Prolonged and Recurrent Fevers in Children

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Chief, Division of Pediatric Infectious Diseases
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University of Louisville School of Medicine
Disclosures

Consultant for Novartis
Objectives

After this lecture, participants should be able to…
- Design a diagnostic plan for children with unexplained fever
- Differentiate intermittent febrile illnesses and periodic fevers
- Manage patients with PFAPA syndrome
Measuring Temperature

Liquid-in-glass
Thermistor-based
Direct contact with patient

Defining Fever

Core body temperature ≥100.4 °F (38.0 °C)

Site of measurement
- Birth to 3 years: rectal
- 3 to 5 years: axillary (add 1 °F or 0.6 °C)
- Ages 5 and above: oral

Rideout. Contemp Pediatr 2001;18:42
Fever is defined as the endogenous elevation of at least one measured body temperature of \( \geq 38 ^\circ C \).\(^2,3\)

\(^2\) The value of \( \geq 38 ^\circ C \) is accepted as reflecting an abnormal elevation of temperature, irrespective of device, anatomic site, age, or environmental conditions.

\(^3\) While it is recognized that this value is to some extent *arbitrary*, it is based upon a conservative interpretation of definitions proposed and used by clinicians, investigators, and the public at large.
Fever is the main complaint
Not associated with a defined clinical illness
Not “fever without source”
Previously healthy
Patient is not having abnormal temperatures
It *is* a fever—
It *is* a fever—
for him!
Undifferentiated Fever

Prolonged

Not-FUO

Recurrent

Causes

- "Temperatures usually run low"
- Diurnal temperature variation
- Meals
- Ovulation
- Tobacco and chewing gum
- Exercise

Undifferentiated Fever

Prolonged

Recurrent

Not-FUO

Clues

- Healthy appearance
- Normal growth/development
- Stable weight
- School absences for subjective complaints
- Vulnerable child

- Behavioral problems
- Misconceptions about health
- Fear of malignancy
- Family stress
- Normal physical exam

Undifferentiated Fever

- Prolonged
  - Not-FUO
  - F-Not-UO
- Recurrent

Diagnosis achievable in the primary care setting
Clues on history, physical exam, or simple laboratory tests
Uncommon presentation of a common disease
Separate illnesses that blend together
Undifferentiated Fever

- Prolonged
  - Not-FUO
  - F-Not-UO

- Recurrent

Diagnoses

- URTI (otitis media, sinusitis)
- LRTI (pneumonia)
- Central nervous system infection
- Tuberculosis
- Histoplasmosis
- Brucellosis
- Ehrlichiosis
- Endocarditis
- Leukemia
- Kawasaki disease
- Juvenile idiopathic arthritis
- Inflammatory bowel disease
Fever for 3 Weeks
Fever for 4 Weeks
Undifferentiated Fever

Prolonged

Not-FUO
F-Not-UO
PUF

Recurrent
ILLNESS $>$3 weeks
Fever $>$101 °F on several occasions
Diagnosis uncertain after 1 week in hospital
# Defining Prolonged Unexplained Fever

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<tr>
<th>Reference</th>
<th>Temperature (≥)</th>
<th>Frequency</th>
<th>Duration</th>
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<tr>
<td></td>
<td>°C</td>
<td>°F</td>
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<tr>
<td>McClung, 1972</td>
<td>38.9</td>
<td>102.1</td>
<td>Multiple occasions</td>
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<td>Pizzo, 1975</td>
<td>38.6</td>
<td>101.4</td>
<td>≥5 occasions</td>
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<td>Lohr, 1977</td>
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<td>Steele, 1991</td>
<td>38.1</td>
<td>100.5</td>
<td>≥2 occasions/wk</td>
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<td>Jacobs, 1998</td>
<td>38.1</td>
<td>100.5</td>
<td>Daily</td>
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Operational Definition of FUO in Children

Core body temperature $\geq 38.1 \, ^\circ C \, (\geq 100.5 \, ^\circ F)$

$\geq 1$ occasion every day

$\geq 14$ consecutive days

Made up by Dr. Marshall
Factors Affecting Cause of FUO

Geography
Age
Host factors
New diseases
Physician experience
Referral patterns
Availability of laboratory tests and imaging
Managed care
Causes of FUO in Children—U.S.

