

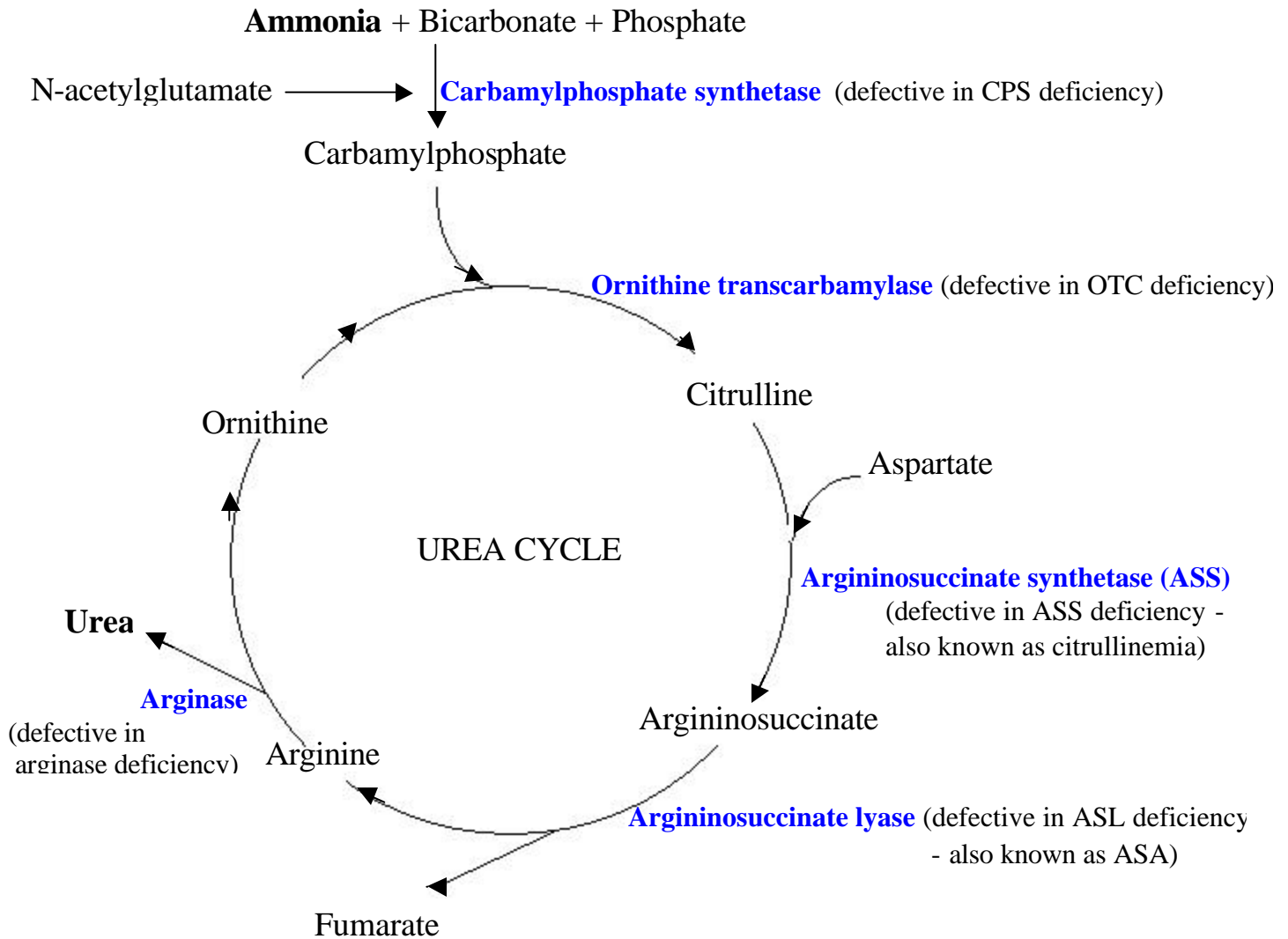
**EMERGENCY PROTOCOL  
UREA CYCLE DISORDERS  
THE NEONATE WITH HYPERAMMONEMIA**

**INTRODUCTION**

This protocol is for the neonate who is considered at risk for a urea cycle defect (UCD). Hyperammonemic crises in infants with UCDs are medical emergencies and must be treated as such to avoid death or serious brain injury.

**PATHOPHYSIOLOGY**

Each of the five biochemical reactions within the urea cycle is associated with a known enzyme deficiency and a related clinical disorder as shown in the diagram below



Carbamyl phosphate synthetase (CPS) and ornithine transcarbamylase (OTC) are located in the mitochondria. Arginase, argininosuccinate synthetase (ASS) and argininosuccinic acid lyase (ASL), also known as argininosuccinase, are cytosolic in location. The major site of complete urea cycle activity is the hepatocyte. The most common UCD is OTC deficiency and it is the only one, which is X-linked in inheritance; hemizygote males are usually severely affected and carrier females (heterozygotes) may be symptomatic to varying degrees depending on the extent of random X chromosome inactivation (lyonization). The other defects are autosomal recessive in inheritance; males and females are equally affected.

