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Minireview

Nitrogen sparing therapy revisited 2009

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ABSTRACT

Although the protocol that most experienced metabolic centers in the United States follow for treating acute hyperammonemia in urea cycle disorders (UCDs) is similar to that proposed by Brusilow and Batshaw in the early 1980s, over the years a steady evolution has taken place. Continued developments in intensive care, surgical and hemodialysis techniques, fluid and electrolyte management, cardiovascular support, and emergency transport have contributed to improved management of acute hyperammonemia. Compared to historical data, survival of urea cycle patients has also improved following treatment with alternative pathway therapy, in addition to appropriate supportive care, including the provision of adequate calories to prevent catabolism and promote anabolism and hemodialysis if needed. However, overall neurological outcomes have been suboptimal. There are currently a number of exciting prospective new therapies on the horizon, including novel medications or cell-based treatments. Nevertheless, the therapeutic expertise that is currently in place at centers specializing in management of metabolic emergencies already has the potential to improve survival and outcome in these children significantly. The early identification of UCD patients so that transport to a metabolic treatment center may be carried out without delay continues to be a major area of focus and challenge.

Acute hyperammonemia in urea cycle disorders (UCDs) is a medical emergency that requires rapid institution of multiple treatment modalities, including intravenous "nitrogen-scavenging" medications, provision of adequate calories to prevent catabolism (block production of endogenous ammonium) and promote anabolism, and hemodialysis, in order to treat effectively [1]. Historically, mortality and morbidity associated with UCDs have been high, with survivors often exhibiting devastating neurological sequelae [2]. Alternative pathway therapy has revolutionized the acute and chronic treatment of patients who have UCDs. UCD patients have improved survival following therapy with alternative pathway therapy [3], but overall neurological outcomes have been suboptimal [4,5]. After touching on initial clinical trials using alternative pathway therapy, this review concentrates on current therapeutic strategies for management of acute and chronic hyperammonemia secondary to UCDs, as well as newer developments that have the potential to improve survival and neurological outcome.

Initial studies

In 1979, Brusilow et al. suggested that patients who have UCDs may benefit if the synthesis of non-urea nitrogen-containing metabolites whose excretion rates are high could be promoted [6]. The two main classes of compounds that could utilize alternative mechanisms of waste nitrogen disposal are (i) the urea cycle intermediates arginine and citrulline, and (ii) the amino acid acylation products hippuric acid and phenylacetylglutamine (PAGN) [7].

Brusilow and Batshaw first demonstrated the potential of alternative pathway therapy in two neonates with argininosuccinate lyase (AL) deficiency [8]. They hypothesized that argininosuccinic acid (ASA) might serve as a vehicle for the excretion of waste nitrogen in patients with AL deficiency. ASA contains two waste nitrogen atoms and has a renal clearance similar to the glomerular filtration rate. Because of the location of the enzymatic deficiency in AL deficiency, excess arginine would promote ASA synthesis and, hence, increased waste nitrogen excretion. Indeed, intravenous arginine therapy, in combination with peritoneal dialysis in one of the patients, resulted in a fall of plasma ammonium and glutamine to normal [8]. In essence, ASA served as a 'large urea' molecule.

Soon thereafter, the potential for amino acid acylation products to provide a mechanism for the synthesis and excretion of waste nitrogen was demonstrated in a teenager with carbamyl phosphate synthetase I (CPS I) deficiency and four additional patients in

Abbreviations: AL, argininosuccinate lyase; AS, argininosuccinate synthetase; ASA, argininosuccinic acid; AUC, area under the time concentration curve; CPSI, carbamyl phosphate synthetase I; OTC, ornithine transcarbamylase; PA, phenylacetate; PAGN, phenylacetylglutamine; PB, phenylbutyrate; UCD, urea cycle disorder.

