

TANGO 2 deficiency disorder

Priority patient: must not be kept waiting in the emergency department

Label

In the event of vomiting, diarrhoea, fever or fasting:

Risk of cardiac arrhythmia, heart failure, rhabdomyolysis, hypoglycaemia, neurological regression

Do not wait for signs of decompensation; always initiate the following management protocol

1 EMERGENCY ASSESSMENT

Complete electrolyte panel with **potassium, magnesium, CPK**, blood gases, lactate, liver function tests, PT, factor V, **capillary blood glucose, venous blood glucose**, NH_3 , lipase, amylase, TSH + tests depending on context and triggering intercurrent disease. Treatment must not be delayed.

SYSTEMATIC ECG, BNP, troponin $\pm$ cardiac ultrasound depending on clinical presentation (look for long QT > 500 msec or Brugada pattern in leads V1, V2 or other arrhythmias).

2 START TREATMENT URGENTLY, without waiting for test results

• If **hypoglycaemia < 60 mg/dL (3.3 mmol/L)**: Administer glucose 1ml/kg of G30% (max 30 mL) orally or enterally if conscious, or 3ml/kg G10% IV if unconscious (G30% also possible by IV).

• **Systematic infusion if food intolerance or hypoglycaemia**: Infusion of 10% glucose solution with standard electrolyte supplementation* (not 10% glucose alone). /!\ **Volumes to be adjusted according to hydration status and cardiac function**

Age	0 - 24 months	2 - 4 years	4 - 14 years	> 14 years/adult	MAX. FLOW RATE
Balanced electrolyte solution 10% glucose	5 mL/kg/h (8 mg/kg/min)	4 mL/kg/h (7mg/kg/min)	3.5 mL/kg/h (6 mg/kg/min)	2.5 mL/kg/h (4 mg/kg/min)	<u>120 mL/h</u> (3L/24h)

*e.g.: balanced electrolyte solution such as Bionolyte, B45, Glucidion, etc. if unavailable: 10% glucose solution + 4–6 g/L NaCl (70–100 mEq/L) and 2 g/L KCl (27 mEq/L)

If IV infusion is not possible => Nasogastric tube or gastrostomy: prepare the above IV solutions and administer via the tube at the same rates.

• **Magnesium** supplementation if arrhythmia is present, without waiting for serum magnesium result

• **Do not** infuse lipids. No carnitine

• **Continue** usual oral or IV medication (including any treatment for hypothyroidism and vitamin therapy)

• Specific treatment for any intercurrent infection Specific treatment for hyper NH_3 (see hyperammonaemia protocol)

• If severe acute rhabdomyolysis (CPK > 10,000 IU/L or immediately if myoglobinuria/muscle pain): **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)]. See rhabdomyolysis protocol for adjustment. Adjust K+.

If arrhythmia: consult cardiology. See drug contraindications overleaf

• These patients are at risk of **long QT syndrome (> 500 msec)** and **Brugada syndrome**

• **CORDARONE and SOTALOL ARE CONTRAINDICATED** (they prolong the QT interval and increase risk of ventricular arrhythmia). Verapamil: no proven efficacy in arrhythmias in patients with long QT syndrome or Brugada syndrome.

• In the acute phase of arrhythmias (torsades de pointes in long QT syndrome, electrical storm in Brugada syndrome): **ISUPREL** (isoproterenol) continuous IV infusion through syringe driver is effective acutely in both long QT syndrome and Brugada syndrome (also used in AV block).

• **Magnesium** supplementation

• If persistent: **electrical cardioversion and consider ECMO**. Transfer to the ICU in a hospital with cardiology and arrhythmology expertise.

• If long QT syndrome: propose **beta-blockers, except Sotalol** (Nadolol preferred if no left ventricular dysfunction, otherwise Bisoprolol). To be introduced in all cases of long QT syndrome on ECG or Holter ECG, to prevent or avoid recurrence of ventricular arrhythmias (no problem if Brugada syndrome is also present).

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

• **Coma or deterioration** of neurological status

• **QTc > 500 msec or arrhythmias**: IV magnesium. Transfer to a hospital with ECMO facilities. See above.

• **Arrhythmia**: Brugada syndrome type I, ventricular extrasystoles (treatment with Isuprel [Isoproterenol]). See above.

• **Heart failure**

• **Rhabdomyolysis**: CPK > 10,000 IU/L; NH_3 > 150 $\mu\text{mol/L}$ (see urea cycle disorder protocol for ammonia scavengers).

4 MONITORING while being treated

• Vital signs monitor

• ECG at least daily. Monitor cardiac function (clinical and echocardiographic).

