British Inherited Metabolic Disease Group

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This protocol has 6 pages

METHYLMALONIC ACIDAEMIA – ACUTE DECOMPENSATION

(standard version)

- **Please read carefully. Meticulous treatment is important as there is a high risk of complications.**

- **If the instructions do not make sense or a problem is not addressed you must discuss your concerns with the consultant on call.**

1. 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 B_{12} (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. Some patients respond to pharmacological doses of vitamin B_{12}.

Decompensation is often triggered by metabolic stress such as febrile illness, particularly diarrhoea or vomiting, fasting or constipation, but an obvious precipitant cause is not always apparent. The early signs of decompensation may be subtle - lethargy, even worse appetite than usual or exacerbation of pre-existing neurological signs (movement disorder, etc). Vomiting is common and should always be taken seriously. However, the signs may be difficult to assess such as irritability or just 'not right'. Always listen to parents carefully. They probably know much more than you do.

2. Admission

Almost all patients who present to hospital will require admission. Only allow the child home if you and the family are entirely happy and you have discussed the problems with the consultant on call. The family must have a clear management plan and be prepared to return if the child does not improve.

- **If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.**

3. Initial plan and management in hospital

⇨ If the child is shocked or clearly very ill arrange for admission to ITU/High dependency at once.

⇨ If admitted to metabolic/general ward make a careful clinical assessment including blood pressure and even if the patient does not appear encephalopathic enter a Glasgow coma score (for details click here). This is important since should the child deteriorate, particularly around the time of a change of shifts, the new team will recognise any change.

The following tests should be considered:

BLOOD (venous unless otherwise indicated)

- pH and gases
- Ammonia
- Glucose (laboratory and bedside strip test)
- Urea & Electrolytes, Calcium, Phosphate and ALP
- Full blood count
- Lactate
- Blood culture
- Amylase/lipase *(if pancreatitis a possibility)*

URINE

- ketones
- Microscopy, culture and sensitivity

(Note: Urine infection is common in young patients with MMA)

Complications

There are many complications of this disorder but some are problematic and need careful management.

1. Dehydration is a common problem because of the renal disease and polyuria. Fluid intakes are adjusted to take account of this.

2. Pancreatitis. This is probably considerably more common than recognised, partly because it is not easy to diagnose with confidence. It should be suspected if there is abdominal pain, shock out of proportion to other symptoms or hypocalcaemia. Plasma lipase and amylase activity should be repeated as these may not be raised, particularly at an early stage. Abdominal ultrasound may be helpful.

3. Cardiomyopathy. This may develop at any time but for reasons not well understood may occur during recovery phase. Patients should be on a cardiac monitor. Arrange echocardiography if there are signs of cardio-respiratory problems

4. Stroke-like episodes. These may occur at any time, frequently of sudden onset and when appearing to recover. They often involve the basal ganglia and present as a movement disorder.

For more information about the complications please click here

4. Management

Management decisions should be based primarily on the **clinical** status.

If the patient is vitamin B_{12} responsive or B_{12} status is not known, give hydroxocobalamin 1-2 mg intramuscularly

The next decision about therapy is whether the child can be treated orally or will need intravenous therapy.

- Factors that will influence the decision include, how ill is the child and whether they have deteriorated suddenly in the past?

- Can the child tolerate oral fluids?

If the child is relatively well - may be treated orally but assess very carefully.
If the child is obviously unwell - must be treated with intravenous fluids

- **If there is any doubt at all, put up an intravenous line.**

4.1 Fluids

A. Oral / Enteral.

If the child is relatively well, not vomiting and has no diarrhoea, oral feeds may be given. The emergency regimen should be used. This may be given as regular frequent drinks but if the patient is at risk of vomiting or is nauseated fluid should be given either continuously or as small boluses more frequently by naso-gastric tube or gastrostomy. For more information about the emergency oral management click here

Age (years)	Glucose polymer concentration (g/100ml) *	Total daily volume**
0-1	10	150-200 ml/kg
1-2	15	100 ml/kg
2-6	20	1200-1500 ml
6-10	20	1500-2000 ml
>10	25	2000 ml

* If necessary, seek help from your local dietitian. In an emergency a heaped 5 ml medicine spoon holds approximately 7g of glucose polymer.

**For each drink the volume will generally be this figure divided by 12 and given 2 hourly but if the patient is nauseated or refuses try frequent smaller drinks or a continuous naso-gastric or gastrostomy infusion.

Electrolytes should be added to the drinks using standard rehydration mixtures following manufacturer's instructions but substituting glucose polymer solution for water.

If a decision is made to give oral fluids, the patient must be reviewed within 4 hours.

