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

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

SIGNATURE:

DATE:

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

SIGNATURE:

DATE:

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

SIGNATURE:

DATE:

NAME/TITLE:

SIGNATURE:

DATE:

CONTENTS

1. PURPOSE: 3

2. DEFINITIONS: 3

3. PRESENTATION: 3

4. DIAGNOSIS: 4

5. MANAGEMENT: 4

6. NURSING MANAGEMENT OF PATIENT WITH MAPLE SYRUP URINE DISEASE 6

7. REVIEW: 17

8. REFERENCES: 17

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:

Maple Syrup Urine Disease (MSUD) is an autosomal recessively 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 (Knerr et al, 2012). Leucine is the most toxic of the offending amino acids in MSUD (Robinson, 1996).

Prevalence:

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

Ireland - 1: 125 000 (National New-born Bloodspot Screening Laboratory, 2011)

3. PRESENTATION:

Historically, the disorder is characterised by a specific odour (maple syrup, burnt sugar) in urine. Patients with 'classical' MSUD usually present with a 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 is manifested within the first few days of life, i.e. feeding difficulties, irritability, drowsiness, hypoglycaemia, seizures and coma (Holmes Morton et al, 2002; Zschocke & Hoffmann, 2011; Oglier de Baulny et al, 2012). Milder forms will 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 (Clow et al, 1981) and length of time exposed to elevated leucine levels at presentation.

4. DIAGNOSIS:

4.1. New-born Screening programme in Ireland

Maple Syrup Urine Disease has been included in the New-born Screening Programme in Ireland since 1971 (National New-born Bloodspot Screening Laboratory, 2011).

4.2. 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. Alloisoleucine is almost pathognomonic of MSUD as it is a by-product of isoleucine (Robinson, 1996).

4.3. 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, 2011).

4.4. 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.

5. MANAGEMENT:

5.1. Acute

5.1.1. 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 doctor or consultant on call.

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

5.1.3. Haemodialysis can be necessary on initial presentation or necessary during episodes of acute leucine toxicity with encephalopathy to quickly reduce elevated branched chain amino acid levels.

5.1.4. Control of electrolyte balance and osmolarity is imperative as brain oedema and hyponatraemia can occur in the acute stage. Serum sodium levels should be kept between 140 – 145 mmol/L (Mitsubuchi et al, 2005).

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

5.1.6. 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).

5.2. On-going

5.2.1. It is vital to measure the blood levels of leucine, isoleucine and valine carefully, i.e. weekly measurement of BCAAs. BCAA levels are monitored twice weekly in children under 2 years.

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

5.2.3. Specialised diet plans are resumed following recovery, in consultation with the metabolic consultant and dietician.

5.2.4. 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).

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

6. NURSING MANAGEMENT OF PATIENT WITH MAPLE SYRUP URINE DISEASE

Nursing observation and attention to detail is vital. The reporting of episodes of vomiting or diarrhoea or headache and instigation of treatment may be life-saving.

ACTION	RATIONALE
1. GENERAL OBSERVATIONS:	
a) SKIN CONDITION:	
• Assess colour, peripheral perfusion	- Pallor and poor peripheral perfusion are signs of shock.
• Assess if intact / dry / broken (especially skinfolds / nappy area)	- Signs of protein deficiency. Prolonged exclusion, over-restriction or imbalance of BCAAs leads to anaemia, desquamation of the skin, diarrhoea (Naglak & Elsas, 1988)
• Ensure skin is kept clean and dry and nappy changed frequently	
b) HAIR:	
• Assess if dry / brittle	- May indicate protein or zinc deficiency.
• Height & weight	- Indicates nutritional & hydration status.
2. NEUROLOGICAL STATUS:	
• Assess neurological status using Glasgow Coma Scale.	
• Report ataxia, slurred speech, visual disturbances and general disorientation.	- Suggests encephalopathy due to elevated levels of branched chain amino acids. Disturbed ratios of the three amino acids occur as leucine rises, causing varied and subtle signs of focal

