

**ACUTE ILLNESS PROTOCOL
UREA CYCLE DISORDERS
THE INFANT/CHILD WITH ARGININOSUCCINATE LYASE DEFICIENCY
(also known as argininosuccinic acidemia)**

TREATMENT

An infant/child at risk from a urea cycle disorder should be treated prospectively. The rationale of treatment includes –

1. Minimize protein intake.
2. Reverse or minimize catabolism.
3. Promote waste nitrogen excretion.

1. MINIMIZE/OPTIMIZE PROTEIN INTAKE

DIET SHOULD BE PLANNED IN CONJUNCTION WITH A METABOLIC DIETICIAN

In 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 1.5-2.0 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 - 1.5g 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 ProPhree.

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

2. 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 (when clinical signs are apparent) and managed vigorously. Avoid valproic acid, as it decreases urea cycle function and accentuates hyperammonemia.

3. PROMOTE WASTE NITROGEN EXCRETION

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 but must NOT BE used in arginase deficiency where there is already an excess of arginine.

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. Also avoid citrulline as it will further exacerbate citrullinemia and ASA in which there already is an excess of citrulline

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

MANAGEMENT OF PROGRESSIVE HYPERAMMONEMIA

If the blood ammonia is > 100 – 125 ug/dl (60-75 µmol/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 ARGININOSUCCINIC ACIDEMIA

Sodium benzoate (250 mg/kg/day or 5.5g/m²)

Sodium phenylacetate (250 mg/kg/day or 5.5g/m²)

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

(Surface area for the benzoate and phenylacetate should provide a more accurate dose in adolescents and adults)

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

- 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 regime

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)

If the ammonia continues to rise >200-250 mg/dl (120-150 mmol/L)

Suggest transfer to PICU 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, to slightly retard ammonia rise and in anticipation of dialysis ASAP.

If the ammonia continues to rise >300 mg/dl (175 mmol/L)

CONSIDER DIALYSIS

Dialysis will clear ammonia at :-

170-200ml/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)

*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.

RECOVERY

As ammonia falls below 125-150mg/dl (60-75µmol/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]).