Acute Illness Protocol for Urea Cycle Disorders

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Abstract: Inborn errors of metabolism (IEMs) are genetic disorders that disrupt enzyme activity, cellular transport, or energy production. They are individually rare but collectively have an incidence of 1:1000. Most patients with IEMs are followed up by a physician with expertise in biochemical genetics (metabolism), but may present outside this setting. Because IEMs can present acutely with life-threatening crises that require specific interventions, it is critical for the emergency physician, internist, and critical care physician as well as the biochemical geneticist to have information on the initial assessment and management of patients with these disorders. Appropriate early care can be lifesaving. This protocol is not designed to replace the expert consultation of a biochemical geneticist, but rather to improve early care and increase the level of comfort of the acute care physician with initial management of urea cycle disorders until specialty consultation is obtained.

Key Words: inborn errors of metabolism, urea cycle disorders, hyperammonemia

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SUMMARY OF THE PROTOCOL

Urea cycle disorders (UCDs) represent a class of inborn errors of metabolism resulting from defects in the metabolic pathway for ammonia detoxification. The most frequent UCD is ornithine transcarbamylase (OTC) deficiency. Additional disorders include the following: *N*-acetylglutamate synthase (NAGS) deficiency, carbamoyl phosphate synthetase 1 (CPS1) deficiency, argininosuccinate synthetase 1 (ASS1) deficiency (citrullinemia), argininosuccinate lyase (ASL) deficiency (arginosuccinic acidemia), and arginase deficiency (ARG deficiency). Untreated hyperammonemia can result in progressive encephalopathy, cerebral edema, and death. The cornerstone of management is dietary restriction of protein, ammonia-lowering medications, supplementation of specific amino acids (L-arginine or L-citrulline depending on the specific disorder), and in severe cases hemodialysis. Metabolic decompensations can be provoked by illness, malnutrition, excess dietary protein, liver dysfunction, medications (eg, valproic acid), treatment noncompliance, and less often gastrointestinal bleeding or menstruation. Early identification and management of a metabolic decompensation is critical to prevent adverse outcomes. A suggested management algorithm is summarized in Figure 1.

BACKGROUND

Urea cycle disorders represent a class of inborn errors of metabolism resulting from defects in the metabolic pathway for ammonia detoxification.[1–3] Urea cycle disorders can be divided into *proximal defects*, which include the enzymes of the urea cycle that are located in the mitochondria, and *distal defects*, which include the enzymes of the urea cycle that are located in the cytoplasm (see Table 1 and Fig. 2 for details). In general, proximal urea cycle defects are associated with more severe and difficult to manage hyperammonia compared with distal defects.

The UCDs can first manifest at different ages depending on the degree of enzyme deficiency. The most severe enzyme deficiencies first present in the neonatal period, milder forms may initially present later in infancy or childhood, and the most attenuated forms may first manifest in adulthood. See Table 2 for a list of the common presenting symptoms for patients with UCDs.

Manifestations of hyperammonemia include headache, emesis, altered sensorium, psychosis, ataxia, and seizures. Untreated hyperammonemia can result in progressive encephalopathy, cerebral edema, and death.

Normal reference values for serum ammonia vary with age, and also to some degree between performing laboratories. The normal range for ammonia levels is generally higher in the neonate, where levels up to 110 μmol/L may be normal. The upper limit of normal for a child older than 4 weeks or for an adult is generally around 50 to 80 μmol/L. Most laboratories will report ammonia units in micromoles per liter, but some laboratories may report levels in micrograms per deciliter; the conversion is as follows: 1 μmol/L = 0.59 μg/dL.

Patients with UCDs are managed with a special low-protein diet that is often supplemented with essential amino acid–based medical food.[2,4,5] In addition, patients are prescribed oral ammonia-lowering medications called *ammonia scavengers* that are often used chronically. Ammonia scavengers work by conjugating with specific amino acids in the blood to form inert compounds that are excreted in the urine. *N*-acetylglutamate synthase deficiency is treated with the medication carbamylglutamate (Carbaglu), which is an analog for the deficient cofactor in this disorder, *N*-acetylglutamate.[1–3]

Metabolic decompensations in the UCDs can be provoked by illness, malnutrition, excess dietary protein, liver dysfunction, medications (eg, valproic acid), treatment noncompliance, and less often gastrointestinal bleeding or menstruation.[1–3]

MANAGEMENT

Laboratory Tests

The following tests should be performed when a patient with a UCD presents with a significant intercurrent illness, poor intake, and/or signs of metabolic decompensation: STAT serum ammonia level, chemistry panel, and venous blood gas. If available, a plasma amino acid profile should also be sent, which can later be reviewed by a metabolism/biochemical genetics specialist, although this will not alter the acute management of the patient. See Table 3 for a list of potential laboratory and imaging investigations and their indications in patients with UCDs.

