Children's Health Ireland at Temple Street

NURSING GUIDELINES FOR MANAGEMENT OF CHILDREN WITH UREA CYCLE DEFECTS

Revision: 1

Policy		Procedure		Protocol		Guideline	x

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1. STATEMENT:

The objectives in preparation of Nursing Guidelines for Management of Inherited Metabolic Disorders (IMD) are to increase the knowledge base of nursing staff involved in the delivery of care to patients with an IMD, provide a resource material for reference and ultimately ensure the consistent delivery of high quality care to patients attending the National Centre for Inherited Metabolic Disorders (NCIMD).

Readers of this document are reminded that prescription of dietary regimes and all medications (including insulin, minerals, vitamins and trace elements) is the responsibility of the Metabolic Consultant. These guidelines may only be used under the supervision and guidance of a Metabolic Consultant.

The document authors wish to thank the various Doctors, Nurses, parents and patients who have worked in and attended the National Centre throughout the years, contributing greatly in the process to our knowledge and experience of Inherited Metabolic Disorders.

2. SCOPE

These guidelines are a point of reference for all nursing and medical staff in relation to the care of a child with a urea cycle disorder or suspected of having a urea cycle disorder.

3. DEFINITIONS:

Urea Cycle Disorders are inherited disorders of nitrogen metabolism. Six enzymes are involved in the process of forming urea from waste nitrogen in the urea cycle.

These enzymes are:

1. N-acetylglutamate Synthase (NAGS)
2. Carbamyl Phosphate Synthetase I (CPSI)
3. Ornithine Transcarbamylase (OTC)
4. Argininosuccinate Synthase (ASS)
5. Argininosuccinate Lyase (ASL)
6. Arginase (Sclune et al. 2015)

Where one of the above enzymes is absent, present in reduced amounts, or only partially works, the Urea Cycle is affected. The formation of arginine and ornithine is reduced with

resulting deficiency, and further accumulation of ammonia will result. Arginine administration corrects the deficiency of both arginine and ornithine.

3.1 PREVALENCE

1: 8,000 cumulative incidence (Zschocke & Hoffmann, 2011).

3.2 INHERITANCE

All urea cycle disorders are recessively inherited, except OTC deficiency which is x-linked (Gropman et al, 2013). For this reason, a carrier mother of OTC has a 50% chance of having an affected male. Daughters have a 50% chance of inheriting the mutation. The expression in females who carry the mutation may vary from clinically asymptomatic / mild / moderate forms of the disorder.

4. PRESENTATION:

Impaired activity in the metabolic pathway results in a build-up of neurotoxic ammonia and glutamine (pre-curser amino acid) in blood and tissue. Patients may present at any age but particularly during;

a. The neonatal period – may have normal antenatal & delivery stages.
b. Late infancy due to less severe mutation and presence of some enzyme activity and reduced exposure to prolonged fasting / protein overloading / protein catabolism.
c. Older children & adults can have recurring encephalopathic presentations, however, commonly present with a chronic neurological disease and developmental delay, psychiatric symptoms or liver disease (Wijburg & Nassogne, 2012).

4.1. Signs & symptoms in the neonatal period;

- Poor feeding
- Lethargy
- +/- irritability
- Vomiting
- Respiratory alkalosis (ammonia is a respiratory stimulant) shifting to an acidosis as condition deteriorates.
- Loss of reflexes
- Seizures

- Coma

(Wijburg & Nassogne, 2012; Zschocke & Hoffmann, 2011)

These symptoms develop after an initial symptom free period.

4.2. Symptoms in older infants:

The clinical picture is often less dramatic;

- Failure to thrive
- Feeding difficulties
- Cyclical Vomiting
- Episodes of encephalopathy with lethargy or seizures
- Impaired development
- Ataxia
- Behavioural disturbances (Braissant et al. 2013)

4.3. Symptoms in older children and adults:

- Episodic metabolic encephalopathy (can be associated with large protein intake)
- Vomiting
- Behavioural changes (irritability, agitation)
- Lethargy
- Headaches
- Ataxia (Wijburg & Nassogne, 2012; Zschocke & Hoffmann, 2011)

Arginase deficiency rarely presents with classical hyperammonemia. The usual presentation is progressive diplegia and developmental delay (Champion, 2000).

