Inborn Errors of Metabolism with Hyperammonemia

Urea Cycle Defects and Related Disorders

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KEYWORDS

• Hyperammonemia • Ammonia • Arginine • Citrulline • Liver • Urea cycle • Ornithine

KEY POINTS

- Symptoms of hyperammonemia include cerebral edema, lethargy, anorexia, hyperventilation or hypoventilation, hypothermia, seizures, neurologic posturing, and coma.
- Clinical awareness and suspicion of hyperammonemia is the most important component in the diagnosis and treatment of inborn errors of metabolism associated with elevated ammonia levels.
- For the pediatrician, recognition, stabilization, and rapid transport to a center with a metabolic specialist is the surest way to achieve an optimal outcome.
- Emergency management of hyperammonemia is based on 3 interdependent principles: physical removal of the ammonia by renal replacement therapy, reversal of the catabolic state, and pharmacologic scavenging of excess nitrogen.

INTRODUCTION

The urea cycle, first described by Krebs and Henseleit,[1] converts into urea the extra nitrogen produced by the breakdown of protein and other nitrogen-containing molecules (**Fig. 1**). A congenital or secondary deficiency of the urea cycle may, thus, result in the accumulation of ammonia and other precursor metabolites. Through a variety of mechanisms, hyperammonemia can cause cerebral edema, lethargy, anorexia, hyperventilation or hypoventilation, hypothermia, seizures, neurologic posturing, and coma.

The urea cycle as a nitrogen clearance system is limited primarily to the human liver and intestine with carbamyl phosphate synthetase (CPS1) and ornithine transcarbamylase (OTC) limited exclusively to those tissues. The enzymes downstream that process citrulline into arginine are ubiquitous in their distribution, because these enzymes participate in the production of nitric oxide (NO).

The authors have no commercial or financial interests. Both Drs M.L. Summar and N.A. Mew have and do receive funding from the NIH.

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Pediatr Clin N Am 65 (2018) 231–246
https://doi.org/10.1016/j.pcl.2017.11.004
pediatric.theclinics.com

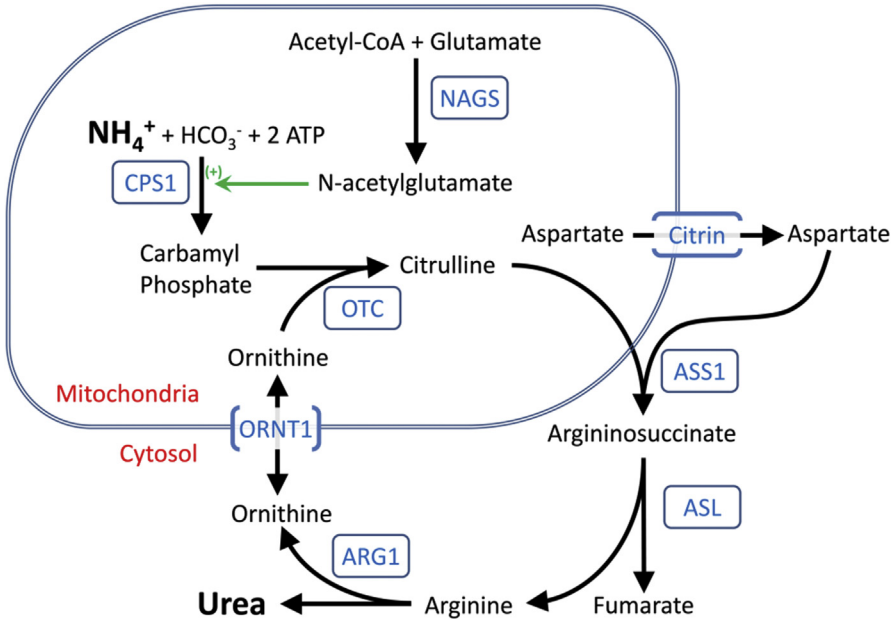

Fig. 1. The hepatic urea cycle. ARG1, arginase; ASL, argininosuccinic acid lyase; ASS1, argininosuccinic acid synthase; ATP, adenosine triphosphate; CoA, coenzyme A; CPS1, carbamyl phosphate synthetase 1; NAGS, *N*-acetylglutamate synthase; ORNT1, mitochondrial ornithine transporter 1; OTC, ornithine transcarbamylase.

A primary urea cycle disorder (UCD) results from an inherited defect in one of the 6 enzymes or 2 transporters of the urea cycle (see **Fig. 1**). Infants with near or total absence of activity of any of these proteins, in particular the first 4 urea cycle enzymes (CPS1, OTC, argininosuccinate synthase [ASS1], and argininosuccinate lyase [ASL]) or the cofactor producer (*N*-acetyl glutamate synthetase [NAGS]), often initially seem to be normal, but within days develop signs and symptoms of hyperammonemia. With partial urea cycle enzyme deficiencies, individuals may go decades before encountering an environmental stress that overwhelms their marginal ureagenesis capacity, resulting in a hyperammonemic episode. Commonly distributed, functional polymorphisms in the urea cycle may not result in hyperammonemia, but instead affect the production of downstream metabolic intermediates (such as arginine) during key periods of need. These variations in intermediate molecule supply can affect other metabolic pathways such as the production of NO from citrulline and arginine, and potentially the tricarboxylic acid cycle through aspartate and fumarate.

