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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.

CPS	Carbamyl phosphate synthetase I
OTC	Ornithine transcarbamylase
UCD	Urea cycle disorder

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.

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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 μmol/L and are often in the range of 500 to 1500 μmol/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 hyperammonemic 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 ammo-

nia determination. Blood for ammonia determination should be collected in a prechilled, ammonia-free tube on ice and delivered to the laboratory immediately. 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 sample 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 collected.

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 acid analyses are the laboratory standards for confirmation of citrullinemia (argininosuccinate synthetase deficiency) and argininosuccinic aciduria (argininosuccinate lyase deficiency).

Arginase deficiency is confirmed with red blood cell enzyme analysis.

RATIONALE. There is a perception that DNA diagnosis for UCD can be performed on a routine basis. This may be available in the future. Currently, routine DNA analysis is available only for OTC deficiency where a mutation can be identified in most patients.

Recommendation

The following Web sites list laboratories offering tests for UCD diagnosis:

- Gene Tests (www.genetests.org)
- University of California at San Diego (www.biochemgen.ucsd.edu)

INTERPRETATION OF RESULTS

Recommendation

Both the plasma ammonia level and the clinical picture should be considered when choosing therapy (dialysis vs intravenous pharmacologic therapy vs management at home with diet and medications).

RATIONALE. There may be lack of concordance between the ammonia level and the clinical condition of the patient. This is especially true for ammonia 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 requirement for intravenous therapy with pharmacologic ammonia scavenging drugs.

RATIONALE. Ammonia levels change rapidly. An elevated ammonia level during a clinic visit in a patient without symptoms, however, does require adjustment of therapy or better compliance with the recommended treatment regimen.

CHRONIC (LONG-TERM) MANAGEMENT

Recommendation

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

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

Recommendation

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

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

Recommendation

Parents should be trained in the placement of nasogastric tubes, and in selected cases consideration should be given to the placement of gastric tubes or buttons to facilitate treatment of patients with severe disorders.

RATIONALE. This practice could reduce the number of times a child has to be admitted to hospital, by permitting dietary and pharmacologic therapy to be continued if oral intake is compromised.

NUTRITIONAL MANAGEMENT

Recommendation

A reduced protein intake is an important 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 argininosuccinic aciduria. Arginine-HCL should preferably be given through a central line and may require simultaneous administration of sodium bicarbonate.

Rationale. In these disorders arginine promotes incorporation of ammonia into the amino acids citrulline 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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