Recurrent fever in childhood
Fever - characteristics

• fever = T > 38.5ºC

  – Protracted:
    • > 5 days

  – FUO (pUO):
    • > 2-3 weeks

  – Recurrent / periodic fever
Really febrile?

• Objectivisation of fever:
  – Measurement technique
  – Fever:
    • Duration
    • Height
    • Dynamics (fever chart)
Associated features

• Clinical symptoms
  – During fever
  – During afebrile interval

• Laboratory
  – During fever
  – During afebrile interval
FUO

• **Infection**
  - Anatomical pre-disposition
    • Congenital anomalies
  - Functional pre-disposition
    • Immune deficiencies
      – Inherited
      – Acquired
  - Unusual / aggressive pathogens
    • leishmaniasis, brucelosis, endocarditis
FUO

• **Systemic malignancies**
  – ALL
  – Neuroblastoma
  – Lymphomas
  – Hemophagocytic lymphohistiocytosis (HLH)
• **ALL - FBC**
  – ! surprisingly „normal“ WBC + high ESR/CRP
  – ! profound anemia (normocytic)
  – ! Normal/low PLT
  – ! CS administration dangerous
  – Initial BM aspirate may be normal...
  – Non-specific features: ↑ LDH, uric acid, ferritin

• **Neuroblastoma:**
  – Age group
  – Screening: abd US, bone scan, urine catecholamines

• **General:**
  – bone pain x mild or no objective joint findings
FUO

• Systemic inflammatory diseases

• Autoinflammatory diseases
Systemic diseases

• „Non-rheumatological“
  – IBD

• „Rheumatological“
  – Still´s disease
  – Systemic vasculitis
  – SLE
S-JIA – Still’s disease

- **Arthritis** + fever or fever prior to arthritis
  + at least 1 of:
    - Evanescent rash
    - Generalized LNpathy
    - Hepatosplenomegaly
    - Serositis
sJIA - complication

• **MAS: Macrophage Activation Syndrome**
  – Life-threatening
  – Excessive proliferation ans activation of T-cells and macrophages
  – Cytokine storm

• Reactive (secondary) lymphohistiocytosis

• In up to 7% sJIA (=10% JIA)

• KDDL: 8x sJIA, 1x systemic leishmaniasis

• Main cause of death in paed rheum
Clinical findings

• Change in fever pattern
• General deterioration, petechie, neurological symptoms
• Labs
  – Decrease of ESR and FBG
  – Cytopenia (hemophagocytosis)
  – Hepatopathy
  – Coagulopathy
  – \text{↑ ferritin} (>10000\text{ ng/ml}), IL-18, triglycerides
• Multiorgan failure
Kawasaki disease

- **Fever** (100%)
  - > 5 days
- **A: conjunctivitis** (85%)
  - Bilat., bulbar, non-suppurative
- **B,C: mucosal changes** (90%)
  - Red cracked lips, strawberry tongue, oropharyngeal erythema
- **D: Lymphadenopathy** (70%)
  - Cervica, acute, non-suppurative, >1,5 cm
- **E: Rash** (80%)
  - Polymorphous
- **F,G: Extremity changes** (70%)
  - Palm and sole erythema / induration, skin peeling
Systemic disease with necrotizing vasculitis on biopsy OR angiography changes + at least 2 from:

- Cutaneous findings
- Myalgia
- Systemic hypertension
- Mononeuropathy / polyneuropathy
- Renal involvement
- Testicular pain
- Vasculitis of other organs
Autoinflammatory diseases

- Periodic fevers
Periodic fever

• Repeat episodes of fever lasting days to weeks

• Asymptomatic intervals

• Hereditary and idiopathic syndromes
„Autoimmune“ x „autoinflammatory“

- Dysregulation of innate immune system
- Recurrency / periodicity
  - Local and general inflammation
  - Asymptomatic intervals
- Early onset
  - Usually before 10 years
- Individual variability
**Periodic fever syndromes in Eastern and Central European countries: results of a pediatric multinational survey**

Nataša Toplak¹, Pavla Doležalova², Tamas Constantin³, Anna Sedivá³, Srdjan Pašić⁴, Peter Čižmar⁴, Beata Woliska-Kušnierz⁵, Miroslav Harjaček⁶, Mariana Stefan⁷, Nicolaino Ruperto⁸, Marco Gattorno⁹, Tadej Avčin¹¹, Eastern/Central European autoinflammatory collaborating group for the Paediatric Rheumatology International Trials Organisation (PRINTO) and Eurofever Project¹⁰

### Table 1 Genetically confirmed and suspected cases of periodic fever syndromes in ECE countries and estimated number of patients per number of children 0-19 years