A secondary defect in the urea cycle may occur if there is a functional deficiency of substrates of one of the urea cycle enzymes. Examples include low intramitochondrial bicarbonate in carbonic anhydrase 5A deficiency, or low ornithine in lysinuric protein intolerance and neonatal ornithine aminotransferase deficiency. Additionally, inhibition of the cofactor producer, NAGS, is a proposed mechanism of urea cycle dysfunction in several conditions, including the organic acidemias, valproate toxicity, and chemotherapy-induced hyperammonemia. Furthermore, generalized liver dysfunction caused by toxin, infection, poor perfusion, or other inborn errors of metabolism, may impair urea cycle function and result in hyperammonemia (**Box 1**).

Box 1
Causes of hyperammonemia

Factors that diminish urea cycle function or augment demands on the urea cycle:
- Genetic defect in an enzyme
- Damage to the liver (both chronic and acutely)
- Chemical toxins (ethyl alcohol, industrial, etc)
- Infectious processes

Drug effects on the cycle
- Direct interference with enzymes
  - Valproic acid
  - Chemotherapy (particularly cyclophosphamide)
- Damage or general disruption of hepatic function
  - Systemic antifungals
  - Chemotherapy from hepatotoxic effects
  - Acetaminophen

Other metabolic diseases
- Organic acidemias (in particular, propionic and methylmalonic acidemias)
- Carbonic anhydrase 5A deficiency
- Lysinuric protein intolerance
- Ornithine aminotransferase deficiency (in neonates)
- Pyruvate carboxylase deficiency
- Fatty acid oxidation defects
- Galactosemia
- Tyrosinemia type I
- Glycogen storage disease

Portosystemic shunt

Nitrogen overload
- Massive hemolysis (such as large bone fracture or trauma)
- Total parenteral nutrition
- Protein catabolism from starvation or bariatric surgery
- Postpartum stress
- Heart lung transplant
- Renal disease
- Gastrointestinal bleeding
- Catabolic stimuli
  - Corticosteroids
  - Gastric bypass
  - Prolonged fast or excessive protein restriction

EFFECT OF AMMONIA ON BRAIN

Ammonia toxicity is thought to cause brain edema, induce neuronal and glial cell death, and alter synaptic growth.[2] The developing brain is much more susceptible to the deleterious effects of ammonia than the adult brain,[3] although the adult brain inside closed cranial sutures is more susceptible to the effects of cerebral edema.

Ammonia diffuses freely from the blood stream across the blood–brain barrier and is rapidly condensed with glutamate to form glutamine by astrocytic glutamine synthetase. Glutamine is osmotically active. In addition, ammonia itself may perturb potassium homeostasis and alter water transport through aquaporin. Therefore, through a variety of mechanisms, acute hyperammonemia results in astrocyte swelling and cytotoxic brain edema.[4] Astrocyte swelling can precipitate pH and $Ca2^{+}$-dependent glutamate release from astrocytes as well as inhibit GLAST (glutamate-aspartate) transporter reuptake of glutamate, leading to an overabundance of glutamate in the synaptic space. This results in excess depolarization of glutamatergic neurons

through the *N*-methyl-D-aspartate glutamate receptor, thereby inducing alterations in NO metabolism and the Na^+/K^+-ATPase. This process precipitates a shortage of adenosine triphosphate, mitochondrial dysfunction, and oxidative stress, which ultimately promote neuronal apoptosis.[2] Acute hyperammonemia may exert effects through metabotropic and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors[5] and also alters cholinergic and serotoninergic systems.[2]

Chronic hyperammonemia may induce adaptive changes in *N*-methyl-D-aspartate receptor-mediated transmission and induction of astrocytosis. In the developing rat, ammonia inhibits axonal and dendritic growth, and disturbs signal transduction pathways.[6] These potential mechanisms may explain the cognitive impairment, behavioral difficulties, and epilepsy observed in older individuals with UCDs, even in the absence of acute hyperammonemia.

Symptoms and Signs of Urea Cycle Disorders

Acute symptoms from hyperammonemia progress from somnolence to lethargy and coma. Abnormal posturing and encephalopathy are often related to the degree of central nervous system swelling and pressure on the brain stem.[7–9] A significant portion of neonates with severe hyperammonemia have seizures, which may be subclinical and nonconvulsive. Hyperventilation, secondary to cerebral edema, is a common early finding in a hyperammonemic attack, which causes a respiratory alkalosis. Hypoventilation and respiratory arrest follow as pressure increases on the brain stem[8–11] (**Box 2**).

