

Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders

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In an effort to develop standards for the treatment of patients with urea cycle disorders, a consensus conference was held in Washington, DC, from April 27-29, 2000. Conference participants included physicians, scientists, nurses, dieticians, and a genetic counselor, all experts in their various medical fields in these diseases. Representatives from the Food and Drug Administration and the National Urea Cycle Disorders Foundation, a parents support group, also participated in the conference. The goals set forth for the conference were to (1) reach a consensus on diagnostic and therapeutic guidelines for urea cycle disorders with the most up-to-date information and the experience of experts in the field, (2) establish a collaborative network of health care professionals to advance the cause of patients with urea cycle disorders in the areas of clinical management and research, and (3) provide help to health care providers in the recognition and management of these complex disorders by publishing the proceedings of the conference in a widely read journal. The articles that follow this introduction represent the current state of knowledge on the topics addressed in the conference and a summary of the discussions that followed each of the presentations. With input from all the participants, we tried to cover those topics that were believed to be the most relevant both to the experts and to patients. As the reader will appreciate, many unresolved and controversial issues pertaining to treatment have yet to be studied by rigorous scientific methods. On the other hand, there are many issues on which the panel agreed. In many instances the availability of reliable information on the respective topics determined whether consensus could be reached. (J Pediatr 2001;138:S6-S10)

A short summary on inherited urea cycle disorders follows to provide the reader with a succinct background to the specific topics on diagnosis and management that make up this supple-

ment. Some of the content of this summary was adapted from Tuchman M, Batshaw ML: Urea cycle and related disorders in Rudolph's Textbook of Pediatrics (in press).

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Urea cycle disorders are each caused by inherited defects in genes encoding enzymes or membrane transporters involved in ureagenesis (Fig 1). Their overall prevalence is considered to be approximately 1:30,000 births; however, there are no population studies to support this frequency. The lack of newborn mass screening programs targeted at these disorders prevents us from obtaining prevalence data. Urea cycle disorders are a common cause of inherited hyperammonemia, but because of the severe consequences of these disorders for the patient, they should be distinguished from other inborn errors of metabolism with secondary hyperammonemia such as fatty acid oxidation disorders, organic acidurias, nonketotic hyperglycinemia, and congenital lactic acidoses. Acquired hyperammonemia can frequently be seen in liver disease of various causes and after chemotherapy and organ transplantation. Finally, there is a rare and severe condition termed transient hyperammonemia of the neonate, found predominantly in premature infants, the cause of which remains obscure.

CPS	Carbamyl phosphate synthetase I
HHH	Hyperornithinemia, hyperammonemia, homocitrullinemia
LPI	Lysinuric protein intolerance
NAGS	N-acetyl glutamate synthase
OTC	Ornithine transcarbamylase

SPECIFIC DISORDERS

The urea cycle disorders are caused by defects in the enzymes carbamyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinate synthetase (citrullinemia), argininosucci-

