CARBAMOYL PHOSPHATE SYNTHETASE DEFICIENCY (CPSD)

RECOMMENDATIONS ON EMERGENCY MANAGEMENT OF METABOLIC DISEASES

Department of Medical Genetics
Carbamoyl Phosphate Synthetase Deficiency (CPSD)

- Patient’s Name:
- Date of Birth:
- MRN in KFSH&RC:

Please read carefully. Meticulous and prompt treatment is important as there is a high risk of serious complications.

Parents of children with diagnosed metabolic disorders know the early signs of decompensation in their children.

**INTRODUCTION:**

Urea cycle disorder causes accumulation of ammonia which is a waste product of protein metabolism. High ammonia levels are extremely toxic to the central nervous system, causing cerebral edema that is a major complication.

Hyperammonemia crises in children with urea cycle defects (UCDs) are medical emergencies and must be treated as such to avoid death or serious brain injury.

In general, decompensation is often triggered by either dietary protein intake beyond bodily requirements or secondary to catabolic processes, e.g. stress of new born period, fasting, dehydration, and/or febrile illness particularly gastro-enteritis and flu.
Each of the five biochemical reaction within the urea cycle is associated with a known enzyme deficiency and a related clinical disorder as shown in the diagram below.

The CPS1 is the first enzyme in the urea synthesis process. Lack of this enzyme will lead to CPSD that is inherited in an autosomal recessive way.

**PRESENTATION:**
The early signs of decompensation include:

- Lethargy
- Poor appetite
- Exacerbation of pre-existing neurological problems (irritability, fits etc)
- Vomiting is common and should be taken seriously
However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen carefully to patient’s family; their knowledge might exceed your expectations.

Later signs and symptoms of decompensation may include:

- Ataxia
- Developmental delay
- Seizure
- Hepatomegaly
- Coma
- Hyperammonemia
- Failure to thrive

At a very early stage the plasma ammonia concentration may not be raised, probably because there is accumulation of glutamine in the brain before ammonia increases in the blood.

Apart from arginase deficiency, which usually presents neurologically rather than as a hyperammonemia syndrome, the other urea cycle defects often present in the newborn period with catastrophic hyperammonemia, seizure and coma secondary to cerebral edema. Typically CPS has the most severe presentation but citrullinemia and argininosuccinic acidemia may also present with severe illness.

**MANAGEMENT:**

If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.

**Initial plan and management in hospital**

- If the child is shocked or clearly very ill, arrange for admission to Intensive Care Unit.
If admitted to metabolic/general ward make a careful clinical assessment including blood pressure and Glasgow Coma Scale even if the patient does not appear encephalopathic.

**ASSESSMENT:**
Assess for cardio-respiratory instability, dehydration, fever, infection, excessive protein intake or any other physical stressor (e.g. surgery), as a potential precipitant for metabolic decompensation. Assess neurological status.

Request following blood tests:

- Plasma ammonia
- Blood glucose
- Blood gas
- Electrolytes, Bicarbonate
- LFTs (AST, ALT, AlkPO4, bilirubin)
- Plasma amino acids (Quantitative)

Plasma amino acid should be drawn first thing in the morning, calling the metabolic lab in advance for urgent samples.

**TREATMENT:**
An infant/child at risk from a urea cycle disorders should be treated prospectively. The rational of treatment includes:

1. Promote waste nitrogen excretion.
2. Reverse or minimize catabolism.

- Management decisions should be based primarily on the **clinical** status. It is particularly important to note any degree of encephalopathy.
The first decision about therapy is whether the child can be treated orally or will need intravenous therapy. Factors that will influence the decision include:

- How ill is the child and whether they have deteriorated suddenly in the past?
- Can the child tolerate oral fluids?
- If the child is relatively well, he/she may be treated orally but assess very carefully.
- If the child is obviously unwell, he/she must be treated with intravenous fluids:
  - Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1 ml/kg of 20% glucose) over few minutes.
  - Give normal saline 5 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give up to 20 ml/kg normal saline instead of the 5 ml/kg. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
  - Continue with glucose 10% at 5 ml/kg/h until next solution ready. see below
  - Quickly calculate the deficit and maintenance and prepare the intravenous fluids
    - Deficit: estimate from clinical signs if no recent weight available
    - Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children): 100 ml/kg for first 10 kg then 50 ml/kg for next 10 kg then 20 ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
    - It is assumed that the patient will be given sodium benzoate and sodium phenyl butyrate at full dose therefore uses 10% glucose. If not given full doses of previous medications, use 0.18% Saline and 10% glucose.

- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
- Recheck the electrolytes every 24 hours if still on intravenous fluids.
1. Promote waste nitrogen excretion:
To help facilitate the excretion of waste nitrogen, the following medications are employed.

a) Sodium benzoate-conjugates with glycine to form hippuric acid which by passes the urea cycle and is excreted in urine.

b) Sodium phenylbutyrate or Sodium Phenyl acetate- conjugates with glutamine to form phenylacetyl-glutamine which bypasses the urea cycle and is excreted in the urine.

c) Arginine-to prevent ARG deficiency and prime any residual CPS activity but most NOT BE used in arniginas deficiency where there is already an excess of arginine.

Do not delay starting ammonia scavenging medications as prognosis is strongly influenced by the duration of illness and peak ammonia levels.

In an emergency, initially the loading dose is given intravenously over 90-120 minutes, followed by an equivalent maintenance infusion given over 24 hours.

Dosage is based on weight and specific enzyme deficiency.

Therapy should continue until ammonia levels are in normal range.

Repeat loading doses are not recommended due to the prolonged plasma levels. Loading dose should be administered along with arginine 10% infusion.

Discontinue administration of oral analogous (eg, sodium phenylbutyrate) before starting the infusion.
### Components of Infusion Solution

Ammonul® must be diluted with sterile 10% dextrose injection at ≥25 mL/kg before administration.

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Dosage Provided</th>
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<tbody>
<tr>
<td></td>
<td>Ammonul®</td>
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<td></td>
<td></td>
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<tr>
<td>Neonate, Infants, Children ≤20 kg</td>
<td></td>
</tr>
<tr>
<td>CPS Deficiency</td>
<td>Loading: Over 90-120 minutes</td>
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<tr>
<td>Maintenance: Over 24 hours</td>
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<tr>
<td>Children &gt;20 kg and Adults</td>
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### Dosage adjustment in renal impairment:
Use with caution; monitor closely

Dialysis: Ammonia clearance is ~10 times greater with hemodialysis than by peritoneal dialysis or hemofiltration. Exchange transfusion is ineffective.

### Dosage adjustment in hepatic impairment:
Use with caution
Once patient is stabilized, ammonia levels are reduced and patient can tolerate oral feeds, intravenous medication should be switched over to oral.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral doses</th>
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<tbody>
<tr>
<td>Sodium benzoate</td>
<td>250-500 mg/kg/day</td>
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<tr>
<td>Sodium phenylbutyrate</td>
<td>450-600mg/kg/day</td>
</tr>
<tr>
<td>Arginine</td>
<td>250 mg/kg/day</td>
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**Potential side effects of sodium benzoate /phenylbutyrate regime:**

- Increased incidence of nausea and vomiting with bolus.
- Overdoses (3-5x recommended dose) can lead to symptoms reminiscent of hyperammonemia, like agitation, confusion and hyperventilation.
- Hyperchloremic acidosis may occur following high-dose treatment.
- Hypokalaemia: Plasma Potassium concentration should be monitored carefully.
- Death has occurred (associated with cerebral edema, hypotension and cardiovascular collapse).

*N.B.*

In CPSD, Citrulline may replace arginine as oral treatment when child is able to have enteral feed (PO, NGT or GT) as it helps pull aspartate into urea cycle and increase nitrogen clearance.

**Avoid Carnitine** as it is not shown to be helpful. Although UCD infants are often low in Carnitine, it is known to conjugate with Sodium Benzoate.

If an IV is required, that solution should NOT contain Sodium as plenty will be provided by the Sodium Benzoate and Sodium Phenylbutyrate.

**Treat any infection and constipation** (which increases ammonia absorption from the gut). Lactulose is recommended as theory suggests this will beneficial although, as yet this unproven.
2. **REVERSE OR MINIMIZE CATABOLISM:**
   The caloric intake for these infants should be kept at least 120-130kcal/kg. Accurate intake and output records 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.

4. **MINIMIZE/OPTIMIZE PROTIEN INTAKE:**
   Stop protein intake initially. Following improvement, gradual reintroduction of protein/essential amino acids within 24-36 hours.

   In CPSD, the infant can start with 0.6gram/kg/d in 1 day using h formula. Protein is administered gradually increased to a maximum of 2.0gram/kg/d.