<table>
<thead>
<tr>
<th>Periodic fever syndrome</th>
<th>Genetically confirmed cases</th>
<th>Suspected cases</th>
<th>Total</th>
<th>Estimated number per number of children 0-19 years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMF</td>
<td>11</td>
<td>49</td>
<td>60</td>
<td>1/465,500</td>
</tr>
<tr>
<td>MKD</td>
<td>14</td>
<td>24</td>
<td>38</td>
<td>1/771,400</td>
</tr>
<tr>
<td>TRAPS</td>
<td>11</td>
<td>16</td>
<td>27</td>
<td>1/1,030,000</td>
</tr>
<tr>
<td>CINCA</td>
<td>4</td>
<td>7</td>
<td>11</td>
<td>1/2,454,500</td>
</tr>
</tbody>
</table>

* Adult patients were excluded from calculation.

FMF- Familial Mediterranean fever
MKD- mevalonate-kinase deficiency
TRAPS- tumor necrosis factor (TNF) receptor associated periodic syndrome
CINCA- chronic infantile neurological, cutaneous and articular syndrome
Etiological insights

• Generalized inflammatory response to an ordinary stimulus
  – Hypersensitive reaction
  – Failure of regulatory mechanisms

• Mutations in 7 different genes in 11 syndromes (since 1997)

• Monogenic syndromes with mendelian inheritance OMIM

• Mutated gene products (DDF superfamily) – participate at
  – Regulation of apoptosis
  – Aktivation of NFκB and production of proinflammatory cytokines
Autoinflammatory diseases – nomenclature
Kastner AL, 2005

• Hereditary periodic fevers
  – FMF, HIDS, FHF/TRAPS, ADPF, MWS, CINCA/NOMID

• Idiopathic febrile syndromes
  – PFAPA syndrome, (SoJIA, AOSD)
  – Snitzler syndrome

• Granulomatous diseases
  – Crohn, Blau syndrome, early onset sarcoidosis

• Pyogenic syndromes
  – CRMO, SAPHO syndrome, PAPA, DIRA

• Hemophagocytis syndromes
  – FHLH, MAS

• Complement disorders
  – Hereditary angioedema

• Vasculitic syndromes
  – Behcet’s disease
FMF

- Most frequent PF, AR
- MEFV gene - Pyrin/marenostrin
- **Short fever attacks** + serositis, arthritis, rash, myalgia, AA amyloidosis
- **Labs:** nonspecific inflammatory
- **Therapy:**
  - NSA
  - Colchicine
  - Blockade of IL-1

KDDL: 1 patient (+parent)

*Kallinich D et al, ARD 2006*  
*Galeazzi M et al, CER 2006*
MAPS /HIDS

• **Mevalonate-Associated Periodic Syndrome / Hyper IgD**

• **Presentations:**
  - Fever episodes + cervical LN, GI complaints, H headache, arthralgia, arthritis, rash
  - Infection or vaccination trigger

• **Labs:**
  - nonspecific + IgD, IgA, MVA in urine

• **Therapy:**
  - CS, immunosuppressives, statins  
    Drenth et al 2001  Simon et al 2004
  - **Etanercept**  
  - **Anakinra**  
    Demirkaya et al 2006, Nevyjel et al 2007

• **Prognosis:** problematic

  KDDL: 7 pts, 3x biologic therapy
HIDS: pathogenesis

- **MVK gene on long arm of** ch 12

- Mutation (v 80% V377I) – *decreased stability* of the protein and catalytic activity to 5-15% (<1% - complete deficit MVK = mevalonic aciduria) Houten et al 1999, 2001, Couissset et al 2001
TRAPS

- **TNFα-Receptor Associated Periodic Syndrome**

- **Presentation:**
  - Protracted fever for weeks, 2-6x per year
  - *myalgia, ocular symptoms, abd pain, pleuritis, rash, arthralgia*
  - AD inheritance

- **Labs:**
  - Nonspecific, ↓ TNFR1

- **Therapy:**
  - CS during attack
  - Cytokine blockade (etanercept, anakinra)

- **Prognosis:** risk of AA amyloidosis (25%)
  
  KDDL: 3 pts

Kallinich D et al, ARD 2006
**CAPS - cryopyrinopathies**

<table>
<thead>
<tr>
<th>Family Cold Urtica (FCAS)</th>
<th>Muckle–Wells Syndrome (MWS)</th>
<th>NOMID/CINCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cold induced</td>
<td>• Rash</td>
<td>• Sporadic</td>
</tr>
<tr>
<td>– Rash</td>
<td>• Deafness</td>
<td>• Chronic meningitis</td>
</tr>
<tr>
<td>– Arthralgia</td>
<td>• AA amyloidosis (25%)</td>
<td>• Deafness</td>
</tr>
<tr>
<td>– Conjunctivitis</td>
<td></td>
<td>• PM retardation, bklindness</td>
</tr>
</tbody>
</table>

