Recurrent Fever in Childhood: What Must Be Considered?

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Disclosures

• Speaker Bureau: Sanofi-Pasteur, Merck, Takeda, Boehringer
• Consultant: Sanofi-Pasteur, Takeda, Pfizer

Objectives

• Upon completion of this lecture, the participant will be able to:
  – Discuss various causes of fever of recurrent fever or fever of unknown origin in children
  – Identify the most common tests to identify etiology of pediatric recurrent fevers
  – Discuss treatment options for children with recurrent fevers
Starting With the Basics

No Single Accepted Definition of Fever

- What is a fever?
  - Rectal temperature above 100.4°F (38°C)
  - Oral temperature above 100°F (37.8°C)
  - Axillary (armpit) temperature above 99°F (37.2°C)
  - Ear (tympanic membrane) temperature above 100.4°F (38°C) in rectal mode or 99.5°F (37.5°C) in oral mode
  - Forehead (temporal artery) temperature above 100.4°F (38°C)

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3287087/ accessed 08-01-2015

No Consensus: Recurrent Fevers in Children

- Recurrent fevers are defined as:
  - Three or more febrile episodes
  - Over a six-month period
  - Occurring at least seven days apart
  - No causative medical illness

Approach to Child with Recurrent Fever

• Extensive History
  — How was temperature obtained
  — Duration
  — Pattern
• Review of Systems
  — Exposures
  — Genetic background
  — Extensive review of system

Comprehensive Physical Examination

• Thorough general examination
  — Growth chart
• Identification of target organ abnormalities
• Notation of:
  — Mouth ulcers
  — Rashes
  — Joint abnormalities
  — Lymph nodes

Laboratory Evaluation

• CBC with differential
• CMP
• Uric acid and LDH
• Urine and culture/sensitivity
• ANA, RF, anti-CCP, Sed rate, CRP
• Blood cultures
• Stool cultures
• Chest X-ray
• Other tests dictated by HPI/ROS/PE
  — Mantoux
  — CMV
  — Epstein Barr Panel
  — Tick borne illnesses
  — Hepatitis panel
  — HIV
Differential Diagnosis

- Recurrent Viral / Bacterial Infections
- Infections suppressed w/ intermittent antibiotics
  - Endocarditis, Occult abscess
- Uncommon Infectious Etiologies
  - Malaria
  - Mycobacteria
- Autoimmune Diseases:
  - Autoimmune Lymphoproliferative Syndrome (ALPS) – JIA, SLE
  - Inflammatory Bowel Disease
- Neoplasia

Case Study: K.E

- 16 year old with 3+ weeks of fever, chills, lethargy and achy joints
- Fevers almost daily; up to 100 – 101
- Recent travel – over past 1 month to Caribbean for vacation; no illnesses while there
- Has seen primary care x 3 with no explanation
- Being seen today requesting referral
- No medications, allergies
- No diarrhea, swollen joints, lymphadenopathy

Today

- T: 100 orally
- P: 80
- Respirations: 16
- BP: 98/60
- Skin: no jaundice, hydrated
- HEENT: normal; no erythema, exudate
- Nodes: nonpalpable, nontender
- Lungs: clear
- Heart: S1S2: RRR; No S3, S4, murmurs, rubs
- Abdomen: + BS, no masses, tenderness, HSM
- PV: normal; no edema
- Neuro: normal
- MS: normal; no edema
Previous Workup

- Chest X-ray: normal
  - Treated with antibiotic for suspected pneumonia without improvement
- Quick strep and throat culture: negative
- Monospot: negative
- CBC: normal WBC with lymphocytosis
- CMP: elevated LFTs: AST and ALT – 3x upper limits of normal
  - Hepatitis panel negative
- Urine normal; negative culture
- Mantoux negative

Where do we go now?