Intravenous Fluids

In a hyperammonemic patient, intravenous (IV) dextrose containing fluids should be used to increase calories and to promote insulin release and anabolism. Generally, IV dextrose 10% containing fluid with half or full normal saline at 1.5 times maintenance rate is used to provide a glucose infusion rate of 8

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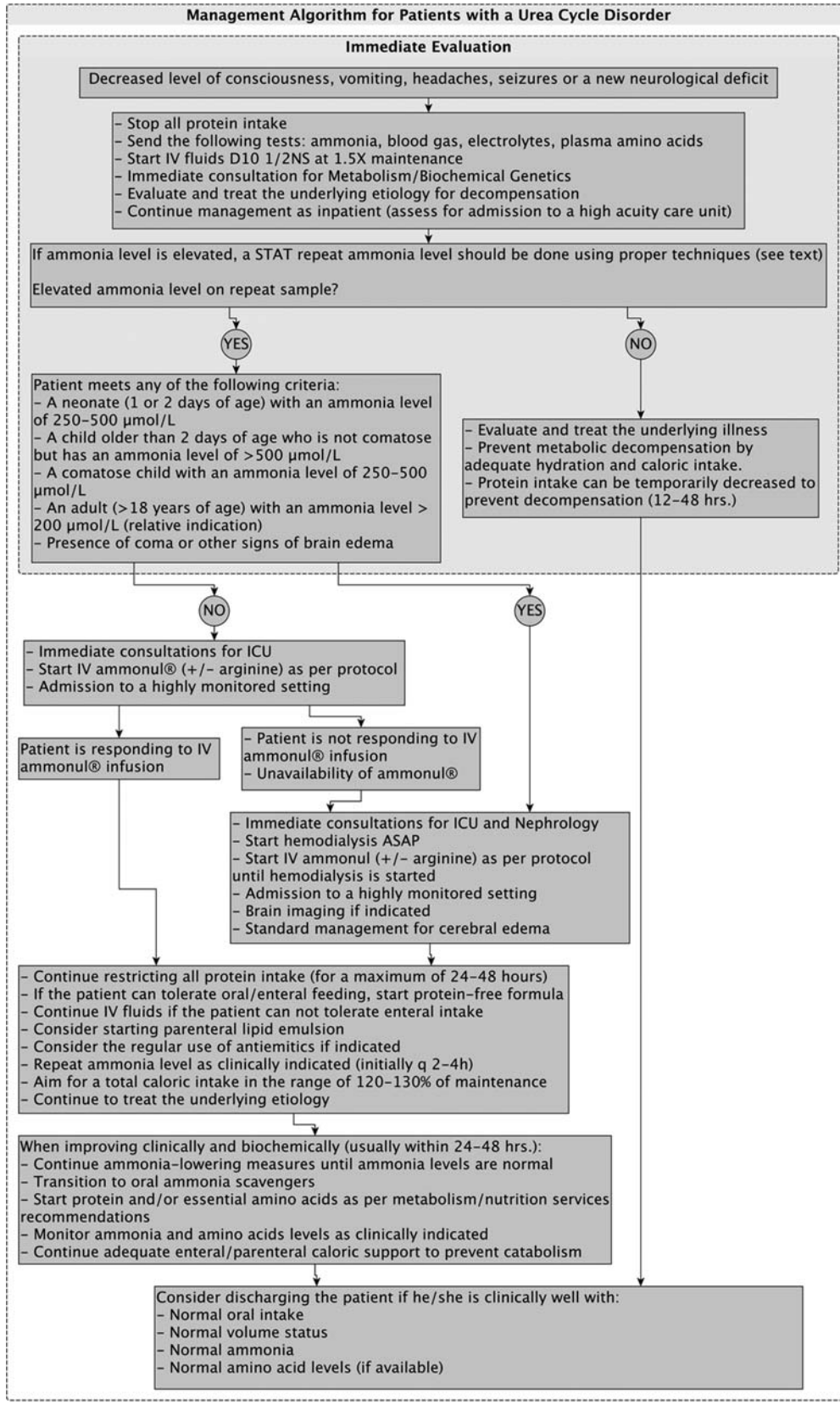

FIGURE 1. Management algorithm for patients with a UCD.