**MILD**

- Therapy: Blockade of IL-1 (anakinra, canakinumab)

**SEVERE**

- KDDL: 1 pt

Lachman H et al, 2010
AD familiar fevers ADPF

- Familial Cold Autoinflammatory Syndrome = (FCAS)
  - *AD, onset before 1 yr*
  - Cold induces non-itchy *maculopapulatus* rash, in 93% with fever; conjunctivitis (84%), arthralgia (96%)
ADPF

- **Muckle-Wells syndrome (MWS)**
  - Not cold-induced
  - Often + progressive sensorineural deafness

- Missense *mutation in CIAS1 gene* on ch 1, protein with pyrin domain
CINCA/NOMID:

- Chronic Infantile Neurological Cutaneous and Articular syndrome
- Neonatal Onset MultiInflammatory Disease
CINCA

• Specific phenotype:
  – Stunted growth
  – Saddfle nose, prominent front
  – Variable CNS disease
  – arthropathy
Clinical picture

- A thriving, healthy-looking toddler referred for recurrent unexplained short fever episodes
- History of recurrent antibiotic exposure for tonsillitis and high CRP
- Absence of positive throat cultures and other microbiology
- Antibiotics make no difference
• Regular episodes similar one to another
• Individually unique combination of features
• Absence of usual URTI symptoms (running nose, cough)
• Striking rapid response to single-dose corticosteroid
• Remission after TE
PFAPA Diagnostic criteria

• Regularly recurring fevers with an early age of onset (<5 years of age)
• Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs:
  – aphthous stomatitis
  – cervical lymphadenitis
  – pharyngitis
• Exclusion of cyclic neutropenia
• Completely asymptomatic interval between episodes
• Normal growth and development
• (Exclusion of monogenic periodic fevers mainly in patients with GI symptoms and rash)
A Diagnostic Score for Molecular Analysis of Hereditary Autoinflammatory Syndromes With Periodic Fever in Children


Differentiating PFAPA Syndrome From Monogenic Periodic Fevers

Marco Gattorno, Roberta Caorsi, Antonella Meini, Marco Cattalini, Silvia Federici, Francesco Zulian, Elisabetta Cortis, Giuseppina Calcagno, Alberto Tommasini, Rita Consolini, Gabriele Simonini, Maria Antonietta Pelagatti, Maurizia Baldi, Isabella Ceccherini, Alessandro Plebani, Joost Frenkel, Maria Pia Sormani and Alberto Martini

*Pediatrics* 2009;124:e721-e728; originally published online Sep 28, 2009;
DOI: 10.1542/peds.2009-0088
Clinical symptoms

- Pharyngitis: 91%
- Adenitis: 78%
- Aphthae: 41%

- Abdominal pain: 23%
- Headache: 15%
- Vomiting: 13%
- Arthralgia: 10%
- Diarrhea: 5%
- Rash: 3%
- Conjunctivitis: 3%
1. Watch-and-wait
   • No specific treatment, symptomatic therapy during febrile attack, avoidance of antibiotics

2. Prednisone
   • Single dose 1mg/kg up to 24-48 hours from onset

3. Second-line treatments
   • Cimetidin, Colchicin
   • Tonsillectomy
Conclusion

• PFAPA syndrome appears to be the most common periodic fever in Caucasians
• Significant morbidity, psychosocial and monetary impact
• Excellent prognosis
• Early identification and adequate management impact grossly patient/family quality of life
• Patient and primary care physicians education necessary
**Child with recurrent unexplained febrile episodes**

- **anatomical change** - ID
  - yes
  - **Infection identified**
  - no
  - **Neonatal onset, urticarial rash**
    - yes
    - SF, fundoscopy
    - **Consider CINCA**
    - no
    - **Fever <3 days, ± serositis, ethnicity**
      - yes
      - **Consider FMF**
      - no
      - **Onset <1 year, abd pain, GI symptoms \(\uparrow\) IgD/A**
        - yes
        - **Consider MAPS**
        - no
      - **Cold urtica, deaf, amyloid**
        - yes
        - **Consider CAPS**
        - no
    - no
    - **Prolonged fever, Ocular symptoms**
      - yes
      - **Consider TRAPS**
      - no
      - **Quotidian fever rash, dur. >7 days**
        - yes
        - **Consider SoJIA**
        - no
      - **Cold urtica, deaf, amyloid**
        - yes
        - **Consider CAPS**
        - no
  - no
  - **Consider PFAPA**
  - no

*Considerations based on specific clinical presentations and laboratory findings.*