Long-term management of patients with urea cycle disorders

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The long-term treatment of patients with urea cycle disorders (UCDs) includes diet treatment and use of specific medications. Guidelines are provided for patients with a severe phenotype. However, treatment must be tailored for each individual, especially with regard to residual enzyme function and in vivo metabolic capacity. This will be reflected in tests used for monitoring therapy that should be performed on a periodic basis. The goal of therapy is to eliminate chronic complications, a laudable but rarely attainable goal. Sick-day rules are discussed. Chronic management also includes diverse services that are essential to the success of the metabolic program. These include neurologic and developmental evaluations, feeding team evaluation and therapy, physical and occupational therapies, speech therapy, school and educational services, social service intervention, psychologic services, and genetic counseling. (J Pediatr 2001;138:S56-S61)

The long-term treatment of patients with urea cycle disorders involves the use of a low-protein diet, supplementation with certain amino acids, and administration of organic compounds to augment waste nitrogen excretion.[1-8] Optimal care, however, necessitates the use of a comprehensive long-term management program that anticipates and responds to a diverse array of needs and complications. The items covered in the treatment of the patients are outlined in Table I.

The list of UCDs is shown in Table II. The most common UCD is ornithine transcarbamylase deficiency.[1] Inherited as an X-linked trait, it affects both males and females. The phenotype is extremely variable, not only because of random X chromosome inactivation in females but also because of many different types of OTC gene mutations and modifying factors such as puberty, pregnancy, labor and delivery, and environmental factors. The spectrum of disease expression ranges from the catastrophically ill 2-day-old boy with an extremely severe form of the disease to the previously healthy adult woman with postpartum hyperammonemia.[1,9,10] The long-term management of each of these forms of OTC deficiency may be different. It is important to be mindful that the type of low-protein diet and amount of medication must be tailored to each individual patient's phenotype and needs.[9] However, in this article we restrict our discussion of treatment to the UCD with a severe phenotype. Also, because the therapy for carbamylphosphate synthetase deficiency is similar to that of OTC deficiency,[1] treatment of both will be addressed as one. The rest of the UCDs will be addressed separately. CPS, argininosuccinate synthetase, argininosuccinate lyase, and arginase deficiencies are all inherited as autosomal recessive traits.[1]

ASL	Argininosuccinic acid lyase
ASS	Argininosuccinic acid synthetase
CPS	Carbamyl phosphate synthetase I
OTC	Ornithine transcarbamylase
UCD	Urea cycle disorder

Diet

The low-protein diet and medications used in the treatment of infants with each of the UCDs are shown in Table III and are based on the recommended treatment as outlined, at least in part, in the book entitled *Metabolic and Molecular Basis of Inherited Diseases*.[1] However, it is important to note that these doses are recommended for severely affected patients and are not suitable for all patients. The treatment must be tailored to the needs of the patient as reflected in the growth rate, plasma ammonia, and amino acid levels and ancillary tests such as blood counts and serum albumin. The biochemical and nutritional rationales that are used for 2 representative patients are depicted in the flow diagrams in

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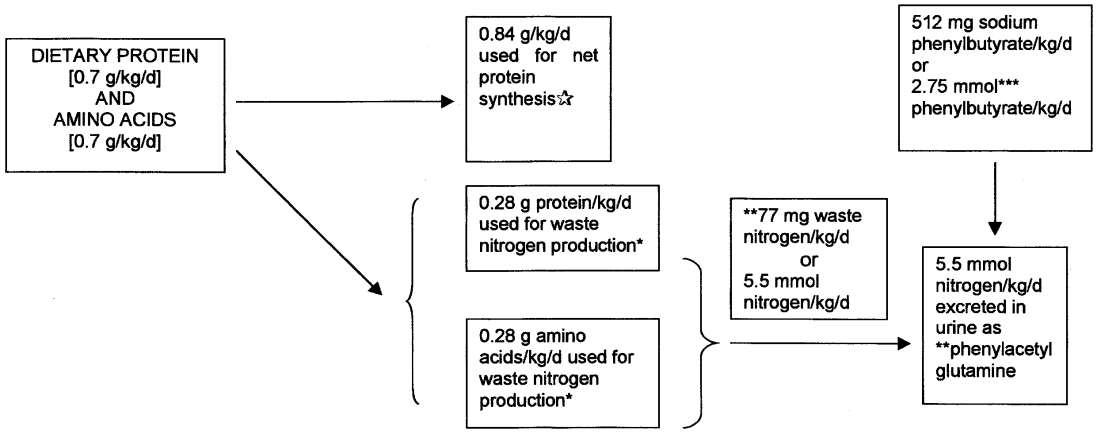

Fig 1. Maintenance therapy and whole body nitrogen economy in patients with severe UCDs. Six-month-old infant with OTC deficiency. *Forty percent to 45% used for waste nitrogen production. **Sixteen percent of protein and 11.5% of amino acids are nitrogen. ***Formula weight: sodium phenylbutyrate = 186. ☆This calculation does not take into account the fact that the nitrogen atom in glutamate derived from essential amino acid catabolism can be reused for synthesis of nonessential amino acids necessary for protein synthesis.