MEDICINES (oral)

- Carnitine 200 mg /kg/24 hours in 4 divided doses
- Metronidazole 7.5 mg/kg every 8 hours
- Treat any infection
- Treat constipation (which increases propionate absorption from the gut)

Medicines to be avoided - Sodium Valproate

B. INTRAVENOUS.

If the child is unwell

- Give Glucose 200 mg/kg **at once** (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes.
- 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/h **ONLY UNTIL NEXT SOLUTION IS READY – do not leave on very high rates for longer than necessary** – 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 0.45% saline/10% glucose or 0.9% Saline/10% glucose depending on sodium levels (for instructions to make this solution click here).

- Having calculated the deficit and the maintenance, administer the appropriate rate of 0.45% saline/10% glucose or 0.9% Saline/10% glucose to correct the deficit within 24 hours
- Recheck the electrolytes every 24 hours if still on IV fluids.

- Hyperglycaemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol rather than reducing the glucose intake. **Strict supervision is essential.**

Potassium is not added initially because of possible pre-renal failure and chronic renal disease. In view of this, potassium is not added at this stage unless plasma potassium is known to be low (<3.5 mmol/l)

4.2 Acidosis

- WARNING severe acidosis (pH <7.2 or base deficit > 10 mmol/l) is potentially very dangerous. Patients who have a respiratory (or cardiac) arrest are usually difficult to resuscitate. **Always** consider elective assisted ventilation

Sodium bicarbonate is not given routinely but if acidosis persists after correction of perfusion, sodium bicarbonate may be needed if the pH <7.2 or the pH is deteriorating rapidly or the base deficit is greater than 10 mmol/l.

Initially give a half correction [0.15 x weight x 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 pH & blood gases. Repeat once if necessary. If this is given keep plasma sodium concentrations under review.

If further doses of sodium bicarbonate appear to be needed, discuss with the consultant. Before doing so 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 haemodialysis), assisted ventilation and inotropes. Such treatment should be under specialist metabolic supervision.

4.3 Continuation of fluids

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 hypokalaemia as necessary.

- Intra-lipid may be added 2g/kg/d (0.4ml/kg/h of 20% solution)

MEDICINES

- If the patient is vitamin B_{12} responsive or B_{12} status is not known, give hydroxocobalamin 1 mg intramuscularly
- Carnitine: Give a loading dose of 100 mg/kg over 30 minutes followed by a continuous infusion of 4mg/kg/hour.
- Metronidazole 7.5 mg/kg every 8 hours oral or intravenous
- Treat any infection
- Treat constipation (which increases propionate absorption from the gut)
- 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. This may be repeated. If persistent hyperammonaemia discuss with regional specialist metabolic service. **Sodium benzoate 250 mg/kg/d** may also be given either as a continuous infusion or enterally. If using sodium benzoate – CLICK HERE for a drug calculator

Medicines to be avoided - Sodium Valproate

5. Progress:
Monitoring: Reassess after 4-6 hours or earlier if there is any deterioration or no improvement
Clinical assessment should include Glasgow coma score (for details click here) and blood pressure.
Blood tests: Blood pH and gases
Ammonia
Glucose (laboratory):
Urea & electrolytes,
Full blood count
Lactate
Calcium, phosphate, alkaline phosphatase and amylase/lipase if pancreatitis possible

⇨ If improving, continue and for intravenous fluids after 6 hours, please refer to the previous section. If Vitamin B_{12} responsive continue to give hydroxocobalamin 1 mg daily intramuscularly whilst on intravenous fluids.

⇨ If there has been no improvement or deterioration (clinical state, acidosis, hyperammonaemia, fluid overload), seek specialist help. Transfer to ICU/HDU is likely to be needed. Additional treatment such as assisted ventilation and haemofiltration (haemodialysis) may need to be considered **urgently**. Note: peritoneal dialysis is less efficient. Exchange transfusion is dangerous and should not be used.
If the patient has been unwell for sometime and has not been getting a vitamin supplement, consider giving a complete vitamin supplement intravenously (as thiamine deficiency may be a particular problem).

6. Re-introduction of enteral feeds: Enteral feeds with some protein should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition. If necessary, consult your local dietitian for more details. 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 specialist metabolic team)

7. Going Home: Only allow the child home if you and the family are entirely happy and you have discussed the problems with the consultant on call. The family must have a clear management plan and be prepared to return if the child deteriorates.

For further information please refer to:

Saudubray J-M, Baumgartner MR, Walter JH. (editors) Inborn Metabolic Diseases. Diagnosis and treatment. 6th Edition. Springer 2016