In milder (or partial) urea cycle enzyme deficiencies, ammonia accumulation may be triggered by illness or stress at almost any time of life, resulting in multiple mild increases in plasma ammonia concentration.[12] The hyperammonemia is less severe and the symptoms more subtle. In individuals with partial enzyme deficiencies, the first recognized clinical episode may be delayed for months or years. Although the clinical abnormalities vary somewhat with the specific UCD, in most, the hyperammonemic episode is marked by loss of appetite, cyclical vomiting, lethargy, and behavioral abnormalities. Sleep disorders, delusions, hallucinations, and psychosis may occur. An encephalopathic (slow wave) pattern on electroencephalography may be observed during hyperammonemia and nonspecific brain atrophy may be seen subsequently on MRI[8,10,12–14] (**Box 3**). The symptoms at first presentation are summarized in **Box 4**.

CAUSES OF UREA CYCLE DISORDERS

A brief review of disorder of the of the urea cycle follows. **Table 1** lists the enzymes and genes of the cycle associated with disease.

Box 2
Symptoms of newborns with urea cycle defects

- Normal appearance at birth
- Somnolence progressing to lethargy then coma
- Loss of thermoregulation (hypothermia)
- Feeding disruption (increases catabolism)
- Neurologic posturing (from cerebral edema)
- Seizures
- Hyperventilation and then hypoventilation

Box 3
Common clinical features for late onset urea cycle disorders

- Dramatic and rapid increase in nitrogen load from
  - Trauma
  - Rapid weight loss and autocatabolism
  - Increase in protein turnover from intravenous steroids
- Avoidance of dietary protein
- History of behavioral or psychiatric illnesses
- Rapid deterioration of neurologic status
- Severe encephalopathy inconsistent with medical condition
- Evidence for cerebral edema by clinical examination or radiograph
- Seizures in most cases
- Decrease in oral intake in leading up to decompensation

Carbamylphosphate Synthetase 1 Deficiency

Carbamylphosphate synthetase 1 (CPS1) is the first enzyme in the urea cycle and is found primarily in the liver. It condenses ammonia, bicarbonate, and adenosine triphosphate into carbamyl phosphate. CPS1 requires its cofactor *N*-acetylglutamate (NAG; see Fig. 1). Individuals with complete CPS1 deficiency rapidly develop hyperammonemia in the newborn period. Affected children who are successfully rescued from crisis are chronically at risk for repeated bouts of hyperammonemia. Individuals with partial CPS1 deficiency can present at almost any time of life with a stressful triggering event. Biochemical analyses may be highly suggestive of CPS1 deficiency, however, molecular testing is often required to make this diagnosis.

N-Acetylglutamate Synthetase Deficiency

NAGS catalyzes the conversion of glutamate and acetyl-CoA to NAG, the required cofactor of CPS1 (see Fig. 1). Without NAG, CPS1 cannot convert ammonia into carbamyl phosphate; thus, NAGS deficiency results in a functional deficiency of CPS1. Individuals with complete NAGS deficiency rapidly develop hyperammonemia in the

Box 4
Presenting symptoms in 260 affected individuals at first presentation of hyperammonemia

- Neurologic symptoms (100%)
- Decreased level of consciousness (63%)
- Abnormal motor function or tone (30%)
- Seizures (10%)
- Vomiting (19%)
- Infection (30%)
- Subjective: decreased appetite, fussy
- Physiologic: respiratory alkalosis (secondary to cerebral edema) followed by apnea

From Summar ML, Dobbelaere D, Brusilow S, et al. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. Acta Paediatr 2008;97(10):1420–5; with permission.

Table 1
Enzymes and genes of urea cycle associated with disease: CPS1 deficiency

Gene Name	Gene Symbol	Location	Protein Name
Carbamyl phosphate synthetase 1	*CPS1*	2q35	Carbamyl phosphate synthase 1
Ornithine transcarbamylase	*OTC*	Xp21.1	Ornithine transcarbamylase
Argininosuccinate synthetase 1	*ASS1*	9q34	Argininosuccinate synthetase 1
Argininosuccinate lyase	*ASL*	7cen-q11.2	Argininosuccinate lyase
Arginase 1	*ARG1*	6q23	Arginase 1
N-acetyl glutamate synthetase	*NAGS*	17q21.3	*N*-acetyl glutamate synthetase
Solute carrier family 25 member 15	*SLC25A15*	13q14	Mitochondrial ornithine transporter 1 (ORNT1)
Solute carrier family 25 member 13	*SLC25A13*	7q21.3	Mitochondrial aspartate glutamate transporter (Citrin)

newborn period. Affected children who are successfully rescued from crisis are chronically at risk for repeated bouts of hyperammonemia. Individuals with partial NAGS deficiency can present at almost any time of life with a stressful triggering event. The use of an analog of NAG, carbamyl glutamate, has proven effective in the treatment of this condition.

Ornithine Transcarbamylase Deficiency

OTC combines carbamyl phosphate with ornithine to make citrulline (see **Fig. 1**). Like with CPS1 deficiency, children with complete OTC deficiency rapidly develop hyperammonemia in the newborn period and thereafter are at risk for repeated bouts of hyperammonemia. OTC is located on the X chromosome; therefore, the majority of severely affected individuals are male. Carrier females may rarely also be affected, owing to skewed lyonization. OTC deficiency is the most common UCD. Individuals with partial OTC deficiency can present at almost any time with a stressful triggering event.