Figs 1 and 2. Please note that the patient whose treatment is depicted in Fig 2 is a 6-year-old child, not an infant. This child serves to illustrate how the protein intake, medication dosage, and partitioning of nitrogen differs according to disease type and age.

In most instances only the broad ranges are given. The first principle is that the amount of whole protein that can be given to the patient will depend on the enzyme deficiency and age. With severe OTC deficiency, it is necessary to restrict dietary protein intake to an amount that is inadequate to permit growth in infancy; the remaining amount of nitrogen must be delivered as essential amino acids. This is analogous to increasing the biologic value of the protein. Therefore the total amount of nitrogen ingested per day can be reduced below the threshold necessary for growth. The types and amounts of medications will also vary but primarily are dependent on the enzyme defect. In OTC and CPS deficiencies, citrulline therapy is used to restore body arginine pools for protein synthesis. Arginine may be used instead of citrulline, but the drawback is that the waste nitrogen atom from aspartate used in the ASS reaction is not used. However, in ASL deficiency arginine is exclusively used not only to maintain adequate arginine levels but also to increase production of argininosuccinate and thereby enhance urinary excretion of waste nitrogen in the form of argininosuccinate. This works much better for ASL than for ASS deficiency, because argininosuccinate, unlike citrulline, is essentially filtered by the kidney and excreted in urine without being reabsorbed.

CLINICAL AND LABORATORY MONITORING

Clinical and laboratory monitoring of each patient is important to the success of the long-term management. The critical parameters in clinical monitoring of therapy are shown in Table IV. These include the growth parameters, weight, height, and head circumference, the developmental and neurologic assessments, and the examination of the liver. In severe ASL deficiency the liver is usually chronically enlarged despite adequate treatment.[1] Some patients may even have cirrhosis. The key tests for laboratory monitoring of therapy are shown in Table V. This testing includes the quantitation of plasma ammonia, plasma amino acids, and in some instances, urine orotate. A complete blood count with a differential serum chemistry panel screen including liver function tests

Table I. Long-term treatment of patients with UCDs

Low-protein diet and medications
Acute episodes
Elective surgery
Neurologic and developmental evaluations
Feeding team evaluation and therapy
Physical and occupational therapies
Speech therapy
School and education services
Social services
Psychologic services
Genetic counseling

Table II. Urea cycle disorders

OTC deficiency
CPS deficiency
ASS deficiency
ASL deficiency
Arginase deficiency
N-acetylglutamate synthase deficiency

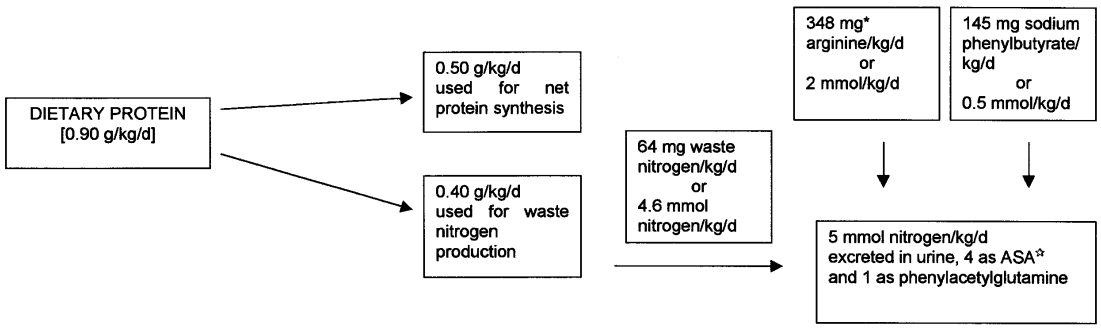

Fig 2. Maintenance therapy and whole body nitrogen economy in patients with severe UCDs. Six-year-old child with ASL deficiency. *Molecular weight arginine = 174. ☆Assuming 100% of ASA is filtered and excreted.