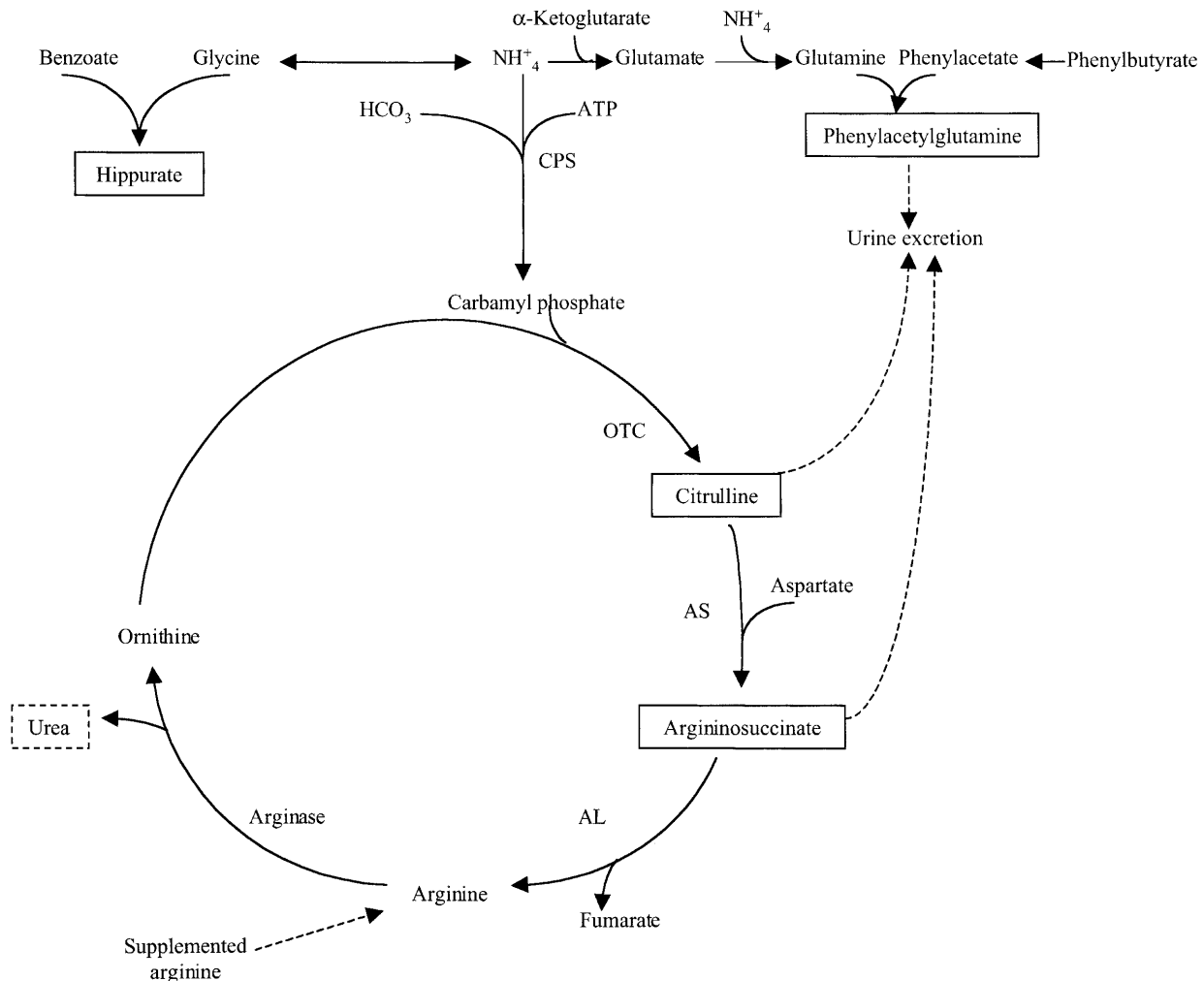


Fig 1. Complete urea cycle pathway that resides in liver is illustrated. Also shown are alternative pathways used to eliminate nitrogen in patients with urea cycle defects. *CPS*, Carbamyl phosphate synthetase; *OTC*, ornithine transcarbamylase; *ASS*, argininosuccinate synthetase; *ASL*, argininosuccinate lyase; *ARG*, arginase; *NAGS*, N-acetylglutamate synthase.

nate lyase (argininosuccinic aciduria), arginase (hyperargininemia), and N-acetylglutamate synthase. Defects in the membrane transporter of dibasic amino acids (lysine, arginine, and ornithine) called hyperdibasic aminoaciduria or lysinuric protein intolerance, the mitochondrial membrane ornithine transporter called hyperornithinemia, hyperammonemia, homocitrullinuria syndrome, and the mitochondrial calcium-dependent transporter called citrullinemia type II should also be included in urea cycle disorders. Awareness by health care professionals of these genetic disorders is very important, because failure to recognize hyperammonemia often leads to brain damage or death and because these disorders

frequently affect more than one family member.

Ammonia is almost exclusively toxic to the brain. The pathophysiology is not well understood, but several hypotheses have been formulated based on biochemical and structural changes that are observed. Interference with energy metabolism or neurotransmitter metabolism has been postulated. Brain edema rapidly develops during hyperammonemic coma, and swelling of astrocytes has been observed on postmortem analysis. Plasma ammonia levels as low as 100 to 200 $\mu\text{mol/L}$ are usually associated with clinical symptoms of lethargy, confusion, and vomiting, and higher levels usually result in coma.

