Prolonged and recurrent fevers in children

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Copenhagen
Normal mean rectal temperature

Mean 37.7°C, SD 0.38

Mean 37.4°C

S. Long, Princ Pract
PID 2012; p 117
Measuring temperature
Measuring temperature
Fever is defined as an endogenous elevation of at least one measured body temperature of $\geq 38^\circ\text{C}$

… irrespective of device, anatomic site, age, or environmental conditions

Marcy. Vaccine 2004;22:551
Undifferentiated fever

- Fever is the main complaint
- Not associated with a defined clinical illness
- Not "fever without a source"
- Previously healthy
Undifferentiated fever

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

Recurrent
- Intermittent
- Periodic
Patient is NOT having abnormal temperatures
Undifferentiated fever

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

Causes
- Temperatures usually runs low
- Diurnal temperature variation
- Meals
- Ovulation
- Tobacco and chewing gum
- Exercise
- Environmental conditions

Undifferentiated fever

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

- Recurrent
  - Intermittent
  - Periodic

Clues
- Healthy appearance
- Normal growth/development
- Stable weight
- School absences for subjective complaints
- Behavioral problems
- Fear of malignancy
- Family stress
- Normal physical exam

Undifferentiated fever

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

Recurrent
- Intermittent
- Periodic

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
  - FUO

- Recurrent
  - Intermittent
  - Periodic

Diagnoses
- URTI (otitis media, sinusitis)
- LRTI (pneumonia)
- CNS infection
- TB
- Leukemia
- Kawasaki disease
- JIA
- IBD
Fever for 3 weeks

- 8 year old girl
- Turnes up at the Paediatric Department
- Headache, back pain, leg pain, stomach pain
- Tired, 3 kg weightloss
- Normal examination except dry cough and temp. 38.0°C

- Previously: asthmatic bronchitis
- Pakistan for 4 months 1 year ago
Fever for 3 weeks
Undifferentiated fever

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

Graph showing temperature vs. days before referral.
Defining prolonged fever of unknown origin

- Illness > 3 weeks
- Fever > 38.3°C on several occasions
- Diagnosis uncertain after 1 week in hospital
Defining prolonged fever of unknown origin

<table>
<thead>
<tr>
<th>Reference</th>
<th>Temperature (≥)</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>°C</td>
<td>°F</td>
<td></td>
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<tr>
<td>McClung, 1972</td>
<td>38.9</td>
<td>102.1</td>
<td>Multiple occasions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pizzo, 1975</td>
<td>38.6</td>
<td>101.4</td>
<td>≥5 occasions</td>
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<tr>
<td>Lohr, 1977</td>
<td>38.4</td>
<td>101.1</td>
<td>Multiple occasions</td>
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<tr>
<td>Steele, 1991</td>
<td>38.1</td>
<td>100.5</td>
<td>≥2 occasions/wk</td>
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<tr>
<td></td>
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<tr>
<td>Jacobs, 1998</td>
<td>38.1</td>
<td>100.5</td>
<td>Daily</td>
</tr>
</tbody>
</table>
UpToDate definition of FUO in children

- Core body temperature of $\geq 38.3^\circ\text{C}$
- $\geq 1$ occasion every day
- $\geq 8$ consecutive days
- No diagnosis after initial outpatient or hospital evaluation including careful history, physical examination and initial laboratory assessment

Factors affecting cause of FUO in case series

- Geography
- Age
- Host factors
- New diseases
- Physician experience
- Referral patterns
- Availability of laboratory tests and imaging
- Managed care
Causes of FUO in children - USA

Marshall, J infection 2014;S84
Causes of FUO in children - USA

Marshall, J. Infection 2014; S84
FUO in adults

Horowitz H, NEJM 2003; 368:3
Infectious causes of FUO in children - USA

Marshall, J infection 2014;S84
Bacterial infections in children with FUO
If it’s infection there is always a source
- Travel
- Raw foods
- Ill persons
- Insect bites
Undifferentiated fever

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

Recurrent
- Intermittent
- Periodic

Inflammatory and autoimmune diseases
- Inflammatory bowel disease
- Juvenile idiopathic arthritis
  - Rheumatic fever
- Kawasaki disease (incomplete)

- Wegeners granulomathosis
- Sarcoidosis
- Behcet disease
- Lupus
- HLH
Undifferentiated fever

Prolonged
- Not FUO
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- FUO

Recurrent
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Malignancies
- Leukemia
- Lymphoma
- Neuroblastoma