Viral vs. Bacterial Infections

- Streptococcal pharyngitis
- Viral URIs
- Bacterial URI
- AOM
- ABRS
- CAP
- UTI
- Tuberculosis
- Hepatitis B
Epstein Barr Virus

- HHV4
- 50% of children < 5 years of age and 90% of adults have evidence of previous infection
- Highly contagious
- When contracted in adolescence, mono
- Can reactivate at any type and cause symptoms
- Implicated in Burkitt’s lymphoma, certain types of Hodgkin’s lymphoma, meningitis
- Labs: Epstein Barr Panel

Epstein Barr Panel

<table>
<thead>
<tr>
<th>Test results most likely indicate the following:</th>
<th>VCA IgM</th>
<th>VCA IgG</th>
<th>EA-D, EBNA-</th>
<th>Possible Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>No infection, symptoms due to another cause, susceptibility to EBV infection</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Early primary infection</td>
</tr>
<tr>
<td>Negative or positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Active infection, though EBV-D or EBNA may persist for rts in about 22% of those infected</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Post-infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>May indicate reactivation of virus</td>
</tr>
</tbody>
</table>


Her EBV panel – old, inactive disease

Urinary tract infection

- Need to consider UTI
- Children may present with incontinence
- May have atypical symptoms
- Always consider pyelonephritis in children; often result of ureteral reflux
- One pyelonephritis case in the reference – urology referral

**Streptococcal Infection**

- She has consistently tested negative with quick strep tests x 2 and throat cultures x 2
- Consider obtaining:
  - ASO titer
  - ADNase-B (Antideoxyribonuclease-B Titer)
- If positive, may need to consider recent strep infection and its complications such as rheumatic fever

**Additional Tests Performed Today**

- ASO and ADNase-B: negative
- Blood cultures: Negative
- Malarial smear: Negative
- Parvovirus B19 IgG and IgM: IgG – positive
- Dengue Virus by PCR: negative
- Chikungunya Antibodies (IgG, IgM) with Reflex to Titers: negative
- CMV Titer:
  - IgM: 2.0: normal < 1.2
  - IgG: 4.8: normal < 1.1

**CMV**

- Cytomegalovirus
- Human herpes virus
- Most people who contract this virus have no idea or no symptoms
- Can cause protracted fevers and hepatitis
- Treatment:
  - Antivirals for individuals with HIV, immunocompromised
    - Ganciclovir (first antiviral approved to treat CMV; administered IV)
    - Valganciclovir (oral; prevention and for those less ill)
More Complex Differential Diagnoses

PFAPA
(Periodic fever, Aphthous-stomatitis, Pharyngitis, Adenitis Syndrome)

PFAPA Syndrome
• Periodic fever, Aphthous-stomatitis, Pharyngitis, Adenitis (PFAPA) Syndrome
  — Also called Marshall Syndrome
  — Described by Marshall in 1987
• Important information:
  — PFAPA onset typically occurs before five years of age with children experiencing episodes of high fever lasting three to six days
  — Recurs every three to eight weeks
  — Clockwork cycle

Causes of PFAPA

• Postulated that IL-1, IL-6, TNF, and interferon gamma play a role in the inflammatory process
• Peripheral lymphoid tissue, such as tonsils may play a role as a reservoir for a pathogen to which there is a dysregulated immune response
• Tonsils may be a microbial reservoir or a source for local immune dysregulation or both

Descriptions of Child

• Glassy eyed
• Clingy
• Fevers > 39°C – 41°C
• Decreased appetite
• Mouth ulcers
• Cervical lymphadenopathy
• Pharyngitis (may have erythematous, edematous tonsils)
• Completely normal between episodes
• Normal growth and development

Must Rule Out

• Rule-outs
  – Malignancy
  – Other inflammatory conditions
  – Cyclic neutropenia
  – Infection
• Laboratory evaluation
  – CBC, UA, Culture, Strep cultures, RF, ant-CCP, ANA, Sed Rate, CRP

Diagnosis of EXCLUSION!