5. DIAGNOSIS:

5.1. Suspicion:

a. **Check serum Ammonia levels.** If an infant, child or adult presents with above symptoms, a blood sample for ammonia levels should be taken.

Plasma ammonia concentrations (levels >100 micromoles in adults & older children, levels >150 micromoles in neonates & infants require investigation for the possibility of a Urea Cycle Defect (Wijburg & Nassogne, 2012). Hyperammonemia (250-500 micromoles/l)

correlates to irreversible neurological damage in neonates and infants (Wijburg & Nassogne, 2012).

b. Obtain a blood gas sample for analysis and p H - Respiratory alkalosis is caused by central stimulation by ammonium ion, followed by metabolic & respiratory acidosis in severely ill patients (Wijburg & Nassogne, 2012).
c. Obtain serum glucose, urea and electrolytes, creatinine, transaminases, coagulation, full blood count.

5.2. Confirmation:

- Plasma amino acids (elevated Alanine & Glutamine)
- Urinary organic acids (OTC, ASS, ASL & arginase deficiency – orotic acid and orotidine present)
- Acylcarnitine
- Mutational Analysis
- Enzyme activity

Hyperammonemia can be present in a number of other metabolic disorders in the neonatal period, but a raised glutamine in the absence of acidosis is strongly suggestive of a Urea Cycle Defect (Haeberle et al, 2012).

Diagnosis and early instigation of treatment is critical to avoid permanent neurological damage or even death (Braissant et al. 2013, Gupta et al, 2011).

6. MANAGEMENT:

6.1. Emergency Treatment:

a. Stop natural protein intake (infant formula / breast feeding / food products which are a source of protein).
b. Ensure adequate calorie intake to prevent catabolism and promote anabolism.
c. Administer intravenous glucose and lipids in order to minimise ammonia production from endogenous protein breakdown (Haeberle et al, 2012).
d. Administer Arginine* and citrulline* supplementation to optimise the function of the urea cycle and administer Sodium Benzoate and Sodium Phenylbutyrate to provide alternative pathways for the excretion of ammonia (Wijburg & Nassogne, 2012). *N*-

Carbamylglutamate may be administered to patients with a suspected NAGS deficiency (Gessler et al., 2010).

e. Haemodialysis or haemofiltration may be recommended on initial presentation and on subsequent admissions where ammonia levels are grossly elevated to reduce levels rapidly.

*Note: Arginine should not be administered to patients with Arginase Deficiency (Wijburg & Nassogne, 2012).

*Note: Citrulline supplementation is administered to patients with OTC deficiency.

6.2 Long-term Management:

a. Long term Follow up

i. A multi-disciplinary approach is cultivated i.e. Medical, Nursing, Dietary, Social Work, Psychology etc.

ii. Monitor ammonia, glutamine, glycine and arginine levels as per Consultant.

iii. Symptomatic control of and avoidance of acute episodes.

iv. Emergency regime, emergency letter and family education are all key to long term management.

7. NURSING MANAGEMENT OF THE PATIENT WITH UREA CYCLE DISORDERS

Complete full nursing assessment on admission and continue to observe for signs of patient deterioration e.g. lethargy, abnormal behaviour, diarrhoea or vomiting.

ACTION	RATIONALE
A. EMERGENCY ASSESSMENT Complete patient assessment on admission and document vital signs in Paediatric Early Warning System (PEWS) record. Escalate care as indicated by PEWS score and clinical judgment. Frequency of monitoring will be dictated by patient's condition (i.e.2-4 hourly during initial presentation and acute illnesses - Paediatric Early Warning Score (PEWS) is used in CHI at TS.)	
• **A**irway	Airway may be compromised due to alteration in the Glasgow Coma scale. Neurological features accompanying acute hyperammonemia include changes in behaviour and consciousness in the short term (Gropman et al. 2013).

