

Current strategies for the management of neonatal urea cycle disorders

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The treatment of newborns with urea cycle disorders has evolved over the years into a complex multidisciplinary effort. The complexity derives from the number of issues that must be addressed simultaneously. At the Urea Cycle Disorders Consensus Meeting held in Washington, D.C., a panel of physicians and other professionals with extensive experience in this field was assembled to bring some systematization to this task. This manuscript is a condensation of the collective opinion and experience of that group. The outcome of untreated or poorly treated patients with urea cycle disorders is universally bad. Although a favorable outcome is not always feasible, even with the best therapy, the methods outlined here should help treat such a patient by drawing on the experience of others who have treated patients with urea cycle disorders. This article does not purport to be the final word in treating children with these disorders. However, by establishing some common ground, new methods can be tried and compared with existing ones. In a future that holds the prospect of gene therapy “cures” for these diseases, striving for the best possible outcome in the critical newborn period is a worthy goal. (*J Pediatr* 2001;138:S30-S39)

Neonatal hyperammonemia is a medical emergency requiring advanced planning, sophisticated facilities, and multidisciplinary teamwork. Urea cycle disorders are the primary cause of hyperammonemia during the vulnerable newborn period. Genetic defects in any of the first 4 enzymes of the pathway (carbamyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinic acid lyase), or a cofactor producer (N-acetyl glutamate

synthase) result in accumulations of precursor metabolites including ammonia (Fig 1). Because there is no effective secondary clearance system for ammonia, disruption of this pathway has a rapid clinical course. The catabolism normally present in the newborn period together with the immaturity of the liver combine to accentuate defects in these enzymes. This rapid accumulation of ammonia and other precursor metabolites results in acute cerebral edema with severe neurologic compro-

mise.¹⁻⁵ Thus fast and effective treatment is key to improving the patient's outcome.

A clear, concise protocol is required to treat neonates with severe hyperammonemia caused by UCDs. In reviewing the experience of a number of clinicians who have cared for these patients, several stages of treatment become apparent. These include (1) recognition and supportive treatment, (2) bulk ammonia removal and pharmacologic scavenging, (3) stabilization and catabolic reversal, and (4) transition to home management. These steps are undertaken to accomplish specific therapeutic goals and include rapidly clearing ammonia from the neonate's bloodstream, blocking the production of additional ammonia, removing excess nitrogen, and protecting the neurologic integrity of the baby. All of these goals should be pursued with thoughtful expediency in the context of the patient's clinical situation.

ASL	Argininosuccinic acid lyase
ASS	Argininosuccinic acid synthetase
CPS	Carbamyl phosphate synthetase I
ECMO	Extracorporeal membrane oxygenation
ECMO/HD	Extracorporeal membrane oxygenation driving a hemodialysis machine
NAGS	N-acetyl glutamate synthase
NG	Nasogastric
NJ	Nasojejunal
OTC	Ornithine transcarbamylase
UCD	Urea cycle disorder

During each stage of management there are a number of critical elements to consider, including what is being done, what are the results, and what remains to be done. This article is an attempt to provide guidance on the