The entire urea cycle resides exclusively in periportal hepatocytes. It is an essential biochemical pathway for waste nitrogen excretion. A cascade of enzymatic transformations converts the toxic ammonia molecule to nontoxic water-soluble urea containing 2 amino groups (one deriving from free ammonia and the other from aspartate) and is eliminated in the urine (Fig 1). Ammonia is also taken up by "scavengers" (eg, glutamate, pyruvate, and aspartate) and is also used in the synthesis of nitrogen-containing compounds (eg, glycine and pyrimidines including orotic acid). A block of the urea cycle can result either from an enzyme deficiency (*CPS*, *OTC*, *NAGS*, argininosuccinic

acid synthetase, arginosuccinic acid lyase, or arginase) or depletion of an amino acid essential to the normal function of the cycle resulting from a transport defect (HHH syndrome and LPI). A recently identified separate mitochondrial transporter, the function of which is unknown, causes citrullinemia type II and is seen in Japanese adults.

Except for OTC deficiency, which is transmitted as a partially dominant X-linked trait, all other known urea cycle disorders are transmitted as autosomal recessive traits. The gene associated with the enzyme deficiency has been identified in each of these disorders except NAGS, and deleterious mutations have been found in the respective genes of affected patients. Thus DNA analysis for mutation detection is possible for each, enhancing both prenatal and postnatal diagnosis and carrier detection in affected families. The degree of the deleterious effect the mutation has on the respective protein's function tends to correlate with the severity of the clinical course. However, the milder the mutation, the more heterogeneous the resulting clinical picture. Unfortunately, newborn mass screening is not currently available for the early diagnosis of these disorders.

CLINICAL PRESENTATION

In general, the more proximal the enzyme defect, the more severe and resistant to treatment is the hyperammonemia (ie, CPS and OTC deficiencies are the most severe). However, as noted previously, there is considerable heterogeneity in the magnitude of hyperammonemia and age of initial presentation based not only on the position of the block within the urea cycle but also on the degree of the enzyme deficiency. The most severe cases have no enzyme activity and present with hyperammonemic coma in the first week of life, whereas patients with the milder forms have some residual enzyme ac-

tivity, and their clinical presentation occurs later in life (ranging from infancy to adulthood) with recurrent episodes of hyperammonemia. Approximately 15% of OTC-deficient heterozygous female patients have symptoms of hyperammonemia sometime in their lives, presumably as a result of skewed liver X-inactivation. Conversely, adults with no symptoms occasionally have been found with the same genetic defect that causes symptoms in a family relative.

Neonatal-onset Urea Cycle Disorders

Infants with complete enzyme deficiencies are usually born at term with no prenatal complications, because the maternal circulation detoxifies the accumulating ammonia. Between 1 to 5 days of age, however, they start feeding poorly, vomit frequently, become lethargic and hypotonic, and may hyperventilate. The diagnosis of sepsis is frequently considered, and workup fails to detect evidence of infection. These babies will progressively have tremor, stupor, seizures, apnea, coma, increased intracranial pressure, and death if the hyperammonemia is not diagnosed and treated effectively. Plasma ammonia levels on acute neonatal presentation may reach levels higher than 1000 $\mu\text{mol/L}$ (normal <35). Other clinical findings may include hepatomegaly, mild serum liver enzyme elevations, and a coagulopathy, but liver function is frequently normal except for hyperammonemia. Initial blood gas measurement typically shows a respiratory alkalosis (caused by hyperventilation). Pulmonary bleeding has been reported as a terminal event, but more frequently the cause of death is vascular compromise of the central nervous system.

Late-onset Urea Cycle Disorders

In patients with partial enzyme deficiencies, the first recognized clinical episode may be delayed for months or years; the hyperammonemia is less severe, and the symptoms are more sub-

tle. The clinical abnormalities vary somewhat with the specific disorder. In most urea cycle disorders, the hyperammonemic episode is marked by loss of appetite, cyclical vomiting, lethargy, and behavioral abnormalities. Sleep disorders, delusions, hallucinations, and psychosis have also been reported. An encephalopathic (slow wave) electroencephalogram pattern may be observed during hyperammonemia, and nonspecific brain atrophy may be seen subsequently on magnetic resonance imaging.

Associated Clinical Abnormalities

In addition to the symptoms of hyperammonemia, a number of hyperammonemic disorders have other, more specific clinical abnormalities. In hyperargininemia there is a progressive spastic diplegia, or quadriplegia that has also been observed in HHH syndrome. Tremor, ataxia, and choreoathetosis have also been reported in hyperargininemia, whereas retinal depigmentation and chorioretinal thinning have been observed in HHH syndrome. Interstitial pneumonia caused by pulmonary alveolar proteinosis is seen in LPI, as are glomerulonephritis and osteoporosis; there may also be an underlying immune deficiency in this disorder. Trichorrhexis nodosa, a node-like appearance of fragile hair, is pathognomonic for arginosuccinic aciduria.

