, urea, lactate, and creatinine and can theoretically attenuate cerebral edema (27). Although artificial liver support systems have garnered attention since their advent in 1996, there is conflicting data about their survival benefit, particularly in patients without fulminant hepatic failure (27,28). Although studies involving both albumin dialysis and molecular adsorbent recirculating system have their limitations, they have shown that these techniques are safe and associated with a significant decrease in measurable hepatic toxins, thus potentially paving the way for a more significant role for dialysis modalities in hyperammonemia.

Dialytic Properties of Ammonia

There are several factors that determine whether a toxin or medication can be removed successfully from human blood by a particular dialysis technique. Among these factors are the molecular weight of the molecule as well as the extent to which it is protein bound (29). Compounds that have a high molecular weight or are highly protein bound to albumin or fat tissues (lipophilic) result in a high volume of distribution and accordingly, are less or poorly dialyzable. Furthermore, when intermittent HD is discontinued, there may be a rebound effect, where the drug that was initially distributed to the tissues may re-enter the vascular space. When RRT is performed for metformin overdose, for instance, there is presumably a large reservoir of this drug within erythrocytes, leading to a significant rebound effect after the discontinuation of dialysis (30).

Post-HD rebound has been observed and attributed to delayed ammonia shifts from secondary compartments (i.e., the movement from cells to plasma) (31). To minimize this effect, intermittent HD has been used in conjunction with CRRT in children with significant blood ammonia concentration reduction (32). However, unlike metformin, ammonia does not significantly bind proteins and is amenable to dialysis, because it is a small molecule (molecular mass is 17 g/mol).

Currently, there is no consensus as to when it is appropriate to initiate dialysis in clinically significant hyperammonemia. Generally, the primary goals of RRT are to reduce blood ammonia concentrations and achieve resolution of clinical symptoms related to hyperammonemia. It has been proposed that, when the blood ammonia level is three times greater than the upper limit of normal or when the patient shows severe encephalopathy, it is worth considering RRT (9). Alternatively, it has also been suggested that dialysis should be implemented early in the progression to hyperammonemia and before the development of AKI, so that the concentration of ammonia will not rise to clinically significant levels (33). Because ammonia is similar to urea in terms of diffusive clearance, both modalities of continuous venovenous hemofiltration (CVVH) and intermittent HD should be effective in clearing ammonia, differing only by the rate of removal. One can suggest that the therapy with the highest clearance is of greatest utility, because the goal is to reduce abnormal levels as quickly as possible (to a goal of <60–70 μmol/L) (33). Cordoba et al. (34) described in vitro clearance of ammonia by intermittent HD and calculated its clearance at variable blood dialysate flow rates. An ammonia clearance of 225 ml/min was obtained at a blood flow (Qb) of 350 ml/min and a dialysate flow (Qd) of 500 ml/min. Under optimal conditions, ammonia could be extracted by the hemodialyzer >80% by setting both parameters at maximal flow rates. Clearance of ammonia was dependent on blood flow, the dialysate flow rate (as for any highly diffusing substance), and the dialyzer membrane surface area (milliliters per minute). The lowest of these three clinical parameters generally determines the overall clearance for highly cleared substances, which is typically the Qb. Indeed, the clearance of urea and glutamine is similar to that of ammonia, suggesting that these molecules have high diffusive clearances, which are all determined by Qb with any moderate-sized dialyzer (dialyzer membrane surface area ≥800 ml/min). Because intermittent HD is very...
effective at clearing ammonia concentrations rapidly, it is often considered the preferred modality on the basis of the concern that the longer hyperammonemia persists in a patient, the higher the likelihood of potential mental impairment (29,33).

Because the Qb of CRRT is typically much lower than that for intermittent HD, one might think that it would serve a lesser role in treating hyperammonemia. However, one consideration in favor of CRRT is that there are fewer treatment interruptions. Because ammonia is continuously being produced, the temporary cessation of clearance from intermittent HD may lead to increased blood concentrations of ammonia or a cycling of ammonia levels. Furthermore, with intermittent HD in the setting of cerebral edema, there may be a loss of continuous control not only over ammonia concentrations but also, of the serum sodium concentration, pH level, body core temperature, and overall fluid balance while the patient is not dialyzing. In fact, Davenport et al. (35) postulated that, in patients with liver failure and increased intracranial pressure, the rapid fluid shifts associated with HD may, in fact, worsen cerebral edema, thereby arguing for a greater role for CRRT in these situations.

