



The Physician's Guide to **Urea Cycle Disorders**

Visit website at:
nordphysicianguides.org/urea-cycle-disorders/



NORD
National Organization for Rare Disorders

For more information about NORD's programs and services, contact:

National Organization for Rare Disorders (NORD)

PO Box 1968

Danbury, CT 06813-1968

Phone: (203) 744-0100

Toll free: (800) 999-NORD

Fax: (203) 798-2291

Website: www.rarediseases.org Email: orphan@rarediseases.org

NORD's Rare Disease Database and Organizational Database may be accessed at www.rarediseases.org.

Contents ©2012 National Organization for Rare Disorders®



What are Urea Cycle Disorders?

The urea cycle disorders (UCD) result from genetic mutations causing defects in the metabolism of the extra nitrogen produced by the breakdown of protein and other nitrogen-containing molecules. Severe deficiency or total absence of activity of any of the first four enzymes (CPSI, OTC, ASS, ASL) in the urea cycle or the cofactor producer (NAGS) results in the accumulation of ammonia and other precursor metabolites during the first few days of life. Infants with a urea cycle disorder often initially appear normal but rapidly develop cerebral edema and the related signs of lethargy; anorexia; hyperventilation or hypoventilation; hypothermia; seizures; neurologic posturing; and coma. 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 to moderately severe elevations of plasma ammonia concentration. The hyperammonemia is usually less severe and the symptoms more subtle. Patients with Arginase deficiency may present with hyperammonemia with severe stress, but are more likely to present with progressive neurologic symptoms unrelated to hyperammonemic episodes.

The urea cycle was first described in 1932 by Krebs and Henseleit. Classic urea cycle deficiency with no enzyme activity invariably presents with overwhelming hyperammonemia in the newborn period with little effect from the environment. Patients with residual activity may go decades before encountering an environmental stress strong enough to overwhelm their marginal ureagenesis capacity and 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 nitric oxide (NO) from citrulline/arginine and potentially the tricarboxylic acid cycle through aspartate and fumarate.

As shown in figure 1, the urea cycle is composed of five primary enzymes, one cofactor producer and two transport molecules across the mitochondrial membrane. Inborn errors of metabolism are associated with each step in the pathway and have been well described over the years. The cycle has the interesting property of having a subset of the enzymes participate in another metabolic pathway which produces nitric oxide. The urea cycle as a nitrogen clearance system is limited primarily to the human liver and intestine with carbamyl phosphate synthetase and ornithine transcarbamylase limited exclusively to those tissues. The enzymes downstream which process citrulline into arginine are ubiquitous in their distribution. As the rate-limiting enzyme in the urea cycle, CPSI functional changes would have the greatest impact on cycle function from environmental and pharmacologic stress (like valproic acid and cyclophosphamide). Hepatotoxins, both chronic and acute, have long been known to affect the clearance of ammonia from the bloodstream. Through loss of liver tissue and direct effects on the enzymes of the urea cycle, the ability to clear excess nitrogen is compromised. This often results in hepatic encephalopathy which compromises the neurologic integrity of the patient. Alcohol is one of the leading causes of hepatic encephalopathy, and chronic hyperammonemia one of the more debilitating results of chronic cirrhosis. The point at which these toxins result in elevated ammonia levels is a factor of the extent of the liver damage but also the genetically determined baseline capacity of the cycle. Other agents such as the seizure medication, valproic acid, are already established as urea cycle toxins.

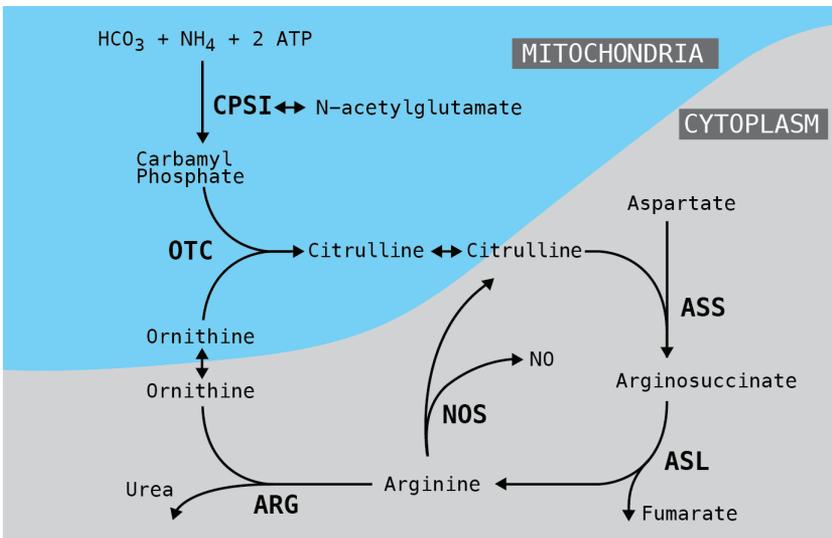


Figure 1

Symptoms & Signs

Symptoms progress from irritability to somnolence to lethargy and coma. Abnormal posturing and encephalopathy are often related to the degree of central nervous system swelling and pressure upon the brainstem. A significant portion of neonates with severe hyperammonemia have seizures. 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 brainstem.

Symptoms of Newborns with Urea Cycle Defects

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

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 to moderately severe elevations of plasma ammonia concentration. The hyperammonemia is usually less severe and the symptoms more subtle than in severe urea cycle enzyme deficiencies. In patients 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 urea cycle disorder, 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) EEG pattern may be observed during hyperammonemia and non-specific brain atrophy may be seen subsequently on MRI.

Common Clinical Features for Late Onset Urea Cycle Disorders

- Dramatic and rapid Increase in Nitrogen Load from
 - Trauma
 - Rapid weight loss and auto-catabolism
 - Increase in protein turnover from steroids
- Tend to avoid protein in their diet
- Often have history of behavioral or psychiatric illnesses

- Rapid deterioration of neurologic status.
- Severe encephalopathy inconsistent with medical condition.
- Usually involve defects in first part of urea cycle.
- Evidence for cerebral edema by clinical exam or radiograph
- Seizures in some cases.
- Decrease in oral intake leading up to decompensation

Presenting Symptoms in 260 Patients 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

Causes

A brief review of disorders of the of the urea cycle follows: Table 1 lists the genes of the cycle associated with disease.