DIFFERENTIAL DIAGNOSIS

The diagnosis of congenital hyperammonemia should be considered on finding an elevated plasma ammonia level in association with only mild or no liver dysfunction and in the absence of ketoacidosis. A precipitating catabolic event such as an infection, traumatic injury, ingestion of large amounts of protein, or other yet unknown metabolic stresses can precipitate hyperammonemia in these pa-

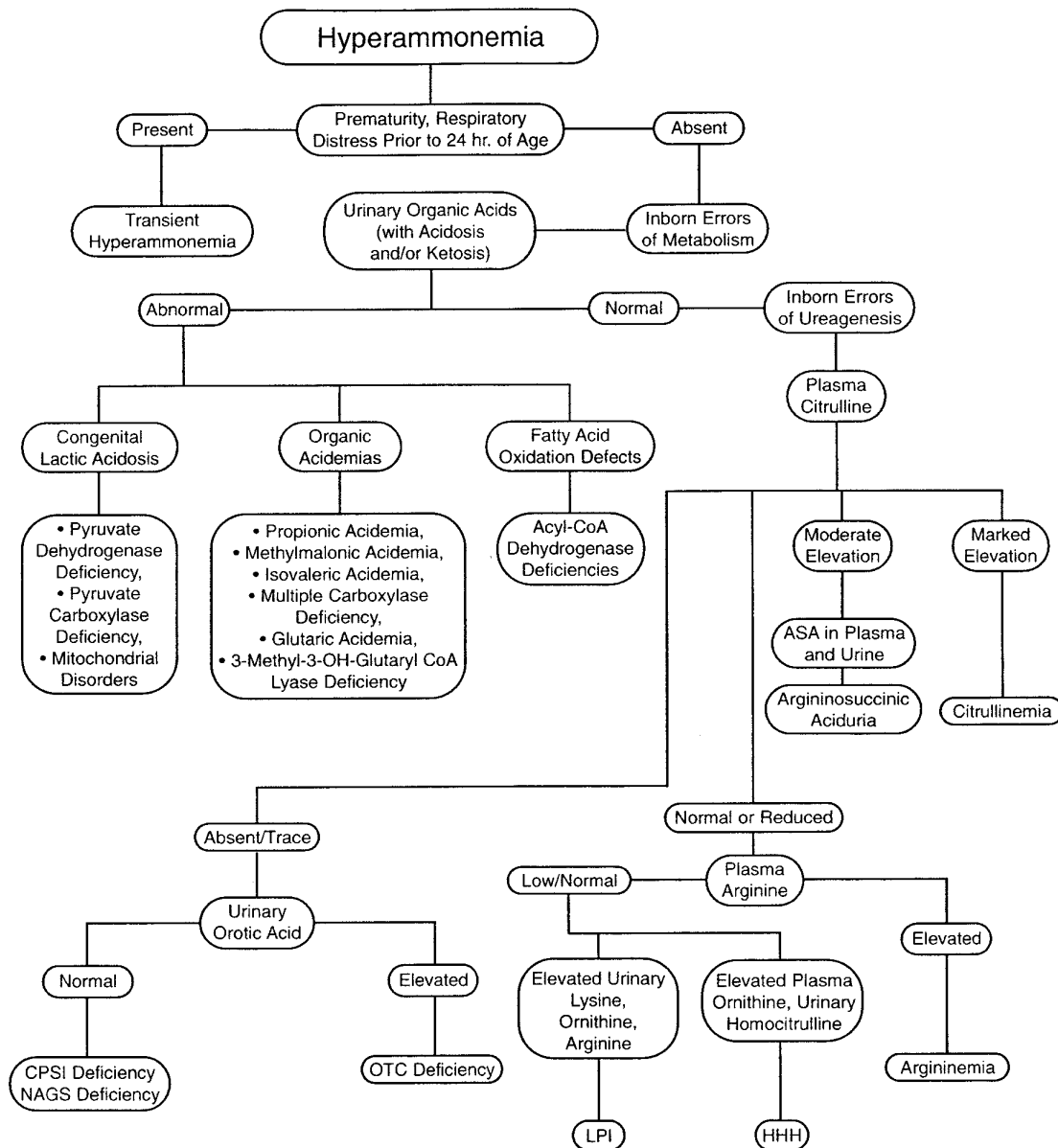


Fig 2. Flow chart for differential diagnosis of congenital hyperammonemia. *LPI*, Lysinuric protein intolerance; *HHH*, hyperornithinemia hyperammonemia and homocitrullinuria syndrome.

tients. Valproate and haloperidol have unmasked previously undiagnosed urea cycle defects in some patients, whereas other patients have erroneously been given the diagnosis of Reye syndrome.