Table III. Treatment of infants with UCDs

	Diet		Medications		
UCD	Protein (g/kg/d)	Essential Amino Acids (g/kg/d)	Sodium phenyl-butyrate (g/kg/d)	Arginine (g/kg/d)	Citrulline (g/kg/d)
OTC deficiency					
CPS deficiency	0.7	0.7	0.45-0.60 (9.9-13.0)*	—	0.17 (3.8)*
ASS deficiency	1.5 – 2.0	—	0.45-0.60	0.4 – 0.7 (8.8-15.4)*	—
ASL deficiency	1.5 – 2.0	—	0.45-0.60	0.4 – 0.7	—
Arginase deficiency†	0.7	0.7	0.30-0.60	—	—

*(g/m^2/d)
†N.B. data on treatment of infants with arginase deficiency are not available, especially for prospective use in asymptomatic newborns.

Table IV. Clinical monitoring of therapy.

Weight, height, and head circumference
Developmental assessment
Neurologic assessment
Liver examination

Table V. Laboratory monitoring of therapy

Plasma ammonia
Plasma amino acid quantitation
Urine orotate

and urinalysis should be obtained on a yearly basis. Every 5 to 10 years each patient should be screened specifically for iron deficiency, vitamin B_{12} deficiency, or both, because of the low-protein, low-meat intake diet.

The goal of treatment is to maintain normal levels of plasma ammonia through the use of the low-protein diet and medication while allowing for normal growth. As the body's burden of waste nitrogen increases, certain amino acid levels will rise, along with or preceding the rise in plasma ammonia. The most prominent is glutamine, the amino acid that is used to monitor the whole body waste nitrogen burden.[1,11,12] The finding of both an elevated plasma ammonia and glutamine level indicates that body ammonia is elevated and the patient is at risk for hyperammonemic encephalopathy.[1] The other amino acids that may be elevated in plasma include alanine, glycine, glutamate, asparagine, aspartate, and lysine. Except in arginase deficiency, plasma arginine may be decreased in the patient with inadequate treatment with arginine or citrulline. The latter may be low in some patients with OTC or CPS deficiency despite therapy. Occasionally, levels of the essential amino acids and, most important, the branched-chain amino acids, leucine, isoleucine, and valine, may fall below the normal range because of the use of a strict low-protein diet. It is important not to allow such deficiency to remain chronic and severe; otherwise, a nutritional deficiency state may ensue. Manifestations may include poor growth, anemia, rash, and hypoalbuminemia.

The biochemical targets for optimal UCD control are noted in Table VI. These include a plasma ammonia level of <40 μmol/L, a plasma glutamine level of <1000 μmol/L, normal plasma levels of alanine, glycine, lysine, and arginine, and no subnormal concentration of any of the essential amino acids. When arginine therapy is used, the serum levels will vary, depending

Table VI. Biochemical targets for optimal UCD control

Plasma ammonia <40 μmol/L
Plasma glutamine <1000 μmol/L
Normal plasma levels of alanine, glycine, lysine, and arginine (except arginase deficiency)
No subnormal concentrations of essential amino acids (eg, leucine, isoleucine, valine)
Normal urinary orotate excretion (<3 μmol/mmol creatinine)
Normal plasma protein concentrations (eg, albumin)

These goals are not always attainable, or even appropriate in every patient. Treatment **must** be individualized.

Table VII. Chronic complications in patients on UCD therapy

Poor growth
Developmental delay
Learning problems
Speech disorder
ADHD
Mental retardation
Spasticity
Seizure disorder
Hepatomegaly

ADHD, Attention deficit hyperactivity disorder.

on the dosage schedule (usually 4-times daily) and timing of the blood sample, but the per-dose values should be <200 μmol/L. Some patients appear to maintain good metabolic control with higher glutamine levels, that is, >1000 μmol/L (personal communication, J.V. Leonard). Ideally, the urinary orotate excretion will be <3 μmol/mmol creatinine. Plasma concentrations of proteins such as albumin should be in the normal range. Measurement of plasma prealbumin may be necessary at times to ascertain the presence of an incipient protein deficiency. It is important to note that citrulline levels will always be markedly increased in patients with ASS deficiency, and both argininosuccinate and citrulline may be elevated in patients with ASL deficiency. It is almost impossible to achieve chronic normal levels of arginine in patients with arginase deficiency while on a protein-restricted diet, even when supplemented with an essential amino acid powder mixture.