Gene Name	Gene Symbol	Location	Protein Name
Carbamylphosphate synthetase I	CPS1	2q25	Carbamoyl-phosphate synthase ammonia
Ornithine transcarbamylase	OTC	Xp21.1	Ornithine carbamoyltransferase
Argininosuccinate synthase	ASS	9q34	Argininosuccinate synthase
Argininosuccinate lyase	ASL	7cen-q11.2	Argininosuccinate lyase
Arginase	ARG1	6q23	Arginase 1
N-acetyl glutamate synthase	NAGS	17q21.3	N-acetyl glutamate synthetase
Ornithine Transporter Mitochondrial 1	ORNT1	13q14	Ornithine Transporter Mitochondrial 1
Citrin	Citrin	7q21.3	Proposed hepatic mitochondrial asparatate transporter

Deficiencies of CPS1, ASS, ASL, ARG, NAGS, ORNT1 and Citrin are inherited in an autosomal recessive manner. OTC deficiency is inherited in an X-linked manner.

N-Acetylglutamate Synthetase Deficiency (NAGS)

N-acetylglutamate synthetase deficiency affects the body's ability to make n-acetylglutamate (NAG) which is a required cofactor for the function of carbamyl phosphate synthetase I. Without NAG, CPSI cannot convert ammonia into carbamyl phosphate. Along with OTC deficiency and CPSI, deficiency of N-acetylglutamate is the most severe of the urea cycle disorders. Patients with complete NAGS deficiency rapidly develop hyperammonemia in the newborn period. Patients who are successfully rescued from crisis are chronically at risk for repeated bouts of hyperammonemia.

Carbamoylphosphate Synthetase I Deficiency (CPSI Deficiency)

Carbamoylphosphate synthetase I deficiency affects the liver's ability to convert nitrogen to urea. This enzyme takes ammonia and through the use of bicarbonate and ATP produces carbamyl phosphate. This enzyme requires the presence of its cofactor n-acetylglutamate. Along with OTC deficiency and NAGS, deficiency of CPSI is the most severe of the urea cycle disorders. Patients with complete CPSI deficiency rapidly develop hyperammonemia in the newborn period. Patients who are successfully rescued from crisis are chronically at risk for repeated bouts of hyperammonemia. Patients with partial CPSI deficiency can present at almost any time of life with a stressful triggering event.

CPSI is the first enzyme in the urea cycle and is found primarily in the liver. It requires the cofactor N-acetylglutamate to function. Currently, diagnosis is based on enzymatic assay of liver tissue. Sequence analysis is available on a research basis only.

Ornithine Transcarbamylase (OTC) Deficiency

Ornithine transcarbamylase deficiency affects the liver's ability to convert ammonia into urea. OTC combines carbamyl phosphate with ornithine to make citrulline which is subsequently processed to urea (see: cycle diagram). Along with CPSI and NAGS deficiency, OTC deficiency is the most severe of the urea cycle disorders. Patients with complete OTC deficiency rapidly develop hyperammonemia in the newborn period. Patients who are successfully rescued from crisis are chronically at risk for repeated bouts of hyperammonemia. OTC is located on the X-chromosome which results in the majority of severe patients being male. Females can

also be affected but tend to present outside the neonatal period. Carrier females can also be affected (unlike the other urea cycle disorders) due to switching off on one of the X chromosomes in females. Patients with partial OTC deficiency can present at almost any time of life with a stressful triggering event.

Argininosuccinate Synthetase Deficiency (ASSD) (Citrullinemia I)

Defects in argininosuccinate synthetase (ASS) affect the ability to incorporate ammonia into urea. This enzyme combines citrulline with aspartate to form argininosuccinate. Patients with complete ASSD present with severe hyperammonemia in the newborn period. The use of arginine in these patients allows some nitrogen (ammonia) to be incorporated into the urea cycle which makes treatment somewhat easier than other defects in the cycle. Citrulline levels in these patients can be 100s of times the normal values. Unlike CPSI, NAGS, and OTC, this enzyme is distributed throughout the body. Diagnosis is by enzymatic assay of fibroblasts. Prenatal testing is performed by enzymatic analysis of amniocytes or CVS sample.

Citrin Deficiency (Citrullinemia II)

Citrullinemia II is an autosomal disorder that results in decreased activity in the liver of a transport molecule for aspartate. This results in limitation of activity for the enzyme argininosuccinic acid synthase which combines aspartate and citrulline to make argininosuccinic acid. Citrin (the defective protein) is an aspartate glutamate transporter across the mitochondrial membrane. This defect can present with classic newborn hyperammonemia, intrahepatic cholestasis, jaundice and fatty liver, but is more likely to present with insidious neurologic findings, hyperammonia, hypercitrullinemia and hyperlipidemia in adulthood. The majority of patients reported have been Japanese or Asian who share a common mutation. These patients can also have the dietary peculiarity of avoiding carbohydrates rather than protein. This probably is due to the overlap of this disorder with glucose metabolism. Treatment for hyperammonemia is the same as the other urea cycle disorders.

Argininosuccinate Lyase Deficiency (Argininosuccinic Aciduria)

Argininosuccinate lyase deficiency affects the body's ability to clear the nitrogen already incorporated into the urea cycle as argininosuccinate. This causes hyperammonemia. Severe defects often present with rapid-onset hyperammonemia in the newborn period. This enzyme defect is

past the point in the metabolic pathway at which all the waste nitrogen has been incorporated into the cycle as argininosuccinate (see figure). Treatment of these patients is based on a reduction in nitrogen intake and supplementation with arginine to complete a partial cycle. This disorder is 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 patients can also develop trichorrhexis nodosa, a node-like appearance of fragile hair, which usually responds to arginine supplementation. Reports exist of affected patients who have never had prolonged coma, but nevertheless have significant developmental disabilities. Clinical trials are underway to determine if the use of nitrogen scavengers will improve the outcome in these patients.

Deficiency of this enzyme prevents the conversion of argininosuccinate to the amino acid arginine which affects the urea cycle and other biochemical pathways.

Diagnosis is based on the presence of large amounts of argininosuccinic acid in the bloodstream and direct enzymatic analysis of fibroblasts. Prenatal diagnosis is available by enzymatic analysis of amniocytes or CVS sample.

Arginase Deficiency (Hyperargininemia)

Arginase deficiency is not typically characterized by rapid-onset hyperammonemia. These patients often present with the development of progressive spasticity with greater severity in the lower limbs. They also develop seizures and gradually lose intellectual attainments. Growth is usually slow and without therapy they usually do not reach normal adult height. Other symptoms that may present early in life include episodes of irritability, anorexia and vomiting. Severe episodes of hyperammonemia are seen infrequently with this disorder, but can be fatal.

Diagnosis is made by the elevated levels of arginine in the blood and by analysis of enzymatic activity in red blood cells.