ACTION	RATIONALE
Signs of altered neurological status include ataxia, anorexia, slurred speech, high pitched cry, hallucinations, dilated pupils, vomiting, lethargy or irritability (Robinson and Drumm, 2001). Swollen anterior fontanelle is a sign of cerebral oedema.	cerebral oedema (which could be fatal).
3. VITAL SIGNS: Frequency of observation will be determined by child's condition	
a) TEMPERATURE:	Pyrexia may indicate underlying infection. Temperature >38.5 degrees Celsius requires a full blood workup including FBC, U+E, L.F.Ts, CRP, branched chain amino acids, blood gas, blood cultures, urine sample and any other tests as requested to assess and evaluate clinical and metabolic status.
b) PULSE:	Tachycardia may indicate infection, shock, metabolic acidosis, fluid overload. Bradycardia can occur in cases of an increase in intracranial pressure.
c) RESPIRATION:	Tachypnoea may indicate infection / acidosis / overload. Decreased respiratory rate may be related to level of consciousness/intracranial pressure. Irregular rate occurs late in leucine toxicity.
d) BLOOD PRESSURE:	Check baseline, usually within normal limits unless shocked. Monitor as clinically indicated. Increase in systolic blood pressure and bradycardia indicates raised intracranial pressure.

ACTION	RATIONALE
OXYGEN SATURATION: Monitor continuously in acutely ill child.	Low oxygen saturation may be present with acidosis.
4) 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 frequency of Branched Chain Amino Acids analysis. Dialysis (Haemodialysis) may be necessary at the time of initial presentation and at times of grossly elevated leucine levels to ensure rapid decrease in levels.	Measured frequently during periods of acute illness (usually 4-8 hourly) to evaluate effectiveness of prescribed dietary and intravenous regime and monitor metabolic status.
5) BLOODS: **a) BLOOD GLUCOSE:** Monitor blood glucose levels. If glycosuria is present and if on multiple infusions / high concentration dextrose record at 4-6 hourly intervals.	Hyperglycaemia may be related to the concentration and volume of dextrose used to provide calories. Refer to the 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 might not be appropriate in these patients as the

ACTION	RATIONALE
	pancreatic gland is normal. To be decided by the consultant in charge of the patient.
A Glucose-lactate profile is carried out as prescribed by Metabolic Consultant.	Hypoglycaemia +/- hyperlactataemia if present requires immediate intervention and the metabolic consultant needs to be contacted as soon as possible.
b) BLOODS: Four-six hourly analysis of urea and electrolytes and plasma osmolarity may be required by Metabolic Consultant while on multiple infusion therapy.	To assess effect 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.
6) URINE: **a) 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. **b) MSU** if infection suspected **c) Urinalysis** : pH	Elevated urine pH and metabolic acidosis in blood may indicate renal tubular acidosis with increased bicarbonate losses (tubulopathy).

ACTION	RATIONALE
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 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	Related to intake of high concentrations of dextrose. Where present check blood glucose. Where elevated, **inform doctor** and consider need for insulin (see point 5 above). Glycosuria in an acutely ill metabolic child is not an indication to wean / stop fluids unless otherwise instructed by Metabolic Consultant.
7. INTAKE AND OUTPUT	
Calculate mls / kg / 24hrs	To ensure adequate intake and monitor fluid balance. Fluid overload may occur due to high fluid intake.
Record losses - vomit - urine - stool	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).
Observe closely for signs of fluid overload.	May exacerbate cerebral oedema.
8. DIET Initial assessment helps to determine child's	

ACTION	RATIONALE
immediate needs and on-going Management.	
a) 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.	**Do not exceed prescribed number of exchanges.** Full daily intake is essential, as this helps reduce the levels of branched chain amino acids and prevents protein deficiency.
Protein allowance is counted in 'exchanges' 1 leucine exchange = 100 mg leucine = 1 gram protein	
b) 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.

ACTION	RATIONALE
c) <u>LOW PROTEIN / PROTEIN FREE PRODUCTS</u>	
Carbohydrate and fat Solution (CHO & Fat)	Provides calorie requirements not supplied in the diet. Do not contain amino acids. Prevention of catabolism.
Extra water may be added to feeds to ensure correct osmolarity (decided by consultant and dietetic team).	
A wide selection of low protein products are also available	
d) <u>EMERGENCY / UNWELL REGIME</u>	
Try to continue usual method of feeding – oral and / or nasogastric feeding.	May need intravenous dextrose 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 400) 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. Nasogastric feeding may be necessary where a patient is incapable or reluctant to take oral diet. Continuous feeds may be necessary when vomiting. Calorie requirements are greater during periods of illness. Extra calories may be administered using high energy drinks, i.e. CHO & Fat or lucozade.	To ensure the patient is receiving prescribed calorific requirements and to prevent protein deficiency. Ensures that prescribed amount of calories are taken over 24 hour period to prevent catabolism.
9. 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.	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 (Naglak and Elsas, 1988). Isoleucine and valine are required to reduce leucine-related toxicity.