Infectious Causes of FUO in Children—U.S.

- URTI
- LRTI
- UTI
- CNS
- TB
- SBE
- Mono
- Osteo
- Cat Scratch
- Tularemia
- Lyme
- Ehrlichiosis
- Other

Percent

1970s (N=99)

1990s (N=72)

Fever for 2 Months

ESR >130 mm/hr
Inflammatory and autoimmune diseases

- Inflammatory bowel disease
- Juvenile idiopathic arthritis
- Lupus
- Rheumatic fever
- Wegener granulomatosis
- Sarcoidosis
- HLH
- Behcet disease
Malignancies
- Leukemia
- Lymphoma
- Neuroblastoma

- Hepatoma
- Soft tissue sarcoma

Long. Principles and Practice of Pediatric Infectious Diseases; 2008:126
Miscellaneous

- Munchausen by proxy
- Factitious fever
- Drug fever
- Central fever
- Pulmonary embolus

- Dysautonomia
- Diabetes insipidus
- Ectodermal dysplasia
- Hyperthyroidism
- Hematoma
Approach to diagnosis
- Severity of findings dictates pace of evaluation
- Serial evaluations
- Avoid antimicrobials
- Use time as a diagnostic tool

If it’s infection, there’s always a source
- Travel
- Raw foods
- Ill persons
- Insect bites
- Animals
- Transfusions
- Recent procedures
- Unusual activities

Questions Only an ID Doc Could Ask
Questions Only an ID Doc Could Ask

Tried unpasteurized goat’s milk?

http://eatdrawlive.com/raw-goat-milk/
Questions Only an ID Doc Could Ask

Tried unpasteurized goat’s milk?

[Image of a goat]

http://eatdrawlive.com/raw-goat-milk/

Brucellosis
Questions Only an ID Doc Could Ask

Jumped on any beaver dams?

http://www.ridacritter.com/beavers.php
Questions Only an ID Doc Could Ask

Jumped on any beaver dams?

Blastomycosis

http://www.ridacritter.com/beavers.php
Questions Only an ID Doc Could Ask

Been around any discarded sheep placentas?

http://animals-backgrounds.blogspot.com/2012/08/sheep.html
Questions Only an ID Doc Could Ask

Been around any discarded sheep placentas?

Q fever

http://animals-backgrounds.blogspot.com/2012/08/sheep.html
Diagnostic Approach

**First Visit**
- Initial Hx and PE
- Previous lab results
- CBC with smear
- CMP
- ESR and CRP
- U/A and UCx
- BCx
- CXR

**Targeted studies**
Diagnostic Approach

First Visit

- Initial Hx and PE
- Previous lab results
- CBC with smear
- CMP
- ESR and CRP
- U/A and UCx
- BCx
- CXR

Targeted studies

Second Visit

- Interval Hx and PE
- CBC with smear
- CMP
- ESR and CRP

Targeted studies

Fever/symptom diary
<table>
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<th>AM</th>
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<th>Time</th>
<th>Temperature</th>
<th>Symptoms</th>
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Pediatric Infectious Diseases
Fever Journal
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Diagnostic Approach

First Visit
- Initial Hx and PE
- Previous lab results
- CBC with smear
- CMP
- ESR and CRP
- U/A and UCx
- BCx
- CXR

Targeted studies

Fever/symptom diary

Second Visit
- Interval Hx and PE
- CBC with smear
- CMP
- ESR and CRP

Targeted studies

Fever/symptom diary
Diagnostic Approach

First Visit
- Initial Hx and PE
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- CBC with smear
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- BCx
- CXR
- Targeted studies

Second Visit
- Interval Hx and PE
- CBC with smear
- CMP
- ESR and CRP
- Targeted studies

Third Visit
- Interval Hx and PE
- CBC with smear
- CMP
- ESR and CRP
- Targeted studies

Fever/symptom diary

Targeted studies
# Targeted Studies

## Infectious Diseases
- TST  
- Histoplasma serology  
- EBV and CMV serology  
- Bartonella serology  
- Brucella serology  
- Toxoplasma serology  
- Tularemia serology  
- HIV antibody or PCR  
- Stool Cx

