British Inherited Metabolic Disease Group

This guideline has 5 pages

PROPIONIC ACIDAEMIA - ACUTE DECOMPENSATION

IMMEDIATE ACTION

- **Triage to high priority**
- **The major complications are hyperammonaemia, encephalopathy, stroke-like episodes, pancreatitis and cardiomyopathy/ arrhythmias. Meticulous treatment is very important as there is a high risk of neurological complications, including cerebral oedema.**
- **Use clinical status: '2. CLINICAL ASSESSMENT' to guide management '3. MANAGEMENT IN HOSPITAL'**
- **If the child is unwell and/or vomiting start intravenous fluids: '3.2. INTRAVENOUS'**
- **Ongoing management should be guided by the child's specialist metabolic team. Contact them as soon as possible for advice.**

1. BACKGROUND AND SIGNS OF DECOMPENSATION:

- Propionic acidaemia (PA) is caused by a deficiency of propionyl CoA carboxylase, an enzyme on the catabolic pathway of amino acids (isoleucine, valine, threonine and methionine) as well as cholesterol side chains, odd chain fatty acids and free propionate from the gut.
- Decompensation is often triggered by states causing metabolic stress such as febrile illness, diarrhoea or vomiting, fasting, or constipation. However, an obvious cause is not always apparent.
- Early signs of decompensation may be subtle. Vomiting is common and should be taken seriously.
- Long-term management aims to reduce the sources of the precursors, with a protein-restricted diet and medicines – L-carnitine and metronidazole.
- Decompensation of PA may cause severe neurological complications (including cerebral oedema and stroke-like episodes). Other complications include pancreatitis, cardiomyopathy and arrhythmias.
- **Treatment of acute illness is therefore urgent.**

2. CLINICAL ASSESSMENT:

Clinical assessment should focus on the following:

- **Signs of hyperammonaemia** – the early signs of encephalopathy may be subtle and may include lethargy and behavioural change. Listen to the parents' concerns carefully.
- Vomiting - as a cause or result of metabolic decompensation. This will guide further management.
- Constipation - may lead to decompensation due to increased propionate absorption from the gut.
- Intercurrent infection or other illness triggering metabolic decompensation.
- Signs of 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 may not be raised, particularly at an early stage. Abdominal ultrasound may be helpful.

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- Neurological status – there is a high risk of neurological sequelae with decompensation, including cerebral oedema and stroke-like episodes. These may present during the recovery phase as a new-onset movement disorder. Document the initial GCS and ensure ongoing monitoring.
- Cardiovascular status – high risk of cardiomyopathy and cardiac arrhythmias. Cardiomyopathy may develop at any time, including during the recovery phase. Cardiac arrhythmias (especially long-QT syndrome) are an important complication which may lead to sudden death. All unwell patients with PA should be on a cardiac monitor. If there is any cardio-respiratory compromise, organise for an urgent ECG/ echocardiogram.

For more information about the complications please click here

Almost all patients who present to hospital will require admission (as they will likely have been self-managing at home with their emergency regimen prior to presenting). **If there is any doubt at all, the child must be admitted, even if only for a short period of observation.**

3. MANAGEMENT IN HOSPITAL:

- If the child is shocked or clearly very ill, consider admission to ITU/ High Dependency.
- If admitted to a 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 very 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:

    - Gas (pH, glucose, lactate).
    - **Ammonia** (urgent, free-flowing sample), Glucose, lactate, urea and electrolytes, calcium, phosphate, ALP, Amylase/ lipase (if pancreatitis symptoms), Blood spot acylcarnitines.
    - Full blood count.
    - Urine ketones.

- Consider other tests as clinically indicated.

- The first decision about therapy is whether the child can be treated orally (Section 3.1) or will need intravenous (IV) therapy (Section 3.2). If there is any doubt, start IV fluids.
- Factors that will influence the decision include: How ill is the child? Can they tolerate oral fluids/ medications? Have they deteriorated suddenly in the past?
- Intravenous fluids are indicated if: the child is unable to tolerate oral fluids, or there is moderate or severe clinical dehydration.

3.1 PATIENT TOLERATING ORAL/ ENTERAL FEEDS:

If the child is relatively well and not vomiting, oral/ enteral fluids may be given. For young children (typically under 2 years) or those who already have enteral feeding tubes, the emergency feed can be given via such tubes.

FULL ENTERAL EMERGENCY REGIMEN (ER) – GLUCOSE POLYMER SOLUTION

Use patient's own ER recipe wherever possible. If not available, then use age-based recipe:

- Click Here for Emergency Regimen for Age ≤ 1 year (10% carbohydrate)
- Click Here for Emergency Regimen for Age 1- 2 years (15% carbohydrate)
- Click Here for Emergency Regimen for Age 2-9 years (20% carbohydrate)
- Click Here for Emergency Regimen for Age ≥ 10 years (25% carbohydrate)

If ER products not available, use IV guidelines.

