

Anaesthesia recommendations for patients suffering from

## **Methylmalonic acidemia (or aciduria)**

**Disease name:** Methylmalonic acidemia

**ICD 10:** E71.1

**Synonyms:** Methylmalonic aciduria, MMA, isolated methylmalonic acidemia

Methylmalonic acidemia (MMA) is a group of rare (approx. 1:50,000) autosomal recessive disorders of amino acid metabolism, involving defects in the conversion of methylmalonyl-CoA to succinyl-CoA (which would normally enter the Krebs cycle). The defect is genetically heterogeneous, and can be due to the lack of the enzyme methylmalonyl-CoA mutase ( $mut^0$ ), partial reduction in its activity ( $mut^-$ ), or to defects in cobalamin metabolism (vit B<sub>12</sub> is a cofactor required in the conversion of methylmalonyl-CoA to succinyl-CoA). These defects result in the accumulation of methylmalonic acid.

Clinical presentation varies and depends on the genetic diagnosis. The most severe form is  $mut^0$ , which usually presents in the neonatal period, while other forms may present later in infancy and childhood, when triggers of increased protein catabolism (infection, dehydration, trauma, surgery, stress) cause metabolic decompensation. The presentation may be non-specific, such as vomiting, lethargy and tachypnoea. Neurological manifestations include encephalopathy, seizures, hypotonia and stroke. Gastrointestinal complaints include recurrent vomiting, failure to thrive, and pancreatitis. If the acute crisis is untreated it may progress to coma and death.

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Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

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Find more information on the disease, its centres of reference and patient organisations on Orphanet: [www.orpha.net](http://www.orpha.net)

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## Disease summary

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Biochemical hallmarks of an acute metabolic decompensation are metabolic acidosis, an increased anion gap (caused by lactate, ketones and organic acids), elevated lactate and ketones ± hyperammonaemia.

Long-term complications include failure to thrive, chronic kidney disease or renal failure, pancreatitis, pancytopenia, osteopenia and intellectual disability. Cardiac involvement is rare, but includes dilated cardiomyopathy and prolonged QTc interval. Several patients have been reported with metabolic stroke and optic atrophy.

Long-term management is aimed at preventing metabolic decompensation. Patients are placed on a protein-restricted diet, given carnitine supplements (to promote the increased excretion of toxic metabolites) and hydroxycobalamin if cobalamin responsive. Administration of metronidazole is aimed at reducing the burden of acid-producing bacteria in the gut. Ammonia scavenging drugs including carglumic acid, a synthetic analogue of N-acetyl glutamate, can be used to manage hyperammonaemia.

Kidney, liver, or combined kidney-liver transplantation is increasingly being performed in patients with MMA. While transplanting either or both organs does not “cure” the disease, the aim is to supply a certain amount of the missing enzyme. Methylmalonyl–CoA mutase is mainly expressed in the liver, but renal transplantation will partially replace some mutase activity. Transplanting kidneys in MMA patients with renal failure both restores the impaired renal function and improves the metabolic enzyme defect, and thus reduces the number of episodes of metabolic decompensation and hospitalisation, and allows liberalisation of the diet. It does not prevent neurological complications. Liver transplantation is considered as a treatment option particularly in patients with frequent decompensations. Combined liver–kidney transplantation is a potential treatment option but is associated with more postoperative complications than single organ transplantation.

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## Typical surgery

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- Insertion of long term intravenous access lines or ports (for treatment, fluids, blood sampling or TPN)
- Gastrostomy or GJ tube insertion
- Imaging studies, including CT and MRI
- Skin biopsy (usually done under local anaesthesia)
- Examination under anaesthesia (e.g. eyes) or brainstem auditory evoked responses (for hearing loss)
- Placement of haemodialysis catheters
- Transplantation (kidney, liver or both)

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## Type of anaesthesia

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General or loco-regional anaesthetic techniques may be used where appropriate.

