Consensus statement from a Conference for the Management of Patients With Urea Cycle Disorders

The Urea Cycle Disorders Conference Group*

DIAGNOSIS AND TREATMENT OF A UREA CYCLE DISORDER

The recommendations made in this consensus statement reflect the opinions and experience of the conference participants. The participants are aware that some of the recommendations have not been scientifically studied and thus cannot be regarded as evidence-based medicine.

NEONATAL PRESENTATION

Recommendation

Always consider the diagnosis of an inborn error of metabolism, including urea cycle disorder, in a sick neonate.

Rationale. The initial symptoms of a neonate with hyperammonemia are failure to feed and somnolence, which can be a finding in many other diseases. These symptoms progress quickly to lethargy and coma unless hyperammonemia is recognized and therapy initiated.

Recommendation

The plasma ammonia level should be measured at the time of any sepsis workup in a patient without an obvious infection.

Rationale. Almost all neonates with a UCD are initially thought to be septic.

Recommendation

Respiratory alkalosis is an important initial clue for the diagnosis of a UCD.

Rationale. Respiratory alkalosis is not usually seen in sepsis or in other causes of severe illness in the neonate. The alkalosis results from stimulation of the respiratory center by hyperammonemia and is a frequent but often subtle occurrence.

Recommendation

All neonates with symptomatic hyperammonemia should be transferred as quickly as possible to a level III neonatal unit with hemodialysis facilities.

Rationale. With no effective clearance system for ammonia, levels increase rapidly, resulting in cerebral edema with severe neurologic compromise. Dialysis is the only means of rapid removal of ammonia from blood in acute neonatal hyperammonemia, and hemodialysis is preferred over peritoneal dialysis because it is much more effective. If hemodialysis is not available, hemofiltration can be used, although ammonia removal may be slower.

Recommendation

If time permits, and without delaying the transport of the patient, samples should be sent for plasma amino acid analysis and for urinary amino acid, organic acid, and orotic acid determination. Plasma and urine should be frozen for future testing.

Rationale. These tests will help identify the cause of the hyperammonemia.
**Recommendation**

Administration of intravenous glucose and fluids should be started before transport. Tracheal intubation and placement of an umbilical venous catheter are recommended; however, transport should not be delayed if central venous access is not available.

**Rationale.** Many neonates are dehydrated at presentation. Intravenous access permits rapid rehydration and allows for administration of drugs and fluids during transport. Intubation and a central venous catheter are useful in case of circulatory collapse during transport.

**Recommendation**

All feedings containing protein should be discontinued. Calories should be provided as intravenous glucose and lipid.

**Rationale.** Caloric supplementation is needed to reverse catabolism and to reduce the protein turnover rate. Protein feeds are stopped to prevent an additional nitrogen burden but are restarted within 48 hours, because depletion of essential amino acids will result in further protein catabolism and ammonia formation.

**Hospital Management of Hyperammonemia**

**Recommendation**

Measure plasma ammonia level.

**Rationale.** A normal blood ammonia level during symptoms of vomiting and lethargy eliminates UCD from the differential diagnosis. Note that an elevated ammonia level (2 to 3 times normal) may be factitious if the sample was not properly obtained. In neonatal-onset UCD, ammonia levels are usually >300 \( \mu \text{mol/L} \) and are often in the range of 500 to 1500 \( \mu \text{mol/L} \).

**Recommendation**

Intravenous therapy with ammonia scavenging drugs should be started when ammonia elevation causes any central nervous system symptoms. However, there is no consensus at what ammonia level intravenous therapy should be started if no symptoms are present. For acute neonatal hyperammonemia coma, a loading dose of 600 mg/kg L-arginine-HCL and 250 mg/kg each of sodium benzoate and sodium phenylacetate in 25 to 35 mL/kg of 10% dextrose solution given over a 90-minute period is recommended. This is followed by a sustained infusion (250 mg/kg L-arginine-HCL and 250 mg/kg each of sodium benzoate and sodium phenylacetate over a 24-hour period for carbamyl phosphate synthetase I and ornithine transcarbamylase deficiency; 600 mg/kg L-arginine-HCL and 250 mg/kg each of sodium benzoate and sodium phenylacetate over a 24-hour period for citrullinemia and argininosuccinic aciduria). For argininosuccinic aciduria, arginine therapy alone may suffice. If locally available, monitoring drug levels will help reduce the risk of toxicity.

**Rationale.** Hyperammonemia associated with symptoms must be treated as soon as possible to avoid further increases in ammonia and to reduce the risk of brain damage.

**Recommendation**

Preparation for dialysis should be made as soon as possible, even before the arrival of the patient. The preferred method for ammonia clearance is hemodialysis. In centers where hemodialysis is not available, hemofiltration or other forms of dialysis should be used.

**Rationale.** Preparation for hemodialysis may require several hours. Peritoneal dialysis, although helpful, may not remove ammonia quickly enough to be clinically effective in severe cases.