Oral rehydration solutions are low in carbohydrate and not suitable

Emergency regimen administration

- Give feeding volume for body weight (see recipe)
- Feed orally: 2 hourly day and night
- If fluid requirements not met, administer continuously by tube.
- If vomits – switch to intravenous fluids (Section 3.2).
- Administer bolus or continuous tube feed, without delay for a maximum of 24-36 hours
- Introduce usual diet/feeds as soon as clinically stable

Medications

- Antipyretics: as clinically indicated
- Consider antiemetic such as ondansetron.
- Give the child's usual medications if not vomiting.
- Treat any constipation (increases propionate absorption from the gut) or infection.

Drug (enteral)	Doses in ill patients
Levocarnitine	100 – 200 mg/kg/day in 4 divided doses
Metronidazole	7.5 mg/kg (max dose 400 mg) three times daily

Seek specialist help if uncertain about management.

Contact the child's specialist metabolic team and dietitian for further advice on the ER and re-introduction of usual diet/feeds

3.2 PATIENT REQUIRES INTRAVENOUS THERAPY:

If the child is unwell and not tolerating oral/ enteral feeds, start IV fluids.

IMMEDIATE FLUID RESUSCITATION:

- **If the peripheral circulation is poor, if the patient is obviously dehydrated, or if the patient is frankly shocked**, give a 10 ml/kg bolus of plasmalyte/ balanced crystalloid as per Advanced Paediatric Life Support guidance (use 0.9% Sodium Chloride if plasmalyte not available). Repeat the bolus if the poor circulation persists, as for a shocked non-metabolic patient.

FLUIDS AFTER INITIAL RESUSCITATION:

- Run IV fluids of 10% Glucose/ 0.45% Sodium Chloride at 5ml/kg/hour ONLY until accurate fluid rates have been calculated **– do not leave on this high rate longer than necessary**.
- For instructions on how to make this solution, click here.

FURTHER FLUID MANAGEMENT IN FIRST 24 HOURS:

- Ongoing fluid management in based upon administering maintenance fluids as 10% Glucose/ 0.45% Sodium Chloride (For instructions on how to make this solution, click here.), plus any calculated fluid deficit plus maintenance over 24 hours.
- Deduct the fluid already given from the total for the first 24 hours.
- Potassium can be added, if appropriate, once the plasma potassium concentration is known and the child is passing urine.
- Hyperglycaemia can be a problem, but **it is important not to reduce the glucose intake**. If the blood glucose persistently exceeds 10 mmol/L, keep the glucose content of IV fluids as 10%, but start an insulin infusion using the local diabetic protocol. **Strict supervision is essential.**
- Reassess hydration status and the need for ongoing IV fluids after 24 hours. Recheck the electrolytes every 24 hours as per local guidance.
- To further promote anabolism in a decompensated patient not responding to IV fluids alone, intra-lipid may be added 2g/kg/day (0.4 ml/kg/hour of 20% solution).

CORRECTION OF HYPERAMMONAEMIA:

- If hyperammonaemic (Ammonia > 100 µmol/L), consider **N-carbamylglutamate** (Carglumic acid) **250 mg/kg** as a single oral/ enteral dose. This may be repeated.
- If persistent hyperammonaemia, discuss with regional specialist metabolic service.
- **Sodium benzoate 250 mg/kg/day** may also be given either as a continuous infusion or enterally. If using sodium benzoate – CLICK HERE for a drug calculator

CORRECTION OF METABOLIC 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, 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 but this solution should be diluted *at least* 1ml to 5ml of 5% glucose. Then review and check U&E and pH & blood gases.
- The acidosis normally corrects fairly quickly so that repeat doses of sodium bicarbonate should only occasionally be needed.
- If the patient remains persistently acidotic, potentially requiring further doses of sodium bicarbonate, discuss with the consultant first. Before doing so, ask: Why is the acidosis persisting? Is the 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.

OTHER MEDICATIONS:

- L-Carnitine: continuous infusion of 4 – 8 mg/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)
- **Medicines to be avoided - Sodium Valproate**

4. 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.
- Repeat tests used to monitor progress:
    - Gas (pH, glucose, lactate).
    - **Ammonia** (urgent, free-flowing sample), Glucose, lactate, urea and electrolytes, calcium, phosphate, ALP, Amylase/ lipase (if pancreatitis symptoms).
    - Full blood count.
- If improving, continue. Refer to the previous section regarding IV fluids beyond 6 hours.
- If there has been no improvement or deterioration (clinical state, acidosis, hyperammonaemia, fluid overload), seek specialist IMD help. Haemofiltration (haemodialysis) and other treatment 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 some time and not getting a vitamin supplement, consider giving a complete vitamin supplement intravenously (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.
- The Metabolic dietetic team will provide guidance regarding re-introduction of enteral feeds.
- 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. DISCHARGE PLANNING:

- Only allow the child home if you and the family are entirely happy and you have discussed with the consultant on call.
- The family must have a clear management and safety-netting 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. 7th Edition. Springer 2022