Treatment is similar to other urea cycle disorders (limitation of protein, use of essential amino acid supplements, diversion of ammonia from urea cycle) with the exception that arginine supplementation is not indicated due to the excessive arginine levels already present in this condition.

Ornithine Translocase Deficiency (HHH Syndrome)

The HHH (hyperornithinemia, hyperammonemia, homocitrullinuria) syndrome is an autosomal recessive inherited disorder described in more than 50 patients. The clinical symptoms are related to the hyperammonemia and resemble those of the urea cycle disorders. Plasma ornithine concentrations are extremely high. 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 and orotic aciduria. Homocitrulline is thought to originate from transcarbamylation of lysine. Most patients 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. Adult patients are found with partial activity of the enzyme. They typically self-select low protein diets.

Common Stressors that affect urea cycle function

- Genetic defect in an enzyme
- Damage to the liver (both chronic and acutely)
- Chemical toxins (ETOH, industrial etc.)
- Infectious or viral processes
- Drug effects on the cycle
 - Direct Interference with Enzymes
 - Valproic acid (Depakote)
 - Chemotherapy (particularly cyclophosphamide)
 - Damage or general disruption of hepatic function
 - Systemic antifungals
 - Chemotherapy from hepatotoxic effects
 - Acetaminophen
 - Corticosteroids (catabolic effects)
- Other Metabolic Diseases
 - Organic acidemias (such as methylmalonic, propionic, etc.)
 - Pyruvate carboxylase deficiency
 - Fatty acid oxidation defects
 - Galactosemia
 - Tyrosinemia
 - Glycogen storage disease
- Vascular bypass of the liver by scarring or vascular bypass

- Nitrogen overload of the System
 - Massive hemolysis (such as large bone fracture or trauma)
 - Total parenteral nutrition
 - Protein catabolism from starvation or bariatric surgery
 - Post partum stress
 - Heart Lung Transplant
 - Renal Disease
 - GI bleeding

Diagnosis

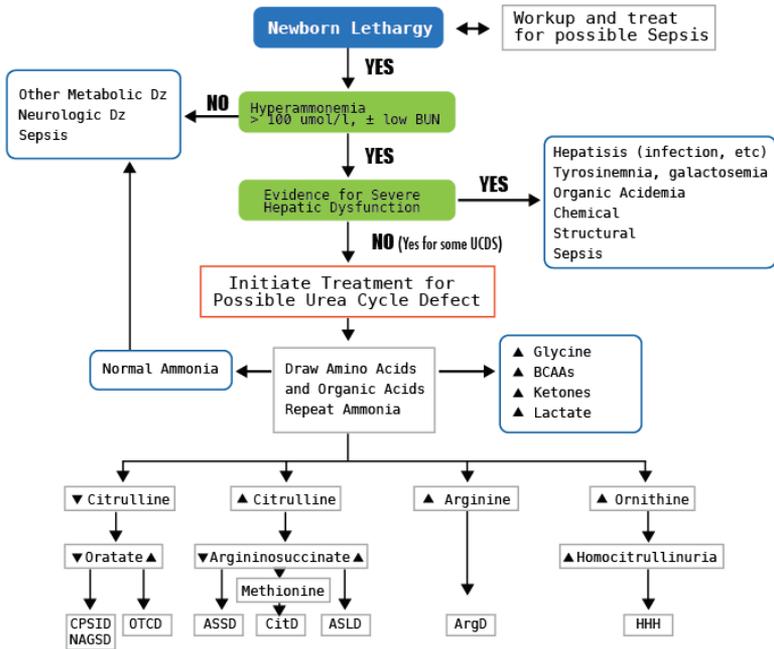
The most important step in diagnosing urea cycle disorders is clinical suspicion of hyperammonemia. A blood ammonia level is the first laboratory test in evaluating a patient with a suspected urea cycle defect. Particular care should be taken in drawing a blood ammonia since there is significant variability depending on proper technique and handling. 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, laboratory data useful in the diagnosis of UCDs include pH, CO₂, the anion gap, blood lactate, plasma acylcarnitine profile acylcarnitines, plasma and urine amino acids, and urine organic acid analyses including the specific determination of orotic acid. Patients with true urea cycle defects will typically have normal glucose and electrolyte levels. The pH and CO₂ can vary with the degree of cerebral edema and hyper- or hypo-ventilation.

In neonates it should be remembered that the basal ammonia level is elevated over that of adults, which typically is less than 35 $\mu\text{mol/L}$ (less than 110 $\mu\text{mol/L}$ in neonates). An elevated plasma ammonia level of 150 $\mu\text{mol/L}$ (>260 $\mu\text{g/dl}$) or higher in neonates and >100 $\mu\text{mol/L}$ (175 $\mu\text{g/dl}$) 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 urea cycle defect. Quantitative plasma amino acid analysis can be used to evaluate these patients and arrive at a tentative diagnosis. Elevations or depressions of the intermediate amino-containing molecules arginine, citrulline, and argininosuccinate (Figure 2, Diagnostic Flow Chart) will give clues to the point of defect in the cycle.

The amino acid profile in sick newborns can be quite different from those in children and adults, which should be taken into account. The levels of the nitrogen buffering amino acid glutamine will also be quite high and can serve as confirmation of the hyperammonemia. If a defect in NAGS, CPSI, or OTC is suspected, the presence of the organic acid orotic acid in the urine can help distinguish the diagnosis. Orotic acid is produced when there is an overabundance of carbamyl phosphate which spills into the pyrimidine biosynthetic system. The determination of urine organic acids and plasma acylcarnitines will also herald the presence of an organic aciduria. Other genetic defects that affect ammonia detoxification are lysinuric protein intolerance, the hyperinsulinism-hyperammonemia syndrome, hypoprolinemia (paradoxical fasting hyperammonemia) and pyruvate carboxylase deficiency. All of them are very rare and important hints would be obtained through the investigations outlined above.

Diagnostic Flow Chart for Acute Hyperammonemia



CPSID: carbamyl phosphate synthetase | deficiency
 NAGSD: n-acetylglutamate synthase deficiency
 OTC: ornithine transcarbamylase deficiency
 ASSD: argininosuccinic acid synthase deficiency
 CitD: citrin deficiency (citrullinemia type II)
 ASLD: argininosuccinic acid lyase deficiency
 ArgD: arginase deficiency
 HHH: homocitrullinuria, hyperornithinemia, hyperammonemia

Figure 2

Enzymatic and genetic diagnosis is available for all of these disorders. For CPSI, OTC, and NAGS, enzymatic diagnosis is made on a liver biopsy specimen freshly frozen in liquid nitrogen. Enzymatic testing for ASS, ASL can be done on fibroblast samples and arginase can be tested on red blood cells. Clinically approved DNA sequence analysis is only available for OTC at the time of this printing, but its availability for the other disorders is anticipated soon, as it is available outside the US. A frequently updated web resource for testing information can be found at the NIH sponsored site: <http://www.geneclinics.org>

Treatment

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 patient.

