METHYLMALONIC ACIDEMIA (MMA)

RECOMMENDATIONS ON EMERGENCY MANAGEMENT OF METABOLIC DISEASES

Department of Medical Genetics
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• Patient’s name:
• Date of birth:

• Please read carefully. Meticulous and prompt treatment is important as there is a high risk of serious complications.
• Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children.

INTRODUCTION
Methylmalonic acidemia, an autosomal recessive disorder, is caused by a deficiency of a specific enzyme on the catabolic pathway of certain amino acids (isoleucine, valine, threonine and methionine). The co-factor for the enzyme is a derivative of vitamin B12 (hydroxocobalamin). Decompensation is often triggered by metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu. The central emergency features of the MMA are profound metabolic ketoacidosis and hypoglycemia.
Treatment is aimed at reducing the sources of the precursors so the patients are treated with a low protein diet and medicines. Some patients respond to pharmacological doses of vitamin B12.

PRESENTATION
The early signs of decompensation include:
➢ Lethargy
➢ Poor appetite
➢ Vomiting: is common and should always be taken seriously
➢ However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen to parents carefully; their knowledge might exceed your expectations.
Later signs and symptoms of decompensation may include:
- Change/Altered level of consciousness
- Rapid and deep breathing (Kussmaul breathing)
- Seizures
- Hepatomegaly

The constellation of laboratory findings in these organic acid disorders:
- **Ketoacidosis**
- **Hypoglycemia**
- **Neutropenia**
- **Hyperammonemia**
- **Hypocalcemia/hypokalemia**

The ketoacidosis, hyperammonemia and hypoglycemia can explain the lethargy and obtundation. The ketoacidosis also produces vomiting. Mobilization of free fatty acids from stores to the liver produces a fatty liver. The increased organic acids may also be toxic to hepatocytes.

**ASSESSMENT**

**a. Clinical assessment:**
- Vital signs, cardiovascular stability
- STAT glucocheck (blood sugar) to check for hypoglycemia
- Neurologic status (including Glasgow coma score); evidence of increased intracranial pressure
- Hydration status
- Presence of fever; signs of infection
- Hepatomegaly

**b. LABS:**

**Blood**
- Blood gas (arterial or venous)
- Blood glucose
- Ammonia
- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca++, PO₄, Mg)
- Urea, creatinine
- Liver profile (including AST, ALT, AlkPO4)
- CBC differential
- Lipase
Urine
- Urine dipstick for ketones
- Urinalysis for specific gravity

Culture
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.

NOTE: Organic acids and ammonia are toxic to the brain and accumulations of these may result in cerebral edema. Caution should be exercised when considering the need for a lumbar puncture. If meningitis/encephalitis is a possibility, then CT of brain should be considered before lumbar puncture.

TREATMENT
The treatment for acute metabolic decompensation in these disorders includes:

1. Hydration
2. Correction of the biochemical abnormalities (metabolic acidosis, hyperammonemia, hypoglycemia)
3. Reversal of catabolism/promotion of anabolism
4. Elimination of toxic metabolites
5. Treatment of the precipitating factor when possible (e.g. infection, excess protein ingestion)
6. Cofactor supplementation
7. Consider hemodialysis

1. HYDRATION
- Give 20 ml/kg normal saline as a bolus immediately. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
- Continue with normal saline 10 ml/kg/hour until next solution ready. – see below
- Quickly calculate the deficit and maintenance and prepare the intravenous fluids
  - Deficit: estimate from clinical signs if no recent weight available
  - Maintenance: The formula for calculating maintenance fluid
(This is the BNF recommendation for children with 20% added because of the increased requirement in methylmalonic acidaemia) 120ml/kg for 1st 10kg then 60 ml/kg for next 10 then 25ml/kg thereafter using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.

- **Note:** Many patients with methylmalonic acidaemia have a renal tubular defect so that they cannot concentrate or acidify their urine normally. The recommended volumes have been adjusted to take account of this. Additional water, sodium and sometimes bicarbonate may be necessary but beware of oliguria in those with very poor renal function.

- Give 10% dextrose with normal saline 0.45%:
  - Intravenous fluids should be administered with enough glucose to prevent further catabolism and sufficient alkali to treat the acidosis.
  - Consider running 10% dextrose with a piggybacked bicarbonate infusion of 1.25-1.5 X times the maintenance rate. Piggybacking allows individual Adjustment/titration of the IV solutions. Add KCl if renal function is not compromised.

- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.

- After the initial 24 hours, continue with glucose 10% with saline 0.45% (unless evidence of continuing sodium depletion or hypernatraemia). Monitor the urea and electrolytes regularly 6 hourly particularly the plasma potassium concentration. Treat hypokalemia as necessary.

**N.B:** Ringer's lactate should NEVER be used for fluid/electrolyte therapy in a child with a known/suspected metabolic disorder.

### 2. CORRECTION OF BIOCHEMICAL ABNORMALITIES

- **Hypoglycemia:** if hypoglycemic, Give Glucose 200 mg/kg **at once** (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes; follow with (at least) a 10% glucose solution
b. **Metabolic acidosis:** administer Sodium Bicarbonate (NaHCO₃) as a bolus (1 mEq/kg) if acutely acidic with pH < 7.22 or bicarb level < 14, followed by a continuous infusion. If hypernatremia becomes a problem, reduce the rate of the NaHCO₃ drip; replace with K acetate.

- **WARNING** severe acidosis (pH <7.2 or base deficit > 10 mmol/l) is potentially very dangerous.

- Initially give a half correction \[0.15 \times \text{weight} \times \text{base deficit (mmol/l)}\] mmol sodium bicarbonate over at least 30 minutes. 1 ml of sodium bicarbonate 8.4% contains 1 mmol of sodium and bicarbonate and must be diluted *at least* 1ml to 5ml of 5% glucose. Then review and check plasma urea and blood gases. Repeat as clinically needed.

- If further doses of sodium bicarbonate appear to be needed, ask why? Is perfusion normal? What is the blood pressure, capillary refill time and urine flow? Could the patient have pancreatitis or cardiomyopathy? The treatment that will need to be considered is haemofiltration (possibly peritoneal dialysis), assisted ventilation and inotropes. Such treatment should be under metabolic specialist supervision.

c. **Hyperammonemia:** the elevated ammonia reflects a secondary inhibition of the urea cycle. As treatment for the organic acidemia proceeds, the ammonia level should diminish.

- If hyperammonaemic (> 200 μmol/l in first 24 hours or >250 μmol/l thereafter) consider N-carbamylglutamate 250 mg/kg as a single oral dose if available. Alternatively give sodium benzoate 250 mg/kg/day enterally

- For extremely elevated ammonia or persistently elevated levels, dialysis should be considered (see Dialysis- Part 7).

### 3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM

a. **GLUCOSE:** Catabolism can be diminished by providing large amounts of glucose (10% dextrose at maintenance or above), thereby surpassing hepatic glucose production. This therapy should be started as soon as possible after the patient presents to the emergency room.
b. **PROTEIN:** Amino acid therapy may be very beneficial in facilitating clinical improvement but should be implemented only under the supervision of a metabolic nutritionist or physician with expertise in metabolic management.
   - All natural protein (containing all amino acids) should be withheld for 48-72 hours while the patient is acutely ill.
   - Providing specialized diet which includes only "non-offending amino acids" (i.e., avoiding isoleucine, valine, threonine, and methionine) during the initial crisis period may not only stimulate anabolism but help prevent significant weight loss.
   - If the patient is not significantly neurologically compromised, these formulas can be provided enterally (NG or GT).
   - If enteral feeding is contra-indicated, consideration should be given to providing TPN.

b. **LIPID:** If TPN considered, intralipid may be given to supply extra calories; intralipid is composed of even chain fatty acids, so it should not increase concentrations of propionate (a 3-carbon organic acid), a precursor of methylmalonate, or methylmalonate. Intra-lipid of 20% solution may be added at 2g/kg/day (0.4ml/kg/hour)

c. **CALORIES:** A goal for calories during a period of decompensation, in order to support anabolism, would be about 20% greater than ordinary maintenance needs. One must remember that withholding natural protein from the diet also eliminates this source of calories and should be replaced by other dietary or nutritional sources.

d. **INSULIN:** Insulin is a potent anabolic hormone, promoting protein and lipid synthesis. Hyperglycemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol for treatment of DKA rather than reducing the glucose intake. **Strict supervision is essential.**

e. **TREAT CONSTIPATION:** which increases propionate absorption from the gut. Do **not** use lactulose as this can be fermented to propionate by gut bacteria