Laboratory Findings

- WBC is often elevated
- Sedimentation rate – often elevated
- Quick strep and throat cultures – negative


Treatment

- 1mg – 2mg/kg at onset of symptoms can abort fever
  - Often thought to be diagnostic of this condition
- Antipyretic therapies
- IL-1 receptor antagonist (Anakinra) has been shown to be effective in children
- Daily cimetidine
  - Reduced fever cycles by 27% with daily use
- Education
  - These usually resolve by adolescence
  - Benign etiology
  - Spontaneous resolution
    - 4.5 years
    - Intervals lengthen


Adenoidectomy and Tonsillectomy Surgery....Is It Helpful?

- Study conducted to loop at impact of adenoidectomy and tonsillectomy in PFAPA
- Conclusion:
  - Complete resolution of symptoms in 99 of 102 patients with PFAPA syndrome who were treated surgically
- Implications:
  - Patients who meet the clinical criteria for PFAPA syndrome should be offered tonsillectomy and adenoidectomy as part of their treatment options

Authors: Greg Licameli, MD, MHCM; Maranda Lawton, MS, PA-C; Margaret Kenna, MD, MPH; and Fatma Dedeoglu, MD
Hereditary Fever Syndromes

“Rare group of diseases characterized by recurrent episodes of seemingly unprovoked inflammation”

Differential Diagnosis of Hereditary Fever Syndromes

• Familial Mediterranean Fever (FMF)
• Hyperimmunoglobulinemia D Syndrome (HIDS)
• TNF Receptor-associated Periodic Fever Syndrome (TRAPS)
  – Also known as: Familial Hibernian Fever
• Cryopyrin-Associated Syndromes (CAPS)

Familial Mediterranean Fever

• Most common periodic fever syndrome
• First described in 1908
• FMF episodes start before the age of 20 years in approximately 90% of the patients.
  – In more than half of them the disease appears before the age of 10 years
  – Can begin in infancy but norm is 5 – 15 years
• Recurrent episodes of:
  – Fever, abdominal, chest and joint pain and swelling
Familial Mediterranean Fever

- Affects people of Mediterranean and Middle Eastern descent, typically Sephardic Jews, Turks, Arabs and Armenians
  - Since the discovery of the gene defect, it is being diagnosed more frequently, even among populations where it was thought to be very rare, such as Italians, Greeks and Ashkenazi Jews
- Autosomal recessive
  - Mutations in the MEFV gene (MEd FeVer gene) on chromosome 16
  - The MEFV gene affects a protein called pyrin. Pyrin plays a role in the natural control of inflammation

Pathophysiology

- The MEFV gene normally codes a protein named pyrin, which is expressed in circulating neutrophils
  - Its presumed action is to blunt the inflammatory response, possibly by inhibiting neutrophil activation and chemotaxis.
- Gene mutations result in defective pyrin molecules
  - It is hypothesized that the altered pyrin cannot suppress minor, unknown triggers to inflammation that are normally checked by intact pyrin
  - The clinical consequence is spontaneous bouts of neutrophil-predominant inflammation in the abdominal cavity as well as in other sites

Presentation

- Short attacks of fever and serositis
  - Sudden onset, usually lasts 6 – 96 hours
  - Fine between attacks
- Fever and peritonitis are usually first symptoms
  - Pain often begins in one quadrant and will then move throughout entire abdomen
  - Decreased bowel sounds, guarding and rebound tenderness are the hallmarks at the peak of the condition
  - May be concerned re: a perforated viscus (organ) such as an appendicitis, bowel etc.
Presentation

- Pleurisy (about 30%)
  - Can hurt to breathe
- Arthritis (25%)
  - Usually only one joint at a time
  - Knee and ankle are most common
- Testicular pain
- Less commonly pericarditis
  - Subclinical inflammation may persist

Erysipelas-Like Rash

- Lower extremities

FMF

- Treatment
  - Colchicine
    - Inhibits neutrophil chemotaxis
    - Prevents febrile attacks in approximately 60% of children
    - Remission or significant improvement for 85% of individuals
    - Significant reduction in symptoms in another 20–30%
    - 3-6 month trial is often recommended
  - Prognosis: good unless associated with amyloidosis
Colchicine

