TITLE: NURSING GUIDELINES FOR THE MANAGEMENT OF CHILDREN WITH GLUTARIC ACIDURIA TYPE 1

NAME/TITLE: Eilish O'Connell, Clinical Education Facilitator, NCIMD

SIGNATURE:

DATE:

NAME/TITLE: Catherine McDonnell, Clinical Nurse Manager, NCIMD

SIGNATURE:

DATE:

NAME/TITLE: Dr Ahmad Monavari, Director of NCIMD (National Centre for Inherited Metabolic Disorders)

SIGNATURE:

DATE:

CONTENTS

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:

Glutaric Aciduria Type 1 (GA1) is a recessively inherited disorder of amino acid metabolism (Hoffmann & Kolker, 2012). The breakdown of the amino acids, *lysine, hydroxyylisine and tryptophan* is impaired by deficiency of the enzyme Glutaryl Co-A Dehydrogenase (GCDH) (Hoffman, 1996). The result is the accumulation of glutaric and 3-Hydroxyglutaric acid (Hedlund et al, 2006).

2.1. Prevalence:

Approx. 1: 56 000 live births – could be higher as a result of under- diagnosis (Monavari & Naughten, 2000).

3. PRESENTATION:

At an average age of between 6 to 18 months, undiagnosed patients suffer an acute encephalopathic crisis, due to a febrile illness, for example, a respiratory or gastrointestinal infection or illness (Hedlund et al, 2006). Prior to this the child will have been developing normally. GA1 should also be considered if an infant presents with macrocephaly, atrophy changes on MRI / CT and /or dystonia, dyskinesia and dysarthria (Hoffmann & Kolker, 2012). Without treatment, there is a progressive mental and neurological deterioration. Clinical signs may include

- Macrocephaly since birth or increasing head circumference past the 97th percentile (Hoffman et al, 1996)

- Nonspecific developmental delay (Treacy et al, 2003)
- Speech loss (Naughten et al, 2004)
- Dyskinesia (impairment of voluntary movement)
- Dystonia (hypotonia / rigidity)
- Tongue trusting, grimacing and fisting
- Loss of head control
- Mistaken Non Accidental Injury (Morris et al, 1999)

Intellect is generally preserved, but may deteriorate with repeated or frequent episodes of metabolic decompensation.

4. DIAGNOSIS:

4.1. Diagnosis is suspected on:

- Acylcarnitine profile
  - Elevated C5DC (this metabolite is used in new-born screening for GA1 in many countries)
  - Elevated levels of glutarylcarnitine & 3-hydroxyglutarylcarnitine

- Urine for organic acids.
  Increased Glutaric, glutaconic and 3 hydroxyglutaric acid levels occur due to failure to metabolize Glutaryl-CoA.

- Total and Free Carnitine (serum) - Carnitine levels may be low due to the elevated excretion of glutarylcarnitine in the urine and plasma and impaired reabsorption of free carnitine.

- Typical MRI or CT brain or Cranial Ultrasound findings

4.2. Diagnosis is *confirmed* by:

- Enzyme Assay - Skin biopsy (for Glutaryl Co-A dehydrogenase enzyme activity).

And/or

- Mutational Analysis of GCDH (Glutaryl-CoA Dehydrogenase) gene.

4.3. HIGH-RISK SCREENING

Babies born to families with a positive history of GA Type 1 are screened at birth. The Metabolic Team will give guidelines for collection of specimens (urine / blood etc.), management and treatment to the Maternity Units in question.

Glutaric Aciduria Type 1 is not included on the Irish New-born Screening Programme but is currently under discussion for inclusion.

5. MANAGEMENT:

The main goal in long-term treatment is the prevention of encephalopathic crises and neurological deterioration. Management involves mainly:

5.1. Dietary manipulation to;

- Restrict natural protein intake (lysine and tryptophan)
- Provide adequate protein for growth and development by administering a synthetic amino acid drink
- Ensure adequate calorie intake to prevent / suppress catabolism

5.2. Administration of Carnitine

To prevent carnitine deficiency and encourage urine excretion of glutarylcarnitine.

5.3. Neuro-Imaging

Cranial ultrasounds and MRI scan at diagnosis and as indicated thereafter.