Hyperammonemia in Adults

The adult literature on RRT and hyperammonemia is sparse, even among patients with liver failure. Decompensated patients with cirrhosis infrequently develop significant cerebral edema, presumably secondary to astrocyte adaptation in patients with chronically high ammonia levels (36). The data supporting the use of CRRT in hyperammonemia secondary to liver failure are limited, but some authors argue for early institution of RRT to achieve lower ammonia levels with improved fluid balance and temperature control (19,20). A recent review article on the treatment of liver failure purported that ammonia clearance could be achieved by using conventional continuous hemofiltration, with higher rates of clearance correlating with higher rates of hemofiltration (20). The authors (20) cited a study by Slack et al. (3), who conducted one of the first studies evaluating a form of RRT (continuous venovenous hemodiafiltration [CVVHD]) in adult patients with liver failure and hyperammonemia. In this small prospective cohort study, the investigators (3) examined whether there was a meaningful decline in arterial ammonia concentrations with ultrafiltration. In their series, eight of 10 patients had acetaminophen–induced acute liver failure, 10 patients had decompensated chronic liver disease, and four patients had postoperative coagulopathy and hyperammonemia. The patients had ammonia levels of >100 μmol/L and required RRT for treatment of anuria, uremia, and/or metabolic acidosis. Higher rates of ultrafiltration led to greater reduction in ammonia concentrations, presumably related to the greater dilution by the replacement fluid. The investigators (3) noted that most critically ill patients undergo low-volume CRRT, from which they likely derive less clearance, and that higher ultrafiltration rates would allow for greater clearance.

Dialysis has been successfully trialed in the setting of hyperammonemia without liver failure, as in the case of valproic acid (VPA) toxicity in adults. VPA inhibits carbamoyl phosphate synthetase, thereby preventing normal action of the urea cycle and subsequently, leading to hyperammonemia and cerebral edema (37). The Extracorporeal Treatments in Poisoning Workgroup analyzed data from 79 articles and presented a systematic review on the role of extracorporeal treatment (ECTR) in VPA poisoning (38). The investigators (38) found that VPA was moderately dialyzable, and the use of ECTR was associated with clinical improvement with regards to mental status, respiratory depression, and hemodynamics, especially when intermittent HD was used. Clinical improvement occurred faster when ECTR was implemented within the first 24 hours of admission. The workgroup concluded that ECT is indicated with acute hyperammonemia in the context of severe VPA poisoning, although the investigators did not designate an ammonia concentration above which initiation of dialysis should occur (38).

CVVH and intermittent HD have also been trialed in adult patients with other rare conditions characterized by hyperammonemia, but the generalizability of these studies is limited owing to the small number of patients (23,39). Levesque and Leblanc (31) described two patients with urinary diversions who developed hyperammonemia and were treated with intermittent HD. The maximal Qb was maintained at 350 ml/min, whereas the Qd was kept at 500 ml/min. Ammonia levels were sampled every hour. Mean in vivo clearance was 261 ml/min at a Qb of 350 ml/min and Qd of 500 ml/min with a 1.9-m² surface area dialyzer, similar to that cited by the study by Cordoba et al. (34). However, one of the patients did not regain consciousness, despite achieving significant reduction in bold ammonia levels. This suggests that there was either a delay in the resolution of the cerebral edema or potentially, rebound of ammonia levels from secondary storage compartments.

Questions also remain about the optimal timing of initiation as well as the duration of dialysis in adults. In one case series of patients who developed acute hyperammonemia soon after lung transplantation, two of three patients survived after implementing a multidisciplinary approach, which included daily intermittent HD and overnight slow, low–efficiency dialysis (39). Early initiation, increased dose, and augmenting the frequency of dialysis increased survival in these patients. However, in a case report of an adult patient with partial, late-onset ornithine carbamoyltransferase deficiency whose hyperammonemia was triggered by pancreatitis, CVVH with dialysis was initiated only on day 6 (9). This patient showed a decline in his ammonia level from 254 μmol/L on presentation to <50 μmol/L by day 46, with improvement in mental status. Although this patient’s treatment regimen was multidisciplinary and included a protein-free diet and supplemental treatment with sodium benzoate and arginine, the authors felt that the patient benefited from the inclusion of dialysis as part of his multidisciplinary treatment regimen (9).