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hyperammonemic coma [9]. Treatment with sodium benzoate or phenylacetate (PA) resulted in increased urinary nitrogen excretion and clinical improvement with decreased plasma ammonium levels. Hippurate and PAGN, amino acylation products of benzoate and PA respectively, were found to account for the increase in urinary nitrogen [9]. Larger trials confirmed the initial findings. Twenty-six infants with urea cycle disorders were treated with intravenous benzoate and arginine hydrochloride for periods of time ranging from 7 to 62 months. The majority (23/26) also underwent peritoneal dialysis. Chronic management consisted of sodium benzoate supplementation, a low-protein diet, and provision of adequate calories. Overall, 85% (22/26) of the patients survived, but neurological impairment was common with 59% (13/22) demonstrating normal intelligence [10]. In 1984, Brusilow et al. described the response of seven further children with UCDs and moderate hyperammonemia (plasma ammonium levels 101–483 μmol/L) who were treated with a protocol similar to the one still in use today. Intravenous sodium benzoate, sodium PA and arginine hydrochloride were used for treating 12 acute hyperammonemic episodes in these children. In addition, nitrogen-free intravenous fluids containing 10% dextrose were used to provide caloric support (at least 40 kcal/kg/day). Two patients had rebound hyperammonemia within 7 h after their initial response to therapy and required peritoneal dialysis. One patient died despite therapy, but the others recovered following the use of this regimen [11].

Current acute management

Hyperammonemia is a medical emergency that requires immediate, coordinated action by a trained multi-disciplinary team in order to deliver appropriate treatment without delay. Ideally, therapy should be provided by a specialized center with experience in treating acute hyperammonemia. Metabolic centers typically have a protocol in place that outlines each therapeutic intervention in detail. Placement of intravenous lines, preferably central, is essential in order to provide adequate calories through the use of nitrogen-free fluids containing dextrose (e.g. 10% dextrose with appropriate electrolytes initially) and intravenous lipids. In addition, venous access allows for treatment with alternative pathway medications and other support, such as vasopressor agents or buffering agents, depending on the cardiovascular and acid–base status of the patient [1,12]. At Lucile Packard Children's Hospital (LPCH), we now send our transport team out with the appropriate dose of sodium PA and sodium benzoate (Ammonul®) with added arginine hydrochloride so that a bolus infusion of these medications can be delivered en route. Upon arrival at our center, or soon thereafter, a post-bolus plasma ammonium level may be checked in order to help guide the course of further therapy, especially the need for hemodialysis. Often hemodialysis, or at least preparation for dialysis, is initiated concomitantly with Ammonul® and arginine therapy. Hemodialysis (HD) has a very high ammonium clearance rate, as compared with other methods such as peritoneal dialysis or hemofiltration (HF) [13–15]. Following conventional hemodialysis, institution of hemofiltration may prevent rebound hyperammonemia [16]. Both sodium PA and sodium benzoate exhibit high clearance by HD and HF, but this typically does not interfere with resolution of hyperammonemia [16]. Use of a high-flow extracorporeal oxygenation (ECMO) circuit to support HD has also been used successfully in neonates with hyperammonemia. The addition of the ECMO circuit may further increase ammonium clearance while simultaneously improving oxygenation [17].

The importance of providing calories to prevent catabolism and promote anabolism cannot be stressed too highly. A goal of at least 80 kcal/kg/day is often used in neonates [7], although a higher caloric intake (e.g. ~120 kcal/kg/day) may be required. We commence 20% in addition to intravenous lipids (2–3 g/kg/day) in order to achieve this caloric goal. An insulin drip may be needed to control blood glucose levels. Other supportive care includes intubation and ventilation as necessary, correction of anemia, electrolyte and acid/base imbalances, maintenance of blood pressure, and treatment of any intercurrent illness [1].

Complete restriction of protein is also a mainstay of acute therapy, although this should be limited to only about 24 h after the initiation of treatment. Thereafter, protein supplementation is provided via parenteral nutrition or nasogastric feeds. In general, transition to enteral feeds should be done as early as possible. If protein restriction is prolonged, depletion of essential amino acids will occur with resultant further protein catabolism and nitrogen release [1].

Outcome following acute management

In 2005, Nassogne et al. published a report describing the outcome of a large cohort of urea cycle patients who were not treated using alternative pathway medications [18]. Between 1972 and 2000, 217 patients were diagnosed with a UCD; 121 had neonatal-onset disease and 96 had late-onset disease. Overall, outcome was poor with mortality reaching 84% (60% if males with OTC deficiency are excluded) in neonatal-onset cases and 28% in those who had late-onset forms of disease. There was a high risk of neurological impairment in survivors [18]. During the period of study, intravenous Ammonul® and arginine therapy were not readily available in Europe. A difference in philosophy regarding the treatment of patients in hyperammonemic crisis, compared to some centers in the United States, may also have played a role in the choice of management for the UCD patients described in this report. In addition, there may have been delays in transporting hyperammonemic patients to experienced metabolic centers. The possibility of permanent brain damage is high in such cases, so urgent intervention is less likely to lead to good outcome, and, therefore, less likely to be used.