ACTION	RATIONALE
Electrolytes	Sodium, potassium, chloride, 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 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 Refer to metabolic calculations booklet
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 of choice.	Paracetamol is metabolized in the liver (Higgins, 1996). Single stat doses may be prescribed as directed by metabolic consultant.
10. ONGOING EDUCATION: Ensure parents are educated in the following prior to discharge from first admission.	

ACTION	RATIONALE
• Genetic Implications • Well and Unwell Regimes • Medications • Enteral feeding (nasogastric tubes etc. if required). • Blood letting • Preparation of feeds • Implications of untreated illness or delayed management Education is on-going at OPD visits and on subsequent admissions.	25% risk of occurrence in each subsequent pregnancy Parents may need to change feeding regime at home To ensure patient safety
11. MULTIDISCIPLINARY SUPPORT / FOLLOW-UP CARE: • Metabolic clinic for medical, dietetic and nursing support. • **Blood tests** for amino acids etc. on each	To provide support to the family unit, to ensure appropriate entitlements and services are accessed.

ACTION	RATIONALE
visit. • **Psychology / Social Worker** **Other Health professionals may be consulted if necessary (e.g. physiotherapist/ Speech and Language / Ophthalmologist).**	

7. 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.

8. REFERENCES:

Ball, P.A., Booth, I.W., Holden, C.E. (1998) *Paediatric Parenteral Nutrition.* 3rd edn. Milton Keynes: Fresenius Kabi.

Clow, C.L., Reade, T.M., Scriver, C.R. (1981) Outcome of Early and Long-Term Management of Classical Maple Syrup Urine Disease. *Pediatrics*. 68 (6): 856-861.

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

Holmes Morton, D., Strauss, K.A., Robinson, D.L., Puffenberger, E.G. & Kelley, R.I. (2002) Diagnosis and treatment of maple syrup disease: a study of 36 patients. Downloaded from pediatrics.aappulications.org at The Children's Hospital on February 18, 2013. Available: http://pediatrics.aappuplications.org/content/109/6/999.full.html

Knerr, I., Weinhold, N., Vockley, J. & Gibson, K.M. (2012) Advances and challenges in the treatment of branched-chain amino/keto acid metabolic defects. *Journal of Inherited Metabolic Disorders* 35, 29-40.

Mitsubuchi, H., Qwada, M. & Endo, F. (2005) Markers associated with inborn errors of metabolism of branched-chained amino acids and their relevance to upper levels of intake in healthy people: An implication from clinical and molecular investigations on Maple Syrup Urine Disease. 4th Amino Acid Assessment Workshop, American Society for Nutritional Sciences, (downloaded from jn.nutrition.org by guest on December 21, 2011).

Naglak, M. & Elsas, L.J. (1988) Nutrition Support of Maple Syrup Urine Disease. *Metabolic Currents*. 1(3): 15-20.

National Newborn Bloodspot Screening Laboratory (2011) *A Practical Guide to Newborn Bloodspot Screening in Ireland.* 5th Edition, The Children's Hospital, Temple St, Dublin.

Ogier de Baulny H., Dionisi-Visi C. & Wendel U. (2012) Branched-chain Organic Acidurias/Acidaemias. In *Inborn Metabolic Diseases: Diagnosis and Treatment* (Saudubray J.M., van den Berge G. & Walter J.H. eds). 5th edition, Springer, Germany, pp. 277-296.

Poulton, T. & Conti, M.J. (1992) A Rare Event. *Nursing Times.* 88 (28): 40-42.

Robinson, P. (1996) Maple Syrup Urine Disease. *RTMDC News.* 5 (3): 12-16.

Robinson, D. & Drumm, L.A. (2001) Maple Syrup Urine Disease: A Standard of Nursing Care. *Pediatric Nursing*. 27(3): 255-270.

Zschocke J. & Hoffmann G.F. (2011*) Vademecum Metabolicum: Diagnosis and Treatment of Inborn Errors of Metabolism*. 3rd Edition, Milupa Metabolics GmbH & Co, Germany.

Metabolic.ie
National Centre for Inherited Metabolic Disorders