TITLE: NURSING GUIDELINES FOR THE MANAGEMENT OF CHILDREN WITH UREA CYCLE DEFECTS

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1. PURPOSE:

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 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. 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 Synthetase (NAGS)
2. Carbamyl Phosphate Synthetase I (CPSI)
3. Ornithine Transcarbamylase (OTC)
4. Argininosuccinate Synthase (ASS)
5. Argininosuccinate Lyase (ASL)
6. Arginase

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.

PREVALENCE

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

INHERITANCE

All urea cycle disorders are recessively inherited, except OTC deficiency which is x-linked. For this reason, a carrier mother 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.

3. 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;

- Neonatal period – normal antenatal & delivery, with an uneventful first few days of life.
- Late infancy due to less severe mutation and presence of some enzyme activity and reduced exposure to prolonged fasting / protein overloading / protein catabolism.
- 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).

3.1. 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.

3.2. Symptoms in older infants:

The clinical picture is often less dramatic;

- Failure to thrive
- Feeding difficulties
- Cyclical Vomiting
- Episodes of encephalopathy with lethargy/ataxia/seizures
- Impaired development

- Ataxia
- Behavioral disturbances

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

3.3. Symptoms in older children and adults:

- Episodic metabolic encephalopathy (can be associated with large protein intake)
- Vomiting
- Behavioral changes (irritability, agitation)
- Lethargy
- Headaches
- Ataxia

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

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

4. DIAGNOSIS:

4.1. <u>Suspicion:</u>

Plasma ammonia concentrations (levels >100µmol in adults & older children, levels >150 µmol in neonates & infants require investigating possibility of Urea Cycle Defect, (Wijburg & Nassogne, 2012)). Hyperammonaemia (250-500umol/l) correlates to irreversible neurological damage in neonates and infants (Wijburg & Nassogne, 2012).

- Blood gas 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).
- Serum glucose, urea and electrolytes, creatinine, transaminases, coagulation, full blood count.

4.2. <u>Confirmation:</u>

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

Hyperammonaemia 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.

5. MANAGEMENT:

5.1. Emergency Treatment:

- Stop natural protein intake (infant formula / breast feeding / food products which are a source of protein).
- Ensure adequate calorie intake to prevent catabolism and promote anabolism.
- Administration of intravenous glucose and lipids in order to minimize ammonia production from endogenous protein breakdown (Haeberle et al, 2012).
- Arginine* and citrulline* supplementation is administered to optimize the function of the urea cycle and Sodium Benzoate and Sodium Phenylbutyrate are administered to provide alternative pathways for the excretion of ammonia (Wijburg & Nassogne, 2012). Administration of *N*-Carbamylglutamate may be administered for patients with a suspected NAGS deficiency (Gessler et al., 2010).
- 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: Citruilline supplementation is administered to patients with OTC deficiency.

5.2. Long-term Management:

- **Long term Follow up**
  A multi-disciplinary approach is cultivated i.e. Medical, Nursing, Dietary, Social Work, Psychology etc.

- **Monitor ammonia, glutamine and arginine levels.**

- **Symptomatic control of and avoidance of acute episodes.**

6. NURSING MANAGEMENT OF THE PATIENT WITH UREA CYCLE DISORDERS

Nursing observation and attention to detail is vital. The reporting of lethargy, abnormal behaviour, diarrhoea or vomiting may be life saving.

ACTION	RATIONALE
1. GENERAL BEHAVIOUR • Observe for and report poor feeding, lethargy, vomiting, irritability, altered level of consciousness, muscle weakness and seizures.	May indicate increase in toxic levels of ammonia and glutamine.
• Check with parents regarding patient's usual behaviour.	Baseline for comparison.
• Provide periods of rest between nursing care procedures.	Minimizes stress due to excessive handling.
2. NEUROLOGICAL STATUS Assess and record baseline using **Glasgow Coma Scale**, and continue to record especially during further episodes of acute illness.	Severe forms of acidaemia and/or hyerammonaemia can produce seizures and coma.

ACTION	RATIONALE
3. SKIN / HAIR Observe colour, peripheral perfusion of skin and condition and texture of hair.	To identify hydration status and nutritional status and presence of shock.
4. VITAL SIGNS 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 TSCUH.)	
• **TEMPERATURE**	A slight rise may be idiopathic. Pyrexia may indicate sepsis. The following should be performed, blood cultures, F.B.C., U+E, and LFT'S. Hypothermia suggests the need for more calories.
• **PULSE**	Tachycardia – shock, infection, acidosis, fluid overload.
• **RESPIRATION**	Ammonia acts as a respiratory stimulant. Check ammonia levels where tachypnoea is present.
• **BLOOD PRESSURE**	Can be hypertensive during episodes of encephalitis / hypotensive with shock.