This section provides an overview of UCD management. The treatment of these patients requires a highly-coordinated team of specialists trained in caring for patients with inborn errors of metabolism (Table). Emergency management of patients in hyperammonemic coma resulting from a UCD is based on three 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. These are not consecutive but should be pursued independently in parallel as quickly as possible.

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 labs
- Nursing staff
 - Execute complex and rapidly changing management plan
 - Closely monitor patient 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 (OTC particularly)
 - Ensure proper samples are obtained for future prenatal testing
 - Contact research/diagnostic centers for genetic testing

Emergency Management

- Fluids, dextrose, and Interlipid® to mitigate catabolism and typical dehydration (attempt 80 cal/kg/day)
- Antibiotics and septic workup to treat potential triggering events or primary sepsis (continue through treatment course)
- Contact and possible transport to treatment-capable institute as soon as possible
- Remove protein from intake (PO or TPN)
- Establish central venous access
- Provide physiologic support (pressors, buffering agents, etc.). (Renal output is critical to long term success).
- Stabilize airway as cerebral edema may result in sudden respiratory arrest

If ammonia does not fall with high-calorie infusion plus pharmaceutical measures or ammonia is well over 700 μ mol/l, central venous access should be established at once and dialysis/rapid hemofiltration begun immediately at the highest available flow rate. Dialysis is very effective for the removal of ammonia and the clearance is dependent on the flow through the dialysis circuit. In severe cases of hyperammonemia, provision for hemofiltration should be made to follow the dialysis until the patient is stabilized and the catabolic state is reversed. Some patients will reaccumulate ammonia after their initial round of dialysis and may require additional periods of dialysis. Most patients will have a slight rise in ammonia after dialysis since removal by scavengers and the liver will not be as effective. This slight rise usually does not necessitate repeat dialysis.

The importance of the management of the catabolic state cannot be overstressed. Since the catabolism of protein stores is often the triggering event for hyperammonemia, the patient will not stabilize and ammonia will continue to rise until it is reversed. Fluids, dextrose and Intralipid® should be given to blunt the catabolic process. Most patients are dehydrated at initial presentation due to poor fluid intake. The patient should be assessed for dehydration and fluids replaced. Since these patients suffer from cerebral edema, care should be taken to avoid overhydration while avoiding dehydration. The nitrogen scavenging drugs are usually administered in a large volume of fluid which should be taken into consideration. A regimen of 80-120 kcal/kg/day is a reasonable goal. The administration of insulin and glucose are useful but also require experience and should be reserved for the sickest patients. At the same time, protein must be temporarily removed from intake (PO or TPN). 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. Refeeding the patient as soon as practicable is useful since 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. Table 1 is extracted from Singh et al and lists the proposed caloric needs for patients with urea cycle disorders.

Table: Recommended Daily Nutrient Intakes (Ranges) for Infants, Children, and Adults with Urea Cycle Disorders

Age	Nutrient			
	Protein (g/kg)	Patient Kcal Intake (kcal/kg)	Energy (kcal/kg)	Fluid (mL/kg)
Infants				
0 to < 3 mo	2.20-1.25	150-101	150-125	160-130
3 to < 6 mo	2.00-1.15	100-80	140-120	160-130
9 to < 12 mo	1.60-0.90	80-75	120-110	130-120
Girls and Boys				
	(g/day)	(kcal/day)	(kcal/day)	(mL/day)
1 to < 4 yr	8-12	800-1040	945-1890	945-1890
4 to < 7 yr	12-15	1196-1435	1365-2415	1365-2445
7 to < 11 yr	14-17	1199-1693	1730-3465	1730-3465
Women				
11 to < 15 yr	20-23		1575-3150	1575-3150
15 to < 19 yr	20-23		1260-3150	1260-3150
≥ 19 yr	22-25		1785-2625	1875-2625
Men				
11 to < 15 yr	20-23		2100-3885	2100-3885
15 to < 19 yr	21-24		2200-4095	2200-4095
≥ 19 yr	23-32		2625-3465	2625-3465

Table 1

Emergency pharmacologic management with ammonia scavengers and arginine is initiated as soon as possible using the drug combination sodium phenylacetate and sodium benzoate (Ammonul, Ucylyd Pharma), ideally while the dialysis is being arranged and the diagnostic workup is under way. Two agents are used in combination to trap nitrogen in excretable forms. Sodium benzoate combines with glycine to make hippurate which is excreted by the kidneys (or removed in the dialysate), and sodium phenylacetate combines with glutamine to make phenacetylglutamine which is also excreted in the urine. 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. Currently administering a second loading dose to the patient after the initial phase is not recommended. Arginine must also be administered continuously in the acute phase of treatment of urea cycle disorders. In addition to replenishing circulating amino acid levels, arginine can utilize those parts of the cycle not affected by genetic blocks and incorporate some nitrogen. Since arginine is the precursor for nitric oxide production, it is worth considering modification of the arginine dose downward if the patient develops vasodilation and hypotension. Table 2 lists doses for the acute management of these patients according to the diagnosis at the time of treatment (information extracted from FDA package insert). Due to the

potential for toxicity (lethal in extreme cases) of these drugs consultation with an experienced metabolic physician is recommended before starting treatment. 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>

Table: AMMONUL DOSAGE AND ADMINISTRATION						
SUMMARY TABLE						
Patient Population	Components of Infusion Solution			Dosage Provided		
	Ammonul	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 hr	2.0 mL/kg/24 hr	≥ 25 mL/kg	250 mg/kg/24 hr	250 mg/kg/24 hr	200 mg/kg/24 hr
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 hr	6.0 mL/kg/24 hr	≥ 25 mL/kg	250 mg/kg/24 hr	250 mg/kg/24 hr	600 mg/kg/24 hr
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 hr	2.0 mL/kg/24 hr	≥ 25 mL/kg	5.5 g/m ² /24 hr	5.5 g/m ² /24 hr	200 mg/kg/24 hr
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 hr	6.0 mL/kg/24 hr	≥ 25 mL/kg	5.5 g/m ² /24 hr	5.5 g/m ² /24 hr	600 mg/kg/24 hr