5.4. Biochemical Monitoring

Blood

- Serum Total and Free Carnitine and Amino Acids are monitored regularly.
- Urea & Electrolytes, Liver Function tests, +/- glutarylcarnitine. Bone profile is monitored to detect early signs of renal tubulopathy.

5.5. Urine

Measurement of Quantitative Glutarate levels.

5.6. Education & Support

Multi-disciplinary Team i.e. Consultants, Nurses, Dieticians, Psychology and Social Work

These therapeutic goals and management are even more important during periods of illness / stress. Metabolic decompensation may result due to apparently trivial illness such as teething, prolonged fasting or even following routine childhood vaccinations. Aggressive management of suspected underlying intercurrent illness is imperative and cannot be emphasized too strongly.

Prompt recognition and early treatment with an emergency regimen may prevent brain damage and death

6. NURSING MANAGEMENT OF THE PATIENT WITH GLUTARIC ACIDURIA TYPE 1

Nursing observation and attention to detail is vital. The reporting of episodes of vomiting and/or diarrhoea may be lifesaving.

ACTION	RATIONALE
1. GENERAL OBSERVATIONS: **SKIN** Assess and document colour, peripheral perfusion and skin integrity **HAIR** Assess if coarse / brittle / alopecia. **HEIGHT & WEIGHT** Obtain and record for continuous comparison.	Pallor and poor capillary refill may indicate shock / stress. Skin breakdown (nappy rash etc.) in a previously diagnosed child may indicate protein deficiency and need to slowly re-commence / increase protein intake. Protein deficiency or minimal insufficiency may result from restriction of protein / frequent intercurrent illness'. Protein deficiency can affect normal growth and development.
2. NEUROLOGICAL STATUS: Assess neurological status (on initial presentation and acute episodes) using **Glasgow Coma Scale**	Risk of encephalopathy. To demonstrate altered level of consciousness, muscle weakness or seizures. If the patient is ambulant, observe for ataxia and dystonia.

ACTION	RATIONALE
	Children presenting following a cerebral insult caused by an intercurrent illness may exhibit dystonia and high-pitched cry.
Provide periods of rest between Nursing Care procedures.	Minimizes stress due to excessive handling. Stress increases metabolic rate and may exacerbate illness and symptoms.
3. VITAL SIGNS: Frequency of monitoring will be dictated by the patient's clinical condition.	
TEMPERATURE Intermittent episodes of pyrexia are a characteristic of Glutaric Aciduria (Baric et al, 1998) and often accompany loss of Metabolic Control.	Pyrexia may indicate underlying infection (temperature above 38.5 ºC requires a full blood workup including FBC, U+E, LFT'S, bone profile, blood cultures, serum amino acids, urinary Glutarate and any other tests as requested to assess and evaluate metabolic status).
Slight rise may be idiopathic, but always report to Metabolic team or Medic on call. Check temperature 4 hourly (or more often if pyrexial).	Hypothermia may suggest need for more calories.
PULSE	Tachycardia may indicate infection / acidosis / fluid overload / dehydration.

ACTION	RATIONALE
RESPIRATORY RATE	Tachypnoea may indicate infection / acidosis / fluid overload.
4. URINE Check early morning sample	Elevated p H may indicate Renal Tubular Acidosis.
Urinalysis Ketones	Presence of ketones indicates catabolic state and need for higher calorie intake.
Glucose	Glycosuria may result due to use of high dextrose concentration infusions or volumes for calorie provision. Check blood glucose.
Specific Gravity	Indication of hydration status.
5. BLOOD GLUCOSE Monitor blood glucose if glycosuria is present.	Hyperglycaemia may be related to the concentration and volume of dextrose used to provide calories. Consult with Metabolic Consultant regarding need for stabilization with insulin infusion. Guidelines are given in the Medical Metabolic Guidelines Handbook. Each patient will be considered individually. Doses of insulin suitable for patients with Insulin Dependent Diabetes are not appropriate in these patients as the pancreatic gland is normal.