   Enteral feed should be started as soon as practical, may even occur concomitant with IV via NG or G-tube if necessary. Essential amino acids should not be withheld >24hours, 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).

**DIET SHOULD BE PLANNED IN CONJUNCTION WITH A METABOLIC DIETICIAN**

**MONITOR THE PATIENT:**
If there is any hint of incipient encephalopathy (lethargy, unusual behavior, etc.) start neurological observations at least hourly and seek specialist help. Under these circumstances, fluid volumes should be reduced and given via central line as concentrated solutions to minimize risk of cerebral edema.

Reassess after 4-6 hours or earlier. Clinical assessment should include Glasgow coma score and vital signs.

**Blood tests:**
- Blood pH and gases
- Ammonia
- Urea & electrolytes
- If improving, continue intravenous fluids and medicines (see the previous section)
- If deteriorating (clinical state, hyperammonaemia), seek specialist help. Dialysis may need to be considered urgently. Note peritoneal dialysis is less efficient. Exchange transfusion is dangerous and should not be used.

**MANAGEMENT OF PROGRESSIVE HYPERAMMONEMIA:**
If the blood ammonia is elevated, repeat the level. If confirmed:

- Discontinue oral feeding and oral medications
- Administer a 10% (or higher) glucose solution and intralipid
- Administer urea cycle medications as an IV bolus

- These infusions should begin during acute illness regardless of the amount of oral CPS medication already provided. Monitor ammonia level every 4 hours, amino acids daily. Electrolytes, acid-base status and the anion gap should be monitored regularly. If another IV is required that should not contain sodium.
- Glucose level should be kept between 120-170 mg/dl (6.0-9.0 mmol/L). If necessary for control of hyperglycemia insulin can be used (remains controversial) bearing in mind that wide swing in glucose level affects brain osmolality.
- Cerebral edema: Oncotic agents such as albumin will increase the overall nitrogen load and should be avoided.
- 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.

*Avoid valporic acid, as it decreases Urea Cycle function and accentuates hyperammonemia.*
If ammonia continues to rise:

Suggest transfer to PICU/ICU with metabolic and hemodialysis facilities and alert pediatric nephrology team. Remember placement of access lines for dialysis takes time DO NOT DELAY.

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

Dialysis will clear ammonia at:

- 170-200ml/min from ECMO based dialysis. Osmotic shifts have not been observed with rapid rate of clearance. Additionally a hemofilter in the circuit will continue to remove ammonia between dialysis cycles.
- 10-30ml/min hemodialysis.
- 3-5ml/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

*N.B.*

**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 stabilizes and clinical status returns to baseline, patient can switch to oral medications and gradual reintroduction of diet in conjunction with metabolic dietician as described in treatment section. The dose of sodium benzoate and sodium phenylbutyrate is determined based on either 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 normal range.

**ACKNOWLEDGMENT:**
These recommendations have been compiled by Wafa Abusamha, Medical Genetic Clinical Coordinator, KFSH&RC based on protocols and guidelines of the American college of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England consortium on metabolic Programs; and have been revised by Medical Genetic Consultants in the Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in June 2014.

**REFERENCES:**
- ACT SHEET, American Collage of Medical Genetics (ACMG)
- EMERGENCY guidelines, British Inherited Metabolic Disease Group (BIMDG)
Dietary Emergency Protocol for Urea Cycle Disorders (UCD)

- Name:
- Date of birth:
- Weight & date of weight measurement:

1. Discontinue regular diet/feeds

2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   Add ................. Scoops Polycose/Prophree to ................. mls water

3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting

4. When using the available tube feeding, it is preferable to give the solution as:
   - Small boluses: Give ....... mls of emergency solution every ......... hour
   - Or continuously if a feeding pump is available

5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add............ Scoops Polycose/Prophree to.......... mls of Rehydration Solution

6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      - If the child is doing well, go back to normal diet.
      - If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen:
      - If your child appears well, reintroduce amino acid mix excluding natural protein source.
      - If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   c. After 48 hours from starting the emergency regimen:
      - If the child is doing well and amino acid mix is well tolerated, start introducing natural protein in the diet gradually over few days starting with half amount.
      - If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, bring your child to the hospital with all medicines, special dietary products, and scoops.

N.B:
If, at any time from starting this emergency regimen, your child is deteriorating and/or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.
ACKNOWLEDGMENT

Dietary Emergency Protocols have been compiled by Eman Megdad, Metabolic Nutriotionist-Medical Genetics; KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in June 2014.
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