FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Recurrent fever in childhoo

Refer or reassure - A practical approach

Thomas Renson, MD PhD
Pediatric Rheumatology, Ghent University Hospita

Pentalfa, KU Leuven, 01/02/2024



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CASE PRESENTATION: 4 Y/O F

- *History*:
  - High-grade fever for two days
  - Mouth soreness, limited food intake
  - Abdominal pain
  - Two prior similar episodes in the past 2-3 months

- *Clinical exam*:
  - Looks generally ill, unwell during fever attacks
  - Tachycardic
  - Aphthous stomatitis and tonsillitis
  - Cervical lymfadenopathy

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ADDITIONAL INVESTIGATIONS

- *Blood work:* ESR 45 mm/h, CRP 195 mg/dl, leukocytosis with neutrophilia

- *Urine test:* no pyuria, no hematuria, no proteinuria

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FURTHER DISEASE COURSE

… Amoxicilline was started in the context of a suspected bacterial tonsillitis

→ Fever resolved after 2 days, other symptoms 1 day later

BUT … New similar episode 5 weeks later.

PFAPA



- **P**eriodic **F**ever
- **A**denitis
- **P**haryngitis
- **A**phthous stomatitis

→ An idiopathic, autoinflammatory, IL-1 mediated condition characterized by recurrent attacks of fever, oral ulcers, pharyngitis, and/or lymphadenopathy.

Most frequent periodic fever syndrome in childhood.

Underlying genetic basis remains elusive.

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PFAPA: TYPICAL ATTACKS

- Onset often before the age of 5
- Attacks resolve spontaneously
- Duration: 3-6 days
- Interval: 3-6 weeks (“clocklike”)



- Disease-free intervals, normal growth and development
- Benign condition; spontaneous remission during childhood/adolescence

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DIAGNOSIS

- *Typical* constellation of signs & symptoms
- High inflammatory markers
- Negative genetic screening

- Generalized lymphadenopathy, hepatosplenomegaly ≠ PFAPA

Box 1. Diagnostic criteria for PFAPA syndrome

Diagnostic criteria for PFAPA syndrome include the following:

- Onset of disease in early childhood, generally before the age of 5 y
- Regularly recurring abrupt episodes of fever lasting approximately 5 d, associated with constitutional symptoms, and both of the following:
  - -aphthae or pharyngitis (with or without cervical adenitis) in the absence of other signs of respiratory tract infection
  - -acute inflammatory markers such as leukocytosis or elevated erythrocyte sedimentation rate
- Completely asymptomatic interval periods (generally lasting less than 10 wk), benign long-term course, normal growth parameters, and the distinct absence of sequelae
- Exclusion of cyclic neutropenia by serial neutrophil counts, before, during, and after symptomatic episodes
- Exclusion of other episodic syndromes (FMF, hyper-IgD syndrome, TRAPS, Behçet syndrome) by family history and the absence of typical clinical features and laboratory markers
- Absence of clinical and laboratory evidence for immunodeficiency, autoimmune disease, or chronic infection

FMF—familial Mediterranean fever; hyper-IgD—hyperimmunoglobulin D; PFAPA—periodic fever, aphthous stomatitis, pharyngitis, and adenitis; TRAPS—tumor necrosis factor receptor–associated periodic syndrome. Data from Marshall et al.[24]

TREATMENT OF PFAPA

- As conservative as possible (benign and often spontaneously remitting)
- Steroids (trial: prednisolone 1mg/kg at the start of an attack)
- Colchicine
- Tonsillectomy

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(PFS)

- Fever is very common in childhood; often due to infection
- ≤2y: 6-7 respiratory infections per year [1]
- **Recurrent** fever:
  ≥3 episodes of unexplained fever in a 6-month period, occurring ≥7 days apart [2]
- **Periodic** fever:
  Recurring episodes of fever (with either strict periodicity or irregular intervals) lasting days to weeks in which fever is the cardinal feature and other associated features are similar and predictable [3]
- DDx: chronic infection (e.g. TB), recurrent infections and immune deficiencies, malignancies, inflammatory bowel disease

[1] Recurrent of periodic fevers. Don't Forget the bubbles 2018.
[2] Pediatr Infect Dis J 2002;21(11):1071-7
[3] Can Fam Physician 2017;63(10):756-762