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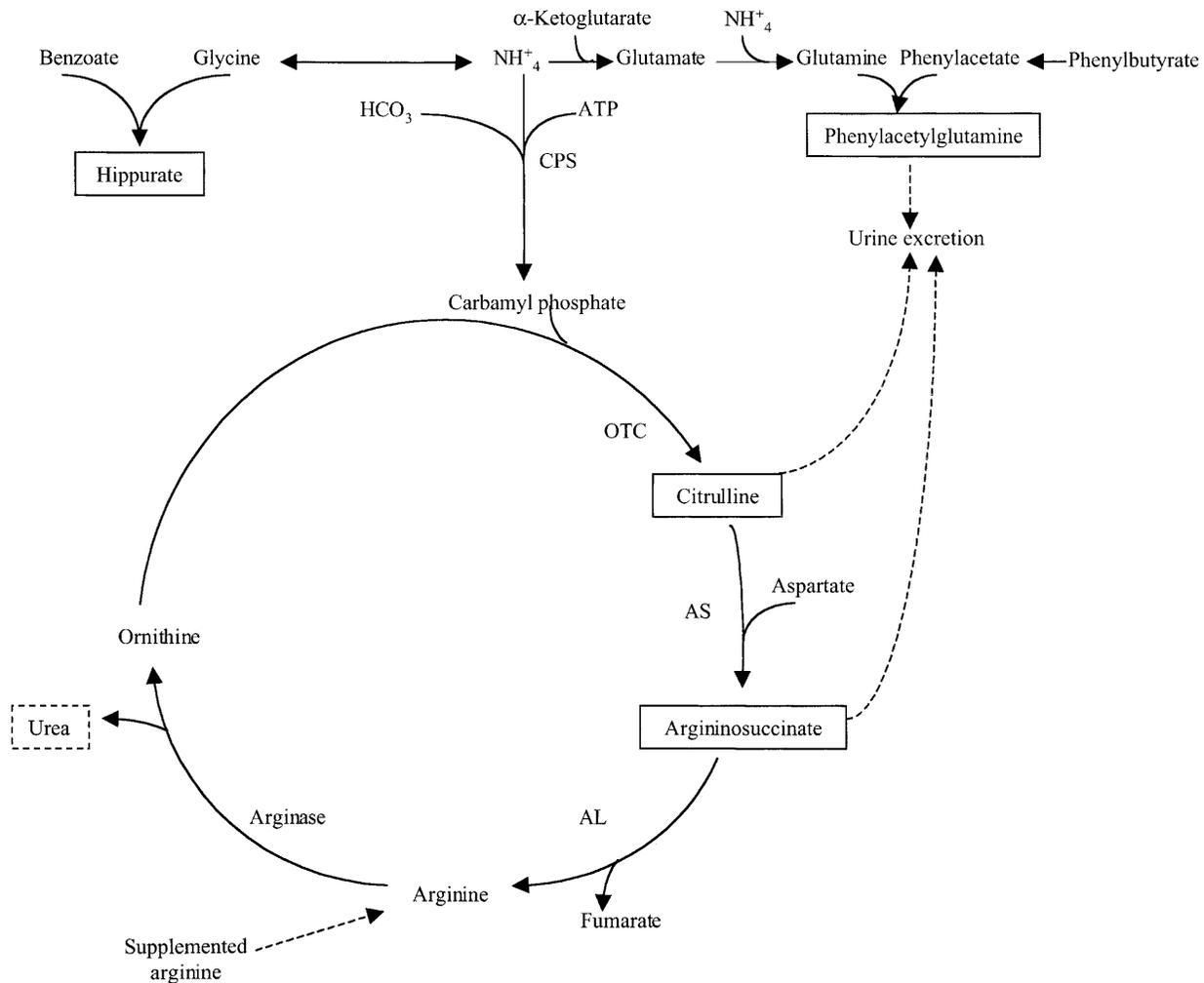


Fig 1. Urea cycle and intermediate components.

specifics of treating a patient with neonatal hyperammonemia.

RECOGNITION AND SUPPORTIVE TREATMENT

Once neonatal hyperammonemia is recognized, the necessary organization and supportive care are initiated to reverse it as soon as possible.

Clinical Presentation

In the immediate newborn period, infants with UCDs will typically look normal. The problems that may have been observed while the child was still in hospital are often not seen until the child is at home because of the current

practice of discharging the mother and newborn baby early. This places much of the burden of recognition on the family and the pediatrician or primary care physician. The typical initial symptoms of a child with hyperammonemia, failure to feed, and somnolence may not be recognized by new parents. As a result, advice and care is sought later when the child's illness has progressed to become more severe.

The progression of symptoms moves from somnolence, through lethargy, and on to coma. There is a loss of thermoregulation with a low core temperature and feeding disruption that correlates with the somnolence.

Abnormal posturing and encephalopathy are often related to the degree of central nervous system swelling and

pressure on the brain stem.^{4,5} Seizures are seen in approximately 50% of severely hyperammonemic neonates. Hyperventilation caused by cerebral edema causes a respiratory alkalosis that is also a common symptom in the early stages of the hyperammonemic attack. This progresses to hypoventilation and respiratory arrest as pressure increases on the brain stem.^{6,7}

The algorithm in Fig 2 may assist with the evaluation of a hyperammonemic newborn, but outside factors can influence the differential diagnosis. Factors such as the overall health of the liver, the duration of hyperammonemia, and pharmacologic agents already given to the patient should be factored into the interpretation of the clinical observations.