## Autoimmune/Inflammatory
- ANA and RF  
- ASOT and anti-DNAse-B  
- C3 and C4

## Malignancy
- Flow cytometry  
- LDH and uric acid  
- Bone marrow

## Miscellaneous
- TFTs  
- Slit lamp exam  
- Sinus CTS  
- Echocardiogram  
- Endoscopy  
- Abdominal U/S or CTS  
- Bone scan  
- PET scan
Clinic visit 1/1/08-12/31/12 (N=4586)

Exclusions

Referred for unexplained fever (221)

“Fever”, “febrile”, “FUO” not included in diagnosis (4118)
Established patient visit (159)
Initial consult in hospital (51)
Not referred for fever (17)
Initial visit before 2008 (8)
Records not available (3)
Referred for typhoid fever (2)
Referred for scarlet fever (1)
Referred for fever blisters (1)
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Referred for unexplained fever (221)

Prolonged (69)

Not having fever (10)

Having fever (59)

Recurrent (152)
Clinic visit 1/1/08-12/31/12 (N=4586)

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Diagnosis apparent on initial visit (11)

Fever of unknown origin (48)

Statler. JPIDS 2015. DOI:10.1093/jpids/piv008
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Not having fever (10)
Having fever (59)

Recurrent (152)

Fever of unknown origin (48)
Diagnosis apparent on initial visit (11)
No diagnosis established (33)
Diagnosis established (15)
Undifferentiated Fever

- Prolonged
  - Not-FUO
  - F-Not-UO
  - PUF
- Recurrent
  - Intermittent

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Sequential, common, self-limited viral illnesses
When did the fever start?
The day he was born.

When did the fever start?
The day he was born.

When did the fever start?

Seriously, he’s had fever every single day since he was born?
When did the fever start?

The day he was born.

Yes.

Seriously, he’s had fever every single day since he was born?
When did the fever start?

The day he was born.

Yes.

Seriously, he’s had fever every single day since he was born?

How old is he?
When did the fever start?

The day he was born.

Seriously, he’s had fever every single day since he was born?

Yes.

How old is he?

12.
Sequential, common, self-limited viral illnesses
- Epidemiological clues (e.g., day care attendance)
- Diagnosis
  - History biopsy
  - Fever and symptom diary
  - Screening laboratory studies
  - Time
Sequential, common, self-limited viral illnesses
Autoinflammatory diseases

Kastner. Cell 2010;140:784
Undifferentiated Fever

Prolonged

- Not-FUO
- F-Not-UO
- PUF

Recurrent

- Intermittent

Sequential, common, self-limited viral illnesses

Autoinflammatory diseases
- Abnormally increased inflammation
- Predominantly mediated by cells and molecules of the innate immune system (as opposed to autoantibodies or autoreactive T-cells)
- Significant host predisposition

*Kastner. Cell 2010;140:784*
Sequential viral illnesses

Auto-inflammatory diseases
Sequential, common, self-limited viral illnesses

Autoinflammatory diseases

– Inflammasomopathies
The Inflammasome

- Macromolecular complex
  - Responds to danger signals
  - Produces inflammatory cytokines
- Monocytes, neutrophils, activated T-cells, chondrocytes

Intrinsic inflammasomopathies (cryopyrin)

— Familial cold autoinflammatory syndrome
— Muckle-Wells syndrome
— Neonatal-onset multisystem inflammatory disease
Extrinsic inflammasomopathies

—Familial Mediterranean fever: pyrin mutation
—Hyper IgD syndrome: mevalonate kinase def
Sequential, common, self-limited viral illnesses
Autoinflammatory diseases
   – Inflammasomopathies
   – Protein folding disorders

Kastner. Cell 2010;140:784
TNF-Receptor Associated Periodic Syndrome (TRAPS)

Proinflammatory gene transcription

NF-κB

TNF-Receptor Associated Periodic Syndrome (TRAPS)

Proinflammatory gene transcription

NF-κB

mTNFR1

TNFR1

NUCLEUS

ER

CELL MEMBRANE

TNF-Receptor Associated Periodic Syndrome (TRAPS)