- Hepatoma
- soft tissue sarcoma
Undifferentiated fever

Prolonged
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- F-Not-UO
- FUO

Recurrent
- Intermittent
- Periodic

Miscellaneous
- Munchausen by proxy
- Factitious fever
- Drug fever
- Central fever
- Pulmonary embolus
- Dysautonomia
- Diabetes insipidus
- Ectodermal dysplasia
- Hyperthyroidism
- Hematoma
Characteristics of Patients Referred to a Pediatric Infectious Diseases Clinic With Unexplained Fever

Victoria A. Statler and Gary S. Marshall
Division of Pediatric Infectious Diseases, University of Louisville School of Medicine, Louisville, Kentucky

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Received December 16, 2014; accepted February 3, 2015; electronically published March 8, 2015.
Unexplained fever

- Prolonged
  - Not FUO, N=10
  - F-Not-UO, N=11
  - FUO, N=48
  - Diagnosis, 31%
- Recurrent
  - Intermittent, N=92
  - Periodic, N=60
  - 9%
  - 35%

75% had no fever, self-limited illness or no diagnosis

5% had a serious illness

Statler V, J Ped Infect Dis Soc 2016;5:249-561
Undifferentiated fever

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- FUO

Recurrent
- Intermittent
- Periodic

Approach to diagnosis
- Severity of findings dictates pace of evaluation
- Serial evaluations
- Avoid antimicrobials
- Use time as a diagnostic tool
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

Third visit
Interval Hx and PE
CBC with smear
CMP
ESR and CRP

Targeted studies

Fever/symptom diary

Fever/symptom diary
Targeted studies

- **Infectious diseases**
  - TST, IGRA
  - EBV and CMV serology
  - HIV Ab/Ag or PCR
  - Bartonella serology
  - Brucella serology
  - Toxoplasma serology
  - Tularemia serology
  - Histoplasma serology
  - Stool culture

- **Autoimmune/autoinflammatory**
  - ANA and RF
  - ASO and anti-DNAse-B
  - C3, C4

- **Malignancy**
  - Flowcytometry
  - LDH and uric acid
  - Bone marrow
  - PET-CT

- **Miscellaneous**
  - Thyroid function tests
  - Sinus CT
  - Echocardiogram
  - Endoscopy
  - Abdominal US or CT
  - Bone scan
  - PET scan
FDG-PET-CT in children with FUO

- Results similar to adults
- Sensitivity 80-90%
- Clinical helpful 45%
- FP
- FN

Houseni M. PET Clin 3, 2009: 605-19
Undifferentiated fever

- Prolonged
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  - FUO
- Recurrent
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  - Periodic

Sequential, common, self-limited illness
- Epidemiological clues (daycare)
- Diagnosis
  - Careful fever and symptom chart
  - Screening laboratory studies
  - Time
Undifferentiated fever

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- Not FUO
- F-Not-UO
- FUO

Recurrent
- Intermittent
- Periodic

Sequential, common, self-limited illness

Autoinflammatory diseases
- Abnormally increased inflammation
- Predominantly mediated by molecules and cells of the innate immune system (as opposed to autoantibodies or autoreactive T cells)
- Significant host predisposition
<table>
<thead>
<tr>
<th>Feature</th>
<th>Inflammasomopathies</th>
<th>Extrinsic</th>
<th>Protein folding disorder</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Intrinsic</td>
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<td>European</td>
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<td>Any</td>
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<td>Age at onset</td>
<td>&lt;1 yr</td>
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<td>&lt;1 yr</td>
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<td>Triggers</td>
<td>Cold</td>
<td>Cold</td>
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<tr>
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<td>Continuous</td>
</tr>
<tr>
<td>Distinctive features</td>
<td>Rash Conjunctivitis</td>
<td>Rash Conjunctivitis</td>
<td>Rash Meningitis Arthropyathy Deafness Deafness</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Treatment</td>
<td>Anti-IL-1</td>
<td>Anti-IL-1</td>
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Undifferentiated fever

- Prolonged
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Cyclic neutropenia

Temperature

Neutrophile count/mL

39°C

Days before arrival
Undifferentiated fever

- Prolonged
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  - FUO
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  - Periodic

PFAPA

Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome
Distinctive Features of PFAPA Syndrome

- Clockwork periodicity
- Fever episodes are stereotypical and unprovoked
- Identifiable prodrome is common
- Upper respiratory tract inflammation
- No rash or arthritis
- Elevated acute phase reactants
- No failure-to-thrive
- Episodes are aborted by steroid therapy
- Episodes resolve after tonsillectomy
- Resolves by adolescence
- No long-term sequelae
Cases
3 year old girl with recurrent fever
Neonatal History