**Medicines to be avoided:** Sodium Valproate, Lactulose
4. ELIMINATION OF TOXIC METABOLITES
Correction of acute metabolic perturbations (acidosis, hypoglycemia) may help clear some of the factors contributing to the encephalopathy associated with acute metabolic crises. However, the presence of large quantities of toxic metabolites, believed to be toxic to the brain as well, is not cleared with glucose or bicarbonate, or rapidly with hydration. Consideration should be given to providing the means to help facilitate the excretion of these compounds:

a. **L-CARNITINE:** Free carnitine levels are low in the organic acidemias. L-Carnitine should be given intravenously - 200 mg/kg/24h given as a bolus of 100 mg/kg in 30 minutes and then 50 mg/kg every 6 hours intravenously. When oral fluids are tolerated, carnitine may be administered PO at a dose of 100 mg/kg/day.

b. **ANTIBIOTICS:** Administering broad-spectrum antibiotic may speed recovery in a patient in acute crisis.

c. **DIALYSIS:** When a patient is comatose, dialysis is indicated to facilitate a more rapid clearance of metabolic toxins (see 7. DIALYSIS)

5. TREATMENT OF PRECIPITATING FACTORS
Infection should be treated vigorously when possible. Note that neutropenia (and thrombocytopenia) frequently accompany metabolic decompensation. Bone marrow recovery is expected once the levels of toxic metabolites diminish significantly.

6. COFACTOR SUPPLEMENTATION FOR METHYLMALONIC ACIDEMIA
Cobalamin (B12) 1mg intramuscularly might be useful in cases of vitamin responsive enzyme deficiencies. In children with established diagnoses, parents will often know whether or not their child is a responder.
7. DIALYSIS
Dialysis (i.e., Peritoneal Dialysis, Hemodialysis, Continuous Renal Replacement Therapy) is indicated in cases with:

- Intractable metabolic acidosis
- Unresponsive hyperammonemia
- Coma
- Severe electrolyte disturbances (usually iatrogenic)

The Renal Service should be alerted early on in the hospital course.

MONITORING THE PATIENT
Clinical parameters:

- Mental status (Glasgow Coma Score)
- Vital signs specifically BP and temperature
- Fluid balance
- Evidence of bleeding (if thrombocytopenic)
- Symptoms of infection (if neutropenic)

Biochemical parameters:

- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca²⁺, PO₄, Mg)
- Urea, creatinine, glucose, ammonia
- Lipase
- Blood gases
- CBC differential
- Urine for ketones and specific gravity

RECOVERY
- The patient should be kept NPO until his/her mental status is more stable.
- If the patient is not significantly neurologically compromised, enteral feeds (NG/GT) with the patient special formula containing all but the offending amino acids should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition (see THERAPY, Part 3).
- If enteral feeds cannot be introduced within 48 hours start total parenteral nutrition (TPN) early to avoid malnutrition. (Note only moderate protein restriction when using TPN is necessary. Discuss with metabolic specialist team)
ACKNOWLEDGMENT
These recommendations have been compiled by Nahya Awada, Advanced Clinical Specialist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the American College of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England Consortium on Metabolic Programs; and have been revised by Medical Genetics Consultants in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011

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Dietary Emergency Protocol

Methylmalonic Acidemia (MMA)

- Name:
- Date of birth:
- Weight & date of weight measurement:

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   Add ................. Scoops of Polycose/Prophree to ................. mls of water

3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
   - Small boluses: Give ........ mls of emergency solution every .......... hour
   - Or continuously if a feeding pump is available
5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add ................. Scoops of Polycose/Prophree to ................. mls of Rehydration Solution

6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      - If the child is doing well, go back to normal diet.
      - If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen:
If your child appears well, reintroduce amino acid mix excluding natural protein source.

If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.

c. After 48 hours from starting the emergency regimen:

- If the child is doing well and amino acid mix is well tolerated, start introducing natural protein in the diet gradually over few days starting with half amount especially if ammonia level is known to be elevated.
- If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, bring your child to the hospital with all medicines, special dietary products, and scoops.

N.B:

If, at any time from starting this emergency regimen, your child is deteriorating and /or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

ACKNOWLEDGMENT
Dietary Emergency Protocols have been compiled by Eman Megdad, Metabolic Nutritionist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011