- Proinflammatory gene transcription
- Unfolded protein response
- Ligand-independent signaling
- Inhibition of apoptosis

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TNF-Receptor Associated Periodic Syndrome (TRAPS)

NF-κB

Unfolded protein response
Ligand-independent signaling
Inhibition of apoptosis

Proinflammatory gene transcription

NUCLEUS

ER

GOLGI APPARATUS

CELL MEMBRANE

mTNFR1

TNFR1

TNF

TNF-Receptor Associated Periodic Syndrome (TRAPS)

- Proinflammatory gene transcription
- Unfolded protein response
- Ligand-independent signaling
- Inhibition of apoptosis

## Inflammasomopathies

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*Kastner. Hematol 2005;74-81
Bodar. Br J Hematol 2008;144:279
Lachmann. Clin Exper Immunol 2011;165:301*
# Clinical Classification Criteria

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<tr>
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<td>Generalised enlargement of lymph nodes or splenomegaly</td>
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<td>Eastern Mediterranean† ethnicity</td>
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<td>North Mediterranean† ethnicity</td>
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<td><strong>Absence</strong></td>
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<td>Duration of episodes &gt;6 days</td>
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<tr>
<td><strong>Cut-off</strong></td>
<td>≥60</td>
<td><strong>Cut-off</strong></td>
<td>≥42</td>
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*The clinical features should be related to the typical fever episodes (i.e., exclusion of intercurrent infection or other comorbidities).†Centrifugal migratory, erythematous patches most typically overlying a local area of myalgia, usually on the limbs or trunk.

†Eastern Mediterranean: Turkish, Armenian, non-Ashkenazi Jewish, Arab. North Mediterranean: Italian, Spanish, Greek.
Clinical Classification Criteria

Data from Eurofever Registry (N=1215)
Undifferentiated Fever

- Prolonged
  - Not-FUO
  - F-Not-UO
  - PUF

- Recurrent
  - Intermittent
  - Periodic

Cyclic Neutropenia

### Undifferentiated Fever

**Prolonged**
- Not-FUO
- F-Not-UO
- PUF

**Recurrent**
- Intermittent
- Periodic

### Cyclic Neutropenia

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Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome
Distinctive Features of PFAPA Syndrome

- Clockwork periodicity
- Episodes are stereotypical, circumspect, and unprovoked
- Identifiable prodrome is common
- Upper respiratory tract inflammation
- No rash or arthritis
- Acute phase reaction
- Failure to fail to thrive
- Episodes are aborted by steroids
- Episodes resolve after tonsillectomy
- Syndrome usually resolves by adolescence
- No long-term sequelae

Syndrome of periodic fever, pharyngitis, and aphthous stomatitis

A syndrome of periodic fever that resembles human cyclic neutropenia in its clinical presentation has been identified in 12 children observed at two major referral centers. Attacks characterized by abrupt onset of fever, malaise, chills, aphthous stomatitis, pharyngitis, headache, and tender cervical adenopathy occur at 4- to 6-week intervals over periods of years. These episodes of illness resolve spontaneously in 4 to 5 days. Mild leukocytosis and elevation of the erythrocyte sedimentation rate during attacks are the only laboratory abnormalities. Affected children grow normally, are not unusually susceptible to infection, and exhibit no long-term sequelae. Attacks may be aborted by short courses of prednisone but do not respond to nonsteroidal anti-inflammatory agents. This syndrome is sporadic and appears to be much more common than cyclic neutropenia. (J Pediatr 1987;110:45-6)

Gary S. Marshall, M.D., Kathryn M. Edwards, M.D., Joseph Butler, M.D., and Alexander R. Lowton, M.D.