Diagnostic Considerations

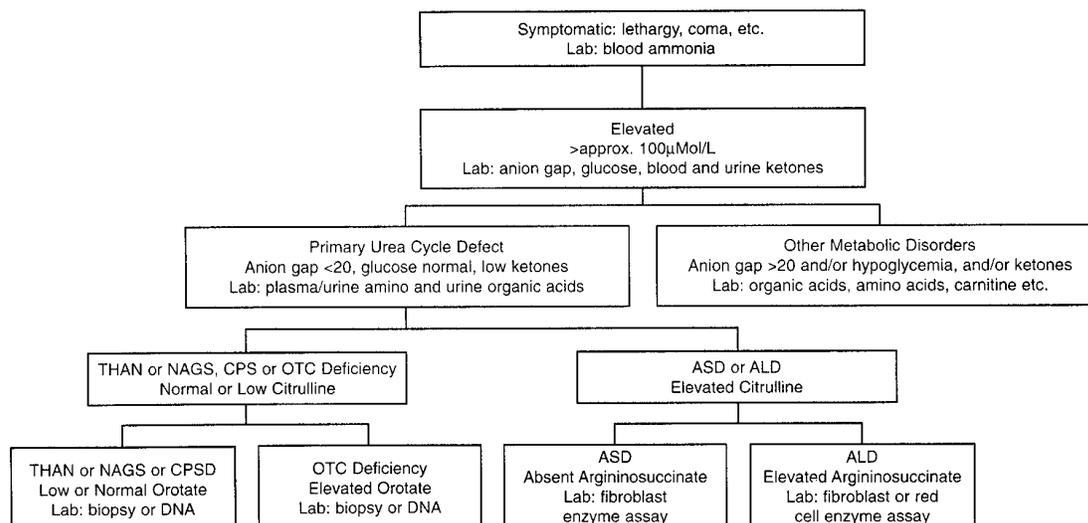


Fig 2. Algorithm for encephalopathic newborns.

Table I. Diagnostic laboratory tests

Ammonia
pH and CO ₂
Plasma quantitative amino acids
Anion gap
Glucose
Urine organic acids and orotic acid
Specific enzymatic or DNA analysis

Laboratory data useful in the diagnosis of UCDs include plasma ammonia levels, pH, CO₂, the anion gap, plasma amino acids, and urine organic acid analyses. Table I lists the recommended diagnostic tests, and Fig 2 highlights their use. The clinician should remember that treatment should begin before a final diagnosis is made, and that later stages of treatment should be tailored to the specific disorder (Table I).

An elevated plasma ammonia level of 150 µmol/L or higher, associated with a normal anion gap and a normal blood glucose level, is a strong indication for the presence of a UCD. Quantitative amino acid analysis can be used to evaluate these patients and arrive at a tentative diagnosis. The amino acids in sick newborns are often quite different from those in children and adults, and

Table II. Laboratory measurements in acutely ill infants without UCD

Parameter	Average	SD
Ammonia	47 µmol/L	(13.5)
Glutamine	581	(182)
Glycine	302	(100)
Alanine	319	(252)
Citrulline	10.3	(7)
Arginine	38.3	(18.4)

Averaged results from 25 babies admitted to the neonatal intensive care unit. All babies were 35 weeks' gestation with respiratory problems (birth asphyxia, respiratory distress, or meconium aspiration syndrome).

Table II lists some of our averaged values obtained in sick, term newborns without UCDs. The required diagnostic laboratory tests and their interpretation are discussed in more detail elsewhere in this supplement.

In summary, infants with a UCD often have an initial normal appearance that progresses to lethargy and coma with the associated features of anorexia, hyperventilation, hypothermia, hypoventilation, seizures, neurologic posturing, and other features of cerebral edema.

Early Supportive Care

These are the initial treatment steps that should be implemented as soon as

the patient is suspected of having a urea cycle defect. They can be performed while the patient is being prepared for transport to a metabolic center or being prepared for dialysis or pharmacologic management. Before care is initiated, some thought should be given to the severity of the patient's condition and to the probable long-term outcome. Patients who have been in a hyperammonemic coma for several days have an extremely poor neurologic outcome. Although the patient may be successfully "detoxified" and stabilized, the damage to the central nervous system is likely to be devastating and permanent. Thus the option of withdrawal of support should be dis-

cussed with parents of patients who have already sustained overwhelming damage to the brain.

Intravenous access should be established as soon as possible. If practical, the patient with a UCD should have a deep line placed such as an umbilical catheter or a multilumen central line. The need to resume feedings rapidly should influence the selection of line type. Stable vascular access will assist with the administration of fluids, medications, and the frequent blood sampling. Many patients with UCDs are dehydrated at presentation as a result of anorexia and poor oral intake. Restoration of normal hydration will serve to protect renal function (critical for effective treatment) and ensure adequate tissue perfusion (to blunt the further catabolic production of nitrogen). Overhydration should be avoided because most patients with UCDs have some degree of cerebral swelling. Intravenous administration of fluids with 10% dextrose with one quarter normal saline solution is preferable to physiological saline solution, because patients treated with ammonia-scavenging drugs will receive large amounts of sodium and chloride ions as part of their medication regimen. Other support (pressors, buffering agents), depending on the cardiovascular and acid-balance status of the infant, is also important. Protection of kidney function is an important aspect of the early treatment of these patients. Many have depleted intravascular volumes and go into shock and have acute renal failure. Once the dialysis phase is complete, the drugs used to scavenge excess ammonia from the bloodstream require normal renal function. The use of boluses of fluid and pressor agents should be balanced against the degree of cerebral edema present at the time. Oncotic agents such as albumin will contribute to the overall nitrogen load but in selected cases, and on a limited basis, can be used.