ACTION	RATIONALE
• **B**reathing (Respiratory rate, effort, oxygen requirements).	Ammonia acts as a respiratory stimulant. Check ammonia levels where tachypnoea is present. CNS oedema first causes hyperventilation and respiratory alkalosis later progressing to hypoventilation and apnoea (Braissant et al. 2013).
• **C**irculation (Pulse, blood pressure, capillary refill time, patient colour). **Include Capillary Refill Time assessment as per PEWS** Observe colour, peripheral perfusion of skin and condition and texture of hair.	Tachycardia – shock, infection, acidosis, fluid overload. Can be hypertensive during episodes of encephalitis / hypotensive with hypovolemic shock. To identify hydration status and nutritional status and presence of hypovolemic shock. Observe for pallor, cool clammy skin, decreased central capillary refill time, mottled extremities, dry mucous membranes and sunken eyes (Schub & Karakashian, 2017).
• **D**isability (level of consciousness and neurological status) Assess and record baseline neurological status using **Glasgow Coma Scale**, and continue to reassess regularly especially during further episodes of acute illness.	Severe forms of acidemia and/or hyperammonemia can produce seizures and coma.

ACTION	RATIONALE
Observe for and report poor feeding, lethargy, vomiting, irritability, altered level of consciousness, muscle weakness and seizures. Check with parents regarding patient's usual behaviour.	May indicate increase in toxic levels of ammonia and glutamine in patients with urea cycle defects. The susceptibility of the developing brain to hyperammonemia, if untreated, leads to severe cognitive impairment, seizures and cerebral palsy (Braissant et al. 2013). Baseline for comparison.
• **E**xposure to ensure full examination (whilst respecting the child's dignity and ensuring body temperature conservation).	
TEMPERATURE	A slight rise may be idiopathic. Pyrexia may indicate the presence of sepsis. Follow Sepsis 6 protocol in PEWS chart. The following should be performed, blood cultures, F.B.C., U+E, LFTS, CRP and blood gas (including lactate) – standard for sepsis. Hypothermia may suggest the need for more calories. However, it may be an indicator for infection in the neonate. As ammonia rises in the blood: hypothermia, lethargy and coma progress rapidly (Braissant et al. 2013).
Provide periods of rest between nursing care procedures.	Minimises stress due to excessive handling.

ACTION	RATIONALE
B. BLOOD GLUCOSE Baseline, then 4-6 hourly while receiving intravenous glucose infusion.	Hyperglycaemia may be related to continuous intravenous glucose infusion, or to stress. Consider need for insulin infusion where hyperglycaemia occurs secondary to high glucose concentrations being infused. Refer to Medical Guidelines for Management of patients with metabolic disorders and contact doctor on call. Insulin dosages appropriate for patients with Insulin Dependent Diabetes Mellitus are ***not suitable*** for these patients as the pancreatic gland is normal. Hypoglycaemia may occur if patient is vomiting or has diarrhoea.
C. WEIGHT AND HEIGHT Weigh on admission. Plot on centile charts at weekly intervals while in hospital and at each OPD visit.	Necessary for drug calculation and to ensure that nutritional requirements are being met. Assess for growth spurts and weight loss.
D. URINALYSIS **Monitor** • Ketones • Protein • Specific Gravity and pH • Glucose	Positive ketones indicate catabolism of fat. Positive protein – possible urinary tract infection. Consider reserving a clean catch urine sample for culture and sensitivity. To assess and monitor hydration status. Gycosuria may occur due to high intake of glucose due to high calorie requirements. Check blood glucose to determine serum level.