From the Department of Pediatrics, Division of Immunology and Infectious Diseases, Vanderbilt University Hospital, Nashville, and the Department of Pediatrics, Division of Cellular Immunology, The University of Alabama at Birmingham

In the late 1940s, Reimann proposed the term “periodic disease” to encompass a heterogeneous group of disorders of unknown cause, characterized by uniform limited periods of illness that recur regularly for many years in otherwise healthy individuals. Since then, several periodic syndromes have emerged as distinct entities with well-defined clinical and laboratory features; among these are familial Mediterranean fever, hereditary angioedema, familial periodic paralysis, and human cyclic neutropenia. Other periodic syndromes, such as Behçet disease, are less well defined in terms of pathologic correlates. Reimann more recently proposed that periodic fever is a distinct heritable clinical entity, although he recognizes considerable overlap with other periodic disorders. Specific associations with periodic fever syndromes have been proposed, including elevated unaggregated plasma c-reactive protein and hyperimmunoglobulinemia D. Finally, some periodic disorders remain poorly characterized, such as the “periodic syndrome” of cyclic vomiting, abdominal pain, fever, and somatic complaints in childhood.

We describe 12 children who have a syndrome of periodic fever associated with symptoms that are strikingly similar to those seen during neutropenic episodes in cyclic neutropenia but in whom this disease has been ruled out by careful serial peripheral blood neutrophil counts. All of these children are asymptomatic between febrile episodes.

| ANA | Antinuclear antibody |

have had normal growth and development, and have remained in good general health. Extensive investigation has failed to discum other known causes of periodic fever. We believe that this syndrome represents a previously undescribed, distinct clinical entity.

METHODS AND RESULTS

The clinical and hospital records of 12 children with a unique periodic syndrome were reviewed. These patients were independently referred to two major academic cen-
Marshall’s syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome

Authors: Dr Marco Berlucchi¹ and Dr Piero Nicolai
Creation date: January 2004

Scientific editor: Dr Anne-Marie Prieur

¹Department of Pediatric Otorhinolaryngology, Spedali Civili, Piazza Spedali Civili 1, 25123 Brescia, Italy. marco.berlucchi@tin.it
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**LABORATORY EVALUATION:**

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## PFAPA Syndrome

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<td>Age at onset</td>
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<td>Symptom-free interval</td>
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PFAPA Syndrome: Natural History

Original Registry 1988-97 N=94

Follow-up 2009 N=59
- Death N=1 Argininosuccinate lyase deficiency

Resolved N=50 Age=9.2 yr Duration=6.3 yr

Continuing N=9 Age=20 yr

Remissions N=8 Duration=13 mo

No remissions N=1

Wurster. J Pediatr 2011;159:958
## PFAPA Syndrome: Diagnostic Criteria

<table>
<thead>
<tr>
<th>Criterion</th>
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<th>Thomas 1999</th>
<th>Garavello 2009</th>
<th>Feder 2010</th>
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<td>Regular</td>
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<td>Duration of episodes</td>
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<td>Response to steroids</td>
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</table>

*Other exclusions variously include: FMF, TRAPS, HIGDS, Behcet's, Immunodeficiency, autoimmune disease, chronic infection, arthritis, rash*
Acute Phase Reaction in PFAPA Syndrome

“The earnestness of this Cochrane review article on the so-called PFAPA syndrome raises the frightening possibility that the American otolaryngology profession has been duped into promoting a brand new acronym for what used to be just called recurrent tonsillitis whose basic prerequisite is the presence of tonsils.”

—Hornibrook J. *Otolaryng Head Neck Surg* 2011;144:649
“The earnestness of this Cochrane review article on the so-called PFAPA syndrome raises the frightening possibility that the American otolaryngology profession has been duped into promoting a brand new acronym for what used to be just called recurrent tonsillitis whose basic prerequisite is the presence of tonsils.”

—Hornibrook J. *Otolaryng Head Neck Surg* 2011;144:649

Is PFAPA a “thing”?
You Know When You’ve Seen One
Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis

PFAPA is the most common recurrent fever syndrome in children. It usually presents between the ages of 2 and 5yr with recurring episodes of fever, malaise, exudative-appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, oral aphthae, and, less commonly, headache, abdominal pain, and arthralgia. The episodes last 4-6 days, regardless of antipyretic or antibiotic treatment, and often occur with clock-like regularity on 3-6wk cycles. Findings during the episodes may include mild hepatosplenomegaly, mild leukocytosis, and elevated acute-phase reactants. Both the frequency and the intensity of the episodes diminish with increasing age.

