:: Type 1 autoimmune polyendocrinopathy

- *This document is a translation of the French recommendations drafted by Dr Néraud, Pr Wémeau and Dr Vantyghem, reviewed and published by Orphanet in 2010.*
- *Some of the procedures mentioned, particularly drug treatments, may not be validated in the country where you practice.*

Synonyms:
APECED (Autoimmune PolyEndocrinopathy Candidiasis Ectodermal Dystrophy) syndrome, Whitaker syndrome

Definition:
Type 1 autoimmune polyendocrinopathy is an autosomal recessive genetic autoimmune disease of juvenile onset, combining **chronic mucocutaneous candidiasis** and v**arious autoimmune endocrinopathies**, the most common of which are **hypoparathyroidism** and **adrenal insufficiency**. Other autoimmune disorders are possible, including premature ovarian failure, type 1 diabetes, autoimmune thyroiditis, lymphocytic hypophysitis, intestinal malabsorption, atrophic gastritis, autoimmune hepatitis and pulmonary involvement. Type 1 autoimmune polyendocrinopathy must be differentiated from other autoimmune polyendocrinopathies (particularly type 2, without candidiasis) and IPEX syndrome. **Treatment is designed to compensate for adrenal deficiency** (mineralocorticoids and glucocorticoids) and for parathyroid deficiency by normalising blood calcium levels; **it often includes** prescription of **antifungal agents**.

Further information:
See the Orphanet abstract

Pre-hospital emergency care recommendations
Call for a patient suffering from type 1 autoimmune polyendocrinopathy

Synonyms

- APECED syndrome (Autoimmune PolyEndocrinopathy Candidiasis Ectodermal Dystrophy), Whitaker syndrome

Definition

- autosomal recessive genetic autoimmune disease primarily combining chronic mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency.

Special risks in an emergency

- hypocalcaemia
- acute adrenal insufficiency
- more rarely: diabetic ketoacidosis, fulminant hepatitis, sepsis

Commonly used long-term treatments

- mineralocorticoids and glucocorticoids
- calcium and vitamin D
- sometimes: immunosuppressants

Complications

- consider signs indicative of hypocalcaemia: neuromuscular hyperexcitability, tetany, heart failure (rhythm or conduction problems), convulsion, laryngospasm, bronchospasm
- be alert to the possibility of acute adrenal insufficiency
- consider associated diabetic ketoacidosis

Specific medical care prior to hospitalisation

- continuous ECG monitoring, particularly in cases involving cardiac drugs
- treat hypocalcaemia prior to admission only if it poses a threat (clinical picture/ECG), preferably using calcium gluconate
- treat acute adrenal insufficiency prior to admission, preferably after specimens have been collected
- depending on the clinical condition, admit to the Intensive Care or Resuscitation Unit in the acute phase (always notify the on-call endocrinologist) then to Endocrinology

For further information

- Please visit www.orpha.net and type the name of the disease -> in the summary page click on "Expert centres" on the right tab -> select "United Kingdom" in the "Country" field in the Expert centres page.

Recommendations for hospital emergency departments

Emergency situations

- Severe hypocalcaemia
- Acute adrenocortical failure
- Chronic mucocutaneous candidiasis, often associated with other manifestations
- Sepsis: **manage in the usual manner**
- Diabetic ketoacidosis: **manage in the usual manner**
- Fulminant hepatitis: **manage in the usual manner**

Emergency recommendations

1. Severe hypocalcaemia and/or neuromuscular signs

Severe hypocalcaemia (blood calcium level < 1.8 mmol/L (70 mg/L)) results in neuromuscular hyperexcitability and myocardial abnormalities, the consequences of which can be severe (respiratory or cardiac complications, potentially life-threatening: distal and peribuccal paraesthesia, tetany of the extremities or generalised tetany, sometimes resulting in bronchial, laryngeal or diaphragmatic spasm, occasionally generalised epileptic seizures, QT segment prolongation, acute myocardial failure, excitability or cardiac conduction disorders).