• Laboratory tests: according to initial results. Check at least every 24 hours: serum electrolytes, CPK, K+ (especially

if infusion without K), liver function (signs may be secondary).

PATHOPHYSIOLOGY:

Patients with *TANGO2* gene mutations present chronic manifestations: neurological impairment (psychomotor delay, dystonia, cerebellar syndrome, epilepsy, deafness...), hypothyroidism, sometimes long QT syndrome, etc. and are at risk of “metabolic crises” with **decompensation during fasting, infections and possibly lipid overload, mimicking a generalised fatty acid oxidation disorder**. They therefore require strict and urgent management with glucose infusion in all situations with a risk of catabolism (fever, gastroenteritis, fasting). Vitamins B5 and B9 (5 mg of each) are now recommended in these patients.

SITUATIONS WITH RISK OF DECOMPENSATION:

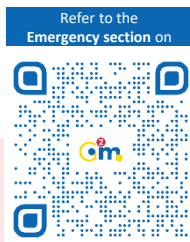
- Intercurrent infection, fever, anorexia, vomiting, surgery **or any state of fasting, calorie deficiency, weight loss or catabolism**.
- **Lipid overload, possibly carnitine administration.**
- **QT-prolonging agents, certain anaesthetics.**
- **In all these situations, the patient must be hospitalised. This is an emergency:** stabilise the patient in the ED before transfer to hospital, and apply the protocol on the previous page.

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

- Acute neurological deterioration, ataxia, impaired consciousness, coma
- **Arrhythmias: Life-threatening arrhythmias** specific to this disorder, combining **Brugada syndrome** and **long QT syndrome** (may occur even without decompensation)
- **Cardiomyopathy:** Note that **cardiac signs may occur later** than metabolic decompensation.
- Severe acute rhabdomyolysis
- Lactic acidosis, hyperammonaemia
- Severe hypoglycaemia with prolonged fasting, Reye syndrome
- Rare cases of pancreatitis and adrenal insufficiency

DRUG CONTRAINDICATIONS / GENERAL ADVICE:**Prohibited medications:**

- salicylic acid, valproic acid
- glucagon in hypoglycaemia (ineffective in prolonged fasting hypoglycaemia and delays treatment)
- any lipid-based medication administered for a prolonged period (Propofol, Medialipids, Intralipids, etc.)
- Levocarnil (L-carnitine)
- QT-prolonging agents - **check QTc before prescribing any drug that may interfere with it** - list available on the website, (regularly updated, account required):
<https://clicktime.symantec.com/3ATrKXhQ5VosjsWtJh372ni6H2?u=https%3A%2F%2Fcrediblemeds.org%2Findex.php%2Fdrugsearch>. E.g. certain antiarrhythmics (**Amiodarone, Procainamide, Sotalol, Quinidine, etc.**), Phenothiazines (Tercian, Largactil), Erythromycin, IV Lidocaine, Ondansetron, Droperidol, Haloperidol, Atropine, Hydroxyzine (Atarax)
- Drugs contraindicated in Brugada syndrome: list available at <https://www.brugadadrugs.org>
- certain anaesthetics (see below)



- **Prolonged fasting contraindicated: never leave the patient without carbohydrate intake for prolonged periods** (infusion or continuous enteral tube feeding).
- All vaccinations are recommended (particularly influenza).

SURGERY/ANAESTHESIA:

- **CAUTION: Never leave the patient fasting without glucose intake** (see infusion protocol above). Maintain usual treatments, including vitamins B5 and B9.
- If possible, schedule surgery in a hospital with cardiology and arrhythmology expertise, and ICU facilities. Check for long QT syndrome and monitor cardiac function.
- **ABSOLUTE CONTRAINDICATIONS:** succinylcholine (depolarising neuromuscular blocker: promotes muscle contraction and therefore rhabdomyolysis and hyperkalaemia); prolonged Propofol infusion (lipid overload). Sevoflurane and other halogenated agents (myocardial depressants)
- **For induction:** prefer **Ketamine and opioids +/- non-depolarising neuromuscular blockers** (e.g. Rocuronium).
- **For maintenance:** prefer **opioids and benzodiazepines**. Prolonged administration of Propofol is CONTRAINDICATED. If neuromuscular blockade with non-depolarising agents: Enhanced monitoring before extubation (TOF).
- As in *RYR1* deficiencies, ensure Dantrolene is available in the operating theatre (IV calcium antagonist, used for rhabdomyolysis due to calcium release). See SFAR recommendations:
<http://sfar.org/recommandations-dexperts-pour-le-risque-dhyperthermie-maligne-en-anesthesie-reanimation/>

NUMBERS AND MEDICAL SPECIALISTS

On-call telephone numbers for metabolic emergencies:

At night, only 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. 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