Fever of Unknown Origin in Pediatrics

Andrew Nowalk MD PhD
Division of Infectious Disease
UPMC Children’s Hospital of Pittsburgh
Disclosure

• This presenter and presentation have no financial conflicts of interest.
### Objectives

<table>
<thead>
<tr>
<th>Understand</th>
<th>Name</th>
<th>Describe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand the definition of fever of unknown origin (FUO) and fever without source (FWS) in children</td>
<td>Name the most common causes of FWS and FUO in children</td>
<td>Describe the appropriate evaluation of children with FWS and FUO</td>
</tr>
</tbody>
</table>

**Case based approach**
Definitions

• Important to differentiate FWS and FUO

• FWS
  – A child with fever and no apparent focus of infection
  – Fever duration is short
  – Pre PCV/HiB vaccines – mostly viral (but occult bacteremia)
  – Post PCV/HiB vaccines – mostly viral (but some UTI)

• FUO
  – Prolonged fever
FUO Definitions

• Original from adult literature
  – Fevers >38.4°C (101.2°F) over ≥3 weeks without cause after ≥ 1 week in the hospital
  • Petersdorf and Beeson, Medicine 1961

• Pediatric – fever of __ for __ without __
  – Temperature – some say 38.0 (100.4), some 38.3 (100.9)
  – Duration – older papers say 21 days, newer say 8-14
  – Signs? Localizing symptoms? Obvious cause?
My FUO definition

• Fevers daily
  
  Have to be, lots of viruses can have biphasic course

• At least 38.0 and higher
  
  Some should be higher, 38.3 or more

• For 2 weeks
  
  I hedge between 2 and 3 weeks, a lot of fevers vanish here

• Without clear source
  
  Leg pain, belly pain, cough means a more focal workup
Approach is as important as science

- Equipment
  - Need rectal/oral temps

- Reassurance
  - Benign nature of FUO in kids vs. adults

- Measured
  - Logical stepwise progression

- Follow-up until resolution
  - One way or another
History and physical most important medical aspects

• Determine pattern of febrile illness:
  – Prolonged fever with few other symptoms/signs (FUO)
  – Longer than expected for known illness (e.g. URI)
  – Recurrent fevers/recurrent illnesses
  – Periodic fever
History: Fever

• How are they taking the temperature?
  – Axillary and adding a degree?
  – Rectal and subtracting a degree?
  – Mom-ometer?
  – Is the child even febrile?
Normal range of body temperature in children

• Daily maximum 100.5°F
  – 100.8° - 102°F in some studies
    • But remember normal curve only includes 95%
• Highest daily maximum in toddlers
• Diurnal variation >1°F
  – Highest in afternoon-evening in young children
Building confidence with parents

• Thorough and careful evaluation
• Be careful what you say and how you say it
  – “Probably a virus” often interpreted as “nothing wrong”
• Plant the seed of resolution early
  – Outpatient, stepwise, no empiric antibiotics
History: Symptoms

**Extensive ROS is critical**
- The more complete, internist-like review
  - Especially ID favorites!

**Small clues may be meaningful**
- Constitutional: weight loss, fatigue, night sweats, etc.
- Persistent respiratory symptoms
- Vague abdominal complaints
- Vague musculoskeletal complaints
History: Exposures

• Animals including home, friends, school, etc
  – Cats, reptiles, birds
• Travel
• Food: unpasteurized, uncooked, foreign
• Contacts: immigrants, incarceration, overseas military
Past History

• Recent dental work or procedure
• Recurrent infections
  – Immunodeficiency?
  – Complications of frequent infections
    (e.g. AOM $\rightarrow$ mastoiditis)
• Previous febrile episodes
• Immunizations
Family History

• Recurrent fevers
• Frequent infections
• Autoimmune/rheumatologic disease
• Ethnicity (Mediterranean, Hibernian)
• Consanguinity
Physical Exam

• Growth charts
• Lymphoid tissue
  – Tonsils, cervical, axillary, inguinal nodes
• Careful cardiac exam
• Hepatosplenomegaly
• Thorough joint exam
  – Earliest sign of arthritis is limited ROM
• Enanthem/ exanthem
Most pediatric FUO are unusual presentations of common infections
## Etiologies of FUO in children