Table 2

After the initial loading phase and dialysis, the patient's dose should be converted to the maintenance doses of the ammonia scavengers listed in the manufacturers packaging insert (Table 1). If the exact enzyme defect is known the amount of arginine administered can be adjusted downward. If chronic therapy is warranted, the patient can then be switched to the oral pro-drug of phenylacetate, phenylbutyrate (Buphenyl). The usual total daily dose of Buphenyl Tablets and Powder for patients with urea cycle disorders is 450 – 600 mg/kg/day in patients weighing less than 20 kg, or 9.9 – 13.0 g/m²/day in larger patients. The tablets and powder are to be taken in equally divided amounts with each meal or feeding (i.e., three to six times per day). Citrulline supplementation is recommended for patients diagnosed with deficiency of n-acetylglutamate synthase, carbamylphosphate synthetase or ornithine transcarbamylase; citrulline daily recommended intake is 0.17 g/kg/day or 3.8 g/m²/day. Arginine supplementation is needed for patients diagnosed with deficiency of argininosuccinic acid synthetase; arginine (free base) daily intake is recommended at 0.4 – 0.7 g/kg/day or 8.8 - 15.4 g/m²/day. In patients with n-acetylglutamate synthetase, the use of carbamyl glutamate has been demonstrated to be very effective, and is now FDA approved 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. Anticonvulsive medication to control seizures and sedation or head cooling to reduce cerebral activity could be of benefit to these patients but has not been clinically evaluated for effect. 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 but this is mainly anecdotal. In canines, opening the blood brain barrier with mannitol resulted in cerebral edema by promoting the entry of ammonia into the brain fluid compartment. Intravenous steroids and valproic acid should be avoided. 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.

Rapid response to the hyperammonemia is indispensable for a good outcome. 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 appears considerably greater than in children. Thus treatment should be aggressive and intensified at a lower ammonia concentration than in children.

Neurologic Evaluation

Cerebral studies should be conducted to determine the efficacy of treatment and whether continuation is warranted. EEG should be performed to assess both cerebral function and evidence of seizure activity. If available, MRI-determined cerebral blood flow can be used to establish if venous stasis has occurred from cerebral edema. Evaluation of brainstem function and higher cortical function are useful to assess outcome. Finally, the decision for continuation is based on baseline neurologic status, duration of the patient's coma and potential for recovery, and whether the patient is a candidate for transplantation. If the basic urea cycle defect is severe enough, liver transplantation should be considered. 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 since 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. As this usually happens at home, it is essential to educate the family about how to react adequately. All patients should carry an emergency card or bracelet containing essential information and phone numbers as well as instructions on emergency measures. Every patient 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 necessary in patients with urea cycle enzyme defects. Patients should also avoid

dehydration, an especially common occurrence among adults in connection with alcohol intake, excessive exercise, hiking, and airline flights. Not all adult patients who recover from a hyperammonemic episode require chronic nitrogen scavengers, but they ought to be considered since many of these patients can become more brittle as time goes on. In particular, IV steroids for asthma and administration of valproic acid are contraindicated.

Should psychiatric problems occur over the long term, caregivers should be alert to the possibility of hyperammonemia. In addition, many patients with citrullinemia type 2, in particular, have presented with mental disturbance.

Clinical observations of patients with argininosuccinic acid lyase deficiency demonstrate a high incidence of chronic progressive cirrhosis with eventual fibrosis of the liver. This finding is not commonly seen in the other urea cycle disorders 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.

Clinical Testing and Work-Up:

For patients with UCD during initial presentation the following are suggested:

- Head Ultrasound
- MRI of the head upon stabilization
- Hearing Screen at Discharge
- Vision Screen at Discharge

For long term management the following are suggested:

- Developmental testing
- For ASS, ASL patients echocardiogram every 2 years looking for pulmonary hypertension
- For patients with all UCD: annual abdominal ultrasound and alpha-fetoprotein after age 20.

For routine clinic visits:

- Dietary history
- Amino acid profile
- Growth parameters
- Ammonia

Investigational Therapies

Information on current clinical trials is posted at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials sponsored by private sources, contact: www.centerwatch.com

NORD does not endorse or recommend any particular studies.

References

1. Bachmann, C. Diagnosis of urea cycle disorders. *Enzyme*.38:Pages:233-241. 1987.
2. Bachmann, C. Interpretation of plasma amino acids in the follow-up of patients: the impact of compartmentation. *J. Inher. Metab. Dis.*31:Pages:7-20. 2008. PM:18236169
3. Batshaw, M. L. and Brusilow, S. W. Evidence of lack of toxicity of sodium phenylacetate and sodium benzoate in treating urea cycle enzymopathies. *Journal of Inherited Metabolic Disease*.4:Pages:231-1981.
4. Batshaw, M. L., MacArthur, R. B., and Tuchman, M. Alternative pathway therapy for urea cycle disorders: twenty years later. *J. Pediatr.*138:Pages:S46-S54. 2001. PM:11148549
5. Batshaw, M. L. and Monahan, P. S. Treatment of urea cycle disorders. [Review] [37 refs]. *Enzyme*.38:Pages:242-250. 1987.
6. Batshaw, M. L., Painter, M. J., Sproul, G. T., Schafer, I. A., Thomas, G. H., and Brusilow, S. Therapy of urea cycle enzymopathies: three case studies. *Johns Hopkins Medical Journal*.148:Pages:34-40. 1981.
7. Ben-Ari, Z., Dalal, A., Morry, A., Pitlik, S., Zinger, P., Cohen, J., Fattal, I., Galili-Mosberg, R., Tessler, D., Baruch, R. G., Nuoffer, J. M., Largiader, C. R., and Mandel, H. Adult-onset ornithine transcarbamylase (OTC) deficiency unmasked by the Atkins' diet. *J. Hepatol.*52:Pages:292-295. 2010. PM:20031247
8. Bezinover, D., Douthitt, L., McQuillan, P. M., Khan, A., Dalal, P., Stene, J., Uemura, T., Kadry, Z., and Janicki, P. K. Fatal hyperammonemia after renal transplant due to late-onset urea cycle deficiency: a case report. *Transplant. Proc.*42:Pages:1982-1985. 2010. PM:20620562
9. Bindu, P. S., Sinha, S., Taly, A. B., Christopher, R., and Kovoor, J. M. Cranial MRI in acute hyperammonemic encephalopathy. *Pediatr. Neurol.*41:Pages:139-142. 2009. PM:19589465
10. Bireley, W. R., Van Hove, J. L., Gallagher, R. C., and Fenton, L. Z. Urea cycle disorders: brain MRI and neurological outcome. *Pediatr. Radiol.*10-12-2011. PM:21989980
11. Braissant, O. Current concepts in the pathogenesis of urea cycle disorders. *Mol. Genet. Metab.*100 Suppl 1:Pages:S3-S12. 2010. PM:20227314
12. Brusilow, S. W. Disorders of the urea cycle. *Hospital Practice (Office Edition)*.20:Pages:65-72. 1985.