In contrast, an open-label, uncontrolled, non-randomized clinical trial of Ammonul® and arginine hydrochloride therapy was performed in 118 hospitals in the United States and Canada from August, 1980 to March, 2005 [3]. Treating physicians were self-selected. To enroll a patient, the investigator contacted Dr. Brusilow at Johns Hopkins School of Medicine (from 1982 to 1996) or Ucyclyd Pharma (from 1997 to 2005). During the 25-year period of study, 299 urea cycle patients (93 neonates, 237 patients >30 days old, including 31 who were treated both as neonates and later) were followed. In total, they sustained 1181 episodes of hyperammonemia. The recommended use of alternative pathway therapy for this study was similar to the initial treatment protocol proposed by Brusilow and Batshaw [11]. Neonates and young children (weighing up to 20 kg) with CPS I deficiency, ornithine transcarbamylase (OTC) deficiency, and argininosuccinate synthetase (AS) deficiency were treated with an intravenous loading dose of 250 mg/kg Ammonul® over a period of 90–120 min. Older children and adults (weighing >20 kg) were treated with an intravenous loading dose of Ammonul® at 5.5 g/m^2 or 250 mg/kg over a period of 90–120 min. After the loading dose, maintenance infusions of the same dose over 24 h were continued until the patient was no longer hyperammonemic and oral therapy could be tolerated. Specific guidelines for administering sodium PA and sodium benzoate were not given for treatment of AL deficiency or arginase deficiency. Loading and maintenance infusions also contained arginine. Dialysis was recommended for any neonate with hyperammonemic encephalopathy or any other patient whose ammonium level did not decrease substantially within 8 h after the load infusion [3].

Overall patient survival was 84% (250 of 299 patients), while hyperammonemic episode survival was 96% (1132 of 1181 episodes). The episode survival rate was lowest (91%) for males with

3.3 ± 6.3 (range 1–79). Patients >30 days old were more likely to survive a hyperammonemic episode compared to neonates (survival rates 98% and 73%, respectively, $P < 0.001$) (Fig. 1). Patients >12 years old were most likely to survive a hyperammonemic episode (survival rate 99%, $P < 0.001$ vs. all other age groups). Among patients who were comatose on admission, no coma was present at the time of discharge in 97 episodes (81%) while 23 episodes resulted in death (19%). Survival of hyperammonemic episodes was lowest for males with OTC deficiency who were comatose on admission (68%). Survival was significantly improved for patients who had episodes with a peak plasma ammonium level ⩽500 μmol/L compared to those with higher peak ammonium levels ($P < 0.001$). Patients <30 days old with a peak ammonium level >1000 μmol/L were least likely to survive a hyperammonemic episode (38% episode survival) ($P < 0.001$) (Fig. 2). Dialysis (including standard hemodialysis, various combinations of arteriovenous and venovenous hemofiltration, and peritoneal dialysis) was used in 136 of 1181 episodes (12%) and in 105 of 299 patients (35%). Dialysis was used more commonly in neonates (60% of episodes) than in older patients (7% of episodes) [3].

Most patients experienced adverse events while being treated for hyperammonemia; metabolism, nervous system, and respiratory disorders were most frequently reported. Co-morbid features were common in patients who died, including seizures (19/49), infection (18/49), cerebral edema or increased intracranial pressure (16/49), disseminated intravascular coagulation (9/49), kidney failure (6/49), multi-organ system failure (5/49), and cerebral hemorrhage (5/49). Although cerebral edema or increased intracranial pressure was documented in only 16 of 49 death narratives, these patients had markedly elevated ammonium levels, so cerebral edema was likely present in nearly all cases. An overdose of Ammonul® was reported in 13 patients who died. Massive overdose was uncommon, being noted in two episodes (doses between 9 and 17 times the recommended dose of Ammonul® were given in these instances). It is likely that the instances of mild overdosing (e.g. one or two additional bolus infusions given over several days) reflected the severity of the hyperammonemic episode and poor clinical status of patients who eventually died [3].