## **Necessary additional diagnostic procedures (preoperative)**

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Blood tests include:

- Blood gas, lactate and ammonia (metabolic acidosis / hyperammonaemia is a sign of decompensated disease, and should prompt a review and discussion about the timing of elective surgery).
- Glucose and ketones reviewing anabolic state
- Full blood count - looking for chronic anaemia, neutropaenia, thrombocytopenia.
- Urea and electrolytes – chronic renal failure occurs in up to 50% and is most reliably assessed by the glomerular filtration rate. Hyperkalaemia has been associated with ventricular tachycardia and cardiac arrest after induction of anaesthesia in a child with MMA.
- Amylase and lipase (particularly in patients with history of previous acute or acute on chronic pancreatitis)

Cardiac evaluation: while cardiac involvement is considered to be rare, prolonged QTc and cardiomyopathy have been described. A baseline ECG and echocardiogram would be recommended (children may be asymptomatic if they perform very limited exercise).

Careful assessment and consultation with the patient's specialist is advised to determine metabolic stability and timing of surgery. Patient's metabolic status should be optimised prior to elective surgery.

## **Particular preparation for airway management**

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There are no specific airway complications described with MMA per se.

## **Particular preparation for transfusion or administration of blood products**

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Patients with MMA may have a chronic anaemia or be pancytopenic as a result of acute or chronic bone marrow suppression. This may or may not require transfusion, depending on the surgery being performed. There are no specific requirements described for transfusion of blood products.

## **Particular preparation for anticoagulation**

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No particular concerns around anticoagulation are described. The disease is not typically associated with thrombosis or the need for anticoagulation.

## **Particular precautions for positioning, transport or mobilisation**

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Patients may be osteopaenic and at risk of fractures, and are also at risk of poor wound healing. Careful positioning is required.

## **Probable interaction between anaesthetic agents and patient's long term medication**

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Patients may be on anticonvulsants that may alter the metabolism of some anaesthetic drugs. Patients with movement disorders may be on L-dopa, clonazepam, or baclofen.

## **Anaesthesiologic procedure**

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**Preoperatively**, the aim is to avoid prolonged fasting as it may cause protein catabolism and a metabolic crisis. Patients should be fasted as per standard guidelines, but prolonged fasting and dehydration should be avoided. The individual day-to-day fasting tolerance of the patient can be used as a baseline. Encourage the intake of clear, glucose polymer-containing fluids until two hours preoperatively, or provide intravenous 10% glucose in 0.45% or 0.9% saline, as follows:

- 8-10 mg/kg/min for neonates and infants
- 6-7 mg/kg/min for children
- 5-6 mg/kg/min for adolescents
- 4-5 mg/kg/min for adults

It is recommended that this infusion is continued throughout the surgical procedure and postoperatively until feeds are re-established. TPN should be continued if the patient is TPN-dependent.

All chronic medication should be continued in the perioperative period.

If the child is unwell or in the setting of metabolic decompensation (metabolic acidosis, elevated lactate and hyperammonaemia revealed on preoperative blood tests), elective surgery should not be performed. In the setting of emergency surgery, preoperative and perioperative haemodialysis should be considered.

### **Intraoperatively:**

- Induction can be inhalational or intravenous.
- Some children may be overweight, making intravenous access difficult.
- There is no contraindication to the use of the volatile agents.
- While it is unlikely to be a problem if used for the induction of anaesthesia, avoid nitrous oxide for maintenance, especially in patients with cobalamin metabolism defects, as it inhibits vitamin B<sub>12</sub> dependent enzymes.