Hyperammonemia in Neonates

The majority of literature on using any form of RRT involves neonates with IEM and urea cycle disorders. However, even studies on neonatal hyperammonemia are scant and mostly retrospective because of the rarity of these conditions. These diseases comprise organic acidurias or urea cycle defects that are characterized by a deficiency of urea cycle enzymes, such as carbamyl phosphate synthetase or ornithine transcarbamylase. Without these enzymes, nitrogen cannot be converted to urea for subsequent excretion by the body, ultimately leading to elevated serum levels of ammonia.
Nevertheless, they did not show that there was a persistently high rate of endogenous production of ammonia and that high levels at the start had already produced irreversible brain damage in the patient.

Since the 1970s and 1980s, there has been limited literature directly comparing peritoneal dialysis, intermittent HD, and CRRT in neonates (43–45). CRRT is sometimes better tolerated in sick neonates compared with intermittent HD, because neonates are prone to hypotension and hypothermia. CRRT has traditionally been difficult to perform in low–birth weight infants because of difficulties with access as well as the size of the circuits relative to the infant’s blood volume (46). However, both CRRT and intermittent HD have been successfully performed in low–birth weight neonates weighing <5 kg (47,48). Many publications favor intermittent HD over peritoneal dialysis and CRRT because of the superior clearance with HD, although there is a paucity of outcome studies (49,50). Lai et al. (50) examined eight infants with acute neurologic deterioration caused by ammonia or organic acid accumulation, applying different forms of RRT. Intermittent HD reduced ammonia levels by as much as 50% after 1–2 hours compared with 2–14.5 hours with CVVH. Lai et al. (50) similarly found that peritoneal dialysis and continuous arteriovenous hemofiltration were much less efficient at reducing ammonia levels. Nevertheless, they did find that CVVH was associated with better clearance if high–replacement volume hemofiltration (hemodiafiltration) was applied (>35 ml/kg per hour) (50).

The higher clearance achieved with HD techniques suggests why this modality may sometimes be preferred. In a larger retrospective analysis, Arbeiter et al. (43) showed that CVVHD led to a faster reduction in ammonia levels than cyclic peritoneal dialysis, with long-term outcomes showing a mortality rate of 13% in the CVVHD group compared with 50% among the patients who underwent peritoneal dialysis. Dialysis was initiated quickly, within 2–21 hours after presentation. The authors (43) also found a significant correlation between the time–averaged mean ratio of solute flows to dialysate flows and the percentage of ammonia decay from initial values at 6 hours (consistent with the high diffusive clearance of ammonia). In a 2006 retrospective review, McBryde et al. (32) identified 18 patients with IEM who underwent 21 RRT treatments of either CRRT or intermittent HD after their hyperammonemia could not be controlled with medications alone. The Qd was set at 500 ml/min, with a Qb of 5–10 ml/kg per minute. Only one patient was treated with peritoneal dialysis. Seven of the initial 14 HD treatments required conversion to CRRT for continued control of hyperammonemia, whereas three of the initial six patients with CRRT required intermittent HD to keep ammonia levels <200 μmol/L. The choice of HD as the initial RRT modality trended toward improved overall survival at 2 years, and the time required to reach the end point of an ammonia level <200 μmol/L was 15 times longer with CRRT compared with HD. The authors, therefore, concluded that intermittent HD should be the first–line RRT modality for the treatment of IEM, with CRRT used to prevent rebound only after HD is discontinued (52).

