Children's Health Ireland at Temple Street

TITLE: NURSING GUIDELINES FOR THE MANAGEMENT OF CHILDREN WITH METHYLMALONIC ACIDURIA

Revision: 1

Policy [ ] Procedure [ ] Protocol [ ] Guideline [X]

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Contents

1. STATEMENT

The objectives in the 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 Methylmalonic Aciduria or suspected of having Methylmalonic Aciduria.

3. DEFINITION:

Methylmalonic Aciduria (M.M.A) is a recessively inherited disorder which is caused by a deficiency of Methylmalonyl-CoA Mutase (Ogier de Baulny et al., 2012). The enzyme is a vitamin B_{12} dependant enzyme. Patients with M.M.A are unable to metabolise the amino acids isoleucine, methionine, threonine, valine and some fats.

This condition is caused by:

i. Decreased or absent enzyme (methylmalonyl CoA mutase) activity.
ii. Decreased or absent enzyme (methylmalonyl CoA epimerase) activity.

iii. (Adenosylcobalamin (vitamin B12) deficiency which acts as a co-factor for mutase enzyme which leads to secondary mutase deficiency.

In MMA, the offending organic acid metabolites of Propionic acid and Methylmalonic acid accumulate in body fluids. These substances then spill into the urine. The excessive build-up of these substances causes a secondary deficiency of Co-enzyme A (CoA) causing the symptoms of Methylmalonic Aciduria.

PREVALENCE 1: 50,000 – 1: 80,000 (Han et al. 2017).

4. PRESENTATION:

Symptoms of M.M.A. may occur in the first days of life, intermittently later in infancy, or chronically, as the child grows. Acute infection or excessive protein intake may trigger symptoms such as;

- Refusal to eat
- Poor sucking reflex
- Vomiting
- Dehydration is a frequent finding in patients with MMA (Ogier de Baulny et al. 2012).
- Acidosis
- Failure to thrive
- Lethargy
- Seizures
- Developmental delay (Lin et al. 2018; Mahmud et al. 2015).

Where left untreated, M.M.A. may result in developmental delay and/or death.

5. DIAGNOSIS:

5.1. SUSPECTING A DIAGNOSIS OF METYLMALONIC ACIDURIA

Diagnosis is **suspected** on the clinical presenting signs & symptoms of the patient and on examination of laboratory investigation results which may present some of the following;

- Metabolic acidosis
- Hypoglycaemia
- Ketosis
- Hyperlactataemia
- Hyperglycinaemia
- Elevated Urea and Creatinine
- Hyperammonaemia
- Raised lactate, pyruvate
- Neutropenia (bone marrow depression is caused by Propionic acid metabolites).
- Thrombocytopenia
- Hepatomegaly

5.2. CONFIRMATION OF THE DIAGNOSIS

Diagnosis is **confirmed** on the following;

- Clinical presentation
- Acylcarnitines (increased propionylcarnitine)
- Analysis of urine organic acids. Highly suggestive diagnostic metabolites are methylmalonic acid & methyl citrate. The organic acids are nearly always abnormal during times of stress/ illness and can be otherwise commonly normal between acute illnesses (Van Gosen, 2008)
- Serum amino acids. Glycine and Alanine accumulates in plasma (Ogier de Baulny et al, 2012).
- Skin biopsy – to detect decreased amounts of enzyme activity and complementation studies.
- Mutational analysis

- Further tests will determine if the problem is due to deficiency of the enzyme **or** deficiency of adenosylcobalamin vitamin B_{12}

5.3 New born Screening / High Risk Screening

Methylmalonic Aciduria is currently not screened for in the Irish New born Population. High Risk Screening will be performed in the Maternity Hospital on siblings born to families with a known positive history (in consultation with the Metabolic Consultant). Prenatal diagnosis is possible by chorionic villi sampling in the first trimester or direct measurement of metabolites in amniotic fluid in 2nd trimester (Ogier de Baulny et al. 2012).