ACTION	RATIONALE
6. DIET AND DIETARY EDUCATION:	
Each admission provides a valuable opportunity for assessment of knowledge base and identification of knowledge deficits.	
Diet is planned to meet needs for :	
NATURAL PROTEIN Infants will receive their protein from their infant formula alone pre-weaning and from solids consumed following weaning.	Necessary for essential amino acids.
1 gram of Protein = 1 exchange	Total protein intake i.e. Natural + Synthetic Protein is necessary for normal growth and development. Individually, neither is sufficient.
SYNTHETIC PROTEIN (Amino acid drink)	
PROTEIN-FREE PRODUCTS • Carbohydrate and Fat Solution **or** • Energyvits (Proprietary formula)	Provides calorie requirements not supplied in the diet. Does not contain amino acids. Prevention of catabolism.

ACTION	RATIONALE
• Extra water may be added to feeds to ensure correct osmolality (decided by consultant and dietetic team).	Attention to fluid intake is particularly important where the child has dyskinetic movements due to cerebral insult pre-diagnosis.
EMERGENCY / UNWELL REGIME	Emergency regimes are introduced when the patient becomes unwell and involve the reduction or discontinuation of natural protein, and an increase in calorie requirements to prevent catabolism. Catabolism may lead to encephalopathy.
Calorie Count Chart	
Different dietary regimes will be prescribed depending on child's condition.	Regimes are altered and updated to allow for weight gain, growth spurts etc.
Check relevant diet sheets for instructions re. Volume to be administered and recipes.	To ensure the patient is receiving prescribed calorific requirements and to prevent protein deficiency.
Dietitians will keep patient diet folders updated.	Regimes are altered and updated to allow for weight gain, growth spurts etc.
Nasogastric feeding may be necessary if patient is incapable or reluctant to take oral diet.	To ensure the patient is receiving prescribed calorific requirements and to prevent protein deficiency.
The Metabolic Team may recommend insertion of a gastrostomy feeding tube to parents of patients who will require long term nasogastric feeding.	To ensure adequate intake and monitor fluid balance.

ACTION	RATIONALE

7. INTAKE AND OUTPUT
• Calculate mls / kg / 24hrs
• Record losses
  ○ vomit
  ○ urine
  ○ stool
	May need to adjust diet to compensate for losses.
	A high intake of fluid is required to overcome fluid loss associated with increased muscle tonus, involuntary movements and sweating (Monavari and Naughten, 2000).

8. MEDICATIONS: • **Carnitine** Administer orally or intravenously as prescribed.	Patients with GA1 are carnitine deficient as Glutarate and carnitine combine and are excreted in the urine as glutarylcarnitine. Carnitine is normally synthesized endogenously from lysine and methionine, and is also derived from our diet, especially red meat and dairy products. Within the body, carnitine is located primarily in skeletal and cardiac muscle (98%) and small amounts are stored in the liver. Its main role is the transport of fatty acids into the mitochondria (Medicines for Children, 2003). Clinical findings in carnitine deficiency include cardiomyopathy, myopathy and acute encephalopathy. In GA 1 these may be secondary effects of low carnitine levels. The primary use is to facilitate excretion of glutarylcarnitine. Carnitine has few side effects, but patients on high dose therapy may develop a fishy odour. Diarrhoea may occur following increase of oral dosage.

ACTION	RATIONALE
• **Baclofen / Diazepam**	May be prescribed if child has dyskinetic movements as a result of neurological insult.
• **Electrolytes**	Sodium, Potassium, phosphate, calcium and magnesium supplements may be prescribed for infusion in intravenous fluids to prevent depletion caused by infusion of large fluid volumes or vomiting and diarrhoea.
• **Diuretic Therapy**	To prevent fluid overload due to infusion of large volumes.
• **Soluble Insulin**	May be required if patient is hyperglycaemic and has glycosuria. Refer to Metabolic Medical Guidelines and consult Metabolic Consultant on call.
• **Solvito**	Water soluble vitamins
• **Peditrace ® & Additrace ®**	Trace elements
• **Vitlipid Infant & Vitlipid Adult**	Fat soluble vitamins. **Please refer to Paediatric Parenteral Nutrition book for correct doses and Common Metabolic Calculations Booklet.**
• **I.V. Dextrose and / or Intralipid**	Prescribed if prescribed calories cannot be administered using oral / nasogastric feeds.
• **Intravenous Lysine and Tryptophan- free amino acids Solution.**	May be prescribed if patient is unable to tolerate synthetic feed.

