:: Familial Mediterranean fever

- *This document is a translation of the French recommendations drafted by Prof Gilles Grateau, Dr Véronique Hentgen, Dr Katia Stankovic Stojanovic and Dr Gilles Bagou 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:

Periodic disease, FMF

Definition:

Familial Mediterranean fever (FMF) is an **auto-inflammatory disease** of genetic origin, affecting **Mediterranean populations** and characterised by recurrent attacks of **fever accompanied by polyserositis** that causes the symptoms. **Colchicine** is the **basic** reference **treatment** and is designed to tackle inflammatory attacks and prevent **amyloidosis,** the **most severe complication** of FMF.

Further information:

See the Orphanet abstract

Pre-hospital emergency care recommendations
Call for a patient suffering from Familial mediterranean fever

Synonyms

- periodic disease
- FMF

Mechanisms

- auto-inflammatory disease that affects Mediterranean populations in particular, due to mutation of the *MEFV* gene that codes pyrin or marenostrin, this being the underlying cause of congenital immune dysfunction; repeated inflammatory attacks can lead to amyloidosis, particularly renal

Specific risks in emergency situations

- acute inflammatory attack, particularly abdominal (pseudo-surgical), but also thoracic, articular (knees) or testicular
- fever as an expression of the acute inflammatory attack

Commonly used long-term treatments

- colchicine
- some patients receive an IL1-inhibitor: Anakinra (Kineret®) or Canakinumab (Ilaris®)

Complications

- do not overlook surgical abdominal emergencies that may be mimicking frequent inflammatory attacks in patients suffering from FMF

Specific pre-hospitalisation medical care

- lay the patient down flat in a calm and warm place
- prescribe a combination of paracetamol and NSAIDs
- sometimes, level 2 analgesics, even level 3, are required
- maintain baseline treatment
- intravenous rehydration sometimes required in children

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 issues and recommendations

1. Acute inflammatory attacks manifest themselves in the form of:

- **fever**, which may be **moderate** (38°C) or very **high (>40°C)**, and is rarely absent
- **pain** associated with one or more serous disorders
  - most frequently, localised or generalised abdominal "pseudo-surgical" abdominal pain, sometimes accompanied by nausea, vomiting, transit problems
  - chest pain with dyspnoea, linked to pleurisy, less commonly to pericarditis
  - joint pain or even true arthritis, generally affecting medium-sized joints (knees+++ and ankles)
  - orchitis
  - less commonly, an extremely painful skin disorder known as "pseudo-erysipelas", generally adjoining a malleolus
- an inflammatory reaction revealed in laboratory results, in the form of raised ESR and CRP (hyperleukocytosis may be moderate or even absent)

2. Emergency diagnostics

- Emergency investigations: if suspected, mainly if the clinical manifestations and the manner in which they developed are unusual, use **diagnostic imaging** and **appropriate investigations** to **rule out** an alternative cause of:
  - abdominal pain (surgical, gynaecological, pyelonephritis, cholecystitis,…)
  - chest pain
  - infectious arthritis if there is a clear entry portal

3. Immediate treatment

- **lay the patient down flat** in a calm and warm place
- **Give a combination of analgesics and antipyrexial agents (paracetamol-type) with nonsteroidal anti-inflammatory agents:**
  - Children:
    - paracetamol: 15 mg/kg every 6 h without exceeding 4 g/24 h
    - in conjunction with NSAIDs, e.g. ibuprofen 8 mg/kg/6 h (alternating every 3 h) without exceeding 1200 mg/24 h
  - Adults: paracetamol 1 g/8 h alternating with NSAIDs, e.g. ibuprofen 400 mg/8 h (alternating every 4 h)
  - Sometimes, the parenteral route is required, mainly if nausea/vomiting develops
- **If the pain is not relieved** by the above medicines, level 2, or even level 3 analgesics may be used:
  - Children:
    - Codeine syrup : 0.5 to 0.75 mL/kg every 4 to 6 h, without exceeding 6 mg/kg/24 h
    - If necessary, administration of morphine (adjust in line with the case history):
      - i.v. route: give a bolus 50 μg/kg loading dose, then administer 25 μg/kg bolus doses in line with the pain, up to a maximum of 8 bolus doses every 4 h
      - IR route: 0.3 mg/kg every 3 to 6 h
  - Adults: tramadol hydrochloride (Non-propietary, Zamadol®, Zydol®) or a combination of paracetamol and codeine, even morphine by separate injections, using the i.v. or s.c. route, depending on how the pain develops
- Intravenous **rehydration** in the event of vomiting and high fever (paediatric dosage: 1500 to 2000 mL/m^2/24 h)
- If the fever remains very high and if pain remains severe, despite the foregoing action, **corticosteroids may be used as a last resort**:

