ADULT EMERGENCY MANAGEMENT
METHYLMALONIC ACIDAEMIA

IMMEDIATE ACTIONS

Triage to high priority

Start 10% dextrose intravenously and measure ammonia

Please contact the patient’s metabolic team for specific advice

These guidelines are intended for immediate emergency management only

BACKGROUND
Methylmalonic acidaemia is caused by a deficiency of methylmalonyl CoA mutase, an enzyme on the catabolic pathway of aminoacids (isoleucine, valine, threonine and methionine) and cholesterol side chains, odd chain fatty acids and free propionate from the gut. The co-factor for the enzyme is a derivative of vitamin B12 (hydroxocobalamin). Treatment is aimed at reducing the sources of the precursors so the patients are treated with a low protein diet and medicines - carnitine and metronidazole. Note: Some patients respond to pharmacological doses of vitamin B12.

Principles of treatment:
1. Avoidance of triggers of metabolic decompensation such as fasting – always ensure adequate carbohydrate intake – either orally or intravenously. Prompt treatment of fever and intercurrent illness.
2. Low protein diet – many adult patients self-impose a moderate reduction in protein intake with avoidance of high protein foods such as meat, fish and dairy. Some others are on a more formal low protein diet and use some prescription low protein food products.
3. Carnitine replacement – generally 50-100mg/kg/day for an adult. Carnitine may not be available in every hospital pharmacy - further information is available from the pharmacy at Great Ormond Street Hospital for Children.

SIGNS OF DECOMPENSATION
Decompensation is often triggered by metabolic stress such as febrile illness, particularly gastroenteritis, fasting, or constipation but an obvious cause is not always apparent. The early signs of decompensation
may be subtle, such as lethargy, worsening appetite or exacerbation of pre-existing neurological signs (movement disorder, etc). However, the signs may be difficult to assess such as *irritability* or just ‘*not right*’. Always listen to patients and their families carefully as they generally recognise early changes more quickly than medical professionals.

**If there is any doubt at all, the patient should be admitted, even if only for a short period of observation**

**INITIAL ASSESSMENT AND MANAGEMENT IN HOSPITAL**

If the patient is shocked or clearly very ill arrange for admission to ITU / HDU.

Management decisions should be based primarily on the *clinical* status. If the patient is relatively well - may be treated orally using their oral emergency regimen but assess very carefully – generally give 200ml of a 25% glucose polymer (eg Maxijul) solution every 2 hours. If the patient is obviously unwell or clinical status is unsure - must be treated with intravenous fluids.

Record the *Glasgow coma score*. This will allow early identification of encephalopathy and deterioration.

**INITIAL INVESTIGATIONS**

Blood pH and gases  
Glucose  
Full blood count  
Renal, liver, bone profiles  
Amylase/lipase (if pancreatitis a possibility)  
Ammonia  
Lactate  
Plasma and/or urine MMA levels (store appropriate samples – contact your laboratory for advice)  
Urine culture - urinary tract infections are common and should be considered and treated  
Other tests as clinically indicated (eg. CRP, blood cultures)

**TREATMENT**

1. Correct volume depletion with 0.9% NaCl. Fluid balance is particularly important in this group of patients, particularly in patients with renal impairment – contact your renal team early for advice if needed. Haemofiltration may be necessary.

2. Start intravenous 10% dextrose as soon as possible at a rate of 2mls/kg/hr (e.g. 140 mls/hr in a 70 kg person).

3. Continue oral carnitine if possible (100mg/kg/day in divided doses) – if unable to tolerate then start carnitine 100mg/kg/day iv maintenance infusion.

4. Reduce oral protein intake initially (aim to restart protein intake by 24 hours after presentation – for further advice contact the patient’s metabolic dietitian).

5. Start metronidazole 400mg three times daily oral or intravenous.

6. If hyperammonaemic - start sodium benzoate 250 mg/kg/day either as a continuous infusion or enterally.

7. If B12 responsive continue to give hydroxocobalamin 1mg intramuscularly daily.

8. Treat any underlying infection or other clinical problem.

9. Be aware of the possibility of refeeding syndrome in susceptible patients.
MONITORING
Reassess frequently, including Glasgow coma score and blood tests:

Blood pH and gases
Ammonia
Amylase / lipase
Lactate
Urea & electrolytes: Potassium concentration should be monitored and corrected appropriately.
Glucose: Hyperglycaemia can occur. If the blood glucose exceeds 10 mmol/L, start an insulin infusion according to your local protocol. Do not reduce the glucose intake.

Failure of improvement of clinical state, ongoing acidosis, hyperammonaemia, fluid overload – consider haemofiltration (haemodialysis) and seek specialist help.

COMPLICATIONS
If patients are not responding to treatment then consider the following early and institute appropriate treatment:

Volume depletion – is common. Adjust fluid intake as needed.
Acidosis – pH and gases should be monitored carefully. If acidosis persists after perfusion deficits are corrected then consider the use of sodium bicarbonate. Severe acidosis may be associated with respiratory/cardiac arrest and consideration should be given to elective assisted ventilation.
Pancreatitis - should be suspected if there is abdominal pain, shock out of proportion to other symptoms or hypocalcaemia.
Cardiomyopathy - may develop at any time but for reasons not well understood may occur during recovery phase. Arrange echocardiography if there are signs of cardio-respiratory problems. Cardiac monitoring is advised.
Stroke-like episodes - may occur at any time, frequently of sudden onset and when the patient is appearing to recover. They often involve the basal ganglia and present as a movement disorder.
Nutritional deficiencies – may be an issue if patients have had a poor appetite for some time, especially if not taking vitamin/mineral supplements. Consider supplements, particularly of thiamine.
Seizures - Avoid the use of sodium valproate.

RE-INTRODUCTION OF ORAL OR ENTERAL FEEDING
As the patient improves, oral or enteral feeds should be introduced as early as possible. Parenteral feeding can be used if enteral feeding is not possible. Protein intake should be reintroduced as early as possible and increased as tolerated. Anti-emetics may be needed. Consult your local metabolic dietitian or specialist centre for more details. See the BIMDG oral emergency regimen for more details.

MORE USEFUL INFORMATION
http://www.bimdg.org.uk/ and click on the red tab for emergency guidelines.

Genereviews: http://www.ncbi.nlm.nih.gov/books/NBK1116/