ACTION	RATIONALE
• **Vaminolact**	Source of natural protein. May be prescribed for intravenous use if patient is unable to tolerate diet or if protein deficiency is suspected.
• **Analgesia / Anti-pyretics** Paracetamol is not recommended for use in patients with GA1.	Paracetamol is metabolized in the liver (Higgins, 1996).
9. EDUCATION: Prior to discharge ensure parents have received teaching on • Well and unwell regimes	
• Medications (side effects etc.)	To ensure patient safety and therapeutic effect.
• Enteral feeding (if required)	Many patients require nasogastric feeding due to need to provide high calorie intake and limit length of fasting periods.
• Genetic implications for future pregnancies	Autosomal recessive condition. This means that there is a one in four chance with each pregnancy that the child may be affected.

ACTION	RATIONALE
• Dressing and care of central lines (if applicable) • Potential complications of untreated or delayed management of intercurrent illnesses	Prompt action can be taken to reduce the risk of encephalopathy.
10. MULTIDISCIPLINARY FOLLOW UP: • Metabolic clinic for medical, nursing, dietetic support and assessment • **Ophthalmology** may be necessary if initial consult showed retinopathy • **Psychology and Social Work**	Chronic illness may adversely affect the family unit and relationships within the family. Psychometric assessment of child. Support to family and siblings. To ensure the family receive appropriate entitlements and access to services. To provide support and advice.

ACTION	RATIONALE
• **Speech and Language**	Due to strict dietary management, oral feeding difficulties may result and warrant nasogastric feeding. Some patients experience speech and language difficulties and oral feeding aversions as a result. Symptomatic patients i.e. patients presenting after an encephalopathic crisis may require and benefit from use of speech boards etc.

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.

7. REFERENCES:

Glutaric Aciduria Type 1

Baric, I., Zschocke, J., Christensen, E., Duran, M., Goodman, S.I., Leonard, J.V., Muller,

E., Morton, D.H., Superti-Furga, A., Hoffman, G.F. (1998) Diagnosis and management of glutaric aciduria type 1. *Journal of Inherited Metabolic Disease.* 21 (4): 326-340.

Higgins, C. (1996) Measurement of aspirin and paracetamol metabolites. *Nursing Times* 92 (8): 40-41.

Hoffman, G.F., Athanassopoulos, S., Burlina, A.B., Duran, M., de Klerk, J.B.C., Lehnert, W., Leonard, J.V. Monavari, A.A., Muller, E., Muntau, A.C., Naughten, E.R., Pleako-Starting, B., Superti-Furga, A., Zschocke, L., Christensen, E. (1996) Clinical course, early diagnosis, treatment, and prevention of disease in Glutaryl-CoA Dehydrogenase Deficiency. *Neuropediatrics.* 27: 115-123.

Hoffmann G.F. & Kolker S. (2012) Cerebral organic acid disorders and other disorders of lysine catabolism. In *Inborn Metabolic Diseases: Diagnosis and Treatment* (Saudubray J.M., van den Berge G. & Walter J.H. eds), 5th edition, Springer, Germany, pp 334-347.

Hudlund, G.L., Longo, N., Pasquali M. (2006) Glutaric Aciduria Type I. *American Journal of Medical Genetics Seminars in Medical Genetics*, 142C(2), 86-94.

Morris A.A.M., Hoffmann G.F., Naughten E.R., Monavari A.A., Collins J.E. & Leonard J.V. (1999) Glutaric aciduria and suspected child abuse. *Archives of Diseases in Childhood*, 80: 404-405.

Monavari, A.A. & Naughten, E.R. (2000) Prevention of cerebral palsy in glutaric aciduria type 1 by dietary management. *Archives of Disease in Childhood.* 82(1), 67-70.

Naughten ER, Mayne PD, Monavari AA, Goodman SI, Sulaiman G, Croke DT. (2004) Glutaric aciduria type I: outcome in the Republic of Ireland. *Journal of Inherited Metabolic Dis*orders, 27(6), 917-920.

Treacy EP, Lee-Chong A, Roche G, Lynch B, Ryan S, Goodman S. (2003) Profound neurological presentation resulting from homozygosity for a mild glutaryl-CoA dehydrogenase mutation with a minimal biochemical phenotype. *Journal of Inherited Metabolic Disorders,* 26(1), 72-74.

Royal College of Paediatrics and Child Health (2003) *Medicines for Children.* London:

Royal College of Paediatrics and Child Health Publications Ltd.