

TEMPLE STREET CHILDREN'S UNIVERSITY HOSPITAL		DOCUMENT REF NO:	PP-CLIN-NUR-108
TITLE:	Nursing Guidelines for the Management of Children with Methylmalonic Aciduria	REVISION NO:	0
LEAD AUTHOR:	Eilish O'Connell	EFFECTIVE FROM:	07/07/2016
APPROVED BY:	Dr Ahmad Monavari	REVIEW DATE:	07/07/2018
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**TITLE: NURSING GUIDELINES FOR THE MANAGEMENT OF CHILDREN
WITH METHYLMALONIC ACIDURIA**

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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:

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 B12 dependant enzyme. Patients with M.M.A are unable to metabolise the amino acids isoleucine, methionine, threonine, valine and some fats (Yannicelli, 1988)

This condition is caused by:

- Decreased or absent enzyme (methylmalonyl CoA mutase) activity.
- Inadequate amounts of adenosylcobalamin (Vit. B12) due to dietary limitations, poor intake or inherited defects of Vit. B12 metabolism.

With 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 (Ogier de Baulny et al, 2012)

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3. 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

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

4. DIAGNOSIS:

4.1. Diagnosis is **suspected** on the clinical presenting signs & symptoms of the patient and on examination of laboratory investigation results i.e.

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

4.2. 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 (Harris, 1988; Ogier de Baulny et al, 2012).
- Skin biopsy – to detect decreased amounts of enzyme activity.

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- Mutational analysis

Further tests will determine if the problem is due to deficiency of the enzyme **or** deficiency of adenosylcobalamin vitamin B₁₂

4.3. Newborn Screening / High Risk Screening

Methylmalonic Aciduria is currently not screened for in the Irish Newborn 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).

5. MANAGEMENT:

Emergency Treatment

5.1. 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.
- 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 amino acidopathies occur.

5.2. After initial treatment for acidosis, **long-term treatment** consists of:

- Restrict intake of isoleucine, threonine, methionine and valine (natural protein) and odd-chain fatty acids.
- Supplement natural protein intake with a synthetic amino acid drink, which is free from the offending amino acids.
- Ensure 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.

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- If tests show adenosylcobalamin (Vit. B₁₂) aides M.C.M. activity, it may be given intramuscularly, either daily or on alternate days (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.
- Metronidazole (antibiotic) is used to clear the gut bacteria, which is responsible for 40% of propionic acid production (Ogier de Baulny et al, 2012).

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6. NURSING MANAGEMENT OF THE PATIENT WITH METHYLMALONIC ACIDURIA

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
<p>1. GENERAL OBSERVATIONS:</p> <p>SKIN</p> <ul style="list-style-type: none"> Assess colour, peripheral perfusion Assess if intact / dry / broken (especially skin folds and nappy area). Ensure skin is kept clean and dry and nappy is changed frequently. <p>HAIR</p> <ul style="list-style-type: none"> Assess if coarse / brittle / alopecia present 	<p>Decreased peripheral perfusion and pallor may indicate shock/stress.</p> <p>Red or broken areas may be early signs of protein deficiency.</p> <p>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.</p>

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ACTION	RATIONALE
<p>WEIGHT</p> <ul style="list-style-type: none"> Measure weight 	To assist in assessment of hydration status. To ensure medications dosage and dietary prescriptions are correct.
<p>2. NEUROLOGICAL STATUS:</p> <p>Assess neurological status using Glasgow Coma Scale to demonstrate altered levels of consciousness, muscle weakness or seizures. If ambulant observe for ataxia and report to medical team.</p>	Risk of encephalopathy secondary to hyperammonaemia. Seizures resulting from hypoglycaemia.
<p>3. VITAL SIGNS:</p> <p>TEMPERATURE</p> <p>Monitor temperature 4 hourly or more frequently if indicated.</p>	Pyrexia of over 38.5° Celsius may indicate underlying infection. F.B.C., L.F.T'S, blood cultures, serum amino acids, blood gas and urine for quantitative MMA. Levels should be obtained to evaluate condition.

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ACTION	RATIONALE
<p>(5-10 mls – Universal container – must be frozen until transfer to the laboratory) If on I.V. Dextrose infusion, test urine regularly for glucose. Inform Metabolic team if glycosuria is present.</p> <p>Urinalysis carried out on admission & daily thereafter.</p>	<p>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).</p> <ul style="list-style-type: none"> - Ketonuria is a common finding and indicates catabolism – prompt action is required. - 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 catabolic / ketoacidosis.
<p>5. BLOOD GLUCOSE & LACTATE</p> <p>Measure 4-6 hourly when unwell and while on intravenous therapy.</p>	<p>Hypoglycaemia and hyperlactataemia are frequently found in patients with MMA (Ogier de Baulny et al, 2012).</p> <p>Hyperglycaemia may occur as a result of high dextrose concentration / volumes required to fulfil calorie requirements.</p> <p>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.</p>