• Needs to be taken prophylactically
• 0.6 mg two times daily; although some have to take four times daily
• If it works for the child, the child will likely be on for lifetime


Additional Treatment for FMF

• Medications which block interleukin-1 may be effective for the many
  – Rilonacept (Arcalyst)
  – Anakinumab (Ilaris)
  – Anakinra (Kineret)

Complications of FMF

• Amyloidosis
  – Amyloid is a protein that develops and deposits itself into major organs when an inflammatory disorder is not controlled
  – Affects lungs, kidneys, heart and intestines
  – Colchicine lowers this risk significantly
  – Obtain urine and consult rheumatology for these patients

HIDS
(Hyperimmunoglobulin D syndrome, also called Mevalonate Kinase Associated Periodic Fever Syndrome)

- First identified and described in 1984
- Most individuals are from Western European decent
  – Dutch and French descent account for 60% of individuals with this syndrome
- Autosomal recessive condition
  – Mutations in MVK gene - long arm Chromosome 12
  – Key enzyme in cholesterol metabolic pathway
- Quite rare
- Boys and girls equally affected

Clinical Manifestations of HIDS
- Onset usually < 1 years old
- Recurrent episodes of unexplained high fever, chills, cervical adenopathy, abdominal pain, diarrhea, vomiting
  - Usually starts as chills, followed then by fever
    – Fever last 3-7 days
  - Fevers recur every 4 – 6 weeks (range 2 – 12wks)

Clinical Manifestations of HIDS

• May have hepatosplenomegaly
• Headaches
• Arthralgia/arthritis of the large joints (knees)
• Rash
• Minority with painful oral/vaginal aphthous ulcers
• Precipitating events
  – Vaccination, minor trauma, surgery, stress


Laboratory Findings

• IgD level continuously elevated
  – Usually > 100 IU/ml (0 – 5300)
  – May be normal in children < 3 years
  – Two elevated levels separated 1 month apart should make clinician suspect this condition
• IgA elevated in 80% of children, in addition to IgD
• Elevated Total WBC count during attacks is common
• Increased CRP and Sed rate
Treatment

• NSAIDs during acute attack
• Prednisone 1 mg/kg/day during attack
• Simvastatin (HMG-CoA reductase inhibitor)
  — Placebo-controlled trial underway
• Reduce Cytokine signaling
  — Etanercept
  — Recombinant human IL-1-receptor antagonist
• Prognosis – Attacks throughout life, highest frequency in childhood and adolescence

Long Term Prognosis

• HIDS is a severe disease that starts early in life with lifelong recurrent attacks of fever
  — There was a significant decrease in frequency of attacks with increasing age, although no patients had a remission
  — After the age of 20 years, 17.8% of patients continued to have attacks more than 12 times per year, while 50% of patients still had more than 6 attacks per year
  — Thirty-three of 45 patients above the age of 20 years had fewer attacks after the age of 20 years than in the first decade of life


Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)

**TRAPS**

- First identified and described in 1982
- Also referred to in literature as Familial Hibernian Fever
- Autosomal dominant
  - Mutations in TNFRSR1A (gene for Type 1 TNF receptor)
  - Chromosome 12
  - This gene provides instructions for making a protein called tumor necrosis factor receptor 1 (TNFR1)
  - Causes an increase in the individuals normal inflammatory response

**TRAPS**

- Clinical criteria/features
  - Longer duration of attacks (> 1 week) than FMF; often lasting up to 3 weeks
  - Intense chills
  - Fever, abdominal pain, pleurisy, ocular inflammation (conjunctivitis, periorbital edema)
  - Large joint arthralgia
  - Centrifugally migrating myalgia & erythematous rash

**TRAPS**

- Equal prevalence in boys and girls
- Most commonly seen in late childhood to early adolescence
- Triggers
  - Often triggered by vaccinations, stressors, illness/infections, minor injury
Treatment

• Corticosteroid response wanes with time
• Preliminary trial with Etanercept:
  – Binds TNF-alpha
  – Significant decrease in episode frequency, duration and severity (McDermott, et al)
• Prognosis dependent on development of amyloidosis
  – Up to 25% of individuals will go on to develop amyloidosis