Argininosuccinate Synthetase Deficiency (Citrullinemia I)

ASS1 conjugates citrulline and aspartate to form argininosuccinate (see **Fig. 1**). Individuals with complete ASS1 deficiency present with severe hyperammonemia in the newborn period. Citrulline levels in these individuals can be hundreds of times the normal values. Unlike CPS1, NAGS, and OTC, this enzyme is distributed throughout the body. ASS1 has also been shown to be involved in the production of NO.

Citrin Deficiency (Citrullinemia II)

Citrullinemia II results from a deficiency of the mitochondrial membrane glutamate-aspartate transporter, SLC25A15 (see **Fig. 1**). The reduced availability of aspartate for the enzyme argininosuccinic acid synthase results in a functional deficiency of the urea cycle. This disorder presents in adolescence or adulthood with recurrent hyperammonemia and neuropsychiatric symptoms. However, biallelic mutations in *SLC25A15* more commonly present in newborns as neonatal intrahepatic cholestasis or in older children as failure to thrive and dyslipidemia. The majority of reported affected individuals have been Asian, owing to a common mutation.

Argininosuccinate Lyase Deficiency (Argininosuccinic Aciduria)

The products of ASL are arginine and fumarate. This enzymatic step is past the point in the urea cycle at which all the waste nitrogen from 1 revolution through the cycle has been incorporated (see **Fig. 1**). Because argininosuccinate is freely excreted in the urine, thereby disposing of 4 nitrogens, hyperammonemia is typically less severe and less frequent than the disorders proximal to this step in the urea cycle. This disorder is often marked by chronic hepatic enlargement and elevation of transaminases. Biopsy of the liver shows enlarged hepatocytes, which may over time progress to fibrosis, the etiology of which is unclear. These children can also develop trichorrhexis nodosa, a nodelike appearance of fragile hair, which usually responds to arginine supplementation.[8,10] Reports exist of affected individuals who have never had prolonged coma, but nevertheless have significant developmental disabilities, possibly owing to impairment of NO synthesis or the deleterious effects of argininosuccinic acid.

Arginase Deficiency (Hyperargininemia)

Arginase is the final step in urea synthesis. It cleaves arginine into ornithine and urea (see **Fig. 1**). Arginase deficiency is not typically characterized by rapid-onset hyperammonemia. Instead, affected individuals often present with developmental delay and progressive spasticity, in particular of the lower limbs. They also may develop seizures and gradually lose intellectual attainments. Growth is usually slow and without therapy they do not reach normal adult height. Other symptoms that may present early in life include episodes of irritability, anorexia, and vomiting.

Ornithine Translocase Deficiency (Hyperornithinemia, Hyperammonemia, Homocitrullinuria Syndrome)

The hyperornithinemia, hyperammonemia, homocitrullinuria syndrome is described in more than 50 individuals. The defect in ornithine translocase results in diminished ornithine transport into the mitochondria with ornithine accumulation in the cytoplasm and reduced intramitochondrial ornithine causing impaired ureagenesis, hyperammonemia, and orotic aciduria (see **Fig. 1**). Plasma ornithine concentrations are extremely high. Homocitrulline is thought to originate from carbamylation of lysine. Most affected individuals have intermittent hyperammonemia accompanied by vomiting, lethargy, and coma (in extreme cases). Growth is abnormal and intellectual development is affected. Spasticity is common, as are seizures.

DIAGNOSIS OF UREA CYCLE DISORDERS

The most important step in diagnosing UCDs is clinical suspicion of hyperammonemia. Time is not on the side of the clinician or the affected individual. Particular care should be taken in drawing blood ammonia, because there is significant variability depending on proper technique and handling, frequently resulting in false-positive results. The clinician should remember that treatment should not be delayed in efforts to reach a final diagnosis, and that later stages of treatment should be tailored to the specific disorder. In addition to plasma ammonia, helpful laboratory data include, pH, CO_2, anion gap, blood lactate, plasma acylcarnitine profile, plasma amino acids, and urine organic acids, including the specific determination of orotic acid.[15] Individuals with UCDs will typically have normal glucose and electrolyte levels. The pH and CO_2 can vary with the degree of cerebral edema and hyperventilation or hypoventilation; however, hyperammonemia in the context of a respiratory alkalosis is highly suggestive of a UCD. In neonates, it should be remembered that the basal ammonia level is elevated over that of adults, which typically is less than 35 μmol/L (less than