**Recommendation**

A protocol should be available for placement of catheters for hemodialysis by a pediatric surgeon. The catheters (or a single double-lumen catheter) should be placed in large vessels to allow the high flows required for effective dialysis. If 2 catheters are used, one should be placed above and one below the diaphragm.

**Rationale.** Effective hemodialysis depends on good blood flow, which in turn relies on correct placement of adequate-sized catheters. Placement of catheters into different vessels will avoid recirculation and ineffective dialysis.

**Recommendation**

Intravenous therapy with ammonia scavenging drugs should be continued while dialysis is being performed.

**Rationale.** The use of these medications provides a synergistic action for ammonia removal, and they are less likely to accumulate during dialysis.

**Recommendation**

A repeat loading dose of ammonia scavenging drugs within 24 hours should be given only in neonates with severe disorders who are receiving dialysis. If drug level monitoring is not available, repeated loading in the previously described setting should only be considered with evaluation of risks versus benefits for a particular clinical picture. All orders for intravenous medications should be carefully checked for correct dosage.

**Rationale.** Toxicity is associated with high drug doses (750 mg/kg/d and higher). Deaths have been reported from accidental overdosing of these rarely used medications.

**Blood Sampling and Laboratory Testing**

**Recommendation**

Sodium, potassium, lithium heparin, or tubes containing EDTA should be used. Serum is not adequate for amo-
nia determination. Blood for ammonia
determination should be collected in a
prechilled, ammonia-free tube on ice
and delivered to the laboratory imme-
diately. Samples should be kept on ice,
and plasma should be separated within
15 minutes of collection. If the assay is
not run immediately, plasma should be
stored frozen at –70°C.

RATIONALE. Hemolysis, delay in sam-
ple processing, and exposure to room
temperature all factitiously increase
the plasma ammonia level. Correct
handling is more important than
whether arterial or venous blood is col-
lected.

Recommendation

Capillary blood is not suitable for the
accurate measurement of ammonia
level.

RATIONALE. The great variability in
mode of collection and tissue damage
frequently causes factitious elevation
of ammonia.

Recommendation

Assay of liver enzyme activity is the
standard for confirmation of N-acetyl
 glutamate synthase, CPS, and OTC
deficiencies. Plasma and urine amino
cid analyses are the laboratory stan-
dards for confirmation of citrullinemia
(argininosuccinate synthetase deficien-
cy) and argininosuccinic aciduria
(argininosuccinate lyase deficiency).
Arginase deficiency is confirmed
with red blood cell enzyme analysis.

RATIONALE. There may be lack of
concordance between the ammonia
level and the clinical condition of the
patient. This is especially true for am-
monia levels <200 µmol/L.

Observation

There is no consensus on whether an
elevated plasma ammonia level (> 3 ×
normal) in a patient with chronic
asymptomatic disease indicates a re-
quirement for intravenous therapy
with pharmacologic ammonia scaveng-
ing drugs.

RATIONALE. Ammonia levels change
rapidly. An elevated ammonia level
during a clinic visit in a patient with-
out symptoms, however, does require
adjustment of therapy or better com-
pliance with the recommended treat-
ment regimen.

CHRONIC (LONG-TERM)
MANAGEMENT

Recommendation

Plasma glutamine level is a useful
marker for effective therapy. Most par-
ticipants agreed that the plasma gluta-
mine level should be maintained at <1000
µmol/L. Glutamine levels are obtained
by quantitative plasma amino acid analy-
sis, preferably in a preprandial state.

RATIONALE. Glutamine appears to be a
better marker than ammonia for
chronic management, but scientific ev-
idence to support a threshold value is
lacking.

Recommendation

Protein intake should be reduced
temporarily (for 24 to 48 hours) dur-
ing an infection. Use of ibuprofen for
fever relief is preferred over aceta-
minophen. Extreme caution should be
exercised in the use of antiemetics.

RATIONALE. Protein-free diets are nu-
ritionally inadequate. Acetaminophen
in high doses is potentially toxic to the
liver. Antiemetics may mask signs of
hyperammonemia.

Nutritional
MANAGEMENT

Recommendation

A reduced protein intake is an im-
portant part of therapy.

RATIONALE. The Recommended Daily
Allowance for dietary protein is higher
than the minimum needed for normal
growth. Most patients with a UCD can
receive less than the Recommended
Daily Allowance of protein and still
maintain adequate growth patterns.

Recommendation

Patients with severe disorders may
need essential amino acids as part of
their protein intake (25% to 50%).

RATIONALE. This recommendation is
based only on theoretical considera-
tions and anecdotal experience. It has not been carefully studied.

Recommendation
Restricted diets should be supplemented with minerals, vitamins, and trace elements.

RATIONALE. Although commercial formulas are nutritionally complete, there may be a requirement for supplementation when the restricted dietary intake comes largely from natural food.