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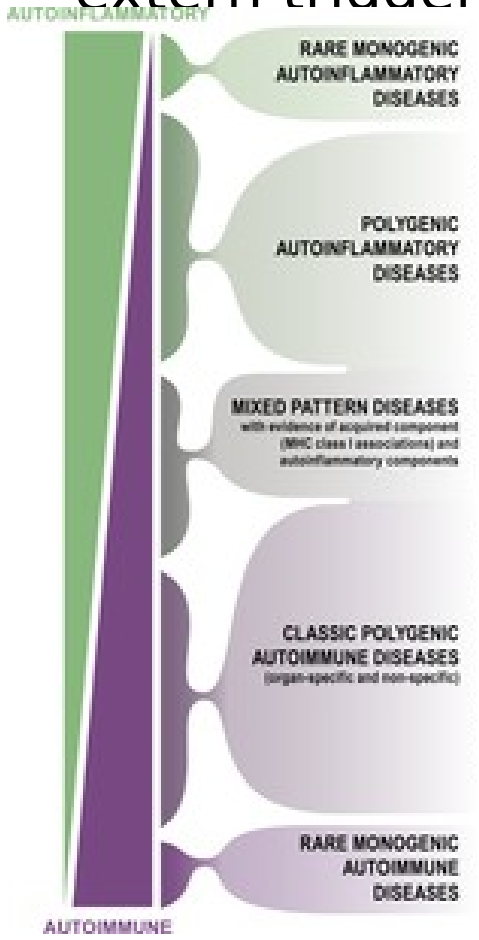
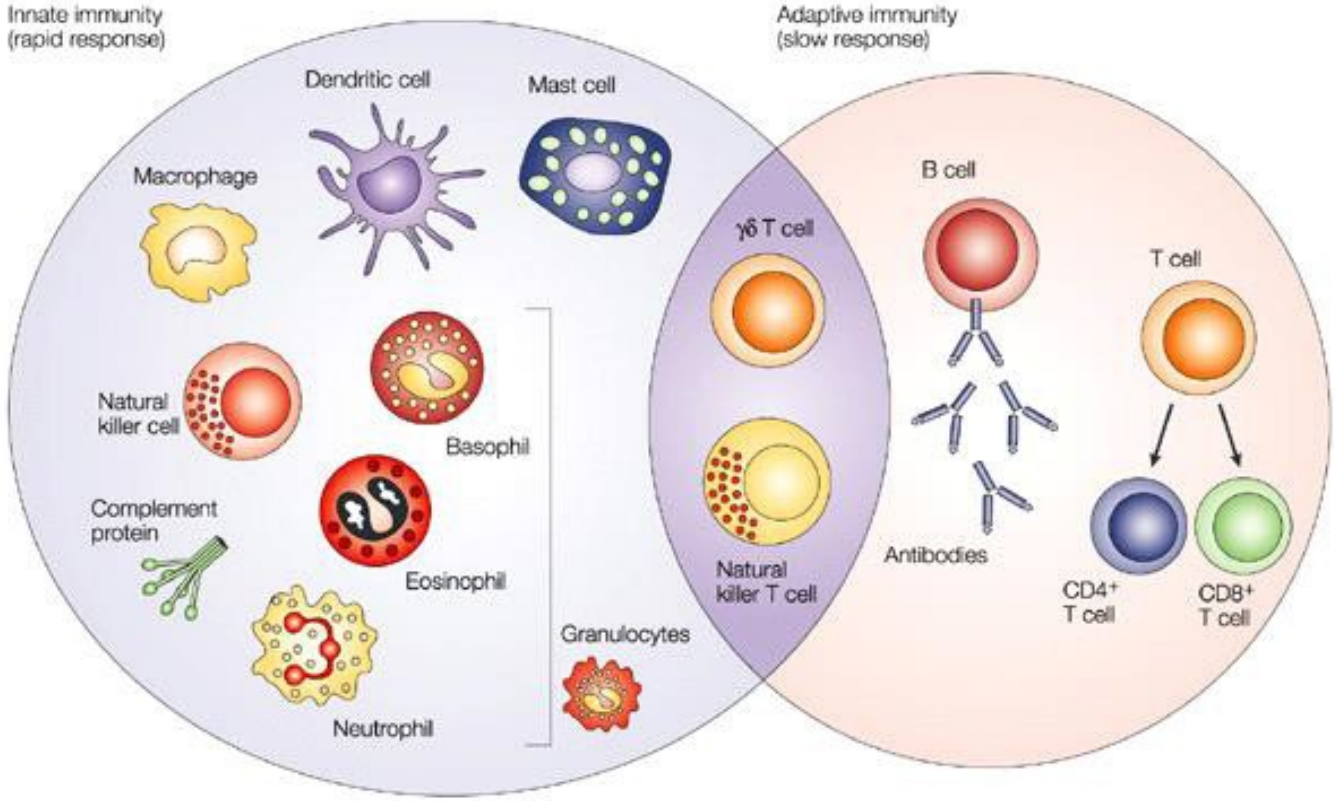
PATHOPHYSIOLOGY