ACTION	RATIONALE
5. BLOOD GLUCOSE Baseline, then 4 -6 hourly while receiving intravenous dextrose infusion.	Hyperglycaemia may be related to dextrose infusion, or to stress. Consider need for insulin where hyperglycaemia occurs in relation to high glucose concentrations. Refer to Medical Guidelines for Management of patients with metabolic disorders and contact doctor on call. Doses appropriate for patients with Insulin Dependant Diabetes are not suitable to these patients as the pancreatic gland is normal. Hypoglycaemia may occur if patient is vomiting or has diarrhoea.
6. WEIGHT AND HEIGHT Plot on centile charts at weekly intervals while in hospital and at each OPD visit.	Assess for growth spurts and weight loss. Necessary for drug calculation and to ensure that nutritional requirements are being met.
5. URINALYSIS • Ketones • Protein • Specific Gravity and pH • Glucose	**Positive ketones indicate catabolism of fat.** Positive protein – possible UTI. To assess and monitor hydration status. Positive glucose – may be due to high calorie requirements. Check blood glucose to determine serum level.
6. FLUID BALANCE Strict monitoring of Intake and output	To assess for signs of fluid overload / dehydration

ACTION	RATIONALE
7. DIET **3 Components :**	
• **NATURAL PROTEIN** Babies 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 protein is referred to as an 'exchange'.**	Needed for growth and development
• **SYNTHETIC PROTEIN** e.g. Dialamine (contains reduced amount of nitrogen)	Nutritional needs cannot be adequately met by limited amount of natural protein tolerated by patients with Urea Cycle Defects.
• **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.	Large feed volumes may be required even when well.

ACTION	RATIONALE
• Regular feeds and avoidance of prolonged fasting periods	Optimize metabolic control
UNWELL REGIME	
• Instigation of an **emergency regime** (during times of metabolic stress) which includes the reduction or elimination of natural protein temporarily from the diet.	Withdraw nitrogen source as much as possible from diet (on Consultant's instructions) This will help to reduce ammonia and glutamine levels.
• I.V. Dextrose 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 intake.	
• 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	Because synthetic protein supplement is nitrogen sparing (i.e. contains nitrogen). This will help to reduce ammonia and glutamine levels.

ACTION	RATIONALE
improves and serum ammonia and glutamine levels return to normal.	
7. MEDICATIONS	
• **Arginine** Administer orally or intravenously as per metabolic guidelines / BNF (2011)	Arginine is a non-essential amino acid. It is derived from the diet and can also be synthesized in the urea cycle. In disorders of the urea cycle (except in arginase deficiency) arginine becomes an essential amino acid. Its administration supplements the urea cycle (BNF, 2011). 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** Administer orally or intravenously as per metabolic guidelines. Administer as a continuous infusion when prescribed intravenously. **Must be given as 'push' dose when given via nasogastric tube as stability of drug cannot be guaranteed when added to feed.**	Sodium Phenylbutyrate conjugates with glutamine to form phenylacetylglutamine, which is rapidly excreted in the urine (Wijburg & Nassogne, 2012). Two mol of nitrogen are excreted for each mol 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 improvement. Dosage is aimed to reduce plasma ammonia concentrations below 60µmol/l, and plasma glutamine less than 800µmol/l.
• **Sodium Benzoate**	Sodium Benzoate is conjugated with glycine to form hippurate, which is rapidly excreted in the urine (Wijburg & Nassogne, 2012).

ACTION	RATIONALE
Administer orally or intravenously as per metabolic guidelines.	With complete conjugation, one mol of nitrogen is cleared for each mol 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. Plasma ammonia falls, accompanied by improvement in symptoms such as appetite, lessened vomiting and irritability.
NOTE : **Intravenous Arginine, Sodium Phenylbutyrate and Sodium Benzoate can be given simultaneously via one cannula / lumen of a central line.**	
• **Sodium and Potassium supplements** may be prescribed for addition to infusions (based on electrolyte results).	Sodium and Potassium supplements may be added to intravenous infusions to prevent depletion secondary to large fluid volumes
• **Diuretic Therapy** • **Soluble Insulin**	May be required if large fluid volumes are required to prevent catabolism May be required if patient is hyperglycaemic – Refer to Metabolic Medical Guidelines and consult Metabolic Consultant on call.
• **Solvito** • **Paeditrace** • **Vitlipid**	Water soluble vitamins Trace elements Fat soluble vitamins **Please refer to Paediatric Parenteral Nutrition book for correct doses (Ball et al. 1998: Dunne, 2008).**
• **Analgesia / Ant-pyretic therapy** Paracetamol is not advocated for use in	Paracetamol is metabolized in the liver (Higgins, 1996).

ACTION	RATIONALE
patients with Urea Cycle Defects.	
8. ONNGOING 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. • Psychology • Social Work • Genetic Counselling Other Health professionals may be consulted as needed (i.e. Speech and Language, Ophthalmology etc).	To assess effectiveness of diet. To determine need for dietary adjustment. Chronic illness may adversely affect the family unit and relationships within the family. Dietary regime can cause elevated levels of stress. To ensure appropriate entitlements and services are accessed. To provide support at times of crisis. Implications for future pregnancies

6. REVIEW:

This procedure shall be reviewed and updated at least every two 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.

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