A Mélange of Pediatric ID Topics

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UTHSCSA
Pediatric Grand Rounds
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Topics
- Kawasaki Disease
- Murine Typhus
- Tuberculosis Skin Tests
- Syphilis serology in Neonates
- FUO

Kawasaki Disease

- Described by Tomisaku Kawasaki in 1967 as Mucocutaneous lymph node syndrome

  Tomisaku Kawasaki

Epidemiological case definition (classic clinical criteria)*

1. Fever persisting at least 4 days
2. Presence of at least 5 principal features:
   a. Changes in extremities
      Acute: Erythema of palms, soles; edema of hands, feet
      Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
   b. Polymorphous exanthem
   c. Bilateral bulbar conjunctival injection without exudate
   d. Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
   e. Cervical lymphadenopathy (>1.5-cm diameter), usually unilateral

& Exclusion of other diseases with similar findings

Case 1

- An 11 month old infant with fever for 27 days was admitted to SRCH
- He had 5 clinic/ER visits over the period of 27 days and was given antibiotics 3 times for……..?
- A thorough history and exam revealed that he had manifested all 6 Kawasaki criteria
- At admission he was extremely irritable and had been for weeks

To be continued..............
**KD SIGNS & SYMPTOMS**

- **Kawasaki Disease**

  - **Hand/feet**
    - Indurated
    - Painful

  - **Rash**
    - Occurs within 5 days of onset of fever
    - Variable
      - Maculopapular
      - Scarlatiniform
      - Erythoderm-like
      - Micropustular (rare)
    - Bullous/vesicular rashes do not occur

  - **Kawasaki - bulbar conjunctivitis**
    - Spares limbus
    - Painless
    - No exudate

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_CDC Weekly/ Monthly d Disease Reports_ 2000:49

_Kawasaki Disease Guidelines_ Committee on Infectious Diseases et al. Red Book Online 454-460

**Lymphadenopathy**
- Least common of the 6 signs/symptoms
- Usually unilateral, anterior cervical triangle
- >1 node of >1.5 cm

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**Other manifestations**
- Irritability**
- Abdominal pain
- Vomiting
- Meningismus
- Hydrops of gallbladder
- Arthralgia
- Anterior uveitis
- Sterile pyuria

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**Late Manifestations**
- Peeling skin—occurs at formerly edematous sites (hands, feet, other)
- Typically late (2-3 weeks) finding

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**Differential Diagnosis**
- Viral exanthems
- Toxic Shock Syndrome
- Scarlet Fever
- Leptospirosis
- RMSF
- Measles
- Stevens-Johnson
- Drug Reaction
- Juvenile Idiopathic Arthritis (JIA; JRA)

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**Laboratory in KD**
- Usually have ESR > 40 (or CRP > 3)
  - May persist for 6-8 weeks
- Sterile Pyuria (35%)
- Mildly elevated transaminases
Laboratory in KD

- Mild liver dysfunction
- Hypoalbuminemia
- CSF pleocytosis
- Platelets → 7 days after onset, thrombocytosis (>450,000)
  - Begins in 2nd week
  - Peaks at 3 weeks (mean of 800,000)

KD Variants

- Incomplete (Atypical) Kawasaki
  - Fever + fewer than 4 of 5 other criteria
  - Sometimes as few as 1-2 other criteria
- Kawasaki Shock Syndrome *

* Recognition of a Kawasaki Disease Shock Syndrome; Kanegaye, JT et al. Pediatrics Vol. 123 No. 5 May 1, 2009 pp. e783-e789

Atypical KD

- Originally described in infants with CAD, who previously lacked the standard criteria for KD
- Most common < 12 mo
- Consider in all children with > 5 days fever with 2-3 of the classic sx of KD
- Lab findings may ↓ or ↑ suspicion for KD

KD COMPLICATIONS

Case 1

Continuing.........