- **Emergency diagnostics**
  - **Assess the severity**:
    - Clinical examination: generalised tetany, convulsions, impaired consciousness, laryngospasm
    - Electrocardiogram (ECG): QT prolongation
    - Laboratory results: total blood calcium < 1.8 mmol/L (70 mg/L) is an indicator of severity
  - **Emergency laboratory tests**:
    - total calcium
    - phosphorus
    - magnesium
    - electrolytes
    - protein or albumin levels
    - renal function
- **Immediate therapeutic measures**
  - **Symptomatic and aetiological treatment:**
    Aim: to eliminate clinical/ECG signs attributable to hypocalcaemia, not to normalise the blood calcium level
    - **Observe using ECG monitor**
    - **Infused patient**
    - **Administration of i.v. calcium**: rapid administration of between 5 and 7.5 mmol elemental calcium (equivalent to approx. 200 to 300 mg). 10 % injectable calcium is available in two forms:
      - **calcium gluconate** [2.3 mmol (= 93 mg) elemental calcium per 10 mL ampoule, the best option in terms of venous tolerability]: administer **2 to 3 ampoules of calcium gluconate diluted in 100 mL 5% dextrose solution as a slow i.v. injection over 10 to 20 mins**.
      - **calcium chloride** [4.5 mmol (= 180 mg) elemental calcium per 10 mL ampoule, also available in a 30 mL ampoule]
    - **If taking** cardiac treatments (**digitalis, quinine,** …), **monitor closely via ECG**

N.B.: i.v. injection of calcium salts must be performed slowly and cautiously. In the event of accidental injection into soft tissue, necrosis may develop, mainly with calcium chloride, for which reason calcium gluconate is preferred.

- **Maintenance therapy:**
  - **Prolonged continuous administration of 1 to 2 mg/kg/h of elemental calcium (6 ampoules of calcium gluconate diluted in 500 mL of 5% dextrose) over 6 to 12 h** repeated until such time as calcium levels have improved (several days' treatment are sometimes required). The total required elemental calcium dose may be as much as 2000 mg in 12 to 24 hours.
  - **Measure calcium levels** every 4 to 6 h, then every 12 to 24 h once a level of 2 mmol/L has been reached
  - **Administration of magnesium**: in the event of severe associated hypomagnesaemia (< 0.7 mmol/L = 14 mg/L), inject 12 to 24 mmol of elemental magnesium (= 300 to 600 mg) over 24 h. Injectable magnesium is available in three forms:
    - **10% magnesium sulphate** which delivers approximately 4 mmol (= 100 mg) of elemental magnesium per 10 mL ampoule
    - 10% magnesium chloride which delivers approximately 5 mmol (= 120 mg) of elemental magnesium per 10 mL ampoule
    - **0.8% magnesium pidolate** which delivers approximately 3 mmol (= 81 mg) of elemental magnesium per 10 mL ampoule

    N.B.: it is better to administer magnesium and calcium in separate infusions
- **Observation during the first 48 hours:**
  - **ECG scope monitoring** whilst blood calcium remains at < 1.8 mmol/L
  - **Blood calcium testing every 6 to 12 h** then every 12 to 24 h once a value of 2 mmol/L has been reached
  - **Monitoring of renal function** every 12 to 24 h
  - **Treatment for hypoparathyroidism must be initiated to avoid recurrence of the hypocalcaemia once the infusion has been stopped**, i.e. switch to oral calcium administration at 1 to 4 g (mean 2 g/24 hrs), combined with a vitamin supplement (oral 1.25 hydroxy-vitamin D, i.m. if there is significant mucocutaneous candidiasis)

2. Acute adrenocortical failure

Emergency diagnostics

- **Blood specimens** to be collected **before** the **infusion** is started:
  - Cortisol
  - ACTH
  - PRA
  - aldosterone

- **Do not wait for results before starting treatment**

Immediate therapeutic measures

- Infuse **100 to 200 mg hydrocortisone hemisuccinate i.v. every 24 h** via a syringe-driver, combined with administration of fluid and electrolytes (1 litre of 5% dextrose + 6 g of sodium chloride every 6 to 12 h for the first 48 hours)
- **calcium gluconate** may be added to this infusion
- **monitor blood sugar levels** in view of the possibility of hydrocortisone-induced decompensation of sub-clinical Type I diabetes

3. Exacerbation of mucocutaneous candidiasis

In certain cases, **mucocutaneous candidiasis impairs drug absorption**.

