Mitochondrial fatty acid ß-oxidation disorders

VLCAD, LCHAD, CPT2, Translocase deficiency, Trifunctional deficiency, Glutaric aciduria type 2 (GA2)

Label

Priority patient: must not wait in A&E

If presenting with fever, vomiting, diarrhoea or fasting state
Risk of hypoglycaemia, coma, cardiac rhythm disorders and/or heart failure, liver failure, rhabdomyolysis

Do not wait for signs of decompensation, in all cases initiate management as set out below

1 EMERGENCY

Capillary and venous **blood glucose**, **CPK**, blood ammonia, serum electrolytes, **potassium**, calcium, urea, creatinine, blood gases, lactate, AST, ALT, GGT, PT - **Factor V**. **If cardiac signs** or abnormalities on the electrocardioscope: ECG, BNP, Troponin +/- echocardiogram. Do not delay infusion.

2 TREATMENT TO BE STARTED URGENTLY, without waiting for test results

- If **blood sugar < 3mmol/L**, raise blood sugar with 1ml/kg of 30% glucose orally (max. 30ml) or 2-3 ml/kg of 10% glucose by direct intravenous injection and start the glucose infusion below. (30% glucose possible via central line or intra-osseous route)
- If **hypovolaemia, replenish** with Ringer's Lactate or 0.9% NaCl at **10 ml/kg** (maximum 500 ml) if no cardiac signs - reassess and continue if necessary.
- Set up an infusion without waiting for the test results in order to ensure a **continuous glucose supply**: Give Infusion based on **10% glucose** + NaCl 6g/L (100 meq/L) WITHOUT POTASSIUM until rhabdomyolysis has been excluded.
- IV lipids are contraindicated

Age	0-3 months	3-24 months	2- 4 years	4-14 years	>14 years - adult	**MAX FLOW RATE**
Infusion flow rate	7ml/kg/h (12mg/kg/min)	6ml/kg/h (10mg/kg/min)	5ml/kg/h (8mg/kg/min)	3.5ml/kg/h (6mg/kg/min)	2.5ml/kg/h (4mg/kg/min)	**120ml/h (3L/24h)**

If unable to infuse the patient *=> Nasogastric tube: prepare the IV fluids listed above and pass them through the tube at the same rate in each branch of the Y-Set*

- If there are no gastrointestinal disorders and if the preparation is available: instead of infusion, **emergency diet** by **continuous** enteral feeding using nasogastric tube or gastrostomy (preparation known to the parents from the diet sheet)
- In the absence of rhabdomyolysis (if CPK < 1000) and renal failure: put potassium back into the infusion, following standard intake amounts (e.g.: Polyionic, Bionolyte, B45, Glucidion…)
- **L-carnitine (LEVOCARNIL)**: continue oral carnitine. If oral administration not possible, give the patient's usual doses as continuous IV infusion. Stop if cardiac rhythm disorder
- Continue the other usual treatments (riboflavin, ketone bodies, etc.) if available and if oral administration is possible. If special oil (MCT, triheptanoin, etc.), give it orally when the patient is able to eat, even if receiving glucose infusion.
- Specific treatment for potential intercurrent infection
- If **NH3 > 150µM** (children) **or >100µM** (adults): do a check, and without waiting for the result, start **Sodium Benzoate** continuous IV infusion (or orally / by NG tube if oral route not available): loading dose of 250 mg/kg over 2 hours (Max. 8g) then 250 mg/kg/24h (Max. 12g/24h).

3 SEVERITY SIGNS = Consult / transfer to Intensive Care

- **Neurological disorders, exhaustion, coma** or **severe hyperammonaemia:** Newborn >200 µmol/L – Child & Adult >150 µmol/L
- **Cardiac rhythm disorder:** stop the levocarnil
- **ECG signs** of hyperkalemia, **hyperkalemia > 7 mmol/L:** stop the potassium, give potassium-lowering treatments
- **CPK > 15 000 IU/L:** review hydration, 3L/m²/day if no cardiac failure, see rhabdomyolysis protocol
- **Haemodynamic insufficiency and/or renal failure**
- **Severe hepatic insufficiency:** Prothrombin ratio < 50%, factor V < **30%**
- **In all cases, take care to maintain glucose intake**

4 MONITORING

- **Scope, ECG** - Echocardiogram if signs indicative of cardiac failure
- **Capillary blood glucose every 4 h:** target 1 to 1.8g/L. If blood glucose >2g/L and glyosuria, consider insulin 0.01IU/kg/h with subsequent dose adjustment every hour. Consider reducing sugar intake (20 - 25%) if hyperglycaemia despite insulin therapy at 0.05 IU/kg/h
- **Laboratory workup** to monitor CPK, electrolytes, NH3, PT, liver function:
  - if initial tests normal and clinically stable. Follow-up tests between 12 hours and 24 hours
  - in all other situations: close monitoring and reassessment of fluid and electrolyte intake.