Caloric supplementation should be maximized to try and reverse catabo-

lism and nitrogen turnover. In addition to glucose, Intralipid administration can provide additional calories but should not be allowed to delay progress toward more aggressive treatment. Oral feedings should be discontinued in patients with severe encephalopathy but restarted as soon as practical. Placement of a nasogastric tube should be done during this early phase. Feeding of all protein should be halted temporarily and calories provided as carbohydrate and fat. For patients who are able to tolerate oral feedings, a protein-free formula such as Mead Johnson 80056 or Ross Formula ProPhree could initially be used. Elemental formulas are not appropriate because they contain considerable amounts of nitrogen. This complete restriction of protein should be maintained only for a short period (24 to 48 hours), because depletion of essential amino acids will result in further protein catabolism and nitrogen release. The author has found that maximizing caloric intake has a significant impact on patient stabilization after bulk ammonia removal.

Even an infant who is awake and responsive can progress to coma and cardiovascular or respiratory collapse during transport or preparation for dialysis. Therefore it is preferable to perform intubation on infants with borderline clinical condition before transport or before they have respiratory compromise for 2 reasons: (1) if a patient is breathing rapidly (respiratory alkalosis driven by cerebral edema), excess calories are burned, contributing to catabolism and further nitrogen accumulation, and (2) intubation is a difficult procedure to carry out while an infant is being transported and can lead to hypoxia.

It is usual for a lethargic infant to have undergone a septic workup with the initiation of antibiotic treatment. With the heavy instrumentation and stress patients with UCD undergo, it is probably prudent to continue existing antibiotic coverage or consider initiat-

ing it as prophylaxis. A bacterial infection in a newborn baby with hyperammonemia could well prove fatal.

There are several other important measures to be taken when caring for these infants. Hyperventilation is recommended and steroids are to be avoided, because they will increase the amount of protein turnover and hence increase the nitrogen load. Mannitol has not been demonstrated to be effective in managing cerebral edema caused by hyperammonemia.

The importance of early treatment cannot be overstressed. Ultimately the neurologic dysfunction of the patient is related to the duration of cerebral edema.⁷⁻¹⁰ Most children will have cognitive impairment, but early treatment to remove ammonia and other metabolites from the bloodstream will lessen the severity of this impairment.

Organization and Mobilization

Newborns with UCDs should be treated by a team of experienced personnel and in facilities with special resources (Table III). The community physicians should be aware of these facilities and how to reach them. A metabolic specialist should coordinate the activities of the various team members and maintain continuity of treatment. As with any team approach, the roles of the members and the steps and goals of treatment should be clear before a patient with a UCD presents for treatment. In addition to alerting team members of the impending arrival of a patient with a UCD, the managing physician should also alert the laboratory regarding STAT tests. The pharmacy should also be alerted to ensure that the specific medications are available and can be prepared at short notice. Human subject permits should already be on hand, because treatment with intravenous sodium phenylacetate and sodium benzoate is still considered experimental and is under an FDA investigational new drug permit (contact Ucylyd Pharmaceuticals for details). We have found that having

Table III. Treatment team members and roles and responsibilities

Team member	Roles and responsibilities
Metabolic specialist Pharmacy	Coordinate treatment and management. Formulate ammonia scavenging and dialysis agents. Check dosing orders.
Nephrologist or dialysis team Intensive care team	Dialysis Assist with physiological support, pain management, and ventilator management.
Surgical team	Catheter placement for hemo- and peritoneal dialysis. Obtain biopsy sample for diagnostic testing.
Laboratory staff	Ammonia, amino acids, and organic acids
Nutritionist	Establish dietary prescription with metabolic foods and supplements. Assist with parenteral calorie management and transition to enteral feeding.

the medications from the pharmacy ahead of time and having blood hand-delivered to the chemistry laboratory saves considerable critical time. Delays in treatment or response to changing status may affect the eventual outcome (Table III).

Bulk Ammonia Removal and Pharmacologic Ammonia Scavenging

The best way to remove ammonia rapidly is by dialysis.^{7,11-13} Keeping ammonia from reaccumulating is achieved through the use of nitrogen scavenger drugs, discussed in detail elsewhere in this supplement. Loading with scavenger drugs should be done as soon as possible if urine output is adequate. Exchange transfusion is ineffective in removing ammonia, and dialysis is the treatment of choice for rapid removal of this toxin.^{7,11-13}

Preparation for Dialysis

Dialysis is the primary means by which ammonia is removed from the patient's body during the early management period. Ideally, the surgical and dialysis teams should be waiting for the patient to arrive and initiate treatment

immediately. If dialysis is not immediately available, it is appropriate to use a loading dose of drugs to induce the removal of ammonia. However, in the patient with severe hyperammonemia, pharmacologic agents are not sufficient to remove ammonia quickly.