ACTION	RATIONALE
E. FLUID BALANCE Strict monitoring of Intake and Output and overall fluid balance. Document accurately in fluid balance record. Weigh nappies and weigh patient daily. Calculate cumulative fluid balance. Report findings to medical team.	To assess for signs of fluid overload / dehydration.
F. DIET **3 Components :** • **NATURAL PROTEIN** Infants will receive their daily allowance of protein from infant formula. Once weaning is commenced protein content of food products must be calculated and included in the daily allowance. **Each gram of natural protein is referred to as an 'exchange'.** • **SYNTHETIC PROTEIN** e.g. EAA (contains reduced amount of nitrogen)	Needed for growth and development. Nutritional needs cannot be adequately met by limited amount of natural protein tolerated by patients with Urea Cycle Defects.

ACTION	RATIONALE
• **FREE FOODS (i.e. Low Protein Products) / CHO & FAT** Ensures calorie needs are met. Free foods are introduced as child grows.	Provide energy and heat. Provide variety in diet and satisfy appetite.
• Nasogastric feeding may be necessary. • Regular feeds and avoidance of prolonged fasting periods	Large feed volumes may be required even when well. Optimise metabolic control.
UNWELL (Emergency) REGIME • Instigation of an **emergency regime** (during times of metabolic stress) which includes the reduction or elimination of natural protein temporarily from the diet. (Vara et al. 2018)	Withdraw nitrogen source as much as possible from diet (on Consultant's instructions) This will help to reduce ammonia and glutamine levels.
• I.V. Glucose and lipids may be required if not tolerating enteral diet.	To ensure patient receives adequate calorie intake.
• **Calorie Count Chart** When unwell, calorie intake will be increased to 110 –120 % of normal daily calorie requirements.	

ACTION	RATIONALE
• When patient is unwell, a medical decision will be taken as to whether synthetic protein should be stopped. Both natural and synthetic protein should be reintroduced to diet when condition improves and serum ammonia and glutamine levels return to normal.	Because synthetic protein supplement is nitrogen sparing (i.e. contains nitrogen). This will help to reduce ammonia and glutamine levels.
G. MEDICATIONS **Arginine** Administer orally or intravenously as per metabolic guidelines / BNF (2017-2018) For administration of intravenous Arginine, use in conjunction with guideline (PP-CLIN-NCIMD-24) **Sodium Phenylbutyrate** Administer orally or intravenously as per metabolic guidelines. For administration of Intravenous Sodium	Hyperammonemia in symptomatic individuals usually requires the use of medications which serve as nitrogen scavengers or substrates that may be deficient (Giva et al. 2019). Arginine is a non-essential amino acid. It is derived from the diet and can also be synthesised in the urea cycle. Arginine becomes an essential amino acid In disorders of the urea cycle (except in arginase deficiency). Its administration supplements the urea cycle (BNF, 2017-2018). Arginine reacts with nitrogen-containing substances earlier in the cycle to form less toxic compounds. These compounds are more readily excreted by the kidneys than ammonia itself. Sodium Phenylbutyrate conjugates with glutamine to form phenylacetylglutamine, which is rapidly excreted in the urine (Wijburg & Nassogne, 2012). Two mmol of nitrogen are excreted for each mmol of phenylbutyrate administered. The elimination of glutamine reduces the nitrogen load on the urea cycle. Plasma concentrations of glutamine and ammonia fall and are accompanied by clinical and biochemical