6. MEDICAL MANAGEMENT:

6.1 Emergency Treatment

- Protein Restriction. Stop natural protein intake (infant formula / breast feeding / food products which are sources of protein).
- Rehydration - MMA is very well cleared by urinary excretion; hydration is thus the mainstay of treatment.
- Ensure adequate calorie intake to prevent catabolism and promote anabolism. Prescribed calorie intake may be increased by 10 % or 20% of normal daily calorie intake (referred to as 110% or 120% calories).
- Administration of intravenous glucose, lipids and for more severe presentations, condition specific IV amino acid mixture - to minimize ammonia production from endogenous protein breakdown.
- Haemodialysis or Peritoneal dialysis may be recommended on initial presentation with markedly elevated propionic acid metabolites and elevated ammonia levels.
- Administration of Carnitine – this is essential for the transport of fats across the mitochondria, but is lost in urine bound to organic acids when aminoacidopathies occur.

6.2. LONG TERM TREATMENT

After the presenting metabolic acidosis has been corrected in the acute phase, **the long term treatment** consists of:

- Restricted intake of isoleucine, threonine, methionine and valine (natural protein) and odd-chain fatty acids.
- Supplemented natural protein intake with a synthetic amino acid formula, which is free from the offending amino acids. This can be given orally or via nasogastric tube if required.
- Adequate calorie intake to prevent catabolism
- 'Free foods' (i.e. non-protein) e.g. fruit, vegetables, sugars, fats and specially manufactured low-protein foods.
- Administration of vitamin and mineral supplements which are patient specific. Supplements may be required due to the synthetic nature of the prescribed diet.
- If tests show adenosylcobalamin (Vitamin. B_{12}) aides M.C.M. activity, it may be given intramuscularly, either daily, alternate daily, twice weekly or weekly (as per doctor's prescription). Neonatal forms are rarely vitamin responsive (Ogier de Baulny et al. 2012).
- Large doses of carnitine are given orally or intravenously to assist the excretion of organic metabolites. It transports fatty acid into the mitochondria where they can be utilised for energy.
- Oral Metronidazole (antibiotic) is used to clear the gut bacteria, which is responsible for 40% of propionic acid production (Ogier de Baulny et al. 2012).

7. NURSING MANAGEMENT OF THE PATIENT WITH METHYLMALONIC ACIDURIA

Complete full nursing assessment on admission and continue to observe for signs of patient deterioration such as increased vomiting, diarrhoea and altered Glasgow Coma Scale score (GCS). Early detection of symptoms with prompt escalation of care and treatment may be lifesaving (Mahmud et al. 2015, Zwickler et al. 2014)).

ACTION	RATIONALE
7.1. EMERGENCY ASSESSMENT A systemic process is used when assessing, measuring and recording vital signs. In an acutely unwell child the ABCDE approach should be used (Royal College of Nursing, 2017). 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	

ACTION	RATIONALE
by patient's condition (i.e. 2-4 hourly during initial presentation and acute illnesses - Paediatric Early Warning Score (PEWS) is used in CHITS.)	
AIRWAY	An early symptom of metabolic decompensation is muscular hypotonia and drowsiness (Zwickler et al. 2014). Decompensation in MMA, manifesting as decreased consciousness, can be life threatening and indicates a severe clinical condition (Fujisawa et al. 2013). Airway patency may be compromised with reduced GCS.
BREATHING Monitor respiratory rate, respiratory effort and oxygen requirements as per PEWS. Obtain oxygen saturation levels if concerned and report abnormalities to medical team.	Respiratory distress may be due to metabolic acidosis. 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)
CIRCULATION - **Pulse**	Tachycardia may indicate • Infection • Acidosis • Fluid overload

ACTION	RATIONALE
	• Dehydration
- Include **CRT** assessment as per PEWS. Assess colour and peripheral perfusion.	Decreased peripheral perfusion, decreased central capillary refill time, pallor and skin that is cool to touch may indicate hypovolemic shock (Standl et al. 2018).
- **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 status using **Glasgow Coma Scale**, and continue to record especially during further episodes of acute illness. Monitor GCS 4 hourly or as condition	Risk of encephalopathy secondary to hyperammonaemia.