Survival was clearly improved, compared to historical data, following treatment with alternative pathway therapy, in addition to the provision of appropriate nutrition and, in some cases, dialysis

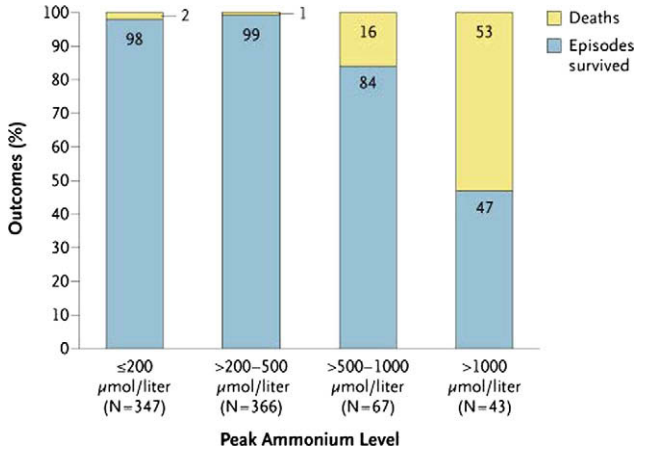
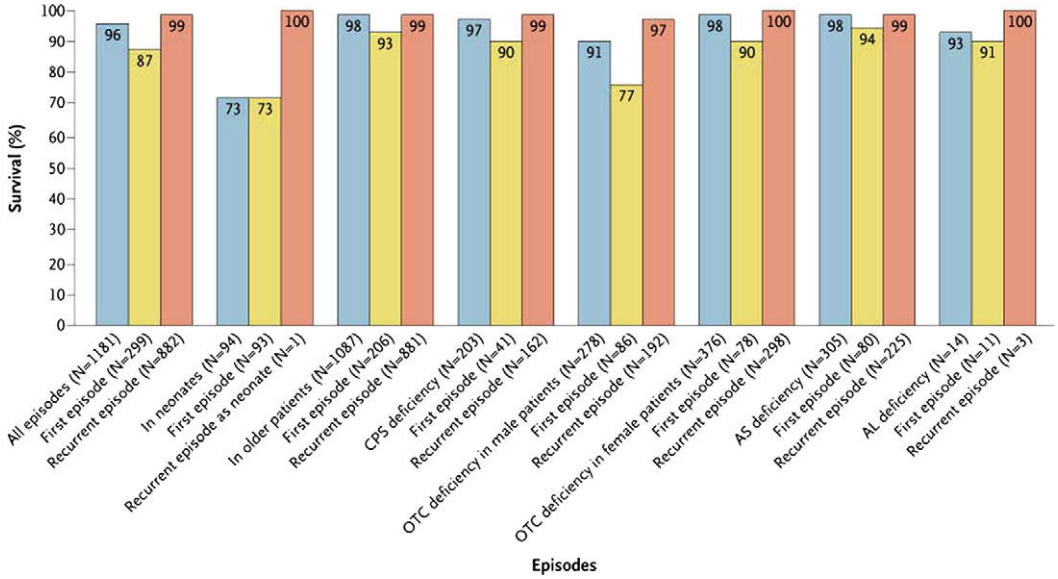


Fig. 2. Hyperammonemic episodes survived according to peak ammonium levels. Patient survival of hyperammonemic episodes depends on peak plasma ammonium level, with significantly improved survival for those with peak plasma ammonium levels of 500 μM or less ($P < 0.001$) [3]. Reproduced with permission from Enns et al., N. Engl. J. Med. 356(22) (2007) 2282–2292. Copyright© 2007 Massachusestts Medical Society. All rights reserved.

[3]. It must be stressed that alternative pathway therapy is only a single component of the coordinated therapeutic regimen necessary for optimal treatment of acute hyperammonemia. Because patients were primarily treated in specialized metabolic centers, the high survival rate likely reflects, at least in part, the expertise available at treating institutions. In addition, these survival statistics apply only to patients who received the study drug and may not necessarily extrapolate to all UCD patients. Some patients may not have been treated because of their poor condition on presentation and others may have died before reaching the hospital.