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ACTION	RATIONALE
<p>6. DIET:</p> <p>NATURAL PROTEIN On initial presentation and during episodes of illness and crisis, protein intake will be discontinued or restricted (decision will be taken by consultant).</p> <p>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.</p> <p>Protein allowance is counted in 'exchanges'</p> <p>1 gram of natural protein = 1 exchange</p> <p>SYNTHETIC PROTEIN (Amino Acid drink).</p>	<p>Necessary for normal growth and development.</p> <p>Supplements natural protein. Contains all amino acids except those that cannot be metabolized.</p> <p>Wide range of low protein products available to provide variety in diet, curb hunger and provide energy.</p>

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ACTION	RATIONALE
<p>LOW PROTEIN / PROTEIN FREE PRODUCTS</p> <p>Carbohydrate and Fat (maxijul and fat solution) or Energyvits (proprietary formula).</p> <p><u>EMERGENCY / UNWELL REGIME</u></p> <p>Different regimes may be prescribed according to patients' status.</p> <ul style="list-style-type: none"> • Natural Protein: may be ¼, ½, ¾, or full (i.e. proportion of normal daily protein intake). • 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). 	<p>Provides calories required to prevent catabolism. Do not contain amino acids.</p> <p>The reduction of natural protein reduces the risk of encephalopathy.</p> <p>Increasing calorie intake prevents catabolism, thus reducing the risk of encephalopathy.</p>

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ACTION	RATIONALE
<ul style="list-style-type: none"> • Calorie intake should be recorded for the child who is unwell. • Nasogastric feeding may be necessary if not taking oral diet. If enteral feeding is not tolerated, intravenous nutrition will be required, <ul style="list-style-type: none"> i.e. - I.V. Dextrose (carbohydrate) - I.V lipids (fat) - I.V. Vaminolact (natural protein) 	<p>Calorie count ensures patient is receiving adequate calories to promote health and prevent catabolism.</p> <p>To ensure adequate amounts of protein, fat and calories are achieved to meet daily requirements.</p>
<p>7. INTAKE AND OUTPUT</p> <p>Calculate mls / kg / 24hrs i.e. Total mls in 24hr period ÷ body weight in kgs.</p> <ul style="list-style-type: none"> • Record losses <ul style="list-style-type: none"> - Vomit & stools & Urine output 	<p>To ensure adequate fluid intake and early detection of fluid overload.</p> <p>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 (Saudubray et al, 1991).</p>

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ACTION	RATIONALE
<p>8. MEDICATIONS</p> <ul style="list-style-type: none"> <p>Adenosylcobalamin (Vit B₁₂) Administered by IM injection. Dose and frequency are titrated according to urinary MMA results.</p> <p>Carnitine Usually administered orally, but may be given intravenously.</p> <p>Vitamins and minerals</p> 	<p>Necessary for the enzyme Methylmalonyl Co-A Mutase to function effectively.</p> <p>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 (Yannicelli, 1988). Usually supplemented orally. Increased oral doses can cause frequent passage of loose stools, IV carnitine can be given as an alternative.</p> <p>Supplementation may be necessary due to synthetic nature of the prescribed diet.</p>
<p>9. EDUCATION Teaching is an on-going process.</p> <p>Involves several members of the multidisciplinary team.</p> <ul style="list-style-type: none"> Diet – includes preparation of feeds. 	

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ACTION	RATIONALE
<ul style="list-style-type: none"> • Well and Unwell Regimes • Medications (side effects, IM administration etc.). • Nasogastric tube insertion and use (if required). • Signs & Symptoms of illness – implications of delayed treatment or untreated illness. 	<p>Volumes and calorific / protein content need to be adjusted according to condition.</p> <p>Ensures patient safety</p>
<p>10. MULTIDISCIPLINARY / FOLLOW UP CARE.</p> <ul style="list-style-type: none"> • Metabolic Clinic for dietetic, medical and nursing support. • Blood testing at each OPD visit e.g. amino acids 	

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ACTION	RATIONALE
<ul style="list-style-type: none"> • Urine samples may be requested at intervals between OPD visits. (Quantitative MMA) • Psychology • Social Work • Speech & Language Therapy • Genetic counselling 	<p>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.</p> <p>To ensure that appropriate entitlements and services are accessed.</p> <p>Implications for future pregnancies 25% risk of occurrence in other pregnancies to same partners.</p>

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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:

Methylmalonic Acidaemia

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

Leonard, J.V. (1995) The management and outcome of propionic and methylmalonic acidemia. *Journal of Inherited Metabolic Disease*. 18 (4), 430-434.

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.

Van Gosen, L. (2006) Organic acidemias: A methylmalonic and propionic focus. *Journal of Pediatric Nursing* 23(3), 225-233.

Yannicelli, S. (1988) Nutritional Support of Methylmalonic Acidemia. *Metabolic Currents*. 1(2), 10-12.