110 μmol/L in neonates). An elevated plasma ammonia level of 150 μmol/L (>260 μg/dL) or higher in neonates and greater than 100 μmol/L (175 μg/dL) in older children and adults, 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 individuals and arrive at a tentative diagnosis. Elevations or depressions of the intermediate amino-containing molecules arginine, citrulline, ornithine, and argininosuccinate (see **Fig. 1**) will give clues to the point of defect in the cycle (**Fig. 2**). The levels of the nitrogen-buffering amino acid glutamine will also be quite high and can serve as confirmation of true hyperammonemia. If a defect in NAGS, CPS1, or OTC is suspected, the presence of elevated orotic acid in the urine

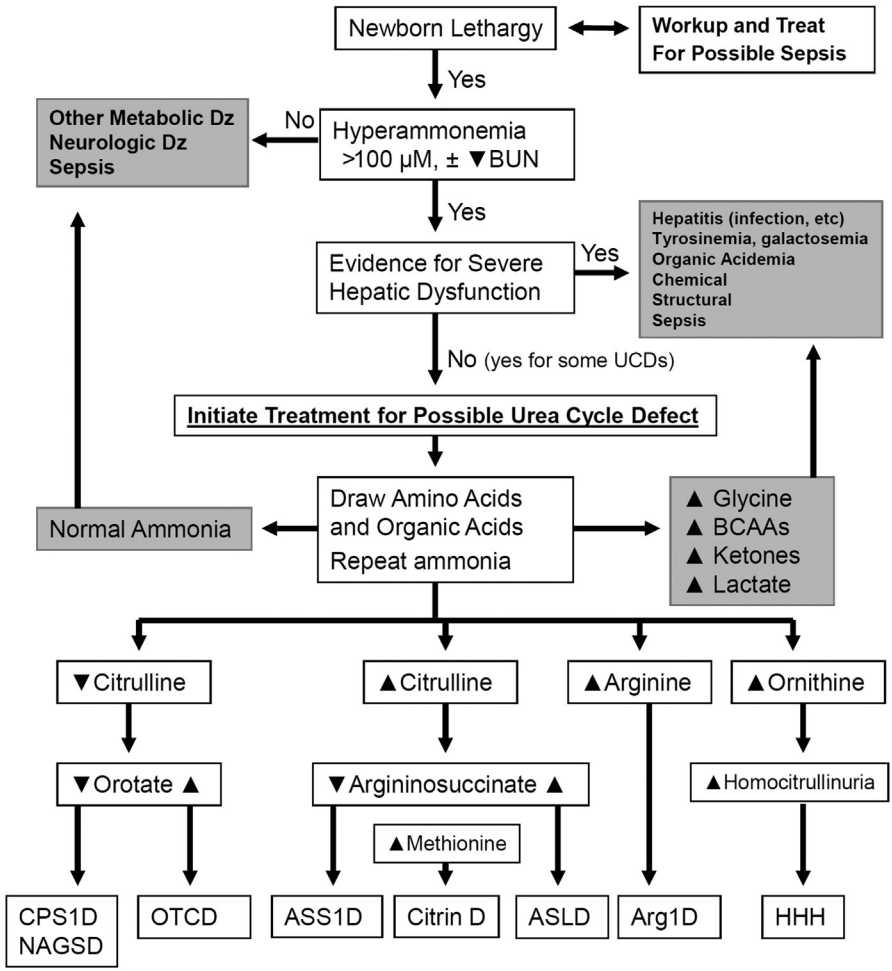

Fig. 2. Diagnostic algorithm for acute hyperammonemia. Arg1D, arginase deficiency; ASLD, argininosuccinic acid lyase deficiency; ASS1D, argininosuccinic acid synthase deficiency; BCAAs, branched chain amino acids; BUN, blood urea nitrogen; citrin D, citrin deficiency (citrullinemia type II); CPS1D, carbamyl phosphate synthetase 1 deficiency; Dz, disease; HHH, homocitrullinuria, hyperornithinemia, hyperammonemia; NAGSD, *N*-acetylglutamate synthase deficiency; OTCD, ornithine transcarbamylase deficiency; UCDs, urea cycle disorders; ▼, decreased; ▲, increased.

is highly suggestive of OTC deficiency. Orotic acid is produced when there is an overabundance of carbamyl phosphate that spills into the pyrimidine biosynthetic system. The determination of urine organic acids and plasma acylcarnitines will also herald the presence of an organic aciduria.

DNA sequence analysis is available for all of these disorders and the clinician should consider a panel approach rather than a gene-by-gene approach. Enzymatic and genetic diagnosis is available for all of these disorders. For CPS1, OTC, and NAGS, enzymatic diagnosis is made on a liver biopsy specimen freshly frozen in liquid nitrogen. Enzymatic testing for ASS1 and ASL can be done on fibroblast samples and arginase activity can be tested in red blood cells.

TREATMENT OF UREA CYCLE DISORDERS

Disclaimer: The treatment of these disorders is complex and best conducted by a specialist in inborn errors of metabolism at a center equipped to do so. For the pediatrician, recognition, stabilization, and rapid transport are the surest way to achieve optimal outcome. Delays in treatment and failure to maximize appropriate treatment will have permanent and damaging effects on the affected individual.