- Monogenic vs polygenic AID
- Dysfunction of innate immune system (autonomous hyperactivation or extern triggers)





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SUBTYPES

- Familial Meditarrenean Fever (FMF)
- PFAPA
- Behçet’s disease
- Hyper IgD syndrome (HIDS)
- CAPS
- TRAPS
- ……

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FMF

- Archetype of monogenic PFS
- Eastern Mediterranean region
- NLRP3 inflammasomopathy caused by MEFV gene mutation
- MEFV gene → pyrin
- Recurrent episodes of fever, polyserositis, arthritis, and erysipelas-like erythema
- Attacks are short-lived! (1-3 days)
- 80-90% symptomatic before the age of 20
- Amyloidosis
- Treatment: colchicine, anakinra (on-demand??), canakinumab

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WHEN TO CONSIDER PFS?

- **Recurring episodes of fever (with either strict periodicity or irregular intervals) lasting days to weeks in which fever is the cardinal feature and other associated features are similar and predictable (= periodic fever)** [1]
- Recurrent fever without infectious focus or positive cultures
- Especially when episodes occur very regularly
- Constellation of recurrent fever (without apparent focus) + skin rash + high inflammatory serum markers + hyperferritinemia ± arthritis ± serositis ± neurological symptoms ± eye manifestations (e.g. uveitis, retinal vasculitis)

- BUT … Irregular, intermittent, recurrent fevers in well-appearing child ≤6y/o are more likely to be triggered by viral infections [2]

[1] Can Fam Physician 2017;63(10):756-762 [2] Recurrent of periodic fevers. Don't Forget the bubbles 2018.

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FACTORS TO CONSIDER IN CASE OF RECURRENT FEVER

- Pattern of fever (current episode and prior episodes)
- Duration of attacks, interval between attacks
- Symptoms during disease-free intervals
- Ethnicity, familial history