The method of dialysis chosen depends on the available expertise and equipment. The fastest removal system uses an extracorporeal membrane oxygenation pump system to drive a hemodialysis machine.^{12,14,15} ECMO has become more widely available because of its use in infant lung disease and cardiac surgery. Other methods include hemofiltration (both arteriovenous and venovenous), standard dialysis, peritoneal dialysis, and continuous-drainage peritoneal dialysis. Each method has its own advantages and drawbacks.^{12,14-18} Because ammonia crosses the dialysis membrane rapidly, the faster the flow rate, the higher the clearance. In critically ill newborns it is difficult to perform standard dialysis for more than a few hours and maintain homeostasis. Peritoneal dialysis clears ammonia at a low rate of 3 to 5 mL/min, and if it is the sole means of ammonia removal, it may take several

days to reduce a significant ammonia burden.¹² Peritoneal dialysis also complicates attempts at early refeeding and increases the risk of infection. However, peritoneal dialysis may be the most widely available form of toxin removal and does not require an entire dialysis team. A variation of peritoneal dialysis with continuous inflow and outflow is effective but requires extremely close monitoring. Hemofiltration produces clearance rates of 10 to 30 mL/min, and clearance rates with ECMO/HD are on the order of 170 to 200 mL/min.¹² With the advent of percutaneous catheter placement for ECMO and the increased pump rates available, the advantages of this method may outweigh the risk of blood vessel damage. Another advantage to the use of an ECMO pump is that a hemofilter can be placed in the circuit to continue removal of ammonia between dialysis runs. We have demonstrated reductions of blood ammonia levels by >1000 $\mu\text{mol/L}$ in a period of 1 to 2 hours with ECMO/HD.¹² Osmotic shifts have not been observed with this rapid dialysis, and recovery of neurologic activity is faster. For patients with less severe hyperammonemia, a hemofiltration pump may suffice for bulk ammonia removal. A review of the literature suggests that approximately 50% of the neonates requiring dialysis for any reason undergo dialysis with a pressure-supported system. The extensive amount of instrumentation arising from the use of any of these methods increases the risk of infection, and prophylactic antibiotic coverage should be considered for all patients.

Dialysis seems to become less effective when the plasma ammonia level falls below 200 $\mu\text{mol/L}$ and can be discontinued. Once dialysis is stopped, and while the patient is still in the acute phase, there may be a rebound of several hundred μmol in the ammonia level. This reflects both the continued catabolic state of the patient with the consequent production of waste nitrogen and the time required for the nitrogen scav-

enging medications to take effect. The use of hemofiltration can blunt or prevent this rebound. It is recommended that the catheters be removed only after the plasma ammonia level has been stable for at least a day. However, this should be balanced by the risk of maintaining the patient in an anticoagulated state. Some patients may require more than one session of dialysis to bring the ammonia level under control. In summary, it is recommended that patients with severe hyperammonemia be treated initially with pump-driven dialysis (ECMO/HD) followed by continuous hemofiltration with the same pump system. In patients who are hemodynamically unstable, this procedure offers pressure support and better control over dialysis flow rates. A further advantage is that enteral feeding through an NG or nasojunal tube can be started.

Pharmacologic Management

RATIONALE. The second line of the treatment for acute hyperammonemia involves the use of compounds that remove nitrogen by alternative pathways. Phenylacetate combines with glutamine to produce phenylacetylglutamine, a compound that is excreted in the urine.^{8,19} The scavenged glutamine is replaced by synthesis in muscle and liver, thus reducing the nitrogen load. In addition, glutamine has been implicated in the neurotoxicity of UCDs; therefore its elimination may have a more direct beneficial effect.²⁰⁻²³ Benzoate combines with glycine to produce hippurate, which is also rapidly cleared by the kidneys.^{24,25} The glycine is replaced by synthesis, thus removing more waste nitrogen from the pool. While the precursor nitrogen is removed from circulation, attention must also be paid to replacing the deficient product(s) of the urea cycle (Fig 1). CPS, NAGS, and OTC defects prevent the formation of citrulline from ornithine and carbamyl phosphate. This in turn decreases the synthesis of arginine, resulting in it becoming an essential amino acid. A