PATHOPHYSIOLOGY

Fatty acid oxidation (FAO) is a major route of energy production by the body, particularly when fasting and in inflammatory states, in the heart, muscles and liver.

Long-term treatment of FAO disorders is based on:

- A LOW-FAT diet, enriched in glucose (except for MCAD deficiency)
- MCT and/or triheptanoin oil (except for MCAD and AG2 deficiencies)
- Limiting fasting times. The fasting time has been determined by the specialist service; it is assessed regularly as a function of the age and individual tolerance of the child (nightly CEF for infants, uncooked corn starch at bedtime for children)
- Carnitine supplementation (LEVOCARNIL 10- 50 mg/kg/day divided into 2 to 4 oral doses, and up to 200-600mg/kg/day for translocase deficiencies.
- +/- Supplementation with synthetic ketone bodies (3-OH- BUTYRATE).
- Riboflavin supplementation (MADD) 100 à 200 mg/j

ASSISTANCE WITH PRACTICAL ADMINISTRATION OF TREATMENTS:

- LEVOCARNIL IV (amp. 1g = 5ml), given neat or diluted in normal saline, using a Y infusion set
- LEVOCARNIL orally (amp. 1g = 10ml), divided into 3 to 4 oral doses/day
- SODIUM BENZOATE IV (amp. 1g = 10ml), for dilution 1:1 by volume with 10% glucose. Warning: contains 7 meq of sodium per gram of benzoate.

CIRCUMSTANCES IN WHICH THERE IS A RISK OF DECOMPENSATION

- Prolonged fasting, intercurrent infection, fever, anorexia, vomiting, surgery, dehydration, **or any fasting state, weight loss or catabolic state.** Rarely strenuous exercise.
- **In all these cases, the patient will be kept in hospital. They represent an emergency:** do the workup on the patient in A&E before admitting him/her to hospital. **ACT QUICKLY** to prevent severe hypoglycaemia or cardiac damage.

CLINICAL AND BIOLOGICAL SIGNS OF DECOMPENSATION: Do not wait for these signs!

- Hypoglycaemia without ketosis, liver failure, hyperammonaemia
- **Gastrointestinal disorders, vomiting**
- Impaired consciousness, exhaustion, coma
- Cardiac rhythm disorders, haemodynamic disorders
- Rhabdomyolysis, muscular pain

DRUG CONTRAINDICATIONS / GENERAL ADVICE:

Prohibited: acetylsalicylic acid (aspirin), valproic acid (Depakin®, etc.), Corticosteroid therapy: weigh up the need if duration > 3 days. No bar to using hydrocortisone hemisuccinate if necessary in intensive care.

- All vaccinations are recommended (particularly influenza).
- **Prolonged fasting is contraindicated, never leave the patient without a supply of carbohydrate (infusion or continuous enteral feeding)**
- Do not forget vitamins and trace elements when intake is exclusively parenteral.
- **In case of admission to hospital** (or attendance at A&E): patients must take with them their usual treatments and the special products that they have in order to prepare an emergency diet.
- The emergency treatment will be reassessed with the metabolic medicine specialist during the day.

SURGERY under General Anaesthesia:

WARNING: never leave the patient fasting without an infusion. Implement the emergency protocol with infusion as above in preparation for surgery, and continue until appropriate nutrition has been resumed (consult with referring service)

- Continuous infusions of propofol and etomidate are to be avoided because they come in the form of a lipid emulsion (but can be used as a single injection for induction); anaesthetic gases can be used.

REFERENCE DOCTORS AND CONTACT DETAILS

On-call telephone numbers for metabolic emergencies of:

At night, only the medical teams can call in emergency situations and only if the emergency certificate has not been understood or if the clinical state or test results are worrying. As far as possible make calls before night time.

Secretarial issues must be dealt with via the medical secretariat during the week or by email addressed to the patient's referring metabolic doctor.

Certificate issued on Dr