

SEVERE RHABDOMYOLYSIS AND MALIGNANT HYPERTHERMIA (mutations in *RYR1* and related genes)

PRIORITY PATIENT: MUST NOT BE KEPT WAITING IN THE EMERGENCY DEPARTMENT

In the event of fever, vomiting, diarrhoea, muscle pain or anaesthesia:
Risk of acute rhabdomyolysis and/or malignant hyperthermia

Label

1 EMERGENCY

Phone call only if the emergency certificate is not understood.

CPK, blood glucose, serum electrolytes, potassium, calcium, phosphate, urea, creatinine, blood gases, lactate, AST, ALT, GGT, PT – factor V. ECG on admission. Note the colour of the urine (myoglobinuria). Further tests depending on the intercurrent illness triggering the episode.

2 START TREATMENT URGENTLY, without waiting for test results:

A- Treatment in all cases

- If there are signs of hypoperfusion, rehydrate with Ringer's lactate or 0.9% NaCl at 10 mL/kg (maximum 500 mL) in the absence of cardiac signs; reassess and repeat if needed.
- IV hydration for at least 6–12 h, even if CPK is initially normal.
 - 10% glucose solution + NaCl 6 g/L WITHOUT POTASSIUM. Intake 2L/m²/day (maximum flow rate 150 ml/hr). Do not use ready-made potassium-containing solutions (balanced electrolyte solutions such as Glucidion, Bionolyte etc.) [BSA = (4W+7)/(W+90)]
 - If infusion is not possible and clinical condition is reassuring : wait for CPK results. If CPK > 6,000 U/L: insert an NG tube for hydration (administer the above solution for infusion at the same rate). If CPK < 6,000 U/L: check again at H4.
- Start specific treatment for any intercurrent infection

B- Adjustment according to CPK

- If CPK remains stable at < 6,000 U/L at H0 and H4 and potassium is normal: an infusion with 10% glucose solution and balanced electrolytes is possible (reintroduce K⁺), to be maintained for a minimum of 12 h according to CPK kinetics.
- If CPK 6,000–20,000 U/L: continue hydration as above, 2 L/m²/day but WITHOUT POTASSIUM
- If CPK > 20,000 U/L or immediately if myoglobinuria is present: arrange transfer to HDU/ICU and start aggressive IV hydration as soon as possible with approval from the ICU physician:
 - Volume 3L/m²/day
 - Preparation for 1 L solution: 200 mL/kg 30% glucose solution + 400 mL bicarbonate 14% + 400 mL NaCl 0.9% No potassium or calcium
- If CPK > 100,000 IU/L, discuss Dantrolene (*RYR1* antagonist, indicated for malignant hyperthermia)
 - PO: 25–50 mg/day
 - or injectable: caution (muscle relaxant and respiratory depressant effect)
 - See SFAR recommendations for IV form: <http://sfar.org/recommandations-dexperts-pour-le-risque-dhyperthermie-maligne-en-anesthesie-reanimation/>

3 SIGNS OF SERIOUS ILLNESS = Specialist opinion/transfer to intensive care

- CPK > 20,000 IU/L (after starting the above infusion)
 - Consider renal replacement therapy if serum potassium > 5 mmol/L despite aggressive IV hydration, any ECG abnormality, anuria/oliguria and positive fluid balances contraindicating continued aggressive IV hydration; renal impairment (creatinine results do not reflect the severity of the kidney impairment, as it is released by muscle breakdown; urea is more reliable)
 - ICU monitoring: capillary blood glucose, sodium, potassium every 2 hours for the first 24 hours, complete electrolyte panel with Ca, phosphate, Mg, urea, creatinine, CPK every 6 hours. Hourly monitoring of urine output > 2ml/kg/h, urine pH and urine specific gravity < 1005. Fluid balance assessment every 3 hours to adjust aggressive IV hydration. ECG in place, hourly trace. Monitor cardiac function (clinical and echocardiographic).
 - Arrhythmia, ECG signs of hyperkalaemia, serum potassium > 7 mmol/L
- Oliguria / anuria, port wine-coloured urine, kidney failure
- Neurological disorders, prostration (risk of hyperosmolar coma)

4 MONITORING (except for severe rhabdomyolysis > 20,000 U/L in ICU)

Temperature (risk of malignant hyperthermia)

- CPK, serum electrolytes, calcium, phosphate, diuresis and urine colour every 4 h. Adjust potassium supplementation according to serum potassium levels and renal function (if not included in the infusion there is also a risk of hypokalaemia).
- Vital signs monitor, ECG every 4 hours if CPK > 6,000 U/L
- If CPK is normal, keep the patient hospitalised for at least 12 h to ensure there is no secondary rise in CPK



SEVERE RHABDOMYOLYSIS AND MALIGNANT HYPERTHERMIA

PHYSIOPATHOLOGY:

Mutations in the *RYR1* gene (which encodes the skeletal muscle calcium channel) and other related genes are responsible for acute rhabdomyolysis and malignant hyperthermia, **particularly during anaesthesia**, but also in situations of stress or catabolic states (fever, fasting, diarrhoea, vomiting, prolonged exertion). **These patients require strict and urgent care in risky situations.**

SITUATIONS WITH RISK OF DECOMPENSATION:

- **Surgery/Anaesthesia**
- Intercurrent infectious disease, fever, anorexia, vomiting or **any fasting or catabolic state** .
- Unusual physical exertion

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

- Muscle pain (may precede elevation of CPK level)
- Inability to walk, prostration
- Arrhythmias, heart failure
- Impaired consciousness
- Hypovolaemic shock
- Myoglobinuria (sign of severe rhabdomyolysis)

DRUG CONTRAINDICATIONS/GENERAL ADVICE:

- Treatments contraindicated during the acute phase of rhabdomyolysis: NSAIDs, all drugs which raise serum potassium
- Statins (increased risk of rhabdomyolysis)
- Some anaesthetic agents: see below

- All vaccinations are recommended (especially influenza).

IF UNDERGOING GENERAL ANAESTHESIA: RISK OF MALIGNANT HYPERTHERMIA

- **Contraindicated anaesthetic agents: Halogenated agents (myocardial depression), depolarising neuromuscular blocking drugs (succinylcholine, induces muscle contraction), prolonged administration of Propofol**
- ***RYR1* mutation = risk of malignant hyperthermia**

- Monitor capnography and core temperature
- Obtain the protocol for injectable Dantrolene (*RYR1* antagonist, see SFAR recommendation)

<http://sfar.org/recommandations-dexperts-pour-le-risque-dhyperthermie-maligne-en-anesthesie-reanimation/>

- Prepare IV Dantrolene
- Monitor CPK before and after surgery

Refer to the **Emergency**
section on the G2M website.

REFERRING PHYSICIANS AND NUMBERS:

At night, only medical teams may call in emergencies and only if the emergency certificate is not understood or if the clinical condition or test results are concerning. Whenever possible, calls should be made before nightfall.

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

Certificate issued on

Dr