block in ASS prevents the condensation of aspartate with citrulline, which accounts for 50% of the nitrogen incorporated into the pathway. ASL deficiency blocks conversion of argininosuccinate to arginine. Therefore arginine is also an essential amino acid in ASS and ASL deficiencies.^{26,27} Even in ASS and ASL deficiency, where there is a partially intact urea cycle, the body rapidly depletes its pool of urea cycle intermediates into which it normally incorporates nitrogen. Therefore arginine serves as a therapeutic agent in UCD. In CPS, NAGS, OTC, ASS, and ASL deficiency, arginine is used to restore its blood levels and prevent the breakdown of endogenous protein.^{26,27} In ASS and ASL deficiency it is used in larger amounts to "prime" the cycle to produce citrulline or argininosuccinate.^{24,28} This has the advantage of incorporating a substantial amount of nitrogen in compounds having a lower toxicity and higher renal excretion. In ASS (citrullinemia), 1 mol of nitrogen can be removed for every mole of arginine metabolized through the cycle, and this doubles in ASL to 2 mol. L-citrulline may serve as a better supplement for patients with OTC and CPS than arginine, because it is converted to arginine while promoting the incorporation of one waste nitrogen; however, an intravenous formulation of citrulline is not currently available. A note of caution concerning arginine. Arginine is a precursor of nitric oxide, a potent vasodilator. Anecdotal evidence and the author's own experience suggest that in CPS and OTC deficiencies, large amounts of excess arginine may accumulate, resulting in overproduction of nitric oxide and leading to extreme vasodilation and hypotension.¹² Reduction in arginine administration corresponded with restored venous tone in 2 patients cared for in our institution.

Administration Protocol

These dose recommendations are based on the Food and Drug Adminis-

tration packaging for intravenous sodium benzoate/sodium phenylacetate and the protocols developed by Dr. Saul Brusilow.^{6,7,11} They are summarized in Table IV.

Loading Dose

The current protocol for the acute management of hyperammonemia includes arginine hydrochloride (600 mg/kg in a 10% solution), and a combination of sodium benzoate and sodium phenylacetate (250 mg/kg of each drug), all infused in 25 to 35 mL/kg of 10% dextrose in water over a 90-minute period. The blood pH should be monitored and buffer added to counteract the acidity of the arginine hydrochloride. The dose of arginine has been increased from previous protocols, because a rapid infusion of arginine is believed to have a significant impact on patients with ASS and ASL deficiency and be relatively safe for patients with OTC, CPS, and NAGS deficiency. Caution should be exercised if additional doses of sodium benzoate and sodium phenylacetate are given within 24 hours of the original dose, but experience suggests that 500 mg/kg each of sodium benzoate and sodium phenylacetate during the first 24 hours is an acceptable regimen (1 loading dose + maintenance infusion). At 750 mg/kg/24 h, there is some toxicity (vomiting, lethargy), and at >750 mg/kg/24 h, the toxicity is essentially invariable and can be life-threatening. Reloading (repeating the initial regimen) should be contemplated only in neonates with severe disorders or those who are undergoing dialysis and, based on the results of pharmacokinetic studies, should be spaced at least 6 hours apart (refer to Dr. Batshaw's article elsewhere in this supplement for more extensive information on the pharmacologic management of UCDs).

Maintenance Infusion

Once the loading dose is given, the patient should be switched to the maintenance infusion. The doses differ only in

Table IV. Recommended doses of pharmacologic agents to be used during dialysis periods

Sodium benzoate/phenylacetate dosage and administration						
Summary table						
Patient population	Components of infusion solution			Dosage provided		
	SB/SA Injection, 10%	Arginine HCl Injection, 10%	Dextrose injection, 10%	Sodium phenylacetate	Sodium benzoate	Arginine HCl
Neonates/Infants/Young children:						
Prospective treatment pending definitive diagnosis of urea cycle enzyme deficiency						
Loading dose	2.5 mL/kg	6.0 mL/kg	~ 25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maintenance dose	2.5 mL/kg	6.0 mL/kg	~ 25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
CPS or OTC Deficiency						
Loading dose	2.5 mL/kg	2.0 mL/kg	~ 25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
Maintenance dose	2.5 mL/kg	2.0 mL/kg	~ 25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
ASS or ASL deficiency						
Loading dose	2.5 mL/kg	6.0 mL/kg	~ 25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maintenance dose	2.5 mL/kg	6.0 mL/kg	~ 25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Older children and adults:						
CPS or OTC deficiency						
Loading dose	55 mL/m ²	2.0 mL/kg	~ 25 mL/kg	5.5 g/m ²	5.5 g/m ²	200 mg/kg
Maintenance dose	55 mL/m ²	2.0 mL/kg	~ 25 mL/kg	5.5 g/m ²	5.5 g/m ²	200 mg/kg
ASS or ASL deficiency						
Loading dose	55 mL/m ²	6.0 mL/kg	~ 25 mL/kg	5.5 g/m ²	5.5 g/m ²	600 mg/kg
Maintenance dose	55 mL/m ²	6.0 mL/kg	~ 25 mL/kg	5.5 g/m ²	5.5 g/m ²	600 mg/kg*

SB, Sodium benzoate; SA, sodium phenylacetate.