TABLE 1. Summary of the UCDs, Deficient Enzymes, Involved Genes, and Their Mode of Inheritance

Name/Acronym	Enzyme Defect	Gene	Inheritance
NAGS deficiency	NAGS	*NAGS*	AR
CPS1 deficiency	CPS1	*CPS1*	AR
OTC deficiency	OTC	*OTC*	XL
Citrullinemia type I	ASS1	*ASS1*	AR
Arginosuccinic acidemia	ASL	*ASL*	AR
Argininemia	Arginase	*ARG*	AR

to 10 mg kg^{-1} min^{-1}.[3,6] In a significant metabolic crisis, if blood glucose is greater than 150 mg/dL, IV insulin infusion can be instituted to further promote anabolism.[3,6] Blood glucose should be maintained between 100 and 150 mg/dL. Glucose infusion rate can be increased if necessary to maintain blood glucose in this range.

If the dextrose 10% is being administered with IV Ammonul (see hereinafter), no additional saline is required in the infusate because Ammonul already has a high sodium content. Depending on plasma potassium levels, it is advisable to consider adding some potassium to maintenance fluids because both high dextrose infusion and Ammonul can reduce potassium levels.

To provide additional calories, IV intralipid can also be initiated at a starting dose of 1 to 3 g kg^{-1} d^{-1}.[3,6] Serum triglycerides should be monitored.

Diet and IV Fluids

In a hyperammonemic patient, dietary protein should initially be held. Generally, protein should not be withheld entirely for greater than 48 hours because this will result in catabolism of endogenous proteins to release essential amino acids, which will further increase ammonia levels. When a patient with a UCD is receiving protein below the recommended daily intake, use of an essential amino acid–based formula (eg, Cyclinex) should be considered to maintain adequate levels of essential amino acids and to effectively use nonessential amino acids for protein synthesis.[3,6]

Total daily calories (IV and enteral) should be increased to promote an anabolic state (consider a 25% increase above maintenance). Protein is generally reintroduced gradually after ammonia levels have normalized (eg, half protein for 24 hours, and then if tolerated, advancing to full protein).[3,6] In practice, the rate of protein advancement has to be tailored to the patient and the specific situation.

Medications

(*a*) *Ammonul*: If a patient has clinical signs of hyperammonemia and/or if ammonia levels are elevated above the patient's baseline, Ammonul should be considered in place of oral scavengers.[2,3,7] Ammonul is a combination of sodium phenylacetate and sodium benzoate. Depending on ammonia level, rate of rise of ammonia, and clinical status, a loading dose may be considered followed by maintenance dosing.

Both loading dose and maintenance dosing (calculated for a 24-hour period) of Ammonul are the same. Dosing depends on body weight as follows[3]:

- Body weight ≤20 kg: 250 mg/kg
- Body weigh >20 kg: 5.5 g/m^2 [BSA sqr[Wt (kg) × Ht (cm)/3600]

The Ammonul dose is diluted in 25 mL/kg of D10W. The loading dose is typically given for 1.5 to 2 hours. Slower infusions can be used if there is concern for cerebral edema or volume overload. If a patient is asymptomatic and has a milder elevation of ammonia, then maintenance dosing of Ammonul can be used without a preceding bolus. If there is worsening clinical status or ammonia level does not improve, then the bolus dose can be given.

Potential adverse effects of Ammonul include nausea (consider premedicating with ondansetron), hypernatremia, and hypokalemia.[8,9] Ammonul toxicity is associated with metabolic acidosis, increased anion gap, ketosis, high lactate, and hyperventilation.[8] Of note, Ammonul is contraindicated in patients with significant electrolyte derangements (hypernatremia, hypokalemia), and hemodialysis should be considered in the latter case.

When normal ammonia levels are achieved, protein should be gradually reintroduced as described previously.[3] If ammonia