Unlike fats and carbohydrates, the body does not store protein. Excess protein is catabolized, releasing liberated nitrogen as ammonia ( $\text{NH}_3$ ). This additional  $\text{NH}_3$  cannot be metabolized by a defective urea cycle and so it accumulates. In general, protein overload comes from either dietary protein intake beyond bodily requirements or secondary to catabolic processes, e.g. stresses of the newborn period, infection, dehydration etc...

Raised ammonia levels appears to be extremely toxic to the central nervous system, causing cerebral edema. It is not clear whether this is a primary effect and/or secondary to elevated glutamine (GLN) which, containing two nitrogenous moieties, functions as a temporary "repository" for ammonia. GLN thus accumulates in excessive quantities in affected untreated individuals, as does alanine (ALA). Amino acid abnormalities may precede hyperammonemia and the onset of symptoms.

## **PRESENTATION**

- Lethargy
- Irritability
- Vomiting
- Ataxia
- Hyperammonemia
- Seizures
- Hepatomegaly
- Coma

Apart from arginase deficiency, which usually presents neurologically rather than as a hyperammonemic syndrome, the other urea cycle defects often present in the newborn period with catastrophic hyperammonemia, hepatomegaly, seizures and coma secondary to cerebral edema. Typically OTC and CPS have the most severe presentation but citrullinemia and argininosuccinic acidemia may also present with severe illness. However, all the UCD disorders may present later in life with a severe acute onset or a more chronic course.

## **ASSESSMENT**

Assess for cardiorespiratory instability, dehydration, fever, infection or any other physical stressor (e.g. surgery), as a potential precipitant for metabolic decompensation. Assess hepatic and neurological status.

- **Blood glucose**
- **Electrolytes, CO<sub>2</sub> and blood gas**
- **Ammonia** (1.5 ml blood in sodium-heparin tube sent STAT to lab on ice)
- **Plasma amino acids**
- **LFTs** (AST,ALT,AlkPO<sub>4</sub>, bilirubin)

If the diagnosis is unclear obtain the following: -

- **Urinary organic acids**
- **Urinary orotic acid**
- **Plasma citrulline**
- **Blood lactate**
- **Newborn screening blood sample**

Plasma ammonia is a direct index of toxicity, important for acute management. A level greater than 250 µg/dl (150 µmol/L), typically with the absence of metabolic acidosis (though may occur secondary to a respiratory alkalosis).

Plasma amino acids should be drawn first thing in the morning, calling the metabolic lab in advance for urgent samples. Glutamine acts as an ammonia buffer and reflects the direction of control of hyperammonemia. It is therefore essential that amino acids are checked daily in the acutely sick child with hyperammonemia secondary to a urea cycle defect.

## **STAT TREATMENT**

Delayed treatment increases morbidity and mortality. Once it is determined that the neonate has a urea cycle defect start treatment **STAT** and then continue to refine the diagnosis.

1. 10% IV dextrose +/- intralipid to provide glucose levels 120-170 mg/dl and prevent catabolism by providing 120-130 kcal/kg/day.
2. Prepare for probable dialysis, contact relevant renal and surgical specialists in anticipation of imminent need.
3. Provide IV sodium phenylacetate, sodium benzoate and arginine as detailed in treatment section (see page 6).

## DIAGNOSIS

To aid in differentiating which UCD is present if the diagnosis is uncertain

<u>Disorder (enzyme deficiency)</u>	<u>AMINO ACIDS</u>	<u>OROTIC ACID</u>
1. N-Acetylglutamate synthetase deficiency (nAGS def.)	- GLN, ALA	absent / normal
2. Carbamyl phosphate synthetase deficiency (CPS def.)	- GLN, ALA - CIT	absent / normal
3. Ornithine transcarbamylase deficiency (OTC def.)	- GLN, ALA - CIT	- - -
4. Argininosuccinic acid synthetase deficiency (citrullinemia)	- - - CIT - ARG	-
5. Argininosuccinic acid lyase deficiency (argininosuccinic aciduria)	- ASA, - CIT - ARG, ORN	-
6 Arginase deficiency	- - ARG, mildly ↑ ASA, CIT	-

Plasma citrulline levels obtained before 24 hours of age may partially reflect maternal citrulline levels (absent levels, however, may be significant). Absent/near-absent (< 5 μmol/L) citrulline at 48 - 72 hours of age are consistent with OTC or CPS deficiency. Marked citrulline elevations (often > 2000 μmol/L) are indicative of citrullinemia whereas a less marked elevation (usually 100-300 μmol/L) is more typical for ASA (the absence of elevated argininosuccinate and related metabolites during the first 48 hours would make the diagnosis of ASL deficiency very unlikely).

