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

Policy ☐ Procedure ☐ Protocol ☐ Guideline ☑

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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 Glutaric Aciduria Type 1 or suspected of having Glutaric Aciduria Type 1.

3. DEFINITION:

Glutaric Aciduria Type 1 (GA1) is a recessively inherited disorder of amino acid metabolism (Hoffmann & Kolker, 2012). The breakdown of the amino acids, *lysine, hydroxylysine and tryptophan* is impaired by deficiency of the enzyme Glutaryl Co-A Dehydrogenase (GCDH) (Piercy et al. 2019). The result is the accumulation of glutaric and 3-Hydroxyglutaric acid which is toxic to the brain, with secondary carnitine deficiency (Ituk et al. 2013).

3.1 PREVALENCE:

Approx. 1: 30,000 – 100,000 live births – could be higher as a result of under-reporting owing to misdiagnosis, where the causative metabolic defect is not suspected from the clinical, laboratory and imaging findings. Incidence may be higher in populations with high rates of consanguinity (Baradaran et al. 2014).

3.2. NEW BORN SCREENING:

GA1 was added to the national new born bloodspot screening programme in Ireland in December 2018. Prior to this, only babies born to families with a positive history of GA Type 1 were screened at birth. The aim of new born screening is to reduce the risk of irreversible neurologic disease following striatal damage (Boy et al. 2017). Early detection can potentially change the natural history of the disease by enabling pre-symptomatic initiation of treatment and management regimes that reduce the likelihood of encephalopathic crises and improve neurological outcome (Piercy et al. 2019). Implementation of new born screening programmes allowing identification of asymptomatic patients and immediate implementation of a metabolic treatment comprising a low lysine diet, carnitine supplementation, and emergency management during episodes that are likely to induce catabolism have significantly improved the neurological outcome of affected individuals (Komatsuzaki et al. 2017).

4. PRESENTATION:

At an average age of between 3-36 months, undiagnosed patients suffer an acute encephalopathic crisis due to an illness, for example, a respiratory or gastrointestinal infection or illness (Vester et al. 2015). Prior to this, the child often 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 intellectual and neurological deterioration. Clinical signs may include

- Macrocephaly which is present from birth in some cases or develops shortly after birth (Kolker et al. 2015).
- Nonspecific developmental delay (Boy et al. 2017)
- Speech loss or dysarthria

- Dyskinesia (impairment of voluntary movement)
- Dystonia (hypotonia / rigidity)
- Tongue trusting, grimacing and fisting
- Loss of head control
- Seizures (Boy et al. 2017)
- Mistaken Non-Accidental Injury. The combination of cerebral atrophy and a large skull produces bridging veins which easily rupture after minor head trauma. Affected children may therefore present with acute subdural and retinal haemorrhages, often misdiagnosed as non-accidental injury (Thomas et al. 2018).

Intellect is generally preserved initially but may deteriorate with repeated or frequent episodes of metabolic decompensation (Piercey et al. 2019).

In some patients, neurologic disease may develop without clinically apparent crises at any age (Boy et al. 2017).

5. DIAGNOSIS:

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

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.

6. MANAGEMENT:

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

a. 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

b. Administration of Carnitine

- To prevent carnitine deficiency and encourage urine excretion of glutarylcarnitine.

c. Neuro-Imaging

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

d. Biochemical Monitoring

Blood

- Serum total and free carnitine, acylcarnitine and amino acids are monitored regularly.
- Urea & Electrolytes, Liver Function tests, +/- glutarylcarnitine. Bone profile is monitored to detect early signs of renal tubulopathy.

Urine

- Measurement of Quantitative Glutarate levels when requested.

e. Education & Support

- Multi-disciplinary Team i.e. Consultants, Nurses, Dietitians, 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 emphasised too strongly.

Prompt recognition and early treatment with an emergency regimen may prevent brain damage and death. Emergency treatment aims to prevent or reverse catabolism, to restore acid-base balance, to reduce the production of toxic metabolites and facilitate their detoxification and urinary excretion and thus protect children with Glutamic Aciduria Type 1 from irreversible brain damage and death (Heringer et al. 2016).

7. 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
7.1 EMERGENCY ASSESSMENT Complete full patient assessment on admission and document vital signs in PEWS record. Escalate care as indicated by clinical judgment and PEWS score. Ascertain if parent (s) have any particular concern and score accordingly. Frequency of monitoring will be dictated by patient's condition (i.e. 2-4 hourly during initial presentation and acute illnesses - Paediatric Early Warning System Score (PEWS) is used in CHI at Temple Street.)	

ACTION	RATIONALE
AIRWAY	Airway competency may be compromised with reduced Glasgow Coma Score.
BREATHING **Monitor respiratory rate, respiratory effort and oxygen requirements as per PEWS. Obtain oxygen saturation levels if concerned and report abnormalities to medical team.**	Tachypnoea, increased respiratory effort, reduced oxygen levels and increased CO_2 levels may indicate; • Infection • Underlying respiratory Illness • Acidosis - can have metabolic acidosis with an increased anion gap (Ogier de Baulny et. al. 2012) • Fluid overload.
Monitor pulse (rate, volume and strength)	Tachycardia may indicate • Infection • Acidosis

ACTION	RATIONALE
	• Fluid overload • Dehydration
Include Capillary refill time (CRT) assessment as per PEWS.	Decreased capillary refill time may indicate shock / stress.
Blood Pressure Report abnormalities in vital signs to the metabolic team.	Can be hypotensive with hypovolemic shock or dehydration.
DISABILITY (Level of consciousness and neurological status). Assess and record baseline neurological	Risk of encephalopathy with GA1.

ACTION	RATIONALE
status using **Glasgow Coma Scale**, and continue to record especially during further episodes of acute illness. Monitor GCS 4 hourly or as condition indicates. Report altered level of consciousness or any deterioration to the metabolic team.	The major neurologic complications in GA 1 are development of a dystonic movement disorder and subdural haematoma occurrence. Frequency of epilepsy is also increased in patients with GA1 and seizures might even be the initial clinical presentation (Boy et al. 2017).
Observe for signs of muscle weakness and for signs of seizure activity. Record seizure type, duration and intervention and record seizure activity in nursing notes. Report any abnormal movements for patient to the medical team. If ambulant observe for ataxia and dystonia and report to medical team. Check with parents regarding patient's usual behaviour.	Children presenting following a cerebral insult caused by an intercurrent illness may exhibit dystonia and a high-pitched cry.

ACTION	RATIONALE
EXPOSURE To ensure full examination (whilst respecting the child's dignity and ensuring body temperature conservation).	
TEMPERATURE Slight rise may be idiopathic, but always report to Medical team. Monitor temperature 4 hourly or more frequently if indicated.	Pyrexia may indicate presence of infection. Consider in conjunction with other signs such as tachycardia and delayed central capillary refill time. Follow Sepsis 6 protocol in PEWS chart. The following should be performed, blood cultures, F.B.C., U+E, LFTs blood gas, serum amino acids, urinary Glutarate and urine for culture and sensitivity. Hypothermia may indicate overwhelming infection (Goldstein et al. 2005). Hypothermia may suggest need for more calories. Normothermia must be maintained because hypothermia with shivering may trigger neurologic crisis by increasing catabolism (Ituk et al. 2013).
SKIN Assess and document colour, peripheral perfusion and skin integrity	Pallor and decreased peripheral perfusion 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.

ACTION	RATIONALE
HAIR Assess if coarse / brittle / alopecia.	Protein deficiency may result from restriction of protein / frequent intercurrent illness.
7.2. INVESTIGATIONS **URINE** ➢ Check early morning sample ➢ Urinalysis ➢ Ketones ➢ Glucose ➢ Specific Gravity **BLOOD GLUCOSE** Monitor blood glucose if glycosuria is present. Measure 4-6 hourly when unwell and while on intravenous therapy or as	Elevated p H may indicate Renal Tubular Acidosis. Presence of ketones indicates catabolic state and need for higher calorie intake. Glycosuria may result due to use of high dextrose concentration infusions or volumes for calorie provision. Check blood glucose. Indication of hydration status. 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
condition indicates. **BLOOD SAMPLING** As directed by the metabolic team. FBC, U &E, LFTs, Bone profile, Venous blood gas, Glucose and lactate, ammonia, serum amino acids, and acylcarnitine profile are bloods routinely required. Additional blood sampling as directed by the metabolic team. Provide periods of rest between Nursing Care procedures.	Individuals with GA1 are at risk for dehydration and electrolyte imbalance during periods of recurrent vomiting, diarrhoea and/ or reduced intake of nutrients and fluids, increasing the risk for an encephalopathic crisis. Blood gases and serum electrolytes should be assessed on admission, and emergency treatment adjusted accordingly (Boy et al. 2017). Quantitative analysis of plasma amino acids helps ensure that patients on a low-lysine diet are receiving a nutritionally adequate diet (Boy et al. 2017). Minimises stress due to excessive handling. Stress increases metabolic rate and may exacerbate illness and symptoms.
7.3. DIET AND DIETARY EDUCATION **Each admission provides a valuable opportunity for assessment of knowledge base and identification of knowledge deficits.**	

ACTION	RATIONALE
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	
SYNTHETIC PROTEIN (Amino acid supplement)	Supplements natural protein. Contains all amino acids except those that cannot be metabolized. Total protein intake i.e. Natural + Synthetic Protein is necessary for normal growth and development. Individually, neither is sufficient.
PROTEIN-FREE PRODUCTS Carbohydrate and Fat Solution **or** • Energyvits (Proprietary formula)	Provides calorie requirements not supplied in the diet. Does not contain amino acids. Essential for the prevention of catabolism.
• 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.

ACTION	RATIONALE
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.
Calorie Count Chart	
Different dietary regimes will be prescribed depending on child's condition.	Catabolism may lead to encephalopathy.
Check relevant diet sheets for instructions re. Volume to be administered and recipes.	
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.	

ACTION	RATIONALE
HEIGHT & WEIGHT Obtain and record for continuous comparison	Regimes are altered and updated to allow for weight gain, growth spurts etc. Protein deficiency can affect normal growth and development.
7.4. FLUID BALANCE Record all intake and output and monitor fluid balance. Calculate mls / kg / 24hrs in infants and percentage maintenance fluid intake in older child. **Record losses** Vomit & stools and urine. Urine output including weighing nappies and measuring urine output. Calculate mls/kg/hr of urine output. Calculate regular and cumulative fluid balances in acutely unwell child. Large	Record all oral, enteral and parenteral intake in fluid balance record to ensure patient is adequately hydrated. To ensure adequate fluid intake and early detection of fluid overload. Losses may need to be replaced. Energy demand and fluid requirements may be increased in patients with severe dystonia (Boy et al. 2012). May need to adjust diet to compensate for losses.

ACTION	RATIONALE
positive or negative balance to be reported to the medical team.	
7.5. 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. Its main role is the transport of fatty acids into the mitochondria (Kepka et al. 2014). Carnitine supplementation is considered to contribute to reduced risk for striatal injury in individuals diagnosed early and reduces mortality rates in symptomatic individuals with GA 1 (Boy et al. 2017). 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. Sodium Valproate is contraindicated in glutaric aciduria type 1 as it aggravates already existing carnitine deficiency and leads to worsening of clinical manifestations (Govender et al. 2017).

ACTION	RATIONALE
Baclofen / Diazepam	Together with benzodiazepines, baclofen orally is the most widely used and apparently effective drug for long term treatment of movement disorders in GA 1 (Boy et al. 2017). It 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.

ACTION	RATIONALE
Intravenous Lysine and Tryptophan- free amino acids Solution.	May be prescribed if patient is unable to tolerate synthetic feed.
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 metabolised in the liver (Malar and Bai, 2012).

ACTION	RATIONALE
7.6. EDUCATION:	
Prior to discharge ensure parents have received teaching on	Effectiveness of a low lysine diet critically depends upon adequate provision of information and education to parents, affected individuals, and caregivers. It is essential that they receive continued support and education from the multidisciplinary metabolic team (Boy et al. 2017).
• Well and unwell regimes	To ensure patient safety and therapeutic effect.
• Medications (side effects etc.)	
• 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.
• 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.

ACTION	RATIONALE
7.7. MULTIDISCIPLINARY FOLLOW UP:	
• Metabolic clinic for medical, nursing, dietetic support and assessment	
• **Ophthalmology** may be necessary if initial consult showed retinopathy	
• **Psychology**	Chronic illness may adversely affect the family unit and relationships within the family. Psychometric assessment of child. Support to family and siblings.
• **Social Work**	To ensure the family receive appropriate entitlements and access to services. To provide support and advice.
• **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.

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 review of this document:

Professor Ellen Crushell, Consultant Paediatrician with Special Interest in Inherited Metabolic Disorders.	Signature: _____ Date: _____
Professor Ina Knerr, Consultant Paediatrician with Special Interest in Inherited Metabolic Disorders.	Signature: _____ Date: _____
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Susan Keane, Clinical Practice Facilitator	Signature: _____ Date: _____

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Document Control / Change Record

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0	01.11.2016	01.11.2018	Eilish O Connell	1st version on Qpulse – superseded local handbook.
1	16.07.2020		Louise Perris	Routine review