EMERGENCY CERTIFICATES - G2M NETWORK

V2 – Nov 2024

Patient with PMM2-CDG (formerly CDG-IA)

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

Risk of thrombosis including cerebral thrombosis/haemorrhage/stroke-like event/epilepsy

Label

Patient monitored for PMM2-CDG _____ Routine haemostasis assessment: AT: %, Factor XI: %

1 IN THE PRESENCE OF ACUTE/UNUSUAL

Phone call only if the emergency certificate is not understood.

- Patients at risk of stroke-like events, stroke (ischaemic or haemorrhagic), seizures, migraine (usually secondary to fever or head tra
- **Laboratory tests:** CBC, **PT, aPTT, antithrombin, factor XI,**
- if possible: Protein C, protein S, fibrinogen, II, V, VII, VIII, IX, X. Liver function tests + assessment depending on intercurrent infection.

Note: the haemostasis workup must be compared with the patient's usual results (see above)

- **Brain MRI: diffusion, T1, T2, FLAIR** and **ASL perfusion** sequences to check for **stroke-like event, thrombosis** and/or **cerebral haemorrhage**, or another differential diagnosis (including **migraine)**
- EEG: to check for **status epilepticus** (differential diagnosis)

2 SPECIFIC MANAGEMENT OF ACUTE INCIDENTS

A. In the event of a thrombotic event

- Anticoagulation with **LMWH** or **UFH** according to current recommendations.
- **Monitoring of anti-Xa is essential** due to possible antithrombin deficiency (target 0.5–1 IU/mL for LMWH or 0.3–0.7 for UFH, 4 hours after the third SC injection in children). If the anti-Xa target is difficult to achieve: discuss administration of **human antithrombin (Aclotine®)** (target after infusion: AT at basal rate).
- If AT < 70% and reduced by 20% of basal rate: balancing anticoagulation may prove challenging. Administer **human antithrombin (Aclotine®)** (target after infusion: AT at the patient's basal rate, check 12–24 hours after administration). Do not wait for this result or for the infusion before starting anticoagulation as this is urgent.
- Switch to VKA or DOAC may be considered after assessment of the patient's bleeding risk.
- If there is a risk of bleeding under anticoagulation: there is no contraindication to FFP if all factors are low.

B. In the event of a stroke-like event: (MRI diagnosis with T2/FLAIR, diffusion and ASL perfusion sequences)

- **FFP if haemostasis is impaired** (decrease of more than 20% of patient's basal rate and AT < 70% and/or FXI < 40%).
- **Avoid Aclotine®** alone (human antithrombin) because of the risk of haemostatic imbalance
- **Corticosteroid therapy**: if impaired consciousness/headache, consider methylprednisolone PO or IV 2 mg/kg/day for 3 to 5 days to reduce vasogenic oedema and ICH.

C. In the event of haemorrhage

Administer **FFP.** If bleeding is uncontrolled despite FFP, human prothrombin complex concentrate (PCC) may be considered only after checking haemostasis factors, and only with products containing protein C and protein S such as Confidex® or Octaplex®. Objectives after infusion: return to the patient's basal rates and consult a clinical haemostasis team.

CAUTION: in all cases the administration of Hemoleven® (FXI concentrate) or Novoseven® is contraindicated due to the thrombotic risk associated with these products.

D. In the event of seizures or status epilepticus

Standard management according to local protocol

E. In the event of migraine:

Symptomatic treatment: **Paracetamol**. Consider **NSAIDs if there is no portal hypertension.** Consider maintenance treatment.

F. In the event of disseminated intravascular coagulation (DIC)

- Administer FFP
- Human antithrombin (Aclotine®) may be considered as clinically indicated and if ATIII is 20% below basal rate

3 IF PRESENTING TO THE ED FOR ANOTHER REASON

- **In the event of head trauma or fever:** Risk of neurological event, which may occur at a later stage. **Clinical monitoring and antipyretic treatment are essential**, on an outpatient or inpatient basis depending on the context.
- **If repeated vomiting: Do not hesitate to give an IV infusion** to maintain normal hydration (risk of thrombosis if dehydration occurs). Usual solutions: no specific infusion, glucose if history of hypoglycaemia.