- Children under 12 years of age: 0.75 to 1 mg/kg (prednisone equivalent) in a single dose, replaced with the aforementioned analgesics and NSAIDs
- Adults and children over 12 years of age: 0.5 to 0.75 mg/kg (prednisone equivalent) in a single dose, replaced with the aforementioned analgesics and NSAIDs

- There is **no indication for a temporary increase in the colchicine dose** (no efficacy in short-lasting inflammatory attacks, also heightened risk of undesirable effects)
- **Colchicine must not be used i.v.** (risk of overdosage and of severe intoxication)
- **In contrast, colchicine should be continued at the usual dose**

Orientation

- **Where?** Generally, inflammatory attacks in FMF are short-lasting (average of 2-3 days) and hospital admission is rarely required
- **When?** In cases of frequent recurrent inflammatory attacks, patients will need to be referred to the doctor who is treating their FMF so that they can be screened for possible trigger factors and so that the baseline treatment can be adjusted

Drug interactions

- No specific drug interactions in the context of medicines used in emergency situations and in baseline treatment
- Drug interactions - colchicine:
  - Combinations that are not recommended (risk of cumulative colchicine toxicity): macrolides and derivatives, apart from spiramycin, statins, cyclosporine
  - Drug combination calling for precautions in use: anti-vitamin K (heightened risk of haemorrhage)

Precautions for anaesthesia

- No specific precautions
- Return to the usual dose of colchicine as quickly as possible (risk of recurrent inflammatory attacks when colchicine is stopped)

Preventive measures

- In the face of certain situations that the patient learns to recognise and that carry a potential risk triggering an inflammatory attack, the idea of preventive use of analgesics/NSAIDs may be suggested
- In certain cases, such as those in which particularly symptomatic patients are sitting school/university examinations and in which onset of an inflammatory attack would also bring about socio-professional consequences, practitioners may sometimes decide to increase the colchicine for one or more weeks prior to the potential trigger event; the dose will then need to be reduced again immediately afterwards

Additional therapeutic measures and hospitalisation

- Put the patient at rest
- If there is abdominal pain:
  - gentle massage with warm or cool undergarments
  - relaxation
- if there is back pain: hot compresses
- if there is a pseudo-erysipelas skin disorder: biafine, rest, hyperelevated limb

Organ donation

- No contraindication to organ or blood donation.
- In the event of amyloidosis, this is systemic and affects the kidneys, the alimentary canal and endocrine glands in particular. Kidney donation is not, therefore, indicated.

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

- Website for the Reference Centre for Childhood Auto-inflammatory Diseases: http://asso.orpha.net/CEREMAI/
- Website for the Association française de la fièvre méditerranéenne familiale [French FMF Association] (AFFMF): www.affmf.org

These recommendations have been compiled in collaboration with Prof Gilles Grateau; Dr Véronique Hentgen (Paediatrics) and Dr Katia Stankovic Stojanovic (adults) - Reference Centre for Childhood and Adult Auto-inflammatory Diseases; the Association française de la fièvre méditerranéenne familiale (AFFMF) and Dr Gilles Bagou SAMU-69, Lyon.

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