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 compromise.[1-3] 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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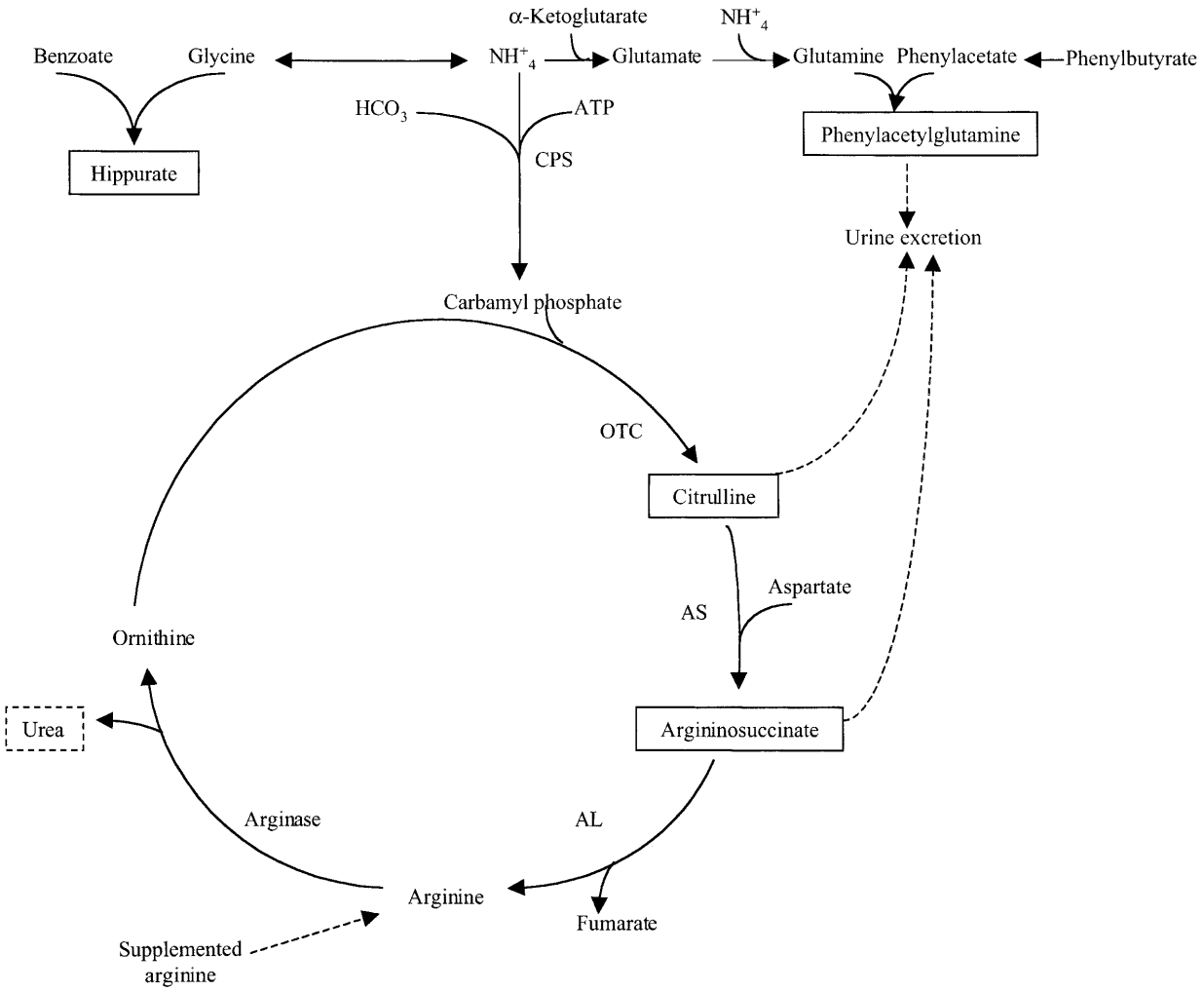

Fig 1. Urea cycle and intermediate components.

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

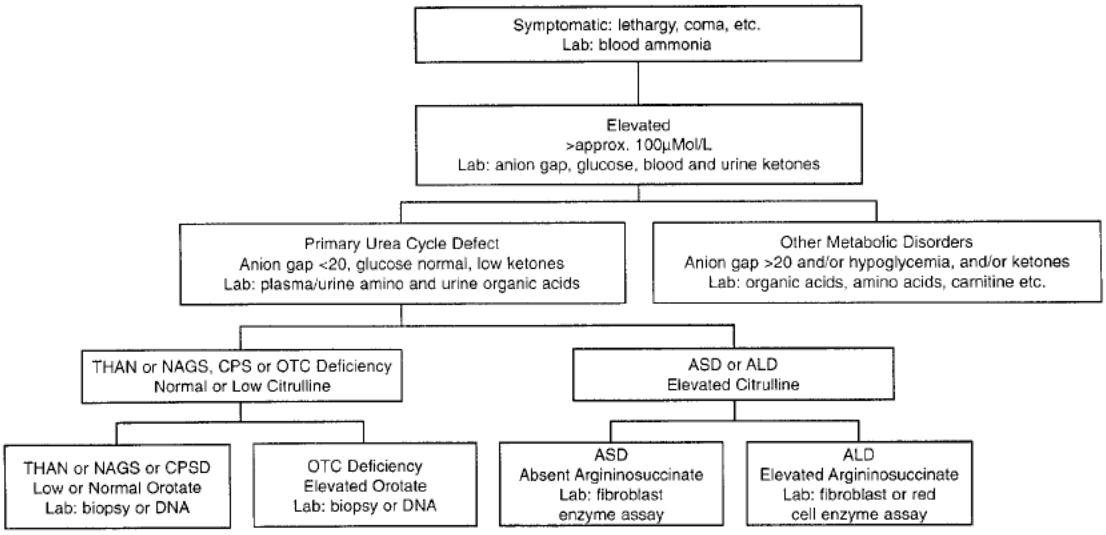

Fig 2. Algorithm for encephalopathic newborns.

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

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).

Laboratory data useful in the diagnosis of UCDs include plasma ammonia levels, pH, CO_2, 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 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 catabolism 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 initiating 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 Ucyclyd Pharmaceuticals for details). We have found that having

Table III. Treatment team members and roles and responsibilities

Team member	Roles and responsibilities
Metabolic specialist	Coordinate treatment and management.
Pharmacy	Formulate ammonia scavenging and dialysis agents. Check dosing orders.
Nephrologist or dialysis team	Dialysis
Intensive care team	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 µmol/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 µmol/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-

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