Despite data suggesting the efficacy of intermittent HD over peritoneal dialysis, some studies suggest that there may be little additional benefit of one modality over the other, depending on the timing of initiation. Schaefer et al. (44) found that infants treated with peritoneal dialysis had ammonia elimination that was similar to that of those treated with CVVHD. The authors (44) attributed this, in part, to small vascular catheters limiting Qb in children. Similarly, Pela et al. (51) found that patients treated with peritoneal dialysis had good outcomes if dialysis was initiated rapidly after presentation. In 2014, Picca et al. (52) retrospectively analyzed data from six Italian centers, focusing on infants with hyperammonemia secondary to IEM treated with dialysis—either peritoneal dialysis or HD. In addition to conventional medical treatment, infants were treated with dialysis if ammonia levels were considered to be too high to be treated with medical treatment alone. There were no criteria as to when dialysis was to be initiated; the threshold ammonia level at which dialysis was initiated was determined by clinical expertise and/or available resources at local facilities. Although neonates treated with intermittent HD had significantly faster ammonia reduction at 4 hours, there were no differences in patient survival or neurologic sequelae, regardless of the dialysis modality. Because HD lowered ammonia levels faster, the authors recommended that intermittent HD should be performed preferentially in neonates if they were in stable condition or when ammonium generation induced a rapid increase in blood levels (52). Nevertheless, they showed that there was no difference in neurologic outcomes when peritoneal dialysis was initiated 10 hours after the diagnosis of an inborn error of metabolism compared with intermittent HD when it was started 20 hours after the onset of hyperammonemia (52). The authors concluded that peritoneal dialysis is often readily available and easy to initiate, and therefore, it may be a viable option in centers where ECT may not be readily available (52). In one editorial on the work by Picca et al. (52), Bunchman (53) agreed that it is reasonable to start with peritoneal dialysis until ECT is available but that peritoneal dialysis is “only a stop gap measure” and should not be used as the sole dialytic therapy (53).

Despite conflicting data, currently, the standard of care for neonates presenting with hyperammonemia entails rapid rehydration, the use of nitrogen scavengers, and high-volume CRRT (54,55). CRRT is often preferred to HD because of the high risks of hemodynamic instability, small patient size, lower systemic pressure, and better management of potassium and phosphorous levels (55). Although HD at high flow rates can successfully reduce levels of ammonia quickly, many patients require CRRT because of the rebound effect, and beginning with CRRT may avoid the risk of treatment delays when switching dialysis modalities (56). Spinale et al. (55) described two patients with ornithine transcarbamylase deficiency, in whom the institution of high-dose CRRT led to a rapid decrease in ammonia levels. The authors presented a helpful CRRT practice algorithm to improve outcomes in neonates with hyperammonemia, recommending that dialysis planning should begin when ammonia levels are >400 μmol/L.
They also recommended that the Qb should be maintained at 30–50 ml/min and that CRRT should be continued until the ammonia level has been reduced to at least 100–200 µmol/L (55). Fleming et al. (54) used data from the Prospective Pediatric Continuous Renal Replacement Therapy Registry to determine whether patients with nonrenal indications for CRRT, such as tumor lysis syndrome and IEM, might benefit from CRRT. The investigators (54) found that CRRT provided initial clearances approximating those of intermittent HD and led to clinically meaningful reductions in ammonia levels (Supplemental Appendix).

Conclusion
Hyperammonemia with cerebral edema is a major contributing cause of mortality among adults with acute liver failure and neonates with IEM or urea cycle deficiencies. There are no firm guidelines for the implementation of RRT owing to the relatively low frequency of conditions characterized by hyperammonemia and the limited outcomes research. It is often difficult to elucidate the effect of one specific intervention, such as RRT, in the setting of multiple other therapies, such as metabolic cocktails and protein-free diets. The most prolific data on the utility of dialysis comes from the neonatal literature. Some authors suggest that intermittent HD reduces blood levels of ammonia most efficiently, which is important, because the rapid resolution of encephalopathy seems to be a major determinant of short-term outcomes (52,57).

Because ammonia seems to be highly diffusively cleared and because its clearance is largely determined by Qb, intermittent HD allows for the highest rate of reduction in ammonia levels and is perceived to be superior to peritoneal dialysis. Currently, the standard of care, however, is to use high-flow CRRT, and more recently, there have been major developments in dialysis technology that will allow for the safe application of CRRT in infants. The Cardiac Renal Pediatric Dialysis Emergency Machine is a miniaturized device used for renal support in newborns with low birth weights (1.5–10 kg) and therefore, low total body volumes (120 ml to 1 L) (58). These revolutionary devices may ameliorate the risk of major hemodynamic derangements that can occur in newborns with AKI or metabolic disorders, like hyperammonemia. Although there are select studies involving neonates that suggest that peritoneal dialysis is effective, especially in less severe patients or where HD is not readily available, this is not considered first-line therapy. At this time, there is still no substitute for the clinical judgment on the part of the treating physician as to when to initiate RRT.

Disclosures
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