Patient with CDG syndrome 1b (MPI-CDG)

Label

Patients with MPI-CDG or CDG 1b are treated with MANNOSE taken orally.

If attending A&E for any reason (e.g. fever) they should be treated in the same way as any other patient. The mannose should never be stopped. This treatment cannot be administered by IV. However, it is important to be aware of certain symptoms that occur if treatment is not complied with, and to counter the risk of thrombosis in at-risk situations.

- **If treatment with mannose is not being administered (and more rarely in case of fever, surgery or prolonged immobility),** they may present with:

- **Coagulation disorders** which mainly carry a **risk of thrombosis** (arterial or venous in any vascular site) but also sometimes a risk of bleeding. Several coagulation proteins (both pro- and anti-coagulant factors) may be reduced, particularly ATIII and factor XI, or proteins C or S.
- Gastrointestinal disorders (vomiting, diarrhoea, abdominal pain with potentially an increased risk of bacterial translocation)
- Liver damage (hepatocellular injury, liver failure, **hepatic fibrosis**). **Hepatic fibrosis progresses even on mannose treatment, with a risk of developing portal hypertension (PH).**
- Hypoglycaemia (usually with hyperinsulinaemia).

1 SPECIFIC MANAGEMENT OF ACUTE INCIDENTS

A. If there is thrombosis

- Anticoagulant treatment with **LMWH or UFH**, depending on current recommendations. The target level of anti-Xa is classically 0.5-1 iu/ml. **Monitoring of anti-Xa is essential** because of potential antithrombin deficiency.
- **If ATIII <70% and reduced by 20% of the baseline level**: it may be difficult to balance anticoagulant therapy. Administration of **human antithrombin (Aclotine ®)** (following infusion, the aim is: ATIII at baseline level for patient, check 12-24 hrs after administration). Do not wait for this result or the infusion before starting anticoagulation, which is urgent!
- A switch to anti-vitamin K is possible after assessing patient's bleeding risk.
- If there is risk of bleeding under anticoagulation treatment (in presence of PH): no contraindication to use of FFP if all the factors are low.

B. If there is gastrointestinal bleeding

Classic management. FBC-platelets and coagulation tests. Transfusion of red blood cells and FFP if necessary. Endoscopic or drug treatment of oesophageal varices (specialist opinion). Radiological or surgical treatment of PH (specialist opinion).

WARNING: in all cases, administration of Hemoleven® (factor XI concentrate) or Novoseven® is contraindicated, due to the risk of thrombosis that is associated with this product.

C. If there is protein-losing enteropathy

- **20% albumin infusion if hypoalbuminaemia < 25g/L (increased risk of thrombosis).**
- **If repeated vomiting: Do not hesitate to give infusion** to maintain normal hydration (risk of thrombosis if dehydrated) and normal blood glucose (risk of hypoglycaemia). Standard solutions: no specific infusion (but increase glucose supply if history of hypoglycaemia).
- Discuss (during working hours - non-urgent): administration of immunoglobulins IV or SC, if hypogammaglobulinaemia.

D. If there is hypoglycaemia

Replenish glucose orally or enterally (NG tube): G30% 1ml/kg, max. 30mL or 1 sugar / 20kg body weight. If enteral route impossible: G10% (10% glucose) 3mL/kg by direct IV injection, then infusion of G10% + usual electrolytes. See suggested glucose intake rates at the back of this protocol

PATHOPHYSIOLOGY:

Patients with MPI-CDG or CDG-1b present with gastrointestinal disorders (protein-losing enteropathy), hepatic disorders, hypoglycaemia, and coagulation abnormalities which carry a risk, mainly of thrombosis, as well as sometimes bleeding. This disease is treatable with mannose, given orally, for life. Hepatic fibrosis alone progresses despite mannose treatment. Mannose has a short half-life, hence it is taken 3 to 5 times per day.