Urinary organic acids: Diagnostic test to help distinguish UCD from organic acidemias (organic acidemias very often produce a secondary hyperammonemia, which can be severe and are associated with a metabolic acidosis). Crucial to carry out during acute period since, if an organic acidemia is the diagnosis, the organic acids may normalize once the patient stabilizes. Requires plastic urine container with no preservative.

Orotic acid. See table above for differential diagnosis. Urine should be collected in 8 or 12 hour aliquots. Two specimens (different days) should be sent for analysis. Requires plastic urine container with no preservative

## **THE DEFINITIVE DIAGNOSIS**

OTCD is currently most readily confirmed by DNA analysis for a mutation in the OTC gene (which can identify approximately 75% of the mutations). In the event that a mutation is not identified, but OTCD is strongly suspected, liver biopsy with measurement of OTC activity is indicated. For analysis of OTC and CPS in liver fresh frozen liver biopsy is required. Warn physician/team carrying out the liver biopsy that it must be snap frozen as quickly as possible to preserve enzyme activity and handled more meticulously than a standard pathological specimen. Other UCDs can be assayed from fibroblasts and arginase can be assayed via red blood cell assay.

For DNA mutation analysis and biochemical assays, check [www.genetests.org](http://www.genetests.org) for the specific laboratories carrying out the individual tests and their specific requirements).

## **TREATMENT**

An infant suspected of or known to have a urea cycle disorder should be treated very aggressively. The rationale of treatment includes –

- Promote waste nitrogen excretion / reduce hyperammonemia.
- Reverse or minimize catabolism
- Minimize protein intake

## **PROMOTE WASTE NITROGEN EXCRETION / REDUCE HYPERAMMONEMIA**

To help facilitate the excretion of waste nitrogen, the following medications are employed.

- (i) **Sodium benzoate** – conjugates with glycine to form hippuric acid which bypasses the urea cycle and is excreted in urine.
- (ii) **Sodium phenylacetate** – conjugates with glutamine to form phenylacetylglutamine which bypasses the urea cycle and is excreted in the urine.
- (iii) **Arginine** – to prevent ARG deficiency and prime any residual OTC activity
- (iv) **Citrulline**. In OTC and CPS, enteral citrulline may pull aspartate into the cycle and increase nitrogen clearance BUT CAUTION, will further exacerbate citrullinemia and ASA in which there already is an excess of citrulline, therefore must be certain about the diagnosis prior to use.

Avoid carnitine as it has not been shown to be helpful. Although UCD infants are often low in carnitine, it is known to conjugate with sodium benzoate

If an IV infusion is required, that solution should NOT contain sodium as plenty will be provided by the sodium benzoate and sodium phenylacetate.

## MANAGEMENT OF HYPERAMMONEMIA

### **If the blood ammonia is >300 mg/dl (>175 mmol/L)**

### **CONSIDER DIALYSIS**

Dialysis will clear ammonia at :-

170-200 ml/min for ECMO based dialysis. Osmotic shifts have NOT been observed with this rapid rate of clearance. Additionally a hemofilter in the circuit will continue to remove ammonia between dialysis cycles.

10-30 ml/min hemodialysis

3-5 ml/min peritoneal dialysis (this rate will however take several days to significantly reduce the ammonia load, at a time when brain damage is related to duration of hyperammonemia toxicity).

While preparing for dialysis administer IV 10% dextrose and UCD medications as described below.

\*note that dialysis itself is associated with significant morbidity/mortality, particularly in the neonate, and decisions to consider using dialysis must balance the risk:benefit ratio for each child.

### **If the blood ammonia is in the range 200-250 mg/dl (120-150 mmol/L)**

Suggest transfer to NICU with metabolic and hemodialysis facilities and alert pediatric nephrology team. Remember placement of access lines for dialysis takes time so do not delay.

If dialysis is not immediately available, give a loading dose of sodium benzoate/phenylacetate as described below, to slightly retard ammonia rise and in anticipation of dialysis ASAP.

### **If the blood ammonia is > 100 – 125 mg/dl (60-75 mmol/L),**

repeat the level. If confirmed:

- discontinue oral feedings and oral medication
- administer a 10% (or higher) glucose solution and Intralipid.
- administer the urea cycle medications as an IV bolus.

## FOR UNKNOWN TYPE OF UCD

Sodium benzoate 250 mg/kg/day

Sodium phenylacetate 250 mg/kg/day

10% Arginine HCl (600 mg/kg/day)

Mix this in 35 cc/kg of 10% dextrose (no sodium) and run as a bolus over 90 minutes. This is then followed by the same solution administered as a 24-hour infusion.