Longitudinal survival data

Summar et al. reported longitudinal survival findings in 260 UCD patients using a subset of the same database used in the study described above [19]. Hyperammonemia presenting in the neonatal period was associated with the worst outcome; only 35% of pa-



tients were still alive at the final follow-up time point (approximately 11 years after the start of the study period). The great majority of deaths in this group (22/26) occurred before age 2 months. In contrast, 87% of patients who presented later in infancy were alive at the final follow-up time point. Seventy-eight percent of patients presenting with hyperammonemia between ages 2 and 16 years survived to the final follow-up time point. When specific disorders were studied, males with OTC deficiency had the lowest survival (53%), compared to OTC females (74%), and those with CPS I deficiency (61%) and AS deficiency (78%) [19].

The Lucile Packard Children's Hospital experience

Over the past decade, we have treated 25 neonates with hyperammonemia at Lucile Packard Children's Hospital at Stanford; 11 with UCDs, 12 with organic acidemias, and two with long-chain fatty acid oxidation defects. Hemodialysis, typically followed by a form of hemofiltration, was performed in most of the UCD patients (9/11, 82%) and in 58% of those with organic acidemias (7/12), but was not required in the fatty acid oxidation patients, even though both of these patients had significant hyperammonemia (~600 to 1000 μmol/L). There was one neonatal death (a girl who presented with seizures and was diagnosed with CPS I deficiency). Three UCD patients died later (two had severe OTC deficiency and the third was given a lethal overdose of Buphenyl® by an outside institution). Three organic acidemia patients also died during childhood (all three had methylmalonic acidemia *mut*^{0} subtype). Both fatty acid oxidation patients have survived to date. In this relatively small cohort of hyperammonemic patients, neonatal survival was 96% and overall survival to date is 72%.

Neurological outcomes

Survival has clearly improved compared to historical outcomes following alternative pathway therapy, when these medications are administered as part of a multi-faceted therapeutic protocol. The goal, however, is not only survival, but also optimization of neurological outcome. Unfortunately, reported IQ data following survival of an episode of neonatal hyperammonemic coma have been sobering. In 24 UCD children tested at ages 12–74 months following treatment with alternative pathway therapy, the mean IQ was 43 ± 6, with only 21% having an IQ > 70 [4]. Moreover, 79% of patients had at least one developmental disability. The depth of coma was found to correlate inversely with IQ, with patients with a history of stage III or IV coma having the worst neurological outcome. Although prolonged hyperammonemic coma was found to be associated with brain damage and impaired intellectual function, the investigators speculated that poor outcomes may be prevented by early diagnosis and institution of appropriate therapy [4].

Chronic therapy

After the initial metabolic crisis has been treated, surviving patients are started on a chronic therapeutic regimen. This consists of protein restriction (along with provision of approximately 50% of protein intake from an essential amino acid formula), supplementation with citrulline or arginine depending on the precise diagnosis, use of alternative pathway medications, and prompt recognition and treatment of any intercurrent illness [20]. The treatment regimen must be individualized. Many centers, including ours, initially administer Buphenyl® (sodium phenylbutyrate) as the primary nitrogen-scavenging medication once Ammonul® has been stopped. In some cases, the addition of sodium benzoate may be required to help control hyperammonemia. The tendency sodium benzoate alone, although in our experience this is usually possible only in the more mild forms of disease, such as manifesting heterozygote females with OTC deficiency.

Poor adherence to the prescribed doses of alternative pathway medications has been a major difficulty in treating patients with urea cycle defects. Buphenyl® requires frequent dosing and has an unpleasant taste and odor. Patients may be faced with taking up to 40 large tablets of Buphenyl® daily in order to manage their underlying disease. Some patients may prefer sodium benzoate, although this medication also has a noxious taste. Another potential problem has been documented more recently; alternative pathway medications may cause a selective deficiency of branched-chain amino acids [21]. Branched-chain amino acid supplementation may improve protein titration in UCD patients and is discussed in detail by Scaglia in this supplement.