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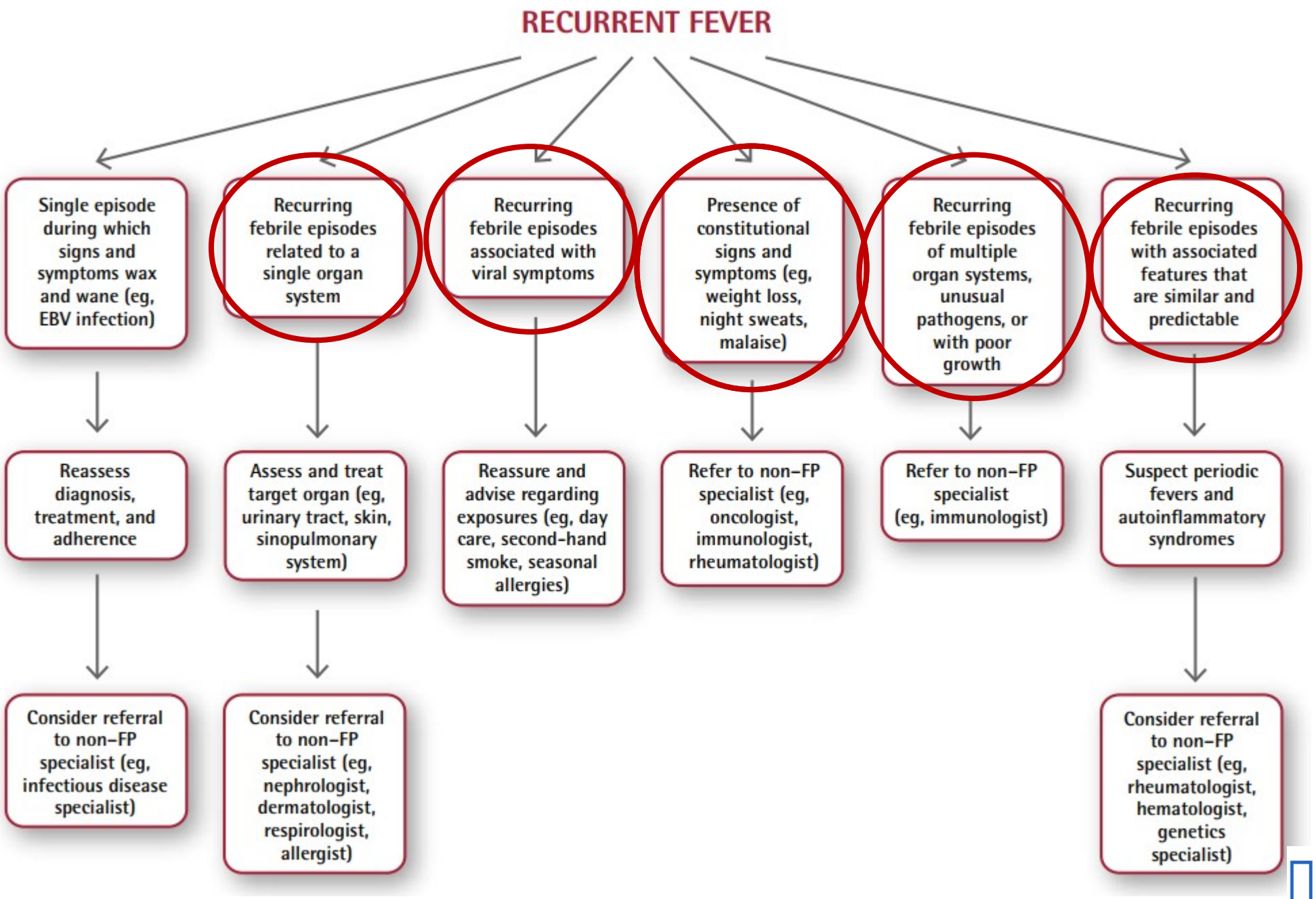

Can Fam Physician
2017;63(10):756-762

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RED FLAGS

- Weight loss and anorexia
- Poor growth
- Night sweats
- General malaise, lethargia
- Lymphoproliferation

→ Additional work-up needed (cave malignancy,



RED FLAGS FOR PID

- ≥4 episodes of otitis within 1 year
- ≥2 episodes of serious sinusitis within 1 year
- ≥2 episodes of pneumonia within 1 yea
- Failure to thrive
- Recurrent deep skin/organ abcesses
- ≥2 deep-seated infections, such as sep
- Persistent oral thrush or fungal skin inf
- Need for IV AB to clear infections
- A positive familial history for PID



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SUSPECTED PFS

At time of disease flare:

- Blood work: erythrocyte sedimentation rate, CRP, peripheral blood count, renal function, liver tests, IgM-A-G-D, C3, C4, ferritin, serum amyloid A (SAA)
- Urine test: mevalonic acid

Any time: SAA, TB screening, AID (or PID) gene panel, thoracic X-ray, abdominal ultrasonography, eye exam

Of note: importance of SAA during clinical remission …

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TAKE HOME MESSAGES

- Recurrent fever is common in young children, most are due to infections
- Think: Infection vs Autoimmunity/Autoinflammation vs Malignancy
- Recurrent infections linked to a single organ → predisposing factors? Specialist referral.
- Recurrent fever ≠ Periodic fever
- Periodic fever = recurrent fever with similar and predictable associated features
- PFS are rare, but should not be overlooked
- PFAPA is most common PFS, FMF is most common monogenic PFS
- Beware of red flags → Malignancy, PID, TB

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ACKNOWLEDGEMENTS

- KU Leuven, Faculty of Medicine, Pentalfa
- Prof. Dr. Lien De Somer, Pediatric Rheumatology, UZ Leuven
- Prof. Dr. Joke Dehoorne, Pediatric Rheumatology, UZ Ghent
- Dr. Rik Joos, Rheumatology en Pediatric Rheumatology, ZNA & UZ Ghent
- Prof. Dr. Benson Ogunjimi, Pediatric Rheumatology, UZ Antwerp & UZ Brussels



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