- Shortly after admission an echocardiogram revealed 5 aneurysms and a very large pericardial effusion
- The infant was transferred to the PICU for drainage of the effusion and further therapy
**KD--complications**

- If untreated within **10 days** after onset, 20-25% develop coronary artery aneurysms.
- Aneurysms in many other arteries (Renal A., Brachial A., etc.) also occur.
- Risk is higher for:
  - infants
  - children > 8 y/o
  - males

- With **incomplete KD**, the cardiovascular risks are the same as for classic KD.
- However, the diagnosis is more difficult and more likely to be missed.

**Therapy**

- **IVIG 2000 mg/kg** over 12 hours
- **High dose aspirin 80-100 mg/kg/day** divided into 4 doses
  - If fever-free >48 hours reduce dose
- **Low dose aspirin 3-5 mg/kg/day** in one dose
  - Discontinue after 6-8 wks if no coronary artery disease is identified
  - Indefinite ASA if aneurysms are present

  * combination of CAD and thrombocytosis necessitates prolonged ASA therapy due to risk for MI

**Cardiac care**

- **Echocardiogram**
  - Diagnosis
  - 1-2 wks after dx
  - 6-8 wks after dx

**Late Diagnosis**

- **Late Intravenous Immunoglobulin Treatment in Patients With Kawasaki Disease**

  Hinomi Muta, Masahiro Ishii, Mayumi Yashiro, Ritei Uehara, and Yosikazu Nakamura; 2012; Pediatrics 129: 291
Study population

- Population studied—75 each with early (<10 days) and late (>10 days) treatment

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Primary Outcome: Coronary Artery Lesions

<table>
<thead>
<tr>
<th></th>
<th>Late IVIG (Days 11-20) (%)</th>
<th>Conventional IVIG (Days 4-8) (%)</th>
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<tbody>
<tr>
<td>CAL (Before IVIG)</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>CAL (after IVIG up to one month)</td>
<td>49</td>
<td>13</td>
</tr>
<tr>
<td>CAL (&gt; one month)</td>
<td>27</td>
<td>1</td>
</tr>
</tbody>
</table>

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- There is increasing evidence that children with normal echocardiograms following KD, still are at significant risk of CAD in later life
- There is no way currently to sort them out from the unaffected children
- There is no consensus about follow-up care

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Occlusion of the RCA —33 y/o male who had apparent KD in infancy

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KD-Short Term Prognosis

- Without treatment 20-25% risk of CA aneurysm
- With treatment < 4% risk
  — Again this may not be as accurate as once believed
Final Note on KD

- Because of the large dose of IVIG and half life > 3 weeks:
  - **No live vaccines for 11 months after therapy for KD**

SYPHILIS SEROLOGY IN NEONATES

Etiology of Syphilis

- *Treponema pallidum* – “pale turning thread”

Syphilis, sive Morbi Gallici (1530)
(Syphilis or the French Disease)

Girolamo Fracastoro

*The first man to display disfiguring sores over his body was Syphilus, who by the shedding of blood instituted divine rights in the king's honour and altars in the mountains sacred to him*

Screening tests

- RPR = rapid plasma reagin
- VDRL = Venereal Disease Research Lab

*The initial antibody test was developed by August Paul von Wassermann, Julius Citron, and Albert Neisser (Koch Institute for Infectious Diseases) in 1906*
Confirmatory test

- **Always** follow screening test with confirmatory test
  - *Treponema pallidum* particle agglutination (TP-PA)
  - fluorescent treponemal antibody –absorbed (FTA-ABS).

AAP Redbook 2009
Algorithm for evaluation and treatment of infants born to mothers with reactive serologic tests for syphilis.

Case

- A woman has a RPR of 1:4 at delivery—you have to make decisions about what to do with the baby
  - What are the decision points?

Key decision points

1. Has a confirmatory test been done?
2. Has the infant been tested by RPR?
3. How does the infant’s RPR compare to the mother’s RPR?
4. Is the physical exam normal or not?
5. Was the mother treated previously?
   a. When?
   b. With what?
Has a confirmatory test been done?

- Reactive maternal RPR/VDRL
- Reactive maternal treponemal test

If negative or reactive, order a confirmatory test.

Next Slide

Physical Exam

- Evaluate physical examination normal
- Evaluates if there is some radiolucency or cupping than found in the maternal RPR/VDRL test

- