NURSING GUIDELINES FOR THE MANAGEMENT OF CHILDREN WITH MAPLE SYRUP URINE DISEASE
Revision: 4

Policy ☐ Procedure ☐ Protocol ☐ Guideline ☑

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1.0 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 evidenced based 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.

2.0 SCOPE

These guidelines are a point of reference for all nursing and medical staff in relation to the care of a child with Maple Syrup Urine Disease or suspected of having Maple Syrup Urine Disease.

3.0 DEFINITION:

Maple Syrup Urine Disease (MSUD) is an autosomal recessive inherited disorder of protein metabolism. The defect occurs in the branched-chain alpha ketoacid dehydrogenase enzyme complex resulting in an accumulation of the three essential branched chain amino acids (BCAA), leucine, isoleucine and valine (and alloisoleucine) and their respective ketoacids in plasma and urine (Mescka et al, 2015). Leucine is the most toxic of the offending amino acids in MSUD (Wang et al, 2015).

Prevalence:

Europe - 1: 200, 000 (Zschocke & Hoffmann, 2011).

Ireland - 1: 155,200 (National New-born Bloodspot Screening Laboratory, 2018).

4.0 PRESENTATION:

Historically, the disorder is characterised by a specific odour (maple syrup, burnt sugar) from the urine. Patients with 'classical' MSUD usually present with metabolic decompensation in the early stages of life (Knerr et al, 2012). The presentation can be difficult to identify/diagnose as the infant is usually born at full term after an uneventful pregnancy, with an initial symptom - free interval and proceeds to deteriorate rapidly with no obvious cause or response to treatment (Oglier de Baulny et al, 2012). Neurological deterioration manifests within the first few days / weeks of life, i.e. feeding difficulties, irritability, drowsiness, encephalopathy, seizures, coma and even death may occur if not diagnosed and treated successfully (O'Reilly et al, 2020). Milder forms may present with developmental delay, recurrent episodes of decompensation and rarely a 'maple syrup like' smell from their urine (Zschocke & Hoffmann, 2011). If untreated, death can occur in the first few weeks of life. Neurological progress is related to the age of the child at time of diagnosis, to the adequacy of metabolic control and length of time exposed to elevated leucine levels at presentation (Patel et al, 2015).

5.0 DIAGNOSIS:

5.1 New-born Bloodspot Screening programme in Ireland

Maple Syrup Urine Disease has been included in the New-born Bloodspot Screening Programme in Ireland since 1972 (National New-born Bloodspot Screening Laboratory, 2018).

5.2 Clinical Presentation

The infant may already be ill with **ketoacidosis**, and present **before** the results of screening are available. Elevated levels of leucine, isoleucine, valine and alloisoleucine are diagnostic of MSUD (Zschocke & Hoffmann, 2011). Plasma levels of the affected amino acids are assessed in suspected cases. Elevated Alloisoleucine is almost pathognomonic of MSUD as it is a by-product of isoleucine (Guo et al, 2015).

5.3 High Risk Screening

Babies born to families with a positive history of this condition will be screened at birth and on subsequent days, but must also have the New-born Screening card performed for the

other conditions included in the screening (National New-born Bloodspot Screening Laboratory, 2018). A plan of care will be put in place for a high risk baby prior to delivery by the Metabolic Consultant. The baby should stay on the prescribed treatment until Maple Syrup Urine Disease has been out-ruled.

5.4 TREATMENT

Early diagnosis and immediate initiation of rigorous therapy yields a satisfactory prognosis (Zschocke & Hoffmann, 2011). Treatment is for life and involves the controlled intake of the branched chain amino acids.

6.0 MANAGEMENT:

6.1 Acute Management

6.1.1 Discontinue all natural protein containing products immediately (i.e. infant formula, all food and food products which contain protein) and discuss this with dietitian and metabolic doctor or Consultant on call.

6.1.2 Extra calories are required to prevent catabolism. Calories are given as protein-free foods, carbohydrate and fat (e.g. via nasogastric tube) or, if administered intravenously, as glucose and lipids (can be given in addition to nasogastric feeds).

6.1.3 Haemodialysis/ haemofiltration may be necessary on initial presentation or during episodes of acute leucine toxicity with encephalopathy to quickly reduce elevated branched chain amino acid levels (Herber et al, 2015).

6.1.4 Control of electrolyte balance and serum osmolarity is imperative as brain oedema and hyponatraemia can occur in the acute stage.

6.1.5 Continue synthetic protein (Leucine, Isoleucine and Valine depleted amino acid mixture) either orally or via nasogastric tube if necessary. Isoleucine and valine supplements are to be given as prescribed by the consultant in charge of the patient.

6.1.6 During acute decompensation episodes or poor biochemical control, cerebral palsy / neurological damage or death in infancy may occur if undiagnosed or treatment delayed (Oglier de Baulny et al, 2012).

6.2 On-going Management

6.2.1 It is vital to measure the blood levels of leucine, isoleucine and valine carefully, i.e. weekly measurement of BCAAs or as frequently as directed by the Metabolic Consultant.

6.2.2 Protein exchanges (1 exchange = approximately 100 mg leucine), valine and isoleucine prescription will be adjusted according to BCAA levels.

6.2.3 Specialised diet plans are resumed following recovery, in consultation with the patient's Consultant and dietitian.

6.2.4 Ensure adequate intake of synthetic protein (i.e. other essential amino acids without leucine, isoleucine or valine). Inadequate intake may result in protein deficiency, which can lead to skin and muscle breakdown (catabolism). The synthetic protein mixture should contain essential vitamins and minerals which are depleted due to the restricted diet (Oglier de Baulny et al, 2012).

6.2.5 Adequate calories are given to suppress catabolism and support growth, development and energy needs.

7. NURSING MANAGEMENT OF PATIENT WITH MAPLE SYRUP URINE DISEASE

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 parents have any particular concern and score accordingly. Frequency of monitoring will be dictated by patient's condition.	Close patient observation and prompt reporting of signs of clinical deterioration e.g. vomiting, diarrhoea, headache and ataxia resulting in early instigation of treatment may be life-saving.
AIRWAY. Seek emergency medical intervention if signs of airway compromise e.g. respiratory distress, reduced $Sp0_2$, absent cough, gag etc.	Airway patency may be compromised with reduced Glasgow Coma Scale score (GCS). Request urgent review of patient if airway compromise is suspected.

ACTION	RATIONALE
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 a metabolic acidosis with an increased anion gap (Ogier de Baulny et al, 2012) • Fluid overload Decreased or irregular respiratory rate/pattern may be related to reduced level of consciousness/ increased intracranial pressure. Irregular rate occurs late in leucine toxicity.
• **Oxygen saturation.** When using pulse oxymetry, ensure frequent rotation of the probe position. Ensure acceptable trace is visible on monitor at all times (particularly in	Low oxygen saturation may be present with acidosis or when patient is shocked. Failure to change position of probe may result in burning of the skin.

ACTION	RATIONALE
neonates). **CIRCULATION.**	
• **PULSE – rate, rhythm, volume.**	Tachycardia may indicate • Infection • Metabolic Acidosis • Fluid overload • Dehydration • Shock • Electrolyte imbalance • Low/high blood pressure Bradycardia may indicate increased intracranial pressure.
• **Include Capillary refill time (CRT) assessment as per PEWS.**	Decreased capillary refill time may indicate infection/ dehydration/shock.

ACTION	RATIONALE
• **Blood Pressure.** Report abnormalities in vital signs to the metabolic team.	Check baseline, usually within normal limits however may be hypotensive due to hypovolemic shock or dehydration. Monitor as clinically indicated. Increase in systolic blood pressure and bradycardia may indicate raised intracranial pressure.
DISABILITY. (Level of consciousness and neurological status). • Assess and record baseline neurological status using **Glasgow Coma Scale**, and continue to record especially during further episodes of acute illness. Monitor GCS 4 hourly or more frequently as condition indicates. Report altered level of	

ACTION	RATIONALE
consciousness or any deterioration to the metabolic team immediately.	
• 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.	Suggests encephalopathy due to elevated levels of branched chain amino acids.
• Report slurred speech, visual disturbances and general disorientation. Bulging anterior fontanelle is a sign of cerebral oedema.	Disturbed ratios of the three amino acids occur as leucine rises, causing varied and subtle signs of focal cerebral oedema (which could be fatal).

ACTION	RATIONALE
EXPOSURE. To ensure full examination (whilst respecting the child's dignity and ensuring body temperature conservation).	
• **TEMPERATURE.** 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, CRP, blood gas, branched chain amino acids and urine for culture and sensitivity. Hypothermia may indicate overwhelming infection (Goldstein et al, 2005).
• **SKIN.** Assess and document colour, peripheral perfusion and skin integrity.	Pallor and poor peripheral perfusion are signs of shock.

ACTION	RATIONALE
Assess if skin is intact / dry / broken (especially skinfolds / nappy area). Ensure skin is kept clean and dry and nappy changed frequently. • **HAIR.** Assess if coarse / brittle / alopecia.	Signs of protein deficiency. Prolonged exclusion, over-restriction or imbalance of BCAAs leads to desquamation of the skin and diarrhoea (Flores et al, 2016; Ross et al, 2016). Dry, brittle hair and alopecia are signs of protein or zinc deficiency.
7.2. INVESTIGATIONS. **BLOOD.** • **BRANCHED CHAIN AMINO ACIDS (i.e. leucine, isoleucine and valine).** Samples may be venous or capillary. Blood tubes are available from St. Brigid's Ward & Laboratory. Metabolic Consultant will specify	Measured frequently during periods of acute illness (usually 4-8 hourly) to evaluate effectiveness of prescribed dietary and intravenous regime and monitor metabolic status. Branched chain amino acids cross the blood brain barrier more readily than other amino acids (Wang et al, 2015).

ACTION	RATIONALE
frequency of Branched Chain Amino Acids analysis.	
Dialysis (Haemodialysis or haemofiltration) may be necessary at the time of initial presentation and at times of grossly elevated leucine levels to ensure rapid decrease in levels.	Haemodialysis or haemofiltration may be necessary to lower plasma Branch Chain Amino Acid levels and remove toxic metabolites rapidly.
• Frequent analysis of urea and electrolytes, LFTs and plasma osmolarity may be required as per Metabolic Consultant whilst patient is receiving multiple drug infusion therapies.	To assess effectiveness of fluid therapy / dialysis on electrolyte balance. Use of intravenous fluids can result in fluid overload and hyponatraemia. Subsequently, water diffuses into the brain causing cerebral oedema. Therefore, plasma osmolarity needs to be checked. Refer to the Metabolic Consultant regarding increased administration of sodium – guidelines are provided in the Medical Metabolic Guidelines Handbook. Each patient will be considered individually depending on their serum sodium concentrations. Consider: Insulin therapy can cause potassium depletion. Elevated levels of leucine can affect water homeostasis within the subcortical grey matter, causing

ACTION	RATIONALE
	swelling within the brain, altering nitrogen levels, further depleting glutamate levels and increasing oxidative stress (Feng et al, 2019).
Other bloods as requested by metabolic consultant.	
BLOOD GLUCOSE.	
Monitor blood glucose levels. If patient is receiving high concentrations of intravenous glucose, monitor and record at 4-6 hourly intervals.	Hyperglycaemia may be related to the concentration and volume of intravenous glucose used to provide calories. Refer to the Metabolic Consultant regarding need for stabilisation 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 might not be appropriate in these patients as the pancreatic gland is normal. To be decided by the consultant in charge of the patient.
A Glucose and lactate profile is carried out as prescribed by Metabolic Consultant.	To check for hypoglycaemia +/- hyperlactataemia: if present requires immediate intervention and the Metabolic Consultant needs to be contacted as soon as possible.
Serum ketones to be carried out as requested by Metabolic Consultant.	