ACTION	RATIONALE
indicates. Report altered level of consciousness or any deterioration to the metabolic team. - 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 report to medical team. Check with parents regarding patient's usual behaviour. **EXPOSURE** Ensure full examination of child is carried	Seizures resulting from hypoglycaemia and encephalopathy

ACTION	RATIONALE
out (whilst respecting the child's dignity and ensuring body temperature conservation).	
TEMPERATURE Monitor temperature 4 hourly or more frequently if indicated.	Pyrexia may indicate the 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, serum amino acids, blood gas and urine for quantitative MMA. Levels should be obtained to evaluate condition. Hypothermia may suggest the need for more calories. It may also indicate overwhelming infection (Goldstein et al. 2005).
7.2. INVESTIGATIONS **URINE:** **If unwell, urine should be obtained for quantitative MMA levels and / or qualitative analysis of Urine for Organic Acids.**	Levels of MMA in the urine alter constantly and normal levels are particular to the individual. Elevated MMA may prompt reduction of natural protein intake (decided by Metabolic Consultant).

ACTION	RATIONALE
(5-10mls – Universal container – must be frozen until transfer to the laboratory).	
If I.V. Glucose infusion is in progress, test urine regularly for glucose. Inform Metabolic team if glycosuria is present.	It may not be possible to reduce rate / concentration of glucose infusion due to calorie requirements. An insulin infusion may be prescribed (decided by Metabolic Consultant).
Urinalysis carried out on admission & daily thereafter.	Ketonuria is a common finding and indicates catabolism – prompt action is required. Elevated urine pH and blood results indicating metabolic acidosis may suggest 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 catabolic / ketoacidosis.
BLOOD SAMPLING As directed by the metabolic team. FBC, U &E, LFTs, Bone profile, Venous blood gas, Glucose and lactate, ammonia, serum amino acids, vitamin B12 and folate	Children with Methylmalonic Acidemia typically present with hyperammonemia and metabolic ketoacidosis during the new-born period (Splinter et al. 2016). Specific changes in the levels of plasma metabolites are the hallmark of the classical forms of MMA including ketoacidosis, hyperlactatemia, hyperammoniemia and cytopenia in variable

ACTION	RATIONALE
and acylcarnitine profile are bloods routinely required. Additional blood sampling as directed by the metabolic team.	proportions (Nizon et al.2013). Ammonia, acid-base balance and anion gap are important biochemical parameters to identify a metabolic decompensation, and to estimate its severity (Zwickler et al. 2014).
BLOOD GLUCOSE & LACTATE Measure 4-6 hourly when unwell and while on intravenous therapy. **BLOOD KETONES** Check ketones on admission and 4-6 hourly when unwell.	Hypoglycaemia and hyperlactataemia are frequently found in patients with MMA (Ogier de Baulny et al, 2012). Hyperglycaemia may occur as a result of high glucose concentration in intravenous fluids/ volumes required to fulfil calorie requirements. Refer to Medical Guidelines handbook regarding prescription of insulin and consult Metabolic Consultant / Registrar on call. Insulin doses appropriate for use in patients with Insulin Dependent diabetes are not appropriate for use in Metabolic Patients.
7.3. DIET: **NATURAL PROTEIN** On initial presentation and during episodes of illness and crisis, protein intake will be discontinued or restricted (decision will be	Necessary for normal growth and development.

ACTION	RATIONALE
taken by consultant). Initially, infants will receive their protein requirements from infant formula. Consequently, protein content of solids introduced from weaning onwards must be included in total daily protein allowance. Protein allowance is counted in 'exchanges'.	
SYNTHETIC PROTEIN (Amino Acid drink).	Supplements natural protein. Contains all amino acids except those that cannot be metabolized.
LOW PROTEIN / PROTEIN FREE PRODUCTS **Carbohydrate and Fat** (maxijul and fat solution) or Energyvits (proprietary formula).	Wide range of low protein products available to provide variety in diet, curb hunger and provide energy. Provides calories required to prevent catabolism. Do not contain amino acids.
EMERGENCY / UNWELL REGIME Different regimes may be prescribed according to patients' status.	

ACTION	RATIONALE
• Natural Protein: may be ¼, ½, ¾, or full (i.e. proportion of normal daily protein intake).	The reduction of natural protein reduces the risk of encephalopathy.
• Synthetic Protein may be reduced only if patient is very unwell.	
• Prescribed calorie intake may be increased by 10 % or 20% of normal daily calorie intake (referred to as 110% or 120% calories).	Increasing calorie intake prevents catabolism, thus reducing the risk of encephalopathy.
• Calorie intake should be recorded for the child who is unwell.	Calorie count ensures patient is receiving adequate calories to promote health and prevent catabolism.
• Nasogastric feeding may be necessary if not taking oral diet. If enteral feeding is not tolerated, parenteral nutrition	To ensure adequate amounts of protein, fat and calories are achieved to meet daily requirements.