- **REVERSE OR MINIMIZE CATABOLISM**

The caloric intake for these infants should run at least 120-130 kcal/g/day. Accurate records of intake and output should be kept to monitor hydration. Infection as a potential but severe catabolic stressor should be considered early and managed vigorously. Avoid valproic acid, as it decreases urea cycle function and accentuates hyperammonemia.

- **MINIMIZE/OPTIMIZE PROTEIN INTAKE**

DIET SHOULD BE PLANNED IN CONJUNCTION WITH A METABOLIC DIETICIAN

**For CPS and OTC deficiency,**

the caloric intake on day 1 is provided by intravenous dextrose and supplemented with Intralipid to provide 120-130 kcal/kg/day. Protein intake should ideally commence after 24 hours to avoid catabolic breakdown of endogenous proteins but may be delayed dependant on clinical status.

Start after 24 hours at 0.6 grams/kg/day, administered as essential amino acids.

After 48 hours, 1.2 grams/kg/day should be supplied, half in the form of essential amino acids, the other half in the form of a natural protein source (i.e., regular infant formula) but, avoid elemental formulas as they are high in nitrogen content. Supplemental calories are added from a non-nitrogenous formula with vitamins and minerals (Mead-Johnson 80056 formula, Ross formula Pro-Phree or equivalent). Water is then added to dilute to the proper concentration. Thereafter, the protein intake is increased gradually in 0.25 – 0.5 gram/kg increments per day to a maximum of 2 grams /kg/day.

**In citrullinemia and argininosuccinic acidemia,**

the infant can start with 0.6 grams/kg/day on day 1, using a regular formula. The administered protein is gradually increased to a maximum of 1.5- 2 grams/kg/day. Supplemental calories are provided as Mead-Johnson 80056 formula or equivalent.

Enteral feeds should be started as soon as practical, may even occur concomitant with IV via NG or NJ tube if necessary. Essential amino acids should not be withheld > 24 hours, to avoid catabolic breakdown of endogenous proteins. To avoid excess amino acid load aim for 1.0 - 1.5 g protein/kg body weight (50% as essential amino acids). Contact the metabolic nutritionist (and discuss with the parent) before starting oral diet such as Mead Johnson 80056 or Ross Pro-Phree.

Once patient stabilized, feedings established and the ammonia not fluctuating may switch to oral UCD medications.

## MONITORING

- These infusions should begin during acute illness regardless of the amount of oral UCD medication already provided. Monitor ammonia levels every 4 hours, amino acids daily. Electrolytes, acid-base status and the anion gap should be monitored regularly. If another IV is required, that solution should not contain sodium.
- Glucose levels should be kept between 120-170 mg/dl. If necessary for control of hyperglycemia can use insulin (remains controversial) bearing in mind that wide swings in glucose levels affect brain osmolarity.
- Cerebral edema; Oncotic agents such as albumin will increase the overall nitrogen load but may in selected cases be considered. Mannitol has not been found to be helpful for edema secondary to hyperammonemia and steroids should not be used. Hyperventilation is recommended, but only under close appropriate supervision.

### **Potential side effects of sodium benzoate/phenylacetate regimen**

Increased incidence of nausea and vomiting with bolus.

Overdoses (3-5x recommended dose) can lead to symptoms reminiscent of hyperammonemia, specifically agitation, confusion and hyperventilation. Death has occurred (associated with cerebral edema, hypotension and cardiovascular collapse)

## RECOVERY

As ammonia falls below 125-150mg/dl (60-75  $\mu\text{mol/L}$ ) and clinical status returns to baseline

Can switch to oral medications and gradual reintroduction of diet in conjunction with the metabolic dietician as described above (in section “therapy”) . The use of oral sodium benzoate and sodium phenylbutyrate (the much less odiferous oral form of sodium phenylacetate) is determined, dependent on the patient, either on body weight or body surface area. The dose should be decided in conjunction with a metabolic physician if the patient does not have an up to date regimen.

NOTE that there may be a rebound hyperammonemia initially with the efflux of intracellular ammonia into the ‘relatively’ ammonia depleted blood. THUS it is important to continue closely monitoring ammonia levels until they remain stable in the normal range. Adapted from : Proceedings of a consensus conference for the management of patients with Urea Cycle disorders. J Peds. Suppl. Vol. 138 (1), 2001

This protocol should be used **ONLY** in conjunction with metabolic consultation. For this please call or have paged the Genetics/Metabolism Fellow-on-call or, failing this, the Metabolic attending on call at your hospital or nearest pediatric tertiary care center (click on “metabolic consultation” at the top of the page to find local contact information [ in the New England area ] ).