The etiology and pathogenesis of PFAPA remain unknown. The majority of patients show dramatic response to a single oral dose of prednisone (0.6-2.0mg/kg), although this approach does not prevent recurrence and may actually shorten the interval between flares. Cimetidine given at doses of 20-40mg/kg/day is effective at preventing recurrences in approximately one-third of cases. Complete resolution has also been reported after tonsillectomy in some but not all patients. A pilot study of anakinra (1mg/kg subcutaneously) given for
Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA)

Epidemiology and Cardinal Clinical Features

PFAPA was first described in 1987 in 12 children from Tennessee and Alabama. More than 700 cases from multiple continents and racial backgrounds have been reported; there are undoubtedly exponentially more cases not reported. PFAPA appears to be predominantly a sporadic disorder. However, history of recurrent fevers or PFAPA-like illnesses (in parent or sibling) is as high as 20% and 45%, and cases in monozygotic twins are reported. In one study, blood samples from PFAPA patients during flares (12) compared with those during asymptomatic intervals (21) and from healthy controls (21) showed overexpression of complement genes during PFAPA attacks, suggesting an infectious trigger with a strong IP-10, and IL-1/IL-18-mediated response of the innate immune system. Activation and probable recruitment of T lymphocytes to peripheral tissues suggest involvement of adaptive immunity in the pathogenesis of PFAPA. Shortening of asymptomatic intervals in up to 50% of steroid-treated PFAPA patients also is compatible with partial infectious pathophysiology. Multiple studies attempting to
Periodic Fever with Aphthous Stomatitis, Pharyngitis, and Adenitis

Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome (also known as Marshall syndrome) was described in 1987. It is a relatively common condition that has a benign prognosis. The precise etiology is unknown; however, it has been suggested that there is a dysregulation of the immune response in patients with PFAPA that may contribute to the etiology. No genetic mutations or ethnic factors have been associated with PFAPA, and although most cases occur sporadically, there have been reports of siblings and parents with similar presentations.

Clinical Manifestations

The onset of PFAPA is usually before the age of 5 years. In an American series, febrile episodes occurred approximately every 28 days and lasted for a mean of 5 days. It is the most clock-like of the periodic fevers in children. Children are healthy between episodes and grow normally. Malaise, chills, fatigue, and oral lesions may herald the onset of a cycle. Fever may appear suddenly and reach a maximum of 40°C to 41°C and then resolve over a 24 to 48-hour period. In the largest series reported, 70% of patients had aphthous
PFAPA Citations in PubMed

![Graph showing the cumulative number of citations for PFAPA in PubMed over publication years from 1985 to 2015. The number of citations increases significantly after 2010.]
PFAPA Milestones

1999  Thomas. Vanderbilt registry (N=94)
      Padeh. Israel (N=28)
2006  Tasher. Israel (N=54)
2010  Feder. University of Connecticut (N=105)
2011  Wurster. Vanderbilt registry follow-up (N=59)
2013  Forsvoll. Population-based study in Norway (incidence 2.3 per 10,000)
2014  Hofer. Pediatric Rheumatology European Society cohort (N=301)

Clinical features, surrogate markers, natural history, epidemiology
**PFAPA Milestones**

- **2002**  Galanakis. PFAPA among children undergoing tonsillectomy
- **2007**  Renko. Randomized controlled trial in Finland (N=26)
- **2009**  Garavello. Randomized controlled trial in Italy (N=39)
- **2010**  Burton. Cochrane Review 1
- **2011**  Garavello. Systematic review
- **2011**  Baugh. AAO-HNS guidelines
- **2012**  Licameli. Case series (N=102)
- **2014**  Burton. Cochrane Review 2

**Graph:**
- **Y-axis:** Cumulative number
- **X-axis:** Publication year (1985-2015)

**Legend:**
- Clinical features, surrogate markers, natural history, epidemiology
- Tonsillectomy
PFAPA Milestones

2006  Stojanov. Cytokine profile
2010  Brown. Inflammatory mediators
2011  Stojanov. Disorder of innate immunity
       Berkun. MEFV mutations
       Yazgan. CRP and procalcitonin
2013  Kolly. Dysregulated IL-1β production
       Forsvoll. Elevated CXCL10
       Sundqvist. Neutrophil oxygen radical production