This section provides an overview of UCDs management.[9,16,17] The treatment of these individuals requires a highly coordinated team of specialists trained in caring for individuals with inborn errors of metabolism (**Box 5**). The emergency management of affected individuals in hyperammonemic coma resulting from a UCD is based on 3 interdependent principles: first, physical removal of the ammonia by dialysis or some form of hemofiltration; second, reversal of the catabolic state through caloric supplementation and, in extreme cases, hormonal suppression (glucose/insulin drip); and third, pharmacologic scavenging of excess nitrogen (**Box 6**). These measures should be pursued in parallel as quickly as possible.

The extracorporeal clearance of ammonia should be considered regardless of ammonia level if the affected individual is grossly encephalopathic, or the increase in ammonia is rapid or refractory to medical therapy. Central venous access should be established at once and dialysis or rapid hemofiltration begun immediately at the highest available flow rate. Dialysis is very effective for the removal of ammonia and the clearance depends on the flow through the dialysis circuit.[18,19] Given the risk of dialysis in a newborn, consideration should be given to arteriovenous or venovenous hemofiltration with a variable speed bypass pump in the circuit. If possible, access to hemofiltration should be maintained until the child is stabilized and the catabolic state is reversed. Some individuals may experience a rebound in plasma ammonia levels and may require additional rounds of dialysis. This effect may be attenuated by converting the affected individual to continuous renal replacement therapy after the initial period of intermittent dialysis. Most affected individuals will have a slight increase in ammonia after dialysis, because removal by scavengers and the liver will not be as effective. This slight increase usually does not necessitate repeat dialysis. With more aggressive reintroduction of protein, the author has seen a reduction in this rebound effect.

The importance of the management of the catabolic state cannot be overstressed. Because the catabolism of protein stores is often the triggering event for hyperammonemia, the affected child will continue to produce ammonia and will not stabilize until the catabolic state is reversed. Fluids, dextrose, and intravenous lipid emulsion should be given to blunt the catabolic process. Most affected individuals are dehydrated at initial presentation owing to poor fluid intake. The affected individuals should be assessed for dehydration and fluids replaced. Because these individuals suffer from

Box 5
Treatment team and organization

- Metabolic specialist
  - Coordinate treatment and management
- Intensive care team
  - Assist with physiologic support
  - Ventilator management
  - Sedation and pain management
- Nephrologist or dialysis team
  - Manage dialysis
  - Manage renal complications
- Surgical team
  - Large-bore catheter placement
  - Liver biopsy as necessary
  - Gastrostomy tube placement (if indicated)
- Pharmacy staff
  - Formulate nitrogen scavenging drugs
  - Cross-check dosing orders in complex management
- Laboratory staff
  - Analyze large volume of ammonia samples in acute phase
  - Analyze amino acids and other specialty laboratory tests
- Nursing staff
  - Execute complex and rapidly changing management plan
  - Closely monitor for signs of deterioration or change
- Nutritionist
  - Maximize caloric intake with neutral nitrogen balance
  - Educate family in management of complex very low-protein diet
- Social work
  - Rapidly identify resources for complex outpatient treatment regimen
  - Work with families in highly stressful clinical situation
- Genetic counselor
  - Educate family in genetics of rare metabolic disease
  - Identify other family members at potential risk (ornithine transcarbamylase particularly)
  - Ensure proper samples are obtained for future prenatal testing
  - Contact research and diagnostic centers for genetic testing

Box 6
Emergency management at first symptoms

- Fluids, dextrose, and intralipid to mitigate catabolism and typical dehydration (attempt 80 cal/kg/d).
- Antibiotics and septic workup to treat potential triggering events or primary sepsis (continue through treatment course). A spinal tap should probably be avoided pending imaging.
- Contact and possible transport to treatment-capable institute as soon as possible.
- Remove protein from intake (by mouth or total parenteral nutrition).
- Establish central venous access.
- Provide physiologic support (pressors, buffering agents, etc). (Renal output is critical to long-term success).
- Stabilize airway; cerebral edema may result in sudden respiratory arrest.

cerebral edema, care should be taken to avoid fluid overload. The nitrogen scavenging drugs are usually administered in a large volume of fluid, which should be taken into consideration. A regimen of 80 to 120 kcal/kg/d is a reasonable goal. The administration of insulin is useful, but also requires experience, and should be reserved for the sickest individuals. At the same time, protein must be temporarily removed from intake (by mouth or total parenteral nutrition), for no longer than 12 to 24 hours. Refeeding the affected individuals as soon as practicable is useful, because more calories can be administered this way. The use of essential amino acid formulations in feeding can reduce the amount of protein necessary to meet basic needs, and should be strongly considered within the first 24 hours of admission. In lieu of introducing food into the gut, parenteral nutrition containing only essential amino acids as a nitrogen source can be used. Delivery through the gastrointestinal tract is the preferred method. These individuals have not shown themselves to be more prone to necrotizing enterocolitis.