Complications of UCD Therapy

The chronic complications that may be seen in patients receiving UCD therapy are shown in Table VII. These include poor growth, developmental delay, learning problems, speech disorder, attention deficit hyperactivity disorder, mental retardation, spasticity as in cerebral palsy, seizure disorder, and hepatomegaly with and without liver function test abnormalities.[1,2,13,14] It is important to note that normal variant short stature such as genetic short stature and constitutional delay of growth and puberty may also occur in patients with UCDs. Whether the latter condition is more prevalent in the UCD population is unknown. Many of the previously described complications may be a consequence of hyperammonemic coma in the newborn period or later, after an acute intermittent illness. In addition, some patients may have been chronically intoxicated because of a delay in diagnosis. This type of patient can present in late infancy or childhood with progressive psychomotor retardation or with what appears to be a progressive neurodegenerative disease such as with arginase deficiency. After the hyperammonemia is corrected or the disease process is stabilized, all of the sequelae such as learning problems, speech defect, cerebral palsy, and seizure disorders will need to be treated, as with any child without a UCD. Patients with ASL deficiency in particular may have developmental delay and seizures despite adequate metabolic control and the absence of a historical episode of hyperammonemic coma. Sometimes poor disease control may result in chronic hepatomegaly with increased accumulation of fat and glycogen in the liver, fibrosis, and abnormal liver function tests. It usually remits after stabilization of the hyperammonemia. As noted previously, this is not the case with ASL deficiency, especially with the neonatal-onset variety.

The intercurrent illnesses or an acute episode of decompensation associated with hyperammonemia must be treated as delineated by Brusilow et al.[6] This may include the use of intravenous sodium phenylacetate, sodium benzoate, and arginine hydrochloride. Hemodialysis therapy may also be necessary. If the patient is not comatose, enteral administration of medications and cessation of protein intake may be effective. Parents are to be instructed in the signs and symptoms of hyperammonemia such as anorexia, vomiting, altered behavior, headache, visual disturbances, ataxia, lethargy, and seizures that may indicate acute hyperammonemia. These may occur during a viral illness or after ingestion of a large amount of dietary protein. If a patient is ill because of an acquired illness but the plasma ammonia level is <100 μmol/L (approximately 3 times the upper range of normal), the family should introduce a sick-day routine.[15] This consists of a decrease, or more commonly a cessation, of protein intake while nonprotein calories are given often in the form

of fruit juices, or even better, the Ross Prophree or Mead-Johnson 80056 formula suspensions. The ammonia scavenging medications should be administered during these periods, and dosages can be increased by approximately 50% if warranted by the clinical findings.

UCD AND SURGERY

If patients require elective surgery, they should be admitted to the hospital on the day before surgery. At this time the plasma ammonia and amino acid levels should be checked to ensure that the patient is not in a decompensated state prior to surgery. Before surgery, when the patient is no longer allowed to eat or drink, an intravenous catheter should be placed to deliver fluids, glucose, and electrolytes at a maintenance rate. This will prevent fasting-induced catabolism and its associated hyperammonemia. In older children and adolescents, the use of a 10% glucose solution may produce hyperglycemia to a degree sufficient to induce an osmotic diuresis and volume contraction. For these instances a 5% glucose solution should be used. Patients may also need to receive the UCD medications before, during, and after the procedure. Depending on the severity of the enzyme deficiency and the nature of the surgery, plasma ammonia levels should be monitored before, during, and after the operation, even in the recovery room. If the procedure is a long one such as an orthopedic scoliosis repair, it may be necessary to administer glucose and Intralipid, with total parenteral nutrition (the equivalent of a low-protein diet) along with intravenous sodium phenylacetate, sodium benzoate, and arginine hydrochloride during the operation.

The rest of the services outlined in Table I should be delivered to the patients and their families. There are exceptions, but the broad and comprehensive approach to care is especially important for the patient with neonatal-onset disease. Many of the patients with OTC and CPS deficiencies are so severely affected that the medical therapies outlined previously are only temporizing measures until liver transplantation can be performed in the first year of life.[16,17] The delivery of chronic care to a patient with this kind of special needs requires a multidisciplinary approach.

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LONG-TERM MANAGEMENT DISCUSSION

Coordinator Role

It was agreed that there is a need to establish a coordinator to oversee all aspects of the treatment of a patient with UCD, so that progress over time is properly reviewed.

Amino Acid Levels

Maintenance is aimed at balancing the amino acid pools. To achieve this, a range of proteins from different sources should be taken by the patient. Determination of amino acid levels should be made with a blood sample taken 2 hours after a meal. The amino acid levels should be as low as possible without being subnormal, providing growth is not compromised

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