- Uncomplicated pregnancy, para 1
- Acute caesarean section at GA 38
- Apgar scores 3/1, 6/5 and 9/10. Birth weight 3,510 g
- Neonatal sepsis and hepatitis
- Treatment: n-CPAP, phototherapy, antibiotics, diuretics, and blood transfusions
- Congenital viral infection?
History & Examination

• From 3 mo: recurrent white coatings and blisters on the tongue
• From 5 mo: episodes of fever 39-40°C every second week, cervical lymphadenitis, rash, and more blisters in the mouth
• Each illness episode between 6 and 14 days
• Adenotonsillectomy no effect
• Normal growth and development

• Normal physical exam, no fever
• CRP 7 mg/L, tbc 505x10⁹/L, leuco 12.7x10⁹/L, hgb 5.8 mmol/L, ESR 29 mm/h
• Negative HIV, CMV and EBV antibodies
1 month later

- Temp 38.5°C
- Rhinitis
- Tender cervical adenitis
- No other physical findings
- Normal chest X-ray
- CRP 142 mg/L, ESR 72 mm/h
<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>5.2 mmol/L</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>10.9x10⁹/L</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>505x10⁹/L</td>
</tr>
<tr>
<td>Urat</td>
<td>0.49 mmol/L (ref. 0.15-0.35)</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>203 U/L (ref. 155-450)</td>
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<tr>
<td>IgD</td>
<td>100 IU/mL</td>
</tr>
<tr>
<td>IgG</td>
<td>12.3 g/L (ref. 3.4-9.1)</td>
</tr>
<tr>
<td>IgA</td>
<td>3.08 g/L (ref. 0.12-1.49)</td>
</tr>
<tr>
<td>IgM</td>
<td>1.64 g/L (ref. 0.39-2.08),</td>
</tr>
<tr>
<td>IgG subclasses</td>
<td>Normal</td>
</tr>
<tr>
<td>Blood culture</td>
<td>Negative</td>
</tr>
<tr>
<td>Blood smear</td>
<td>Reactive, no lymphoblasts</td>
</tr>
<tr>
<td>Complement defect screening</td>
<td>Normal</td>
</tr>
<tr>
<td>Vaccination response to HiB, diphtheria, tetanus</td>
<td>Normal</td>
</tr>
<tr>
<td>Mannan binding lectine (MBL)</td>
<td>220 g/L</td>
</tr>
<tr>
<td>Haemoglobin electrophoresis</td>
<td>Normal</td>
</tr>
<tr>
<td>Tracheal aspirate</td>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Discrete perihilar infiltrates</td>
</tr>
<tr>
<td>Urine culture</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Following 6 weeks

- 3 hospitalizations
- Symptoms: Fever, rhinitis, cervical adenitis, **stomatitis**, macular rash on the legs
- CRP 104-235
- Chest X ray: normal
- Urine dip stick: normal
- Treatment: cefuroxim, gentamyxin, amoxi/clav
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<tr>
<td>Blood smear</td>
<td>Atypical lymphocytes, no malignancy</td>
</tr>
<tr>
<td>Bone marrow aspiration</td>
<td>Hypoplastic marrow, no malignancy</td>
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<tr>
<td>Mutation analysis for FMF</td>
<td>Negative</td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
</tr>
<tr>
<td>ANCA</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>Negative</td>
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<tr>
<td>PCR parovirus</td>
<td>Negative</td>
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<tr>
<td>PCR EBV</td>
<td>Negative</td>
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<tr>
<td>Lymphocyte subpopulations</td>
<td>Normal</td>
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<td>Lymphocyte stimulation tests</td>
<td>Normal</td>
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<tr>
<td>Tuberculin Skin Test</td>
<td>Negative</td>
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<tr>
<td>Sweat test</td>
<td>Sweat Sodium 68 mmol/L (slightly elevated)</td>
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<td>Delta 508 mutation analysis</td>
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<td>X-ray thorax</td>
<td>Normal</td>
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<tr>
<td>Echocardiography</td>
<td>Small mitral insufficiency, not haemodynamic significant</td>
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<tr>
<td>US abdomen</td>
<td>Slight hepatomegaly with hyperechogenic patches</td>
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Diagnosis?