Emergency pharmacologic management with intravenous ammonia scavengers is initiated as soon as possible using the drug combination sodium phenylacetate and sodium benzoate, ideally while the dialysis is being arranged and the diagnostic workup is under way. These 2 agents are used in combination to trap nitrogen in excretable forms. Sodium benzoate combines with glycine to make hippurate, and sodium phenylacetate combines with glutamine to make phenacetylglutamine, which are excreted by the kidneys (or removed in the dialysate).[20,21] The body replaces these amino acids using excess nitrogen. It is suspected that the removal of glutamine by phenylacetate has the additional benefit of removing a compound suspected of having a major role in the neurotoxicity of these disorders.[2,4,22,23] Currently, administering a second loading dose to the affected individual after the initial phase is not recommended, because there is toxicity associated with overdose.

Arginine must also be administered continuously intravenously in the acute phase of treatment of UCDs. Supplementation of arginine serves to replace arginine not produced by the urea cycle (in addition to the partial cycle function it can stimulate) and prevents its deficiency from causing additional protein catabolism. Because arginine is the precursor for NO production, it is worth considering reducing the arginine dose if the affected individual develops vasodilation and hypotension. Before diagnostic confirmation, affected individuals should be also started on the NAG analog carbamyl glutamate, because this agent may be effective in NAGS deficiency, some cases of CPS1 deficiency, and in the organic acidemias.

Table 2 lists doses for the acute management of these individuals according to the diagnosis at the time of treatment (information extracted from the US Food and Drug Administration package insert). Owing to the potential for toxicity (lethal in extreme cases) of these drugs, consultation with an experienced metabolic physician is recommended before initiating treatment.[24] A resource for finding these physicians and other treatment suggestions is found in the home page for this web site at: http://www.rarediseasesnetwork.org/ucdc.

After the initial loading phase and dialysis, the dose should be converted to the maintenance doses of the ammonia scavengers listed in the manufacturer's packaging insert (see **Table 2**). If the exact enzyme defect is known, the amount of arginine administered can be adjusted downward. If chronic therapy is warranted, the affected individual can then be switched to the oral prodrug of phenylacetate, sodium phenylbutyrate, or the pre-prodrug glycerol phenylbutyrate, which has a slower release and no taste. The drug insert packaging should be consulted for proper dosing. The usual total daily dose of phenylbutyrate tablets or powder for individuals with UCDs is 450 to 600 mg/kg/d in individuals weighing less than 20 kg, or 9.9 to 13.0 g/m^2/d in larger individuals. The tablets or powder are to be taken in equally divided amounts with each meal or

Table 2
Sodium phenylacetate and sodium benzoate dosage and administration

	Components of Infusion Solution			Dosage Provided		
Affected Individual Population	**Sodium Phenylacetate and Sodium Benzoate**	**Arginine HCl Injection, 10%**	**Dextrose Injection, 10%**	**Sodium Phenylacetate**	**Sodium Benzoate**	**Arginine HCl**
Neonates to young children						
NAGS, CPS and OTC Deficiency						
Loading dose (90 min)	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/24 h	2.0 mL/kg/24 h	≥ 25 mL/kg	250 mg/kg/24 h	250 mg/kg/24 h	200 mg/kg/24 h
Unknown, ASD and ASL deficiency						
Loading dose (90 min)	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/24 h	6.0 mL/kg/24 h	≥25 mL/kg	250 mg/kg/24 h	250 mg/kg/24 h	600 mg/kg/24 h
Older children and adults						
NAGS, CPS, and OTC deficiency						
Loading dose (90 min)	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^2/24 h	2.0 mL/kg/24 h	≥25 mL/kg	5.5 g/m^2/24 h	5.5 g/m^2/24 h	200 mg/kg/24 h
Unknown, ASD and ASL deficiency						
Loading dose (90 min)	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^2/24 h	6.0 mL/kg/24 h	≥25 mL/kg	5.5 g/m^2/24 h	5.5 g/m^2/24 h	600 mg/kg/24 h

Abbreviations: ASL, argininosuccinate lyase; CPS, carbamyl phosphate synthetase; NAGS, *N*-acetyl glutamate synthetase; OTC, ornithine transcarbamylase.

feeding (ie, 3 to 6 times per day). Citrulline supplementation is recommended for individuals diagnosed with deficiency of NAGS, CPS1, or OTC. The daily recommended dose is 0.17 g/kg/d or 3.8 g/m^2/d. Arginine supplementation is needed for individuals diagnosed with deficiency of ASS1; arginine (free base) daily intake is recommended at 0.25 to 0.3 g/kg/d. In individuals with NAGS, the use of carbamyl glutamate has been demonstrated to be very effective,[25] and is approved by the US Food and Drug Administration for this disorder. The package insert should be consulted for dosing.