Recommendation
Monitoring of linear growth, appearance of hair, skin and nails, and the biochemical tests for essential amino acids, glutamine, hemoglobin, albumin, pre-albumin, and transferrin provide useful criteria to assess the nutritional status of the patient.

RATIONALE. These are all useful markers of nutritional status.

PHARMACOLOGIC MANAGEMENT

Recommendation
The labeling for intravenous sodium benzoate and sodium phenylacetate should be modified to include a new indication for the treatment of patients with argininosuccinic aciduria.

RATIONALE. Clinical experience indicates that these drugs are helpful in reducing ammonia in this condition, acting by a mechanism different from that of arginine.

Recommendation
High-dose arginine is very effective in reducing plasma levels of ammonia in patients with citrullinemia and argininosuccinate, providing an alternative pathway for waste nitrogen excretion. High-dose arginine-HCL may cause metabolic acidosis, and it can cause tissue necrosis if extravasation occurs.

Recommendation
L-citrulline, given by nasogastric tube during the initial phase of intravenous therapy, may be useful in the treatment of CPS and OTC deficiency.

RATIONALE. This recommendation is based on consensus clinical experience. Citrulline is not available in intravenous form. Given (orally) in CPS and OTC deficiency, it has the advantage of removing one nitrogen atom while being converted to arginine.

Recommendation
Written orders for pharmacologic scavenging agents should be double-checked to avoid overdosing.

RATIONALE. Used in higher than recommended doses, these compounds can be highly toxic. Accidental overdosing has resulted in deaths. The clinical picture of toxicity is similar to that seen with salicylate poisoning (ketoacidosis).

Recommendation
Where available, plasma levels of ammonia scavenging drugs should be monitored to avoid toxicity.

RATIONALE. Variable drug excretion may cause toxicity. In the absence of drug levels, a serum anion gap of >15 mEq/L and an anion gap that has risen >6 mEq/L could indicate drug accumulation and increased risk for toxicity.

Recommendation
Intravenous arginine-HCL and sodium benzoate/sodium phenylacetate should be available in hospitals where patients with UCD are treated.

RATIONALE. These medications are not routinely available and may be required on an emergency basis to treat patients with acute hyperammonemia.

Recommendation
Patients should have a written treatment protocol with them. This should outline the steps in acute management and define the specific dosage of medications to be used. The protocol should be updated as the child grows.

RATIONALE. The availability of such a protocol at the time the patient comes to an emergency room because of hyperammonemia can hasten effective treatment and potentially avoid incorrect dosage.

Recommendation
To avoid hyperammonemic crises during intercurrent illness, a “sick day” regimen should be established. This may involve decreasing protein intake, increasing non-protein calories, and adjusting medication dosage. Parents should become knowledgeable about this regimen.

RATIONALE. This approach may prevent hospitalizations during self-limited illnesses. However, any clinical symptom of hyperammonemia should prompt a visit to the hospital.

CHRONIC THERAPY

Recommendation
Three-times-daily dosing of ammonia scavenging drugs is the minimum, with 4 times daily recommended. Administration of the drugs should be linked to meals to maximize the effect of ammonia removal.

RATIONALE. The half-lives of these drugs are approximately 2 to 4 hours. Dosing adjustment to the timing of excessive ammonia production (ie, after a protein load) may be needed.

Recommendation
Risk/benefit for the use of these drugs in patients who may become, or are, pregnant should be carefully considered.
**Rationale.** The safety of these drugs in pregnancy has not been determined.

**Long-term Correction**

**Recommendation**
Liver transplantation should be considered for patients with severe CPS or OTC deficiency, for patients with argininosuccinic aciduria and liver cirrhosis, and for any patient who has recurrent symptomatic hyperammonemic episodes despite optimal medical management.

**Rationale.** The 5-year post-transplantation survival rate for patients with UCD is now approximately 80%. Liver transplantation cures the hyperammonemia but does not correct the arginine deficiency, for which arginine supplements may be required.

**Recommendation**
Families should not delay treatment decisions (including liver transplantation) based on the possibility of gene therapy in the near future.

**Rationale.** It remains to be determined whether long-term correction with gene therapy is feasible and safe.

**Psychosocial Issues**

**Recommendation**
Health care practitioners must be aware of the psychosocial needs to support patient and family. All families should be assessed by a social worker, and approved support programs should be developed.

**Rationale.** This is rarely mentioned in the medical literature but has a profound impact on outcome. All families experience great stress and endure a period of adjustment to the disorder and its complications.

**Recommendation**
All families in which a member has been diagnosed with a UCD should receive genetic counseling.

**Rationale.** These are genetic disorders with a risk of recurrence. Availability of carrier testing and prenatal diagnosis provides a number of reproductive options.

**Recommendation**
Provide assistance to ensure that stable financing of care is in place.

**Rationale.** Support for the intensive, long-term and outpatient care, and the relatively unknown medicines is difficult to organize and is an important problem faced by families.

**Urea Cycles Disorders Conference Group**

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