the amount of arginine hydrochloride given and are dependent on the diagnosis. The 24-hour dose of the combination of sodium benzoate/sodium phenylacetate is 250 mg/kg/24 h of each drug. For patients with CPS, OTC, or NAGS deficiency, the dose of arginine hydrochloride is 200 mg/kg/24 h. For ASS and ASL deficiency the dose of arginine is 600 mg/kg/24 h. For patients awaiting diagnosis, the 200 mg/kg/24 h dose of arginine should be used in conjunction with sodium benzoate and sodium phenylacetate. Attention should be paid to the potassium level of the patient, and the maintenance fluids should have potassium added, because sodium phenylacetate may cause potassium depletion. The maintenance infusion is continued until a conversion to oral medication is made. Cerebral blood flow or electroencephalography analysis may be required to determine whether treatment should be discontinued.

Laboratory Monitoring

Our center measures ammonia plasma levels every hour during high-flow rate dialysis. These samples should be handled expeditiously to get the fastest possible turnaround. Once the ammonia plasma level has stabilized to <200 to 300 $\mu\text{mol/L}$, the monitoring frequency can be reduced to once every few hours. When the patient is receiving a stable drug regimen and no longer requires dialysis, the frequency can be further reduced to every 12 hours and to once-daily before discharge. During the acute phase, electrolytes and acid-base balance should be carefully monitored (every 4 hours). Glucose should be monitored hourly in patients receiving a glucose/insulin infusion to avoid wide swings in glucose levels. Amino acids should be monitored on a daily basis to assess nutritional status and the effectiveness of glutamine removal and citrulline/

arginine replacement. The amount of blood removed should be monitored and transfusion used to avoid iatrogenic anemia.

Other Acute Treatment Issues

Opinion is divided among experts on the use of glucose and insulin in these patients. Glucose and insulin can serve as suppressors of catabolism, but their use requires care. The consensus opinion at this meeting was to administer 6 to 8 mg/kg/min of glucose (administered as 10% dextrose in water) and to use insulin sparingly to maintain the serum glucose level <170 mg/dL. The presence of glycosuria is an indication for continued administration of intravenous regular insulin at a rate that keeps glucose levels between 120 and 170 mg/dL. Wide swings in glucose levels can change the osmolality of the brain and therefore should be avoided.

The use of normal saline solution should also be avoided, because the pharmacologic agents used in ammonia removal contain large amounts of sodium and chloride ions.

The use of carnitine in neonates being treated with sodium benzoate is not believed to be beneficial. There have been no documented cases of carnitine deficiency, even though carnitine levels are low in these neonates, and carnitine is known to conjugate with sodium benzoate.

Valproic acid should be avoided in any patient who has seizures. It is known to decrease urea cycle function and will aggravate the hyperammonemia.²⁹⁻³¹

Enteral citrulline is used in some centers for neonates with UCD and CPS or OTC deficiencies, the rationale being that pulling aspartate into the pathway may increase nitrogen clearance. The dose of citrulline used is 150 to 200 mg/kg/24 h. A clear diagnosis should be made before citrulline is used to avoid providing citrulline to patients with ASS and ASL who already have excessive amounts of this amino acid.

Stabilization and Catabolic Reversal

This phase overlaps with the second phase to some extent. One of the keys to successful treatment of a patient with a UCD is to reverse the catabolic process. This decreases nitrogen turnover and reduces the amount of ammonia that must be detoxified. During this stage there may be fluctuations in the ammonia plasma levels, and often the bulk ammonia removal protocol will have to be repeated. Some form of low-level dialysis (hemofiltration) may be continued during the early parts of this phase while the patient's nitrogen production exceeds removal.

Caloric Management

The author recommends that the patient be started on some form of enteral

feed as soon as is practical. This may occur while the patient is still undergoing cannulation. The placement of an NG or NJ tube may facilitate this. Parenteral nutrition (with reduced amino acid content) should be maximized during the acute phase to transition the patient to enteral feeds. The highest infusion rate of glucose (dextrose) that does not cause hyperglycemia should be used. Intralipid should also be used to maximize parenteral calories. The use of Intralipid may provide a rationale for the use of carnitine to improve cellular transport of fatty acids. Essential amino acids should not be withheld for >24 hours. Most patients with a UCD are nutritionally compromised on admission to the hospital. Although the addition of excess nitrogen in the form of amino acids and protein should be avoided, essential amino acids will be released from the patient's own protein stores if they are not provided, thus increasing the amount of waste nitrogen requiring disposal. Nutritional intake should be managed with the active participation of a nutritionist experienced in metabolic disorders. Targets of 1.0 to 1.5 g of protein/kg body weight (50% as essential amino acids) are a good start during the early phases of treatment. Dr. Leonard's article in this supplement discusses the nutritional treatment of patients with these disorders in more detail. A number of commercial products are available to treat these patients including protein-free formulas (Mead Johnson 80056, Ross ProPhree) and essential amino acid formulations such as SHS UCD-1 and Ross Cyclinex-1.