13. Brusilow, S. W. Urea cycle disorders: clinical paradigm of hyperammonemic encephalopathy. *Prog. Liver Dis.* 13:Pages:293-309. 1995.PM:9224507
14. Brusilow, S. W. and Maestri, N. E. Urea cycle disorders: diagnosis, pathophysiology, and therapy. *Adv. Pediatr.* 43:Pages:127-170. 1996.PM:8794176
15. Cagnon, L. and Braissant, O. Hyperammonemia-induced toxicity for the developing central nervous system. *Brain Res. Rev.* 56:Pages:183-197. 2007.PM:17881060
16. Campeau, P. M., Pivalizza, P. J., Miller, G., McBride, K., Karpen, S., Goss, J., and Lee, B. H. Early orthotopic liver transplantation in urea cycle defects: follow up of a developmental outcome study. *Mol. Genet. Metab.* 100 Suppl 1:Pages:S84-S87. 2010.PM:20223690
17. Cederbaum, S., Lemons, C., and Batshaw, M. L. Alternative pathway or diversion therapy for urea cycle disorders now and in the future. *Mol. Genet. Metab.* 100:Pages:219-220. 2010. PM:20462778
18. Celik, O., Buyuktas, D., Aydin, A., and Acbay, O. Ornithine transcarbamylase deficiency diagnosed in pregnancy. *Gynecol. Endocrinol.* 27:Pages:1052-1054. 2011.PM:21736537
19. Chan, J. S., Harding, C. O., and Blanke, C. D. Postchemotherapy hyperammonemic encephalopathy emulating ornithine transcarbamoylase (OTC) deficiency. *South. Med. J.* 101:Pages:543-545. 2008.PM:18414167
20. Das, A. M., Illsinger, S., Hartmann, H., Oehler, K., Bohnhorst, B., Kuhn-Velten, W. N., and Lucke, T. Prenatal benzoate treatment in urea cycle defects. *Arch. Dis. Child Fetal Neonatal Ed.* 94:Pages:F216-F217. 2009.PM:19000997
21. Deignan, J. L., Cederbaum, S. D., and Grody, W. W. Contrasting features of urea cycle disorders in human patients and knockout mouse models. *Mol. Genet. Metab.* 93:Pages:7-14. 2008.PM:17933574
22. Dutoit, A. P., Flick, R. R., Sprung, J., Babovic-Vuksanovic, D., and Weingarten, T. N. Anesthetic implications of ornithine transcarbamylase deficiency. *Paediatr. Anaesth.* 20:Pages:666-673. 2010.PM:20497355
23. Enns, G. M. Neurologic damage and neurocognitive dysfunction in urea cycle disorders. *Semin. Pediatr. Neurol.* 15:Pages:132-139. 2008.PM:18708004
24. Enns, G. M. Nitrogen sparing therapy revisited 2009. *Mol. Genet. Metab.* 100 Suppl 1:Pages:S65-S71. 2010.PM:20202877
25. Enns, G. M., Berry, S. A., Berry, G. T., Rhead, W. J., Brusilow, S. W., and Hamosh, A. Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N. Engl. J. Med.* 356:Pages:2282-2292. 5-31-2007.PM:17538087
26. Feillet, F. and Leonard, J. V. Alternative pathway therapy for urea cycle disorders. [Review] [42 refs]. *Journal of Inherited Metabolic Disease.* 21 Suppl 1:Pages:101-111. 1998.
27. Ficiocioglu, C., Mandell, R., and Shih, V. E. Argininosuccinate lyase deficiency: longterm outcome of 13 patients detected by newborn screening. *Mol. Genet. Metab.* 98:Pages:273-277. 2009.PM:19635676
28. Funghini, S., Thusberg, J., Spada, M., Gasperini, S., Parini, R., Ventura, L., Meli, C., De Cosmo, L., Sibilio, M., Mooney, S. D., Guerrini, R., Donati, M. A., and Morrone, A. Carbamoyl Phosphate Synthetase 1 deficiency in Italy: Clinical and genetic findings in a heterogeneous cohort. *Gene.* 493:Pages:228-234. 2-10-2012.PM:22173106

29. Gessler, P., Buchal, P., Schwenk, H. U., and Wermuth, B. Favourable long-term outcome after immediate treatment of neonatal hyperammonemia due to N-acetylglutamate synthase deficiency. *Eur.J.Pediatr.* 169:Pages:197-199. 2010.PM:19533169
30. Gropman, A. L., Summar, M., and Leonard, J. V. Neurological implications of urea cycle disorders. *J.Inherit.Metab Dis.* 11-23-2007.PM:18038189
31. Gungor, S., Akinci, A., Firat, A. K., Tabel, Y., and Alkan, A. Neuroimaging findings in hyperargininemia. *J.Neuroimaging.* 18:Pages:457-462. 2008.PM:18321250
32. Haberle, J. Role of carginic acid in the treatment of acute hyperammonemia due to N-acetylglutamate synthase deficiency. *Ther.Clin.Risk Manag.* 7:Pages:327-332. 2011. PM:21941437
33. Ibarra-Gonzalez, I., Fernandez-Lainez, C., and Vela-Amieva, M. Clinical and biochemical characteristics of patients with urea cycle disorders in a developing country. *Clin. Biochem.* 43:Pages:461-466. 2010.PM:20025860
34. Iyer, R., Jenkinson, C. P., Vockley, J. G., Kern, R. M., Grody, W. W., and Cederbaum, S. The human arginases and arginase deficiency. *J.Inherit.Metab Dis.* 21 Suppl 1:Pages:86-100. 1998. PM:9686347
35. Kido, J., Nakamura, K., Mitsubuchi, H., Ohura, T., Takayanagi, M., Matsuo, M., Yoshino, M., Shigematsu, Y., Yorifuji, T., Kasahara, M., Horikawa, R., and Endo, F. Long-term outcome and intervention of urea cycle disorders in Japan. *J.Inherit.Metab Dis.* 12-14-2011.PM:22167275
36. King, L. S., Singh, R. H., Rhead, W. J., Smith, W., Lee, B., and Summar, M. L. Genetic counseling issues in urea cycle disorders. *Crit Care Clin.* 21:Pages:S37-S44. 2005.PM:16227114
37. Klaus, V., Vermeulen, T., Minassian, B., Israelian, N., Engel, K., Lund, A. M., Roebrock, K., Christensen, E., and Haberle, J. Highly variable clinical phenotype of carbamylphosphate synthetase 1 deficiency in one family: an effect of allelic variation in gene expression? *Clin. Genet.* 76:Pages:263-269. 2009.PM:19793055
38. Krebs, H. A. and Henseleit, K. Untersuchungen über die harnstoffbildung im tierkörper. *Hoppe-Seyler's Z. Physiol. Chem.* 210:Pages:325-332. 1932.
39. Krivitzky, L., Babikian, T., Lee, H. S., Thomas, N. H., Burk-Paull, K. L., and Batshaw, M. L. Intellectual, adaptive, and behavioral functioning in children with urea cycle disorders. *Pediatr. Res.* 66:Pages:96-101. 2009.PM:19287347
40. Lee, B., Singh, R. H., Rhead, W. J., Sniderman, King L., Smith, W., and Summar, M. L. Considerations in the difficult-to-manage urea cycle disorder patient. *Crit Care Clin.* 21:Pages:S19-S25. 2005.PM:16227112
41. Lichter-Konecki, U. Profiling of astrocyte properties in the hyperammonaemic brain: shedding new light on the pathophysiology of the brain damage in hyperammonaemia. *J.Inherit.Metab Dis.* 31:Pages:492-502. 2008.PM:18683079
42. Maestri, N. E., Hauser, E. R., Bartholomew, D., and Brusilow, S. W. Prospective treatment of urea cycle disorders. *Journal of Pediatrics.* 119:Pages:923-928. 1991.
43. Maestri, N. E., McGowan, K. D., and Brusilow, S. W. Plasma glutamine concentration: a guide in the management of urea cycle disorders. *Journal of Pediatrics.* 121:Pages:259-261. 1992.