Lyme Disease or Coinfections

Tick Borne Illnesses
Two Sets of Guidelines

- IDSA – http://www.idsociety.org/lyme

Erythema Chronicum Migrans

- Etiology
  - Caused by a spirochete called Borrelia Burgdorferi
  - Transmitted by the bite of certain ticks (deer, white-footed mouse)
  - 1st cases were in 1975 in Lyme, Connecticut
  - Affects many systems
  - Children more often affected than adults

This is NOT a Lyme Bearing Tick
Lyme Bearing Tick

Erythema Chronicum Migrans

- Symptoms
  - 3-21 days after bite
  - Rash (present in 72-80% of cases)-slightly itchy
  - Lasts 3-4 weeks
  - Mild flu like symptoms (50% of time)
  - Migratory joint pain
  - Neurological and cardiac symptoms
  - Arthritis, chronic neurological symptoms

Erythema Chronicum Migrans

- Signs
  - Rash:
    - Begins as a papule at the site of the bite
    - Flat, blanches with pressure
    - Expands to form a ring of central clearing
    - No scaling
    - Slightly tender
  - Arthralgias:
    - Asymmetric joint erythema, warmth, edema
    - Knee is most common location
Erythema Migrans

Systemic symptoms
- Facial palsy
- Meningitis
- Carditis

Erythema Chronicum Migrans

- Systemic symptoms
  - Facial palsy
  - Meningitis
  - Carditis
Erythema Chronicum Migrans

Plan
  – Diagnostic:
    • Sed rate: usually normal
    • Lyme Titer
      – IGM: Appears first: 3-6 weeks after infection begins
      – IGG: Positive in blood for 16 months
      – High rate of false negatives early in the disease
    • Lyme Western Blot

Per ILADS

• “Diagnosis of Lyme disease by two-tier confirmation fails to detect up to 90% of cases and does not distinguish between acute, chronic, or resolved infection”
• “The Centers for Disease Control and Prevention (CDC) considers a western blot positive if at least 5 of 10 immunoglobulin G (IgG) bands or 2 of 3 immunoglobulin M (IgM) bands are positive. However, other definitions for western blot confirmation have been proposed to improve the test sensitivity. In fact, several studies showed that sensitivity and specificity for both the IgM and IgG western blot range from 92 to 96% when only two specific bands are positive”
  – Lyme specific bands: 31, 34, and 39

Erythema Chronicum Migrans

Plan
  – Therapeutic: Per CDC
    • Amoxicillin 500mg three times daily x 21 – 28 days
    • Doxycycline 100 mg 1 po bid x 21 – 28 days
    • If in endemic area and tick is partially engorged, may treat with doxycycline 200 mg x 1 dose with food
ILADS

- Believe in Chronic Lyme Disease
- Treatment may be continued as long as needed to treat symptoms
- Alternative recommendations are made:
  - Doxycycline 100-200 mg bid or TCN 500 mg 1 bid
  - Clarithromycin 500 mg 1 po bid along with hydroxychloroquine 200 mg 1 two times daily
  - Azithromycin 500 mg once daily

Additional Tick Borne Illnesses

Anaplasmosis

- Formerly referred to as ehrlichiosis
- Transmitted by blacklegged tick or Lonestar tick
Anaplasmosis (Ehrlichiosis)

- **Clinical picture**
  - Fever, chills, headaches, muscle aches
  - Occurs 1-2 weeks after a tick bite
  - Additional clues: thrombocytopenia, leukopenia, or elevated liver enzyme levels are helpful predictors of anaplasmosis, but may not be present in all patients
  - Testing: may be negative for first 7-10 days; PCR assay test
  - Treatment: doxycycline 100 mg 1 pill two times daily x 7-14 days (continue for minimum of 3 days after fever subsides)
    - Alternative: rifampin