In all instances, intensive care treatment has to be meticulous. Ventilator or circulatory support may be required, in addition to anticonvulsive medications to control seizures. Sedation or head cooling to reduce cerebral activity could be of benefit to these individuals, but has not been fully clinically evaluated for efficacy. Antibiotic therapy and evaluation for sepsis is recommended because sepsis is an important consideration in the primary presentation and, if present, may lead to further catabolism. Electrolytes and acid–base balance are to be checked every 6 hours during the initial phase of treatment. The use of osmotic agents such as mannitol is not felt to be effective in treating the cerebral edema from hyperammonemia, because this condition is not thought to be osmotic in nature. In canines, opening the blood–brain barrier with mannitol resulted in cerebral edema by promoting the entry of ammonia into the brain fluid compartment.[26,27] Other measures include physiologic support (pressors, buffering agents to maintain pH and buffer arginine HCl, etc) and maintenance of renal output, particularly if ammonia scavengers are being used. Finally, it is imperative to reassess continuation of care after the initial phase of treatment.

Intravenous steroids should be avoided, because they promote catabolism. Valproic acid is also contraindicated because it may impair urea cycle function.

A rapid response to the hyperammonemia is indispensable for a good outcome.[28] Acute symptomatology centers around cerebral edema, disruptions in neurochemistry, and pressure on the brainstem. The resulting decrease in cerebral blood flow plus prolonged seizures, when they occur, are poor prognostic factors. In adults, because the sutures of the skull are fused, sensitivity to hyperammonemia seems to be considerably greater than in children.[29] Thus, treatment should be aggressive and intensified at a lower ammonia concentration than in children.

Cerebral studies should be conducted to determine the efficacy of treatment and whether continuation is warranted. Electroencephalography should be performed to assess both cerebral function and evidence of seizure activity, which may be nonconvulsive. If available, cerebral blood flow as determined by MRI can be used to establish if venous stasis has occurred from cerebral edema. Magnetic resonance spectroscopy may also be useful during the diagnostic stage. Evaluation of brain stem function and higher cortical function are useful to assess outcome. In the authors' experience, the appearance of the MRI in the postacute phase may be worse than what is seen in the long-term clinical outcome. Finally, the decision for continuation is based on baseline neurologic status, duration of coma, and potential for recovery, as well as whether the affected individual is a candidate for transplantation. In severe UCDs, early liver transplantation has become routine. Criteria for transplantation are, of course, linked back to neurologic status, duration of coma, and availability of donor organs. Diagnostic samples of DNA, liver, and skin should be obtained because they can be central in family counseling and future treatment issues.

LONG-TERM MANAGEMENT

Every effort should be made to avoid triggering events. It is imperative to prevent or quickly interrupt a catabolic state at an early stage of impending decompensation

during subsequent illnesses or surgeries, as well as during any event resulting in significant bleeding or tissue damage. Because this conditions usually happens at home, it is essential to educate the family about how to react adequately. All affected individuals should carry an emergency card or bracelet containing essential information and phone numbers, as well as instructions on emergency measures. Every affected person should relate to physicians and a hospital with a dedicated team of metabolic specialists who can be reached at any time. For vacations, it is usually prudent to enquire about metabolic services in the respective destination.

Long-term diet modification with nutritional oversight is often necessary in individuals with chronic episodes of hyperammonemia, and should be done only in collaboration with a metabolic dietitian. Individuals with urea cycle defects should also avoid dehydration, an especially common occurrence among adults in connection with alcohol intake, hiking, and airline flights. Not all affected adults who recover from a hyperammonemic episode require chronic nitrogen scavengers, but they ought to be considered because many of these individuals can become more brittle as time goes on. Recommended evaluations for individuals with UCDs are listed in **Box 7**.

Should psychiatric problems occur over the long term, caregivers should be alert to the possibility of hyperammonemia. In addition, many individuals with UCDs, in particular OTC deficiency and citrullinemia type 2, have presented with mental disturbance.[30–34]

Clinical observations of individuals with ASL deficiency demonstrate a high incidence of chronic progressive cirrhosis with eventual fibrosis of the liver. This finding is not commonly seen in the other UCDs and studies are underway to better determine the exact pathophysiology. It is important to provide genetic counseling in order to assess risk to other family members.

Box 7
Recommended evaluations for individuals with UCD

During initial presentation:

Head ultrasound

Brain MRI (upon stabilization of acute hyperammonemia)

Hearing screen at discharge

Vision screen at discharge

Long term management:

Developmental testing

Echocardiogram every 2 years to evaluate for pulmonary hypertension (for argininosuccinate synthase and argininosuccinate lyase deficiencies)

Annual abdominal ultrasound and alpha-fetoprotein after age 20

Dual energy x-ray absorptiometry scan (every 5 years, starting at age 10)

Routine clinic visits

- Nutrition evaluation to include
  - Growth parameters
  - Dietary history
- Biochemical analysis
  - Ammonia
  - Amino acid profile
  - Pre-albumin
  - Vitamin D (yearly)

SUMMARY

UCDs present the physician with one of the most emergent and intellectually challenging scenarios they are likely to encounter. With optimized teamwork, rapid response, and early diagnosis, affected individuals can have a good outcome. The experts in the Urea Cycle Disorders Consortium, which is sponsored by the National Institutes of Health, are an excellent resource when confronting a newly affected individual, and the UCDC web site is an excellent place to start.

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