Missing metabolites

After an oral dose of sodium phenylbutyrate, the concentration of phenylbutyrate (PB) peaks at 50–90 min and PA and PAGN peak at 150–180 min [22]. Although PAGN is the major product of PA metabolism, by conjugation of phenylacetyl-CoA with glutamine, a small amount of unchanged PA and PB is also excreted in the urine. However, taken together the urinary excretion of PA, PB, and PAGN accounts for less than 50% of the ingested PB. The mystery of the "missing" PB has been solved only partially. In 2002, the novel metabolite phenylbutyrylglutamine was identified, although only about half of ingested PB was accounted for by the addition of this compound [22]. More recently, a number of other PB metabolites, formed by interaction of PB with lipids and carbohydrates, have been identified. These new metabolites are either glucuronides (e.g. phenylbutyryl- or phenylacetyl-β-glucuronate) or β-oxidation side products (e.g. *R*-3-hydroxy-4-phenylbutyrate, phenylisopropanol). Nevertheless, even with the addition of these carbohydrate and lipid derivatives, the total recovery of PB and its metabolites accounted for only 62% of the ingested PB dose [23]. Therefore, it is likely that other metabolites of PB remain to be discovered. In addition, some of the ingested PB, metabolites of PB, or both may be excreted in feces. The fate of the PB glucuronide metabolites excreted in bile is unknown [23].

HPN-100 (glyceryl tri-[4-phenylbutyrate])

HPN-100 (glyceryl tri-[4-phenylbutyrate], glycerol phenylbutyrate) is a new oral medication being developed for hyperammonemia control in UCDs. Clinical trials in adult patients are currently underway. This investigational agent is a pro-drug of PB; glycerol phenylbutyrate is a triglyceride that contains three molecules of 4-phenylbutyric acid joined via ester linkage to glycerol. Importantly, glycerol phenylbutyrate is an organic liquid (oil) with little odor or taste that has the potential to deliver the same amount of phenylbutyrate in a much reduced amount of medication. The maximum anticipated dose of glycerol phenylbutyrate is 5.8 ml three times daily, which provides the equivalent to 20 g of PB (i.e. a little over three teaspoons daily provides the equivalent of 40 tablets of Buphenyl®). Glycerol phenylbutyrate also does not contain sodium. Greater patient acceptance and compliance may result from the combination of improved ease of administration and minimal odor.

Pharmacology data from Cynomolgus monkeys, which have the capacity to convert PA to PAGN, suggest that glycerol phenylbutyrate may act as a 'slow release' compound that may be metabolized to PAGN more efficiently than PB [23]. Ester hydrolysis of glycerol phenylbutyrate results in release of PB, which then can undergo β-

plasma ammonium values, plasma and urine PAGN, and amino acid levels in 10 adult urea cycle patients who switched from their prescribed dose of Buphenyl® to an equivalent dose of glycerol phenylbutyrate based on amount of PB. After seven days of treatment with three times daily glycerol phenylbutyrate, 24-h pharmacokinetic data was obtained and serial plasma ammonium levels were measured. Treatment with glycerol phenylbutyrate resulted in ~30% lower plasma ammonium values as assessed by time-normalized AUC (mean NH_3 on Buphenyl® 38.4 ± 19.6 μmol/L vs. 26.1 ± 10.3 μmol/L on glycerol phenylbutyrate, not statistically significant), similar plasma PAGN and amino acid levels, and similar urinary excretion of PAGN. Urinary PAGN accounted for ~55% of the PB administered as Buphenyl® or glycerol phenylbutyrate. Interestingly, there was a trend towards lower nocturnal ammonium values in subjects while being treated with glycerol phenylbutyrate. Somewhat fewer adverse events were reported during the glycerol phenylbutyrate period of this trial (21 adverse events in seven subjects during Buphenyl® treatment compared to 15 adverse events in five subjects during glycerol phenylbutyrate treatment). The only two hyperammonemic events during this study occurred in subjects being treated with Buphenyl® and both episodes were attributed to medication non-adherence [24]. In conclusion, glycerol phenylbutyrate plasma ammonium control appears to be at least comparable to Buphenyl®. The trend toward lower overnight ammonium values may reflect delayed release of PB following ester hydrolysis. This study also noted that eight of 10 subjects were prescribed Buphenyl® in doses below the recommended treatment guidelines according to the package insert. Because ~30% to 40% of plasma ammonium values were abnormal in these patients, higher medication doses may be beneficial. Further development of glycerol phenylbutyrate is warranted, especially given the difficulties facing urea cycle patients with respect to daily pill burden and the noxious taste of Buphenyl®. If the promise of the initial Phase 2 results is confirmed in larger-scale trials, glycerol phenylbutyrate has the potential to improve both medication adherence and, therefore, control of plasma ammonium levels.