Babesiosis

- **Babesiosis**
  - Parasite which invades, infects, and kills the red blood cells (*Babesia microti*)
  - *Babesia microti* is spread in nature by *Ixodes scapularis* ticks (also called blacklegged ticks)
  - Symptoms: flu-like symptoms, such as fever, chills, sweats, headache, body aches, loss of appetite, nausea, or fatigue. Babesiosis can cause hemolytic anemia (from destruction of red blood cells)
Babesiosis

- Babesiosis
  - Treatment:
    - atovaquone (Mepron) PLUS azithromycin; OR
    - clindamycin PLUS quinine (this combination is the standard of care for severely ill patients)
  - Length: 7-10 days

Babesiosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dosage (usually treat for at least 7-10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>atovaquone</td>
<td>250 mg orally twice a day</td>
</tr>
<tr>
<td>azithromycin</td>
<td>On the first day, give a total dose in the range of 500-1000 mg orally; on subsequent days, give a total daily dose in the range of 250-1000 mg</td>
</tr>
<tr>
<td>clindamycin</td>
<td>600 mg orally 3 times a day of 300-600 mg intravenously 4 times a day</td>
</tr>
<tr>
<td>quinine</td>
<td>500 mg orally 3 times a day</td>
</tr>
</tbody>
</table>

Bartonella

- Bartonella (cat-scratch)
  - Explanation: Bartonella spp. Bacterium
  - Diagnosis: B. henselae DNA may be detected by PCR
  - Symptoms: Fever, chills, headache, lymphadenopathy, and severe pain in the tibia, weight loss, sore throat, rash
  - Treatment:
    - Azithromycin:
      - For adults and children > 45.5 kg: 500 mg on day 1, followed by 250 mg for 4 days
      - For children ≤ 45.5 kg: 10 mg/kg on day 1, followed by 5 mg/kg for 4 days
    - ILADS – consider Levofloxacin

http://www.cdc.gov/parasites/babesiosis/health_professionals/index.html#tx accessed 12-20-2013

Case Study: MA

- 11 year old new patient presents with complaint of joint pain, fevers, changes in bowels (constipation – diarrhea), generalized achiness, chills
- Transferred care from pediatrician for further evaluation
- Symptoms first began at age 7; referred to rheumatology who diagnosed him with RA
  - Has been in Enbrel x 1 year
  - Continues with significant symptoms
- Parents convinced it is Lyme disease causing symptoms

MA

- T: 99; P: 73 and regular; RR -18
- BP: 100/68
- Skin: p/w/d; no rashes, striae
- HEENT: normal
- Nodes: normal
- Lungs: clear
- Heart: S1S2: RRR, No S3, S4, murmurs or rubs
- Abdomen: generalized tenderness; no rebound; + BS; no hsm, negative Markle’s sign
- PV: normal; no edema
- MS: FROM: no edema, warmth

Initial labs (MA)

- CBC:
  - WBC: 14.6; Increased neuts and decreased lymphs
  - Hgb/HCT: 10.4/33.1; decreased MCV, decreased MCHC, elevated RDW
- CMP: normal
- TSH: normal
- ASO titer: elevated; negative quick and full throat culture
- Urine: negative
- Lyme, ehrlichia, babesia, bartonella: negative
- EBV: old infection
Initial labs and Testing (MA)

- RF: negative
- Anti-CCP: negative
- ANA: negative
- CRP: 49.6 (normal < 10)
- Sed: 72 (normal < 20)
- Chest X-ray: negative
- Mantoux: negative

Where Do We Go From Here?

Additional Labs (MA)

- Ferritin: 32
- Total iron: low
- TIBC: elevated
- Hemoglobin electrophoresis normal
- Reticulocyte count: elevated

What Do We Do Now?

What Did I Do?

- Stool cards for blood (all positive)
- Colonoscopy: confirmed IBD (Crohn's disease)
- Switched from Enbrel to Remicade
- Fevers subsided within a week
- 20% of individuals with IBD present with joint pain as their initial symptoms
  - Always have IBD in your differential
End of Presentation!

Thank you for your time and attention

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