ACTION	RATIONALE
URINE. • **Organic acids** (5-10mls required). Must be kept in freezer until sent to lab. Must be stored in universal container. Taken to confirm diagnosis. Not normally used thereafter. • **MSU** if infection suspected. • **Urinalysis**. - pH	Elevated urine pH and metabolic acidosis in blood may indicate renal tubular acidosis with increased bicarbonate losses (tubulopathy).
- Specific gravity	Indication of level of hydration. Increased specific gravity occurs in case of dehydration. Decreased specific gravity occurs in patients with renal failure or after excessive fluid intake. Present if

ACTION	RATIONALE
	catabolic / ketoacidosis.
- Ketones	Ketonuria is an **abnormal** finding in the neonatal period. If found beyond this age group indicates the presence of catabolism which needs to be urgently reported to the metabolic consultant
- Glucose If glycosuria is present and/or patient is receiving high concentrations of intravenous glucose record blood glucose at 4-6 hourly intervals.	Related to intake of high concentrations of dextrose. Where present check blood glucose. Where elevated, **inform doctor** and consider need for insulin. Glycosuria in an acutely ill metabolic child is not an indication to wean / stop fluids unless otherwise instructed by Metabolic Consultant.
7.3. DIET AND DIETARY EDUCATION. Initial assessment helps to determine child's immediate needs and on-going management.	

ACTION	RATIONALE
• **NATURAL PROTEIN.** On initial presentation and during episodes of illness and crisis, all natural protein intake will be temporarily stopped. Discuss special diet/IV treatment with metabolic doctor/Consultant and dietitian.	To prevent intake of precursors to toxic metabolites.
Infants will receive their natural protein requirements from infant formula alone. Protein content of solids introduced from weaning onwards must be included in total daily protein allowance. **Protein allowance is counted in 'exchanges'.** **1 leucine exchange = approximately 100 mg leucine = 1 gram protein.**	**Do not exceed prescribed number of protein exchanges.** Full daily intake is essential, as this helps reduce the levels of branched chain amino acids and prevents protein deficiency.

ACTION	RATIONALE
• **SYNTHETIC PROTEIN.** Synthetic amino acid drink. Contains all amino acids necessary for growth and development **EXCEPT** leucine, isoleucine and valine.	Amino acid drink provides the amino acids, minerals and vitamins that have been restricted by a limited natural protein intake.
• **LOW PROTEIN / PROTEIN FREE PRODUCTS.** Carbohydrate and fat solution (CHO & Fat). Extra water may be added to feeds to ensure correct osmolarity (decided by consultant and dietetic team). **A wide selection of low protein products**	Provides calorie requirements not supplied in the diet. Do not contain amino acids. Prevention of catabolism (Mroch et al, 2014).

ACTION	RATIONALE
are also available.	
EMERGENCY / UNWELL REGIME.	
Try to continue usual method of feeding – oral and / or nasogastric feeding.	May need intravenous glucose if unable to tolerate oral or nasogastric feeding.
Natural protein intake will be reduced or discontinued.	To prevent toxicity.
Continue synthetic amino acid drink. Different dietary regimes will be prescribed depending on child's condition. As plasma levels return to near normal therapeutic values (e.g. leucine below 400µmol/L) small amounts of natural protein may be re-introduced, decided by Consultant in charge.	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 high leucine levels and subsequently encephalopathy. Regimes are altered and updated to allow for weight gain, growth spurts etc.

ACTION	RATIONALE
Check relevant diet sheets for instructions regarding volume to be administered and recipes.	
Dietitians will keep patient diet folders updated.	To ensure the patient is receiving prescribed calorific requirements and to prevent protein deficiency.
Nasogastric feeding may be necessary where a patient is incapable or reluctant to take oral diet. Continuous feeds may be necessary when vomiting.	Ensures that prescribed amount of calories are taken over 24 hour period to prevent catabolism.
Calorie requirements are greater during periods of illness. Extra calories may be administered using high energy drinks, i.e. CHO & Fat or lucozade.	
HEIGHT & WEIGHT.	Regimes are altered and updated to allow for weight gain, growth spurts etc.