DRUG CONTRAINDICATIONS / GENERAL ADVICE:

Drug contraindications Oestrogens, Hemoleven® (Factor XI concentrate) or Novoseven® due to risk of thrombosis. Given that there is liver damage with PH, it is recommended to abstain from alcohol and avoid prescribing drugs which carry a risk of bleeding (acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs).

All vaccinations are recommended (particularly influenza).

IN CASE OF SURGERY:

- Anaesthetics not contraindicated

- The following tests are to be ordered at the anaesthetic consultation: FBC, PT (if PT<70% or INR>1.2, add Factors II, V, VII, X), aPTT, Factors VIII, IX, XI (even if aPTT normal), ATIII.

-Mannose treatment must not be stopped (or for no more than the shortest possible time) due to the risk of hypoglycaemia and thrombosis. Set up a continuous glucose infusion to maintain blood glucose above 4 mmol/L.

-There is an increased risk of peri-operative thrombosis. An infusion of fresh frozen plasma or antithrombin (Aclotine) may be indicated. In the post-operative period: prophylaxis with LMWH should be considered on a case-by-case basis once the coagulation parameters have stabilised, and after assessing the relative risk of bleeding versus thrombosis relating to the individual patient and the surgical procedure.

COUNTERING THE RISK OF THROMBOSIS IN AN AT-RISK SITUATION (bed rest, in plaster etc.)

- Pre-adolescent child: **To be considered on a case-by-case basis,** assessing the relative risk of thrombosis versus bleeding.
- For other patients: routine prophylactic anticoagulation following the recommendations, particularly since there may be antithrombin deficiency.
- If LMWH started: **Monitoring of anti-Xa essential** given the potential antithrombin deficiency (target in children: 0.1-0.3 IU/ml 4 hrs after the 3rd SC injection). If difficulty in achieving the anti-Xa target: consider administering Aclotine (target after infusion: ATIII at baseline level for patient, check 12-24 hrs after administration).

IF PATIENT IS PREGNANT

Specific monitoring:

- Stop mannose (teratogenic).
- Assess the risk of hypoglycaemia (particularly if there is nausea and vomiting).
- Assess the risk of thrombosis as this increases during pregnancy and post-partum, and when treatment is stopped.
- The risk of bleeding due to PH at the time of delivery needs to be considered

Look up the emergency

PRACTICAL GUIDE FOR ADMINISTERING TREATMENT

- Mannose: 150–170 mg/kg/dose 3 to 5 times per day. Extemporaneous preparation
- FFP: transfusion 10-20ml/kg
- Human antithrombin (Aclotine): 50 IU/kg/24 hrs or 48h, by slow IV over 30 mins to 1 hour
- PPSB: 30 IU/kg by direct IV injection
- LMWH: standard dosages depending on the situation: 50IU/kg/12hrs as prophylaxis against the risk of thrombosis or 100 IU/kg/12 hrs for treatment.
- Glucose infusion: G10% with electrolytes

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

NUMBERS AND MEDICAL SPECIALISTS

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. As far as possible, make calls before nighttime.

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

Measurement of plasma mannose as part of the investigation:

- While the patient is fasting, and before administering the oral mannose, take a sample in a grey tube = T0
- Then, take a sample using a grey tube at T + 1 hour after taking the mannose = T + 1
- Then, take another sample using a grey tube at T + 2 hours = T + 2

After taking a sample, centrifuge the tube, decant the plasma and freeze it. Make sure that the sampling time is clearly indicated on each tube. As far as possible, avoid sending tubes at the end of the week.

Send the 3 tubes of decanted plasma in dry ice to the following address:

Dr Dupré / Dr Bruneel / Dr Vuillaumier-Barrot
Hôpital Bichat
Biochemistry Department (CDG section)
La Tour, 3rd floor
46 rue Henri Huchard
75018 Paris

Please advise by email

arnaud.bruneel@aphp.fr
thierry.dupre@aphp.fr
sandrine.vuillaumier@aphp.fr