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Number</th>
<th>165</th>
<th>99</th>
<th>100</th>
<th>20</th>
<th>54</th>
<th>146</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td></td>
<td>63 (38)</td>
<td>29 (28)</td>
<td>52 (52)</td>
<td>7 (35)</td>
<td>18 (33)</td>
<td>64 (44)</td>
<td>47 (59)</td>
</tr>
<tr>
<td>Collagen-vascular</td>
<td></td>
<td>9 (5)</td>
<td>11 (11)</td>
<td>20 (20)</td>
<td>3 (15)</td>
<td>8 (15)</td>
<td>9 (6)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>IBD</td>
<td></td>
<td>0</td>
<td>3 (3)</td>
<td>0</td>
<td>1 (5)</td>
<td>3 (6)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Neoplasm</td>
<td></td>
<td>3 (2)</td>
<td>8 (8)</td>
<td>6 (6)</td>
<td>1 (5)</td>
<td>7 (13)</td>
<td>4 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>18 (11)</td>
<td>16 (16)</td>
<td>10 (10)</td>
<td>2 (10)</td>
<td>8 (15)</td>
<td>5 (3)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td></td>
<td>9 (5)</td>
<td>11 (11)</td>
<td>12 (12)</td>
<td>6 (30)</td>
<td>10 (19)</td>
<td>62 (42)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Resolved during FU</td>
<td></td>
<td>35 (21)</td>
<td>21 (20)</td>
<td></td>
<td></td>
<td></td>
<td>62 (42)</td>
<td></td>
</tr>
</tbody>
</table>

Studies compiled in Long et. al PPPID
<table>
<thead>
<tr>
<th>Infectious</th>
<th>Viral</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
<td>Adenovirus</td>
<td>Blastomyces</td>
</tr>
<tr>
<td>Bartonella</td>
<td>Arbovirus</td>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Cytomegalovirus</td>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Enterovirus</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Mastoiditis</td>
<td>Epstein-Barr Virus</td>
<td>Leishmaniasis</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>Hepatitis Viruses</td>
<td>Lymphogranuloma</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Herpes Simplex</td>
<td>Malaria</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Virus</td>
<td>Psittacosis</td>
</tr>
<tr>
<td>Rat Bite Fever</td>
<td>Human</td>
<td>Q Fever</td>
</tr>
<tr>
<td>Salmonellosis</td>
<td>Immunodeficiency</td>
<td>Rocky Mountain Spotted Fever</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Virus</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Pioconaviruses</td>
<td>Visceral larva migrans</td>
</tr>
<tr>
<td>Tularemia</td>
<td>Non-Tuberculosis</td>
<td>Mycobacteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Infectious</th>
<th>Oncologic</th>
<th>Autoimmune</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Lymphoma</td>
<td>Behcet Disease</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Langerhans Cell</td>
<td>Histiocytosis</td>
<td>Inflammatory Bowel Disease</td>
<td>Insipidus</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Hyperthyroidism</td>
<td>Drug Fever</td>
<td>Factitious Fever</td>
</tr>
<tr>
<td>Hemophagocytic</td>
<td>Granulomatosis</td>
<td>Hyperthyroidism</td>
<td>Familial</td>
</tr>
<tr>
<td>Lymphohistiocytosis</td>
<td>(with polyangitis)</td>
<td>Periodic Fever</td>
<td>Dysautonomia</td>
</tr>
<tr>
<td></td>
<td>Juvenile Idiopathic</td>
<td>Syndromes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kawasaki Disease</td>
<td>Serum Sickness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polycytosis Nodosa</td>
<td>Cyclic neutropenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
<td>Kikuchi-Fujimoto Disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic Lupus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythematous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody Syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute thyroiditis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
High yield infections and FUO

- Respiratory most common: CAP (± lung abscess, empyema), chronic sinusitis, including prolonged resp virus
- Disseminated bacterial and viral – EBV, CMV, parvovirus, Bartonella, Lyme, TB
- Endocarditis (especially CHD, IVDU in adolescents)
- UTI (especially complicated)
- Abscess: especially intra-abdominal, ruptured appy
- Osteomyelitis: vertebral, pelvic, Bartonella
Laboratory studies: First Blood