Cumulative number

Publication year

Clinical features, surrogate markers, natural history, epidemiology
Inflammation
Tonsillectomy
PFAPA Milestones

2008  Gattorno. Diagnostic score for monogenic PFS
2009  Gattorno. Gaslini score to identify patients at low risk for PFS mutations

Clinical features, surrogate markers, natural history, epidemiology

Differentiation
Inflammation
Tonsillectomy
PFAPA Milestones

2010  Cochard. Familial clustering in Europe
2011  Adachi. Family cluster in Japan
       Antón-Martín. Occurrence in sibs
PFAPA Milestones

2015  Di Gioia. Genome-wide SNPs, whole-exome sequencing
      —autosomal dominant
      —incomplete penetrance
      —unlikely monogenic

- Tonsillectomy
- Inflammation
- Differentiation
- Genetics
- Families

Clinical features, surrogate markers, natural history, epidemiology
PFAPA Milestones

- 2013 Valenzuela. Inflammatory mediators in tonsils
- 2015 Petra. Phenotype of T-cells in tonsils
- Forsvoll. Decreased CD8+ T-cells in tonsils

- Clinical features, surrogate markers, natural history, epidemiology
- Tonsillectomy
- Inflammation
- Differentiation
- Families
- Genetics

Publication year:
Cumulative number:
0 20 40 60 80 100 120 140
PFAPA Milestones

- 2014 Freeman. Microbial RNA sequencing in tonsils
- 2016 Tejesvi. Bacterial rRNA gene sequencing

Graph showing cumulative number of publications over time, with peaks for Clinical features, surrogate markers, natural history, epidemiology, Tonsillectomy, Inflammation, Differentiation, Families, and Genetics.
### Gaslini Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coding</th>
<th>Coefficient</th>
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<tbody>
<tr>
<td>Age at onset</td>
<td>Months</td>
<td>-0.067</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Never= 0</td>
<td>+1.494</td>
</tr>
<tr>
<td></td>
<td>Sometimes or often= 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Always= 3</td>
<td></td>
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<tr>
<td>Aphthosis</td>
<td>Never= 0</td>
<td>-1.504</td>
</tr>
<tr>
<td></td>
<td>Sometimes or often= 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Always= 2</td>
<td></td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>Absent= 0</td>
<td>+1.958</td>
</tr>
<tr>
<td></td>
<td>Present= 1</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Never= 0</td>
<td>+0.901</td>
</tr>
<tr>
<td></td>
<td>Sometimes= 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Often= 2</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>Negative= 0</td>
<td>+1.503</td>
</tr>
<tr>
<td></td>
<td>Positive= 1</td>
<td></td>
</tr>
</tbody>
</table>

*Gattorno. Arth Rheum 2008;58:1823*
Differential Gene Expression

Principal Component Analysis

Hereditary Periodic Fever

PFAPA Flare

PFAPA Non-flare

Control

Stojanov. PNAS 2011;108:7148
N=6 in each group
Hereditary periodic fevers: CAPS=3, FMF=2, TRAPS=1
Differential Gene Expression

- **IL-1β and inflammasome-associated genes**
  - CASP5
  - IRAK3
  - IL1B
  - IL1RN
  - IL18RAP
  - CASP1
  - P2RX7

- **Complement-associated genes**
  - SERPING1
  - C2
  - C1QB
  - C1QA
  - CD59
  - CR1
  - C3AR1
  - C1RL
  - CD46
  - CFB