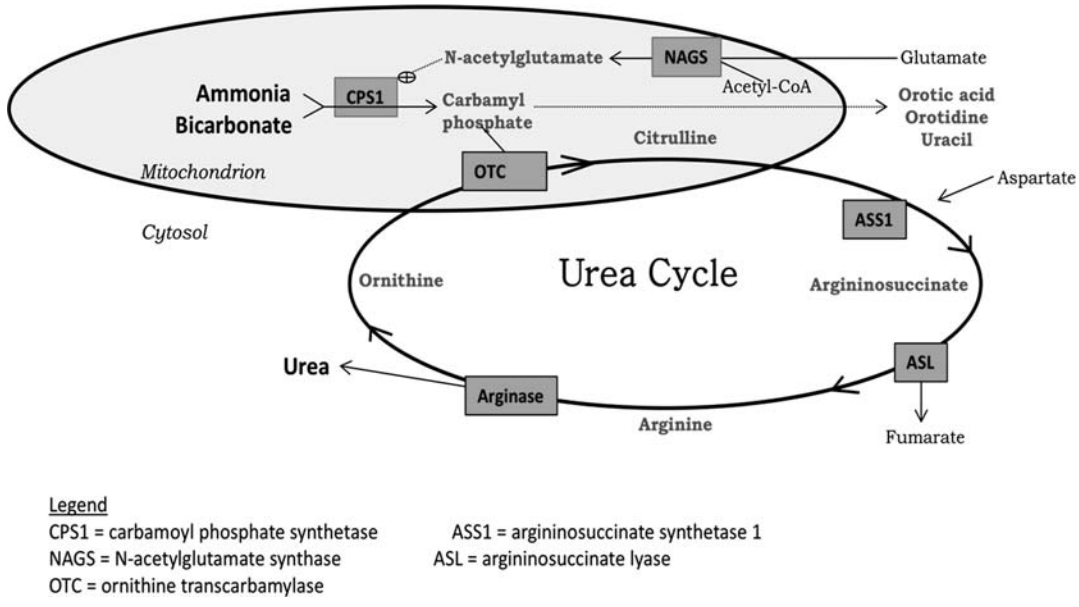

FIGURE 2. Overview of the urea cycle and ammonia metabolism.

TABLE 2. Symptoms and Signs of Patients With UCDs During Acute Decompensation

Body System/ Process	Symptoms and/or Signs*
Metabolic	Hyperammonemia, primary respiratory alkalosis
Neurologic	Headache, psychiatric symptoms, encephalopathy, coma, seizures, ataxia, papilledema
Gastrointestinal	Nausea and vomiting
Respiratory	Hyperventilation

*Close family members of individuals with diagnosed metabolic disorders often know the signs of decompensation in their relatives, and it is important to take this information into consideration.

levels are satisfactory when dietary protein has reached the goal, IV Ammonul may be transitioned to oral scavengers. There may be a rebound hyperammonemia after Ammonul is discontinued, so ammonia levels should be carefully monitored.

If Ammonul is unavailable, then oral scavengers should be continued and the nephrology service should be urgently consulted for hemodialysis.

(*b*) *Carbamylglutamate (Carbaglu)*: Carbamylglutamate, an analog of *N*-acetylglutamate, is indicated in the management of NAGS deficiency. Carbamylglutamate is dosed at 100 to 250 mg kg^{-1} d^{-1} in 3 to 4 divided doses. A loading dose of 100 mg/kg per dose × 1 can be given on the first day of therapy.[2,3]

(*c*) L-arginine *supplementation*: In a hyperammonemic crisis in all of UCDs, except ARG deficiency, IV arginine hydrochloride should be used to sustain the body arginine pool and to act as a substrate to enhance waist nitrogen excretion. The dosing varies depending on the underlying disorder, as summarized in Table 4.[2,3,9] As previously mentioned, L-arginine supplementation is contraindicated in hyperargininemia/ARG deficiency.

Potential adverse effects of IV L-arginine includes severe chemical burn due to extravasation during infusion and, in rare cases, hypotension.

Enteral L-arginine can be used in place of IV arginine hydrochloride if IV arginine is unavailable. Also, patients should be stepped down to enteral L-arginine when Ammonul is discontinued.[2] Arginine dosing should be titrated to maintain plasma levels in the normal range.

TABLE 4. Summary of the Recommended IV Arginine Dosing

Name/Acronym	Enzyme Defect	Dose of IV arginine*
NAGS deficiency	NAGS	<20 kg: 100–200 mg kg^{-1} d^{-1} >20 kg: 2.5–6 g m^{-2} d^{-1} Maximum: 6 g/d
CPS1 deficiency	CPS1	<20 kg: 100–200 mg kg^{-1} d^{-1} >20 kg: 2.5–6 g m^{-2} d^{-1} Maximum: 6 g/d
OTC deficiency	OTC	<20 kg: 100–200 mg kg^{-1} d^{-1} >20 kg: 2.5–6 g m^{-2} d^{-1} Maximum: 6 g/d
Citrullinemia	ASS1	<20 kg: 600 mg kg^{-1} d^{-1} >20 kg: 12 g m^{-2} d^{-1}
Arginosuccinic acidemia	ASL	<20 kg: 600 mg kg^{-1} d^{-1} >20 kg: 12 g m^{-2} d^{-1}

*Dosing of IV arginine should be adjusted to maintain plasma levels between 80 and 150 μmol/L.