- CBC, manual differential/smear, platelets
- ESR, CRP
- CMP
- UA + urine culture
- Blood culture
- Stool culture x 3 only if diarrhea
- Consider:
  - CXR
  - EBV/CMV/Parvovirus/Bartonella titers
  - Lyme titers? PPD?
Close PLANNED follow up essential

• You will call with test results positive or negative

• Parents have clear indications to call you
  – Change in fever pattern, localizing signs/symptoms

• FEVER DIARY

• You will see them weekly until...
One of three things happen

1. Fever resolves with or without an answer
   – Miller time

2. An etiology declares itself
   – Focal bone pain, positive lab result, etc
   – Treat or not as indicated

3. Fever persists without symptoms
   – Follow every 1-2 weeks and repeat tests periodically
   – Consider second round tests
Potential second round tests

- CXR (if not done before)
- HIV
- Quantitative immunoglobulin levels (QUIGs)
- PPD/IGRA if not done first round
- Sinus CT
- Chest/ abdomen/ pelvis CT
- Targeted serology (shotgun not indicated)
What if it just won’t go away? Third round?

• Usually best to stick to weekly follow up and only order tests as indicated after initial
• Rarely fishing expeditions: Gallium scan/fast MRI, bone marrow aspirate, LP
Collagen-vascular diseases

• Systemic onset JIA (Still’s disease)
• SLE
• IBD (Crohn’s)
Malignancies

• Rare compared with adults
• Lymphoma/leukemia 80%
• Other malignancies: Lymphohistiocytosis, Rosai-Dorfman disease, neuroblastoma
• NOTE: if bone marrow obtained, also culture for bacteria, AFB and fungus
Miscellaneous

- Normal physiologic variation
- Immunodeficiency (B cell)
- Drug fever
- Factitious
- Diabetes insipidus
- Hypothalamic (if brain damage)
Periodic febrile syndromes
COMMON periodic fever: PFAPA

- **Periodic Fever, Aphthous stomatitis, Pharyngitis, and Adenitis**
- Usually starts in toddler years
- Every 3-8 weeks, lasts 3-4 days
- Completely well in between
- Treat with prednisone to shorten episode
- If child fits this well, stop here
UNCOMMON periodic fever: everything else

• Familial Mediterranean fever
• Hyper-IgD syndrome (Hibernian fever)
• Cyclical neutropenia
• TNF-receptor associated (TRAPS)
Cases
Case 1

- 4 year old female, previously healthy
- Fever daily 102-103 for two weeks
- Vague abdominal pain but no vomiting or diarrhea, eating and drinking
- Maybe mild abdominal tenderness on exam
Case 1 continued

- Family has a kitten
- She has been scratched
- Bartonella titers elevated 1:512
- Abdominal imaging shows multiple lesions in liver and spleen
The new boss

- CSD is recent series is among the most common causes of FUO
- Often requires no therapy
- Can occur in the absence of adenopathy or abdominal findings
Case 2

• 6 year old previously healthy boy
• Fever x 12 days
• Nonspecific erythematous macular rash
• Well-appearing, not chronically ill
• No complaints of joint pain, but has arthritis in ankles and wrists
Case 2 continued

• CBC reveals anemia, minimally elevated ESR
• Parvovirus IgM strongly positive
Fever and joint findings

• Parvovirus is a good fit
• In Lyme endemic areas (= PA!), *always* think about Lyme
Case 3

• 6 month old previously healthy infant
• Was admitted to OSH for 8 days of fever and leukocytosis, treated with ceftriaxone for a few days, sent home
• Returned one week later with fever, leukocytosis and diarrhea
Case 3 continued

• Family keeps chickens on the property
• One out of 4 stool cultures positive for Salmonella
• Resolves with ceftriaxone
Keep on watching

• New symptoms that develop over time are key
FUO Pediatric take home points

• Mostly benign and most resolve unanswered
• Unusual presentations of common diseases
• Explanation of nature of FUO, approach and concrete plan with parents critical
• Avoid excessive “blind” testing and follow the child