At this stage the patient's neurologic status should be assessed in response to treatment and the degree of impairment that may have occurred from the disease.

Once the patient is stabilized, feedings have been established, and the ammonia level is not fluctuating, the patient can be switched to the oral formulations of the nitrogen-scavenging medications. Dr. Batshaw's article in

this supplement discusses long-term pharmacologic management in greater detail. Current dosing recommendations for newborn patients with CPS or OTC deficiency are sodium phenylbutyrate (450 to 600 mg/kg/d) and citrulline (170 mg/kg/d). Patients with ASS deficiency receive sodium phenylbutyrate (450 to 600 mg/kg/d) and arginine (400 to 700 mg/kg/d). Patients with ASL deficiency receive L-arginine (400 to 700 mg/kg/d), and if their hyperammonemia is not controlled by diet and arginine alone, some patients also receive sodium phenylbutyrate. Of note, some patients with ASL deficiency may have significant hepatomegaly and chronic elevation of transaminases leading to varying degrees of fibrosis. The reason for this is not clearly understood, although in patients treated by the author, it does not appear to significantly affect hepatic function. Some clinicians also use sodium benzoate at a dose of 250 to 500 mg/kg/d if sodium phenylbutyrate is not sufficient to scavenge the excess nitrogen. Sodium benzoate is a caustic substance and will cause a rash if it comes into contact with skin, and a burn reaction if extravasated from an intravenous site.

TRANSITION TO HOME MANAGEMENT

During this phase preparations are made to facilitate the continuing treatment of the patient in the home environment.

Careful consideration should be given to the route of feeding. Patients with severe neurologic impairment usually require the placement of a gastrostomy tube. This is probably safer than repeatedly passing an NG tube and is less stressful for the family. Inadequate protein supplementation may prevent healing of the insertion site with frequent skin breakdown and should be monitored. Placement of the tube before initial discharge may pre-

vent a later admission for nutritional failure. A metabolic nutritionist should build a rapport with the family, because the most stressful issues at home usually center on feeding. A supply of the special formulas must be identified and insurance coverage issues managed. Letters of justification will typically be required for the formulas and medications. Arginine and citrulline are medical supplements rather than Food and Drug Administration drugs, and explanatory documentation will usually be necessary.

The introduction of a patient with a UCD into most families is a very stressful event, and support for the family should be arranged. Most states have programs for home visits by medical professionals, and families with a child with a UCD often benefit from them. The author often recommends prospective family counseling to deal with the changes in dynamics before they become critical. Time also must be spent with close relatives to explain an illness with which few of them will be familiar. Patients with a UCD are perceived as extremely fragile by parents and relatives, and the family should be reassured that physically these children are not more delicate than others. However, exposure to individuals with contagious illness (eg, upper respiratory infections, gastroenteritis) should be minimized.

The patient should follow a normal immunization schedule, and antipyretics can be used prophylactically. A multivitamin should also be used, although the medical foods are well compounded for vitamins and trace elements. Often the formulas are mixed with bottled or sterile water that does not contain fluoride, and some provision for fluoride treatment may be needed. The author has observed the development of extensive dental caries in a number of patients who did not receive fluoride supplementation. The pediatrician or primary care provider plays a crucial role in caring for a patient with a UCD and should be in-

involved well before the patient's discharge. It is useful to prepare a treatment sheet for medical emergencies and to keep it updated at clinic visits. This can save crucial time and prevent confusion.

If liver transplantation is being considered for the patient, the appropriate laboratories and contacts should be made before the patient's discharge.

CONCLUDING REMARKS

The treatment of patients with a urea cycle disorder presents one of the most challenging and rewarding tasks in metabolic disease. The best outcome for the patient can be obtained only by careful planning, coordination, and thought. The stress to the patient can be minimized by planning the transitions between early management, ammonia removal, and stabilization. The combination of physical and pharmacologic removal must be monitored very closely, because each patient will react differently. Advanced preparation is very important, because it is virtually impossible to assemble all of the resources to treat a patient with UCD without preplanning. This preparation includes identification of a laboratory that can rapidly process and report plasma amino acids to confirm the diagnosis and plasma ammonia values to assist with real-time management. Advance planning also means that the roles of potential members of the treatment team are known well in advance. As with all detailed treatment schemes, the clinician must maintain a high degree of adaptability to allow a fast response to the specific patient circumstances. This can be facilitated by contacting others with experience in treating patients with these disorders. A consensus article like this one is only possible with the use of the accumulated knowledge and experience of a large number of individuals who have pioneered this field. As Sir Isaac Newton said, "If I have seen farther than

others, it is because I was standing on the shoulders of giants."

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