Hemodialysis

Hemodialysis is indicated in several situations that are summarized in Table 5.[2,6] If hemodialysis is a potential consideration, the nephrology service should be consulted as soon as possible.

If there is clinical or radiologic evidence of cerebral edema, there should be a strong consideration to continue hemodialysis in the form of continuous venovenous hemofiltration even after plasma ammonia has normalized until there is resolution of cerebral edema, because brain ammonia and glutamine levels may remain elevated even after plasma levels have normalized. In addition, rebound hyperammonemia after stopping dialysis could prove fatal in this precarious situation.

TABLE 3. Laboratory Tests and Investigations That Can Guide Clinical Care During Acute Metabolic Decompensations*

Laboratory Tests	Comments
Plasma ammonia	This should be done immediately on presentation. The blood for the test should be collected from a free-flowing sample, without tourniquet; placed immediately on ice; and analyzed within 15 min.
	Normal ammonia level is 15–35 μmol/L in an older child or adult and <110 μmol/L in a neonate†
Chemistry panel for electrolytes and blood glucose	To evaluate for acidosis/alkalosis and hypoglycemia if present
Venous blood gas	To assess for respiratory alkalosis
Plasma amino acid levels	To determine the levels of arginine, glutamine, and other urea cycle intermediates. Glutamine is one of the body's "reservoirs" for ammonia, and increasing glutamine may precede increases in ammonia.
Serum lactate	Can be elevated in hypovolemia (shock)
Infectious workup (CBC, cultures, CXR, urinalysis, etc)	To assess for the underlying etiology

*Sending laboratory tests should be guided by the clinical presentation of the patient. This is not an exhaustive list and some of the tests listed here may not be indicated.

†To convert from micromoles per liter to micrograms per deciliter, multiply by 1.8 (eg, an ammonia level of 100 μmol/L is equivalent to 100 × 1.8 = 180 g/dL.

CBC indicates complete blood count; CXR, chest x-ray.

TABLE 5. Indications for Hemodialysis in Patients With UCDs

1. Ammonia level of 250–500 μmol/L in a comatose child
2. Ammonia level of 250–500 μmol/L in a neonate aged 1 or 2 d
3. Ammonia level >500 μmol/L in a noncomatose child older than 2 d
4. Increasing ammonia level despite Ammonul therapy and adequate calories/nutritional management for 3–4 h
5. Poor clinical status: coma, cerebral edema
6. Unavailability of Ammonul
7. Hemodialysis or continuous venovenous hemofiltration can be considered first-line therapy in an adult (>18 y) with an ammonia level >200 μmol/L. In this case, the consideration to dialyze should be evaluated in light of the patient's comorbidities and the availability of ammonia-scavenging medications

Management of Possible Neurologic Complications (Decreased Level of Consciousness, Seizure, or Coma)

If there is concern for cerebral edema, then standard neurocritical care principles should be followed. Moderate hyperventilation can be considered. Mannitol has not been demonstrated to be effective in managing hyperammonemia-induced cerebral edema.

Treatment of the Underlying Etiology

Every effort should be made to identify and treat any potential underlying illness or infection that may be contributing to a decompensation. Infections such as gastritis/gastroenteritis, upper respiratory tract infection/bronchitis, and urinary tract infection are common causes for metabolic decompensations. These conditions should be managed according to their usual protocols and recommendations. Commonly used antibiotics and antiemetics can be used safely in patients with UCDs. In those patients with seizures, avoid using valproic acid (Depakote) because of its inhibitory effects on the CPS1 enzyme.

MONITORING

1. If the patient with UCD is ill, then strong consideration should be given to monitoring in an intensive care unit setting.
2. Neurologic status should be monitored, with a frequency indicated by clinical concern.
3. Ammonia levels repeated based on levels and clinical status. A common initial interval is every 2 to 4 hours.
4. Plasma amino acids if available should be monitored to evaluate essential amino acid levels (for nitrogen balance), glutamine, and arginine levels
5. Electrolytes should be monitored on Ammonul therapy.

CONCLUSIONS

Urea cycle disorders are severe metabolic disorders with life-threatening acute complications. Early recognition of metabolic decompensation and institution of appropriate management are critical to ensure good outcome. The acute care physician is usually the first provider to evaluate the patient with a UCD and is in a unique position to improve patient outcome by instituting the appropriate early management while expert opinion from a biochemist geneticist is sought.

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