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PMM2-CDG (formerly CDG-Ia)

PHYSIOPATHOLOGY:

Patients with PMM2-CDG have coagulation disorders that mainly expose them to thrombotic risk, but sometimes also bleeding risk.
Several coagulation proteins (both pro- and anti-coagulant factors) may be reduced, particularly antithrombin and factor XI, but also protein C, protein S and factor IX.
There is also chronic neurological involvement (delay, cerebellar syndrome), and acute neurological risks (particularly stroke-like events, epilepsy and migraine).
Hepatic involvement with moderate elevation of transaminases is possible, but should not raise concerns about hepatic failure or Reye's syndrome (which are rare).

DRUG CONTRAINDICATIONS/GENERAL ADVICE:

Drug contraindications: Oestrogens, Hemoleven® (Factor XI concentrate) or Novoseven® due to risk of thrombosis. In cases of portal hypertension: avoid salicylates and NSAIDs.

All vaccinations are recommended (particularly influenza).

IF SURGERY IS REQUIRED: potential bleeding risk and thrombotic risk:

- **No contraindications to anaesthetics**
- To be performed during the pre-anaesthesia consultation: CBC, PT (if PT < 70% or INR > 1.2, add FII, V, VII, X), aPTT, factors VIII, IX, XI (even if aPTT is normal), AT
- Prophylactic administration of FFP immediately pre-operatively +/- Aclotine® depending on coagulation factor deficiencies, the bleeding risk of the procedure and the post-operative thrombotic risk.
- **Post-operatively:** In the event of post-operative bleeding complications: further FFP transfusion. Prophylaxis with LMWH may be discussed on a case-by-case basis once haemostasis has stabilised, after assessing the bleeding/thrombotic risk ratio inherent to the patient and to the surgical procedure. In the event of prolonged immobilisation: compression stockings, aggressive IV hydration and preventive anticoagulation.

PREVENTION OF THROMBOTIC RISK IN HIGH-RISK SITUATIONS (bed rest, plaster cast, long journeys, etc.):

- Prepubescent children: compression stockings, aggressive IV hydration; consider preventive anticoagulation on a case-by-case basis by assessing the bleeding/thrombotic risk ratio (particularly in patients with a history of thrombosis or antithrombin deficiency). Oral oestrogens are contraindicated.
- In pubescent children and adults: follow the above instructions and give preventive anticoagulation readily
- If LMWH started: **Monitoring of anti-Xa is essential** due to potential antithrombin deficiency (target 0.2–0.4 IU/mL 4 hours after the third SC injection in children). If the anti-Xa target is difficult to achieve: discuss administration of Aclotine® (target after infusion: AT at the patient's basal rate, check 12–24 hours after administration)

IN CASE OF FEVER:

Always give antipyretics and look for a treatable infection, as fever or infections promote acute neurological episodes.

GUIDANCE ON PRACTICAL ADMINISTRATION OF TREATMENTS

FFP: 10–20 mL/kg by slow IV infusion
Human antithrombin (Aclotine ®): 50 IU/kg/24h or 48h, by slow IV bolus injection over 30 mins to 1 hour
PCC: 30 IU/kg by direct IV injection
LMWH: standard doses depending on the situation: 100 IU/kg/day SC to prevent thrombotic risk or 100 IU/kg/12h for curative treatment
Corticosteroid therapy Methylprednisolone PO or IV, 2 mg/kg in a single dose (max 60 mg)
Management of status epilepticus according to local protocol

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

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.
Administrative questions should be addressed to the medical secretariat during the week or by email to the patient's referring metabolic specialist. Certificate issued on Dr