- While propofol was traditionally thought to be contraindicated for patients with MMA, it has recently been shown to be safe for both the induction and maintenance of anaesthesia or sedation in the setting of metabolically stable patients. For major surgery (such as transplantation) or in unwell children, it would seem prudent to avoid propofol for the maintenance of anaesthesia due to its mitochondrial effects.
- Dehydration and hypotension can trigger a metabolic crisis. Patients should be well hydrated with dextrose in saline as above. Despite a theoretical concern over the use of lactate-containing fluids, a recent study has not shown an association between the use of Ringer's Lactate and metabolic decompensation.
- The use of catecholamines may cause catabolism leading to metabolic decompensation. Catecholamine use should be avoided where possible and all parameters closely monitored if catecholamines are required.
- Sufficient depth of anaesthesia and analgesia must be maintained to avoid surgical stress.
- Consider using drugs to decrease ammonia with continuous infusion intraoperatively
- Monitor blood gases, lactate, electrolytes, glucose and ammonia during longer procedures.
- Manage hyperglycaemic patients with an insulin infusion. Be aware that they may be very sensitive to insulin as their pancreases function normally, and hypoglycaemia is a risk. Consider starting insulin at a low dose, eg 0.02 IU/kg/hr and titrate to effect.
- Avoid blood in the gastrointestinal tract that could act as a protein load and trigger decompensation. Consider placing a throat pack or gastric tube where appropriate, e.g. dental work, tonsillectomy.
- Avoid the use of steroids due to their catabolic effects and risk of triggering acute decompensation (there is no evidence as to whether a single dose used to prevent postoperative nausea and vomiting is safe or not, so it would seem prudent to avoid).
- Avoid nephrotoxic drugs due to their potential to precipitate or aggravate renal disease.
- Patients may be neutropaenic increasing the risk of sepsis and line sepsis. Observe local infection control practices and antibiotic guidelines.
- Prolonged QTc interval is a rare complication. Caution with using drugs that prolong the QT interval.
- Anti-emetics: it is recommended that metoclopramide is avoided. Use ondansetron.
- Paracetamol, opiates and loco-regional anaesthetic techniques can be used for analgesia. Avoid non-steroidal anti-inflammatory drugs.
- The use of muscle relaxants is not contraindicated. Monitoring of their effects and of their reversal would seem prudent in hypotonic children.

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### **Particular or additional monitoring**

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Regular measurement of glucose, arterial blood gases, lactate, ammonia and potassium is recommended.

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### **Possible complications**

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Dehydration, hypotension, hypoxia, the stress of surgery and anaesthesia, and the presence of intercurrent illness and infection can all trigger a metabolic crisis, leading to metabolic acidosis, hyperlactataemia and / or hyperammonaemia. Hyperkalaemia secondary to metabolic acidosis has been described as causing intraoperative ventricular tachycardia and cardiac arrest.

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### **Postoperative care**

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Patients should be closely monitored after anaesthesia for signs of clinical deterioration, and should be managed in high-dependency settings where appropriate.

Intravenous fluids should be continued until the child tolerates enteral feeding. Feeding can be commenced as is appropriate for the surgical procedure. Patients should not be without protein > 48hours; if enteral intake is not possible early postoperatively, TPN should be considered. The child should only be discharged after full recovery, once tolerating their usual diet and medication, and with normal metabolic results. The patient's metabolic team should guide dietary management and discharge.

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### **Information about emergency-like situations / Differential diagnostics**

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Differential diagnoses for the acute metabolic crisis in MMA include sepsis, respiratory distress and diabetic ketoacidosis. MMA can also present with seizures or a reduced level of consciousness. Any delay in recovery from anaesthesia should prompt checking of blood gases, glucose, electrolytes and ammonia.

Management of the acute crisis includes rehydration, providing glucose as a metabolic substrate (as above) while avoiding hyperglycaemia, and correcting any electrolyte abnormalities and acid-base disturbances. Consider dialysis for persistent acidosis or hyperammonaemia.

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### **Ambulatory anaesthesia**

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Patients with MMA would not typically be considered for day-case anaesthesia. They should not be discharged home until they are fully recovered and have normal metabolic results. Discussion should be held with the metabolic team before considering ambulatory anaesthesia.

## **Obstetrical anaesthesia**

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The safe use of epidural anaesthesia for labour has been described. No anaesthetic complications are described during anaesthesia for Caesarean sections.

## Literature and internet links

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