* Stojanov. PNAS 2011;108:7148
Inflammatory Proteins in Serum

Stojanov. PNAS 2011;108:7148
Tonsillectomy: Meta-analysis

<table>
<thead>
<tr>
<th>Source, year</th>
<th>Observed/Total</th>
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<tbody>
<tr>
<td>Abramson et al, 1989</td>
<td>4/4</td>
</tr>
<tr>
<td>Thomas et al, 1999</td>
<td>7/11</td>
</tr>
<tr>
<td>Padeh et al, 1999</td>
<td>3/3</td>
</tr>
<tr>
<td>Dahn et al, 2000</td>
<td>0/5</td>
</tr>
<tr>
<td>Galanakis et al, 2002</td>
<td>15/15</td>
</tr>
<tr>
<td>Parikh et al, 2003</td>
<td>0/2</td>
</tr>
<tr>
<td>Berlucchi et al, 2003</td>
<td>5/5</td>
</tr>
<tr>
<td>Tasher et al, 2007</td>
<td>6/6</td>
</tr>
<tr>
<td>Renko et al, 2007</td>
<td>14/14</td>
</tr>
<tr>
<td>Licameli et al, 2008</td>
<td>26/27</td>
</tr>
<tr>
<td>Wong et al, 2008</td>
<td>8/9</td>
</tr>
<tr>
<td>Garavello et al, 2009</td>
<td>12/19</td>
</tr>
<tr>
<td>Pignataro et al, 2009</td>
<td>5/9</td>
</tr>
<tr>
<td>Peridis et al, 2009</td>
<td>8/9</td>
</tr>
<tr>
<td>Feder and Salazar, 2010</td>
<td>11/11</td>
</tr>
<tr>
<td>Overall</td>
<td>124/149</td>
</tr>
</tbody>
</table>

Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA) (Review)

Burton MJ, Pollard AJ, Ramsden JD, Chong LY, Venkamp RP

THE COCHRANE COLLABORATION

This is a preprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2014, Issue 3

http://www.thecochranelibrary.com

WILEY
Clinic visit 1/1/08-12/31/12 (N=4586)

Exclusions

Referred for unexplained fever (221)

“Fever”, “febrile”, “FUO” not included in diagnosis (4118)
Established patient visit (159)
Initial consult in hospital (51)
Not referred for fever (17)
Initial visit before 2008 (8)
Records not available (3)
Referred for typhoid fever (2)
Referred for scarlet fever (1)
Referred for fever blisters (1)

Prolonged (69)

Not having fever (10)
Having fever (59)

Diagnosis apparent on initial visit (11)
Fever of unknown origin (48)

No diagnosis established (33)
Diagnosis established (15)

Recurrent (152)

Not having fever (10)
Having fever (59)

Fever of unknown origin (48)

Statler. JPIDS 2015. DOI:10.1093/jpids/piv008
Clinic visit 1/1/08-12/31/12 (N=4586)

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Recurrent (152)
  Intermittent (92)
  Periodic (60)

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Recurrent (152)
  Intermittent (92)
  Periodic (60)
    Self-limited illnesses or no diagnosis established (84)
      Diagnosis established (8)

Statler. JPIDS 2015. DOI:10.1093/jpids/piv008
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Diagnosis established (15)  

Recurrent  
(152)  
Intermittent  
(92)  
Periodic  
(60)  
Self-limited illnesses or no diagnosis established (84)  
Diagnosis established (8)  
No diagnosis established (39)  
Periodic fever syndrome (21)  
PFAPA (20)  
FMF (1)  

Statler. JPIDS 2015. DOI:10.1093/jpids/piv008
# Undifferentiated Fever in Pediatric ID Clinic

<table>
<thead>
<tr>
<th>Final Diagnostic Category</th>
<th>Fever Pattern</th>
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<td>Prolonged (N=69)</td>
<td>Recurrent (N=152)</td>
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<tr>
<td>No illness, self-limited illness, or no diagnosis made</td>
<td>43 (62%)</td>
<td>123 (81%)</td>
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<td>Mild or moderate illness</td>
<td>18 (26%)</td>
<td>25 (16%)</td>
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<tr>
<td>Serious illness</td>
<td>8 (12%)</td>
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Statler. IDSA Meeting, October 2014
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</tr>
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</table>

Inflammatory bowel disease (3)  
Juvenile idiopathic arthritis (2)  
Acute lymphoblastic leukemia (1)  
Familial Mediterranean fever (1)  
Systemic lupus (1)  
Malaria (1)  
Rheumatic fever (1)  
Typhoid fever (1)  
EBV infection w/HLH (1)
He’s got the fever
Oh, he’s got the fever
Nothing a po’ boy can do