- **Diagnostics**
  - Perform a thorough **clinical examination** (extremities, buccal cavity, anal-genital region)
  - Collect specimens for **fungal and bacterial investigations**
- **Treatment**
  - **Oral fluconazole** (the i.v. route is used in the absence of response to treatment, following adaptation according to fungal culture and sensitivity results)
  - **Topical treatments** (bicarbonate mouth-wash, buccal or genital antifungal agents)
  - In the event of malabsorption, administer vitamin and diet supplements

Orientation

- Where?
  - **If the patient is already being followed up and if there are no life-threatening factors** (laryngospasm, cardiac arrhythmia, significant drop in blood pressure < 90 mmHg), transfer the patient to the **Endocrinology Department where he/she is normally followed up**, given the specific management required for APECED syndromes, having first alerted the department by telephone.
  - **In a life-threatening situation**, transfer to the **Accident & Emergency Department at the nearest hospital** then refer the patient to the Endocrinology Department.
- When? Depending on the severity of the problems (blood calcium level, ECG abnormalities, epileptic seizures, haemodynamic instability, consciousness disturbances)
- How? Choose the type of transport appropriate to the clinical status

Drug interactions and precautions for use

- **If** taking **cardiac medication** (containing digitalis, quinidine etc.), **carefully monitor the normalisation of calcium levels via electrocardiography**
- **Magnesium loading requires great caution in cases of renal failure**
- A certain number of **antifungal agents** (such as itraconazole) are **cytochrome P450 inhibitors** which may cause an accumulation of drugs that are metabolised via this route, with consequent undesirable effects

Precautions for anaesthesia

- **Hypocalcaemia: check the blood calcium level prior to general anaesthesia** and, if necessary, increase oral calcium and vitamin supplementation before authorising the procedure. In the event of emergency surgery in a patient with hypocalcaemia (< 2 mmol/L), administer i.v. calcium
- **Adrenal insufficiency**: during the peri-operative phase, switch from oral treatment to infusion of 100 to 200 mg hydrocortisone hemisuccinate every 24 h via a syringe-driver, plus infusion of 1 litre of 5% dextrose solution containing 6 g NaCl
- **Candidiasis**: screen for and prevent fungal infections (alkalinisation, topical care, possibly antifungal agents) if antibiotics are prescribed

Preventive measures

- **Make sure that there are no other associated endocrine disorders present** (known or unknown) and that supplements are being administered in respect of all deficient vital functions (adrenal/parathyroid insufficiency)
- **Check that the patient is not diabetic**; in particular, look for the features of the primary syndrome and the presence of ketones in urine or perform a capillary blood test
- While managing the patient, remember that **extensive gastrointestinal candidiasis can interfere with the absorption of orally administered drugs**

Additional therapeutic measures and hospitalisation

- Following life-threatening hypocalcaemia, switch to oral administration of calcium and vitamin D derivatives
- Teach the patient about clinical warning signs (paraesthesia of the peribuccal area or extremities, tetany) and tell him/her to seek a consultation quickly in such situations
- Arrange for blood calcium to be monitored regularly so that treatment can be adjusted in the Community
- Refer to the page on treatment of adrenal insufficiency for this condition

Organ donation

- The patient must **not donate organs**

Emergency telephone numbers

- Please visit www.orpha.net and type the name of the disease -> in the summary page click on "Expert centres" on the right tab -> select "United Kingdom" in the "Country" field in the Expert centres page.

Documentary resources

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