ACTION	RATIONALE
Obtain and record for continuous comparison.	Protein deficiency can affect normal growth and development.
7.4. FLUID BALANCE.	
Record all oral, enteral and parenteral intake and all output and monitor fluid balance.	To ensure patient is adequately hydrated.
Calculate mls / kg / 24 hrs in infants and percentage maintenance fluid intake in older child.	To ensure adequate fluid intake and early detection of fluid overload. Fluid overload may occur due to high fluid intake.
• **Record losses.**	
Vomit & stools and urine. Calculate urinary output including weighing nappies. Calculate mls/kg/hr of urine output. Calculate regular and cumulative fluid balances in acutely unwell child. Large positive or negative balance to be	May need to adjust diet to compensate for losses. Lost volumes must be replaced using a high energy feeding solution containing carbohydrate (CHO) & Fat or in the event of large losses "full feed" of their special diet (i.e. extra dietary feed will be made to replace vomits).

ACTION	RATIONALE
reported to the medical team. Observe closely for signs of fluid overload	 May exacerbate cerebral oedema.
7.5 MEDICATIONS. • **Isoleucine and Valine** are given as supplements. Available in powder form. Warm water should be used for re-constitution as boiling water can destroy amino acids. • Intravenous amino acids are available. • **Thiamine** may be given if patient has a thiamine responsive form of Maple Syrup urine Disease or is prescribed Thiamine by Metabolic Consultant. • **Electrolytes**	 Isoleucine and valine levels fall more rapidly than leucine and may reach sub-optimal levels while leucine remains elevated. This can trigger a rebound phenomenon due to muscle catabolism. Isoleucine and valine are required to reduce leucine-related toxicity (Servais et al, 2013; Su et al, 2017). Thiamine responsive MSUD responds to pharmacological doses of thiamine through normalisation of plasma Branch chain amino acid levels (Patel et al, 2015). Sodium, potassium, chloride, phosphate, calcium and magnesium supplements may be prescribed

ACTION	RATIONALE
	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 infusions of large volumes.
• **Soluble Insulin**	May be required if patient is persistently hyperglycaemic and / or has glycosuria. Refer to Metabolic Medical Guidelines and consult Metabolic Consultant on call.
• **Solvito**	Water soluble vitamins
• **Peditrace**	Trace elements
• **Vitlipid infant / adult**	Fat soluble vitamins Prescribed to prevent deficiency of Vitamins and minerals.
• **Analgesia / anti-pyretic Therapy** Paracetamol is not advocated in patients with MSUD. Ibuprofen is the medication	Paracetamol is metabolised in the liver (Malar and Bai, 2012). Single stat doses may be prescribed as directed by Metabolic Consultant.

Refer to NCIMD Calculations booklet for Healthcare professionals (PP-CLIN-NCIMD-28)

ACTION	RATIONALE
of choice.	
7.6 ONGOING EDUCATION. Ensure parents are educated in the following prior to discharge from first admission. • Genetic Implications • Well and Unwell Regimes • Medications • Enteral feeding (nasogastric tubes etc. if required).	Effectiveness of a low protein 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. To ensure patient safety and therapeutic effect. Autosomal recessive condition. This means that there is a one in four chance with each pregnancy that the child may be affected. Parents may need to change feeding regime at home. Many patients require nasogastric feeding due to need to provide high calorie intake and limit length of fasting periods.

ACTION	RATIONALE
• Blood letting • Preparation of feeds • Implications of untreated illness or delayed management Education is on-going at OPD visits and on subsequent admissions.	Prompt action can be taken to reduce the risk of encephalopathy.
7.7 MULTIDISCIPLINARY SUPPORT / FOLLOW-UP CARE. • Metabolic clinic for medical, nursing, dietetic support and assessment • **Blood tests** for amino acids etc. on each visit. • **Psychology**	Chronic illness may adversely affect the family unit and relationships within the family. Psychometric assessment of child. Support to family and siblings.

ACTION	RATIONALE
• **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.
• **Physiotherapy**	
• **Ophthalmology** may be necessary if initial consult showed retinopathy.	

8. MONITORING, AUDIT & EVALUATION

This procedure shall be reviewed and updated at least every three years by the Clinical Nurse 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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