The future of hyperammonemia therapy

In a sense, the future of UCD therapy is now. Specialized metabolic centers already have the clinical and technical expertise in place to cope with acute hyperammonemia, although more of such centers and improved access to those already in place are clearly needed [25]. Experienced metabolic centers typically have hyperammonemia protocols in place so that a coordinated response by multiple care providers (especially specialists in biochemical genetics, neonatology, surgery and nephrology) can proceed smoothly. Electronic order sets may further improve the delivery of multi-disciplinary care. Improvement is still needed with respect to the timeliness of identification of patients with elevated ammonium levels so that care can be instituted without delay. Expanded newborn screening has the potential to detect some UCDs based on elevations of citrulline or arginine, but at present proximal defects (CPSI and OTC deficiencies) are not identified by tandem mass spectrometry, although techniques for doing so are under development. Even so, patients with neonatal onset forms of disease typically become symptomatic before results of newborn screening are known. Therefore, although further expanding newborn screening to include the proximal defects and improving the turn around time for obtaining test results may have some effect on early identification of affected neonates, in practice outcomes may not be changed significantly unless there is increased awareness of these disorders by primary medical care providers. The connection between community hospitals and specialized

Rapid institution of alternative pathway therapy and adequate caloric support has the potential to improve outcome. For example, our institution strives to send transport teams out with a prepared supply of Ammonul® and arginine hydrochloride so that the patient receives the initial bolus during transport. If the initial bolus is provided in such a manner, the treating physician may be able to make a decision on the need to institute hemodialysis upon arrival to the hospital. Of course, in some instances plasma ammonium will be at levels that clearly would not respond to alternative pathway therapy regardless of the time course of the intervention. In such instances, a decision about whether or not to proceed with dialysis will have to be made after careful evaluation of potential risks, benefits, and likely outcome. Hemodialysis, hemofiltration, and hemodiafiltration have been extremely effective treatments for acute management of hyperammonemia and techniques continue to improve [26,27]. Mild systemic hypothermia, in addition to hemodialysis or hemofiltration, is another novel technique that may be useful in correcting hyperammonemia [28], but this modality has yet to be studied in UCD patients in a controlled clinical trial.

Prenatal delivery of nitrogen-scavenging medications may also play a role in the initial care of UCD patients if a diagnosis is known before birth. Two fetuses with a prenatal diagnosis of a UCD were treated by infusing their mothers with intravenous benzoate. Therapeutic benzoate concentrations were detected in umbilical cord blood and in the blood of the neonates. Plasma ammonium and glutamine concentrations were normal in the neonatal period for these children [29]. Novel medications, such as glycerol phenylbutyrate, may also prove useful in the chronic management of UCD patients.

Liver transplantation has become an increasingly utilized therapeutic option for definitive correction of the underlying defect in UCDs, if the patient survives the initial hyperammonemic episode [30]. Advances in immunosuppression, operative techniques, and post-operative intensive care have contributed to improved outcome following transplantation [31]. Post-transplantation survival rates of patients who have inborn errors of metabolism appear to be higher, approaching 100%, when compared to survival following transplantation for other indications, such as acute liver failure, extrahepatic biliary atresia, or postnecrotic liver cirrhosis [32]. Improved survival following liver transplantation in metabolic disorders may be related to the presence of normal anatomy, the ability to perform elective surgery during periods of relative clinical stability, or other factors. Preservation of intelligence is possible if transplantation is performed early, before neurological damage has been sustained [30]. Although hepatocyte transplantation is a promising new approach for the treatment of liver-based metabolic disorders, including UCDs, only limited success has been reported to date [33]. Gene therapeutic approaches also hold promise for the future, but significant hurdles need to be overcome. This topic is discussed more fully elsewhere in this volume.

Braissant has reviewed the mechanisms of neurotoxicity secondary to hyperammonemia comprehensively in this issue. Ammonium exposure alters cerebral energy metabolism and causes increased oxidative stress, nitric oxide synthesis, and mitochondrial permeability transition. In addition, neurotransmitter systems and cellular signal transduction pathways are affected by elevated ammonium levels [5,34]. The elucidation of the molecular pathways related to brain damage may lead to development of novel medications for therapy of hyperammonemia, such as *N*-methyl D-aspartate receptor antagonists, phosphodiesterase inhibitors, anti-inflammatory agents, antioxidants, nitric oxide inhibitors, and creatine. Carbamylglutamate has shown success in treating CPS I patients in Europe [35], but is not yet available in the United States unless provided under the auspices of an exper-

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