44. Mendez-Figueroa, H., Lamance, K., Sutton, V. R., Aagaard-Tillery, K., and Van, den Veyver, I. Management of ornithine transcarbamylase deficiency in pregnancy. *Am.J.Perinatol.* 27:Pages:775-784. 2010.PM:20458665
45. Meyburg, J. and Hoffmann, G. F. Liver, liver cell and stem cell transplantation for the treatment of urea cycle defects. *Mol.Genet.Metab.* 100 Suppl 1:Pages:S77-S83. 2010. PM:20156696
46. Moini, M., Mistry, P., and Schilsky, M. L. Liver transplantation for inherited metabolic disorders of the liver. *Curr.Opin.Organ Transplant.* 15:Pages:269-276. 2010.PM:20489626
47. Nagamani, S. C., Erez, A., and Lee, B. Argininosuccinate lyase deficiency. *Genet.Med.* 1-5-2012.PM:22241104
48. Ozanne, B., Nelson, J., Cousineau, J., Lambert, M., Phan, V., Mitchell, G., Alvarez, F., Ducruet, T., and Juvet, P. Threshold for toxicity from hyperammonemia in critically ill children. *J. Hepatol.* 56:Pages:123-128. 2012.PM:21703182
49. Satwani, H., Raza, J., Hanai, J., and Nomachi, S. Prevalence of selected disorders of inborn errors of metabolism in suspected cases at a tertiary care hospital in Karachi. *J.Pak.Med. Assoc.* 59:Pages:815-819. 2009.PM:20201170
50. Scaglia, F. New insights in nutritional management and amino acid supplementation in urea cycle disorders. *Mol.Genet.Metab.* 100 Suppl 1:Pages:S72-S76. 2010.PM:20299258
51. Seminara, J., Tuchman, M., Krivitzky, L., Krischer, J., Lee, H. S., Lemons, C., Baumgartner, M., Cederbaum, S., Diaz, G. A., Feigenbaum, A., Gallagher, R. C., Harding, C. O., Kerr, D. S., Lanpher, B., Lee, B., Lichter-Konecki, U., McCandless, S. E., Merritt, J. L., Oster-Granite, M. L., Seashore, M. R., Stricker, T., Summar, M., Waisbren, S., Yudkoff, M., and Batshaw, M. L. Establishing a consortium for the study of rare diseases: The Urea Cycle Disorders Consortium. *Mol.Genet.Metab.* 100 Suppl 1:Pages:S97-105. 2010.PM:20188616
52. Serrano, M., Martins, C., Perez-Duenas, B., Gomez-Lopez, L., Murgui, E., Fons, C., Garcia-Cazorla, A., Artuch, R., Jara, F., Arranz, J. A., Haberle, J., Briones, P., Campistol, J., Pineda, M., and Vilaseca, M. A. Neuropsychiatric manifestations in late-onset urea cycle disorder patients. *J.Child Neurol.* 25:Pages:352-358. 2010.PM:19684305
53. Singh, R. H. Nutritional management of patients with urea cycle disorders. *J.Inherit.Metab Dis.* 30:Pages:880-887. 2007.PM:18034368
54. Singh, R. H., Rhead, W. J., Smith, W., Lee, B., King, L. S., and Summar, M. Nutritional management of urea cycle disorders. *Crit Care Clin.* 21:Pages:S27-S35. 2005.PM:16227113
55. Smith, W., Kishnani, P. S., Lee, B., Singh, R. H., Rhead, W. J., Sniderman, King L., Smith, M., and Summar, M. Urea cycle disorders: clinical presentation outside the newborn period. *Crit Care Clin.* 21:Pages:S9-17. 2005.PM:16227115
56. Sniderman, King L., Singh, R. H., Rhead, W. J., Smith, W., Lee, B., and Summar, M. L. Genetic counseling issues in urea cycle disorders. *Crit Care Clin.* 21:Pages:S37-S44. 2005. PM:16227114
57. Summar, M. Current strategies for the management of neonatal urea cycle disorders. *J.Pediatr.* 138:Pages:S30-S39. 2001.PM:11148547
58. Summar, M. and Tuchman, M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. *J.Pediatr.* 138:Pages:S6-10. 2001.PM:11148544