- IgD 2012.6 IU/mL
- Urine mevalonic acid: 21.8 µmol/mmol
- Genetic analysis: compound heterozygote for the V377I and the c.417insC mutations in the MVK gene
- ~ 100 sick days a year
Mevalonate Kinase Deficiency (Hyper IgD Syndrome)

• IgD 2012.6 IU/mL
• Urine mevalonic acid: 21.8 µmol/mmol
• Genetic analysis: compound heterozygote for the V377I and the c.417insC mutations in the MVK gene

• ~ 100 sick days a year

Treatment:
Steroids
Eternacept
Anakinra
### Autoinflammatory diseases

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</table>
10 year old girl with fever
History

- Fever, cough and malaise 2 weeks ago
- Now fever for 7 days
- Coughing
- Itchy rash on legs and arms
- Pain all over the body
- Antihistamines no effect
- Cefur+genta no effect
- Transferred for second opinion
Past history

• Family Hx: Mom has asthma, brother asthmatic bronchitis, no rheumatic diseases
• Exposures:
  • Charter trip to Turkey 1 yr ago
  • 1 Cat, 4 kittens and a turtle at home
  • 3 weeks prior to symptoms slept in an animal park. Hugged a donkey

• No allergies
• Asthma for 1 yr
• Appendectomy 1 yr ago
• + all childhood vaccinations
• Medicine: Pulmicort 200 microg x 2, beta2agonist p.n.
Physical examination day 7 of fever

- Pale
- Superficial breathing, tachypnoeae
- Heart murmur
- Mild cervical adenitis
- Red throat, normal tonsils
- Rash on inner legs and arms
- Pain in left shoulder
- A spider in the left ear
- No visible joint involvement

- Temp. 38.3°C in ear
- RF 60
- P 128
- BT: 106/56
- Sat: 98% → 90%
- CCR 2 sek
Lab results

- CRP 279 → 325
- ESR 100
- Leuco 27 (24 neutro)
- HgB 6.4
- Thrombocytes 464
- Ferritin 602
- Albumin 18
- IgG 9.2
- Normal U&E, Liver parameters
- Normal RF and ANA screen
Chest X-ray day 7

Fluid on left side?  
Cardiomegaly?  
US: 8 mm fluid  
Puncture 12 mL yellow fluid

**ECHO**: small pericardial effusion

→ Meronem + cipro
PET-CT day 9

Bilat. infiltrates in lungs
Bilat. pleural effusion 1 cm
Pericardial effusion 1.5 cm
No other sites of inflammation
Day 10 of (high) fever

- Meropenem & cipro
- Paracetamol, ibuprofen, morphine
- Temp. 40°C
- ECHO: No aneurisms
- IVIG 2 g/kg
Next few days

---

Day 11

- Afebrile
- Good appetite
- Out of bed
- CRP 144
- Leucocytes 17.3

Day 12

- Temp. 38.7°C
- IVIG
Day 13 of fever
Day 14 of fever

- CRP 170 mg/L
- Sep cipro
- Rp. Doxycycline
- Rp. azihromycine
- Rp. Methylprednisolone 15 mg/kg 3 days

→ Afebrile day 15
## Microbiology

<table>
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<tr>
<th>Test</th>
<th>Pathogen</th>
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<tr>
<td>Blood culture</td>
<td>F. tularensis</td>
</tr>
<tr>
<td>Urine culture</td>
<td>Bartonella</td>
</tr>
<tr>
<td>EBV &amp; CMV &amp; parvovirus serology</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Adenovirus PCR</td>
<td>Borrellosis</td>
</tr>
<tr>
<td>Mycoplasma, legionella, c. pneumoniae, c. psittaci</td>
<td>Coxiella</td>
</tr>
<tr>
<td>Throat swap</td>
<td>Paracocci</td>
</tr>
<tr>
<td>Resp. Viruses PCR</td>
<td>IGRA</td>
</tr>
<tr>
<td>BAL for pneumocystis &amp; TB</td>
<td>Galactomannan</td>
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<tr>
<td>LUT, PUT</td>
<td>HBsAg, HAV</td>
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<tr>
<td>Pleural exudate culture + 16S</td>
<td>F-calprotectin</td>
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<tr>
<td>Brucellosis</td>
<td>Faeces culture</td>
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<tr>
<td>Leptospirosis</td>
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</table>
Further investigations- and treatment

- Ophthalmologic exam
- Fibroscan
- LFU: FEV1 31%, FVC 35%
- HRCT lungs
- BAL
- Day 26: US right knee synovitis
- Continues low-grade fever

- Day 27: Methylprednisolone 30 mg/kg 3 days
- Prednisolone

→ Afebrile and well
Final diagnosis?

Systemic juvenile idiopathic arthritis

Started on roActemra (IL-6 inhibitor) 2 months after first hospitalization

Feels better
All inflammation parameters normalized
Lung function improved
Undifferentiated fever

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Undifferentiated fever

Prolonged

Recurrent

Intermittent

Periodic

FUO

F-Not-UO

Not FUO