The flow diagram for the differential diagnosis of a urea cycle defect (Fig 2) shows that the first task is to obtain a plasma ammonia level. The blood sample should be placed on ice and ideally run within 15 minutes of collection. Most hospitals now have automated analyzers that measure a plasma ammonia level in <30 minutes

in <1 mL of blood. Normal plasma ammonia levels are <35 $\mu\text{mol/L}$ (63 $\mu\text{g/dL}$). In symptomatic hyperammonemia, levels are usually >100 $\mu\text{mol/L}$. Other routine laboratory tests may be useful in making the diagnosis. A low blood urea nitrogen and a respiratory alkalosis in a severely ill child are characteristic of urea cycle disorders. On the other hand, a metabolic acidosis or ketoacidosis is more commonly seen in hyperammonemia caused by an organic acidemia or congenital lactic acidosis.

These can be further discriminated by measuring urinary organic acids for the former condition and plasma lactate/pyruvate for the latter. Organic acidemias and fatty acid oxidation defects can be distinguished by measuring acylcarnitine esters in blood.

Quantitative plasma and urinary amino acids are most helpful in establishing a specific diagnosis of a defect in urea synthesis (Fig 2). Levels of glutamine, alanine, and asparagine, which serve as storage forms of waste nitrogen, are frequently elevated. Plasma arginine

may be reduced in all urea cycle disorders, except in hyperargininemia, where it is 10- to 20-fold higher than normal. In partial defects, however, it is frequently normal. Plasma citrulline levels help discriminate between the proximal and distal urea cycle defects, because citrulline is the product of OTC and CPS activity and a substrate for the distal enzymes. Consequently, plasma citrulline is absent or present only in trace amounts in neonatal-onset CPS and OTC deficiencies and is present in low to low-normal levels in late-onset disease, whereas it is markedly elevated in blood and urine in citrullinemia and argininosuccinic aciduria. To distinguish CPS from OTC deficiency, urinary orotic acid is measured; it is significantly elevated in OTC deficiency and normal or low in CPS deficiency. As in OTC deficiency, urinary orotic acid excretion can also be increased in hyperargininemia, citrullinemia, HHH syndrome, and LPI. Patients with citrullinemia have up to a 100-fold elevation in plasma citrulline, whereas those with argininosuccinic aciduria show a more moderate increase in citrulline of approximately 10-fold, associated with the presence in large amounts of the normally absent argininosuccinic acid. The argininosuccinate chromatographic peak may co-elute with leucine or isoleucine, resulting in an apparent increase in one of these amino acids, but its anhydrides eluting later in the run should allow the correct identification of argininosuccinate. In HHH syndrome, plasma ornithine and urine homocitrulline levels are elevated, whereas in LPI urinary lysine, arginine and ornithine levels are elevated and blood levels may be normal or low.

Citrullinemia, argininosuccinic aciduria, hyperargininemia, and LPI and HHH syndrome can be diagnosed on the basis of the amino acid pattern. NAGS deficiency requires enzymatic diagnosis with hepatic tissue. In OTC deficiency approximately 75% of patients have an identifiable mutation by DNA studies, and mutation analysis can

be done for the other disorders as well. A definitive diagnosis of CPS or OTC deficiency depends on enzyme determination from a liver biopsy specimen.

Therapy for these disorders is discussed in detail in the articles that follow.

OUTCOME

Before alternate pathway therapy was developed, virtually all children with neonatal-onset disease died rapidly. Approximately half of affected neonates still die of hyperammonemic coma. However, long-term survival has improved, with approximately half of the infants who survive neonatal hyperammonemic coma living 5 years or more. Survival is obviously better in partial defects, but these children still remain at risk for intercurrent life-threatening hyperammonemic crises. Although mortality has improved, morbidity remains high. There is a significant risk for multiple developmental disabilities including mental retardation, cerebral palsy, and seizure disorders in children with a neonatal-onset disorder. Children with partial defects and those who have been treated prospectively from birth because of a previously affected sibling have a better outcome, although there is a high incidence of more subtle cognitive deficits including learning disabilities and attention deficit hyperactivity disorder.

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