59. Summar, M. L. Presentation and management of urea cycle disorders outside the newborn period. *Crit Care Clin.* 21:Pages:ix-2005. PM:16227116
60. Summar, M. L., Barr, F., Dawling, S., Smith, W., Lee, B., Singh, R. H., Rhead, W. J., Sniderman, King L., and Christman, B. W. Unmasked adult-onset urea cycle disorders in the critical care setting. *Crit Care Clin.* 21:Pages:S1-S8. 2005. PM:16227111
61. Summar, M. L., Dobbelaere, D., Brusilow, S., and Lee, B. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. *Acta Paediatr.* 97:Pages:1420-1425. 2008. PM:18647279
62. Tihtonen, K., Uotila, J., Lahde, J., Salo, M., and Keskinen, P. Risk of hyperammonemic coma in the puerperium: two cases of women with diagnosed and undiagnosed deficiency of urea cycle enzymes. *Acta Obstet. Gynecol. Scand.* 89:Pages:404-406. 2010. PM:20102292
63. Todo, S., Starzl, T. E., Tzakis, A., Benkov, K. J., Kalousek, F., Saheki, T., and Fenton, W. A. Orthotopic liver transplantation for urea cycle enzyme deficiency. *Hepatology.* 15:Pages:419-422. 1992.
64. Tuchman, M., Lee, B., Lichter-Konecki, U., Summar, M. L., Yudkoff, M., Cederbaum, S. D., Kerr, D. S., Diaz, G. A., Seashore, M. R., Lee, H. S., McCarter, R. J., Krischer, J. P., and Batshaw, M. L. Cross-sectional multicenter study of patients with urea cycle disorders in the United States. *Mol. Genet. Metab.* 94:Pages:397-402. 2008. PM:18562231
65. Wakiya, T., Sanada, Y., Mizuta, K., Umehara, M., Urahasi, T., Egami, S., Hishikawa, S., Fujiwara, T., Sakuma, Y., Hyodo, M., Murayama, K., Hakamada, K., Yasuda, Y., and Kawarasaki, H. Living donor liver transplantation for ornithine transcarbamylase deficiency. *Pediatr. Transplant.* 15:Pages:390-395. 2011. PM:21585627
66. Westrope, C., Morris, K., Burford, D., and Morrison, G. Continuous hemofiltration in the control of neonatal hyperammonemia: a 10-year experience. *Pediatr. Nephrol.* 25:Pages:1725-1730. 2010. PM:20495829
67. Wilson, J. M., Shchelochkov, O. A., Gallagher, R. C., and Batshaw, M. L. Hepatocellular carcinoma in a research subject with ornithine transcarbamylase deficiency. *Mol. Genet. Metab.* 105:Pages:263-265. 2012. PM:22129577
68. Wong, Y. C., Au, W. L., Xu, M., Ye, J., and Lim, C. C. Magnetic resonance spectroscopy in adult-onset citrullinemia: elevated glutamine levels in comatose patients. *Arch. Neurol.* 64:Pages:1034-1037. 2007. PM:17620496
69. Yazaki, M., Ikeda, S., Kobayashi, K., and Saheki, T. Therapeutic approaches for patients with adult-onset type II citrullinemia (CTLN2): effectiveness of treatment with low-carbohydrate diet and sodium pyruvate. *Rinsho Shinkeigaku.* 50:Pages:844-847. 2010. PM:21921468
70. Zalba, B., Serrano, T., Velilla, C., Cabrerizo, J. L., Ridruejo, R., and Obon, B. [Encephalopathy by hyperammonemia in teenagers]. *An. Sist. Sanit. Navar.* 32:Pages:447-451. 2009. PM:20094106

Resources

NIH Rare Diseases Clinical Research Network: Urea Cycle Disorders Consortium (treatment, studies, education):
<http://rarediseasesnetwork.epi.usf.edu/ucdc/index.htm>

National Urea Cycle Disorders Foundation (information, referrals, resources, patient/family education and support)
<http://www.nucdf.org/> 75 S. Grand Ave.
Pasadena, CA 91105
Phone: (626)578-0833
Toll Free: (800)386-8233
Email: CureUCD@nucdf.org

European Network and Registry for Intoxicating Metabolic Diseases
<http://www.e-imd.org/en/index.phtml>

GeneTests: <http://www.ncbi.nlm.nih.gov/sites/GeneTests/>

Acknowledgements

NORD is grateful to the following medical expert for serving as author of this Physician Guide:

Marshall Summar, MD
Division Chief, Genetics and Metabolism
Center for Neuroscience and Behavioral Medicine
Children's National Medical Center
Washington DC

NORD also gratefully acknowledges the assistance of Cynthia Le Mons, Executive Director, National Urea Cycle Disorders Foundation, in the preparation of this Guide.

This NORD Physician Guide was made possible by an educational grant from Cytonet.

Patient Support and Resources

National Organization for Rare Disorders (NORD)

55 Kenosia Avenue

PO Box 1968

Danbury, CT 06813-1968

Phone: (203) 744-0100

Toll free: (800) 999-NORD

Fax: (203) 798-2291

www.rarediseases.org

orphan@rarediseases.org

NORD gratefully acknowledges the assistance of the following medical expert in the preparation of this booklet:

Marshall Summar, MD

Division Chief, Genetics and
Metabolism

Center for Neuroscience and
Behavioral Medicine

Children's National Medical Center
Washington DC

NORD Guides for Physicians

- #1 The Pediatrician's Guide to Tyrosinemia Type 1
- #2 The Pediatrician's Guide to Ornithine Transcarbamylase Deficiency...and other Urea Cycle Disorders
- #3 The Physician's Guide to Primary Lateral Sclerosis
- #4 The Physician's Guide to Pompe Disease
- #5 The Physician's Guide to Multiple System Atrophy
- #6 The Physician's Guide to Hereditary Ataxia
- #7 The Physician's Guide to Giant Hypertrophic Gastritis and Menetrier's Disease
- #8 The Physician's Guide to Amyloidosis
- #9 The Physician's Guide to Medullary Thyroid Cancer
- #10 The Physician's Guide to Hereditary Angioedema (HAE)
- #11 The Physician's Guide to The Homocystinurias
- #12 The Physician's Guide to Treacher Collins Syndrome

These booklets are available free of charge. To obtain copies, call or write to NORD or download the text from www.rarediseases.org.

This booklet was made possible through an educational grant from Cytonet.

For information on rare disorders and the voluntary health organizations that help people affected by them, visit NORD's web site at www.rarediseases.org or call (800) 999-NORD or (203) 744-0100.

NORD helps patients and families affected by rare disorders by providing:

- Physician-reviewed information in understandable language
- Referrals to support groups and other sources of help
- Networking with other patients and families
- Medication assistance programs
- Grants and fellowships to encourage research on rare diseases
- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals

Contact NORD at orphan@rarediseases.org.

National Organization for Rare Disorders (NORD)
PO Box 1968
Danbury, CT 06813-1968
Phone: (203) 744-0100
Toll free: (800) 999-NORD
Fax: (203) 798-2291