ACTION	RATIONALE
will be required, i.e. - I.V. Glucose (carbohydrate) - I.V lipids (fat) - I.V. Vaminolact (natural protein).	
7.4.INTAKE AND OUTPUT Record all intake and output and monitor fluid balance. Calculate mls / kg / 24hrs in infants and percentage maintenance fluid intake in older child.	This, along with other clinical signs will identify if patient is adequately hydrated. Clinical signs and strict fluid balance monitoring will allow early detection of patients' fluid volume status
• **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	Losses may need to be replaced. Dehydration in MMA is very common as the renal clearance of Methylmalonic acid is very high and induces diuresis.

ACTION	RATIONALE
fluid balances in acutely unwell child. Large positive or negative balance to be reported to the medical team.	
7.5.GENERAL OBSERVATIONS • **Condition of skin:** Assess if intact / dry / broken especially skin folds and nappy area). Use a suitable skin barrier cream if required. Ensure skin is kept clean and dry and nappy is changed frequently.	Red or broken areas may be early signs of protein deficiency.
• **HAIR** Assess if coarse / brittle / alopecia present	May indicate low serum protein / zinc levels. Natural protein may need to be increased. If not tolerating dietary protein enterally, consider need to administer intravenously.
• **WEIGHT** Measure weight	To assist in assessment of hydration status. To ensure medications dosage and dietary prescriptions are correct.

ACTION	RATIONALE
7.6. MEDICATIONS	
• **Adenosylcobalamin (Vitamin B_{12})** Administered by IM injection. Dose and frequency are titrated according to urinary MMA results.	Necessary for the enzyme Methylmalonyl Co-A Mutase to function effectively.
• **Carnitine** Usually administered orally, but may be given intravenously.	Transports toxic acyl-CoA compounds from the cell for excretion. 100mg / kg per day is recommended to replenish free carnitine used in the excretion of toxic compounds. Usually supplemented orally. Increased oral doses can cause frequent passage of loose stools; IV carnitine can be given as an alternative.
• **Metronidazole**	Oral Metronidazole (antibiotic) is used to clear the gut bacteria, which is responsible for 40% of propionic acid production (Ogier de Baulny et al. 2012).
• **Vitamins and minerals**	Supplementation may be necessary due to synthetic nature of the prescribed diet.

ACTION	RATIONALE
7.7.EDUCATION Teaching is an on-going process. **Involves several members of the multidisciplinary team.** • Diet – includes preparation of feeds.	
• Well and Unwell Regimes	Volumes and calorific / protein content need to be adjusted according to condition.
• Medications (side effects, IM administration etc.).	
• Nasogastric tube insertion and ensuring competencies are completed by parents/carers to ensure safe care is carried out (if required).	Ensures patient safety
• Signs & Symptoms of illness – implications of delayed treatment or untreated illness.	

ACTION	RATIONALE
7.8. MULTIDISCIPLINARY / FOLLOW UP CARE. • Metabolic Clinic for dietetic, medical and nursing support. **Blood testing** at each OPD visit e.g. amino acids. • **Urine** samples may be requested at intervals between OPD visits. (Quantitative MMA). • **Psychology** • **Social Work** • **Speech & Language Therapy** • **Genetic counselling**	Chronic illness may have adverse effects on the family unit and relationships within the family. Psychologist and Social Worker input are necessary to assess coping mechanisms and difficulties with diet etc. (Splinter et al. 2016). To ensure that appropriate entitlements and services are accessed. Implications for future pregnancies 25% risk of occurrence in other pregnancies to same partners.

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:

Maria O' Regan, Clinical Nurse Manager 111, NCIMD.	Signature: _____ Date: _____
Caroline O' Connor, Nursing Quality, Practice and Research Co-ordinator.	Signature: _____ Date: _____
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	
1	20.05.2020	20.05.2023	Louise Perris	Routine Review