ACTION	RATIONALE
Phenylbutyrate, use in conjunction with guideline (PP-CLIN-NCIMD-25).	improvement. Dosage is aimed to reduce plasma ammonia concentrations below 60µmol/l, and plasma glutamine less than 800µmol/l.
Sodium Benzoate Administer orally or intravenously as per metabolic guidelines. For administration of Intravenous Sodium Benzoate, use in conjunction with guideline (PP-CLIN-NCIMD-23).	Sodium Benzoate is conjugated with glycine to form hippurate, which is rapidly excreted in the urine (Wijburg & Nassogne, 2012). With complete conjugation, one mmol of nitrogen is cleared for each mmol of benzoate given. The loss of glycine reduces the load of waste nitrogen to be excreted via the urea cycle (Leonard and Morris, 2000) and, as a result, there is chemical and clinical improvement.
NOTE: **Intravenous Arginine, Sodium Phenylbutyrate and Sodium Benzoate can be given simultaneously via one peripheral intravenous cannula / lumen of a central venous access device.**	
Glycerol Phenylbutyrate **Oral form available only at present** ***Oral/Nasogastric administration***	Medication approved in 2013 for treatment of Urea Cycle Defects. Can be used instead of Sodium Phenylbutyrate at Consultant's discretion. Glycerol Phenylbutyrate was found to have no sodium burden, and offers palatability and pharmacokinetic advantages over sodium phenylbutyrate (Monteleone et al. 2013).

ACTION	RATIONALE
	Glycerol Phenylbutyrate is digested by pancreatic lipases, which release 4-phenylbutyric acid (PBA). PBA is converted to phenylacetic acid (PAA), which is then conjugated with glutamine to form phenylacetylglutamine (PAGN), which is excreted in the urine (Monteleone et al, 2013). Plasma ammonia falls, accompanied by improvement in symptoms such as appetite, lessened vomiting and irritability.
Other medications and supplements: **Potassium supplements** may be prescribed for addition to intravenous fluids (based on electrolyte results).	Must be given as 'push' dose when given via nasogastric tube as stability of drug cannot be guaranteed when added to feed. Some urea cycle disorders - most commonly Argininosuccinic Aciduria are particularly associated with severe hypokalaemia, and higher doses of potassium may be required to avoid life-threatening hypokalaemia. This is dependent on the individual patient need and only performed under specialist direction. Administer higher doses of potassium in conjunction with Potassium guidelines (PP-CLIN-NCIMD-29). Hypokalemia can develop after repeated boluses of scavenger drugs and in long term treatment resulting from increased renal loss of potassium (Haberle et al. 2012).
Diuretic Therapy	May be required if large fluid volumes are required to prevent catabolism
Soluble Insulin	May be required if patient is hyperglycaemic – Refer to Metabolic Medical Guidelines and consult Metabolic Consultant on call.
Solvito	Water soluble vitamins
Paeditrace	Trace elements
Vitlipid	Fat soluble vitamins **Please refer to Paediatric Parenteral Nutrition book for correct doses (Ball et al. 1998: Dunne, 2008).**

ACTION	RATIONALE
Analgesia / Anti-pyretic therapy Paracetamol is not advocated for use in patients with Urea Cycle Defects.	Paracetamol is metabolised in the liver (Malar and Bai, 2012).
H. ON-GOING MULTI -DISCIPLINARY SUPPORTS	
Metabolic Clinic for medical, dietetic and nursing support.	
Blood tests for ammonia, amino acids and any others requested by team. Patients may occasionally attend local hospitals for ammonia measurement between OPD visits.	To assess effectiveness of diet. To determine need for dietary adjustment.
Psychology	Chronic illness may adversely affect the family unit and relationships within the family. Dietary regime can cause elevated levels of stress.
Social Work	To ensure appropriate entitlements and services are accessed. To provide support at times of crisis.
Genetic Counselling	Implications for future pregnancies

ACTION	RATIONALE
Other Health professionals may be consulted as needed (i.e. Speech and Language, Ophthalmology etc.).	

8. MONITORING, AUDIT & EVALUATION

This procedure shall be reviewed and updated at least every three years by the Clinical Education Facilitator, NCIMD in order to determine its effectiveness and appropriateness. It shall be assessed and amended as necessary during this period to reflect any changes in best practice, law, substantial organisational change and professional or academic change.

9. KEY STAKEHOLDERS

The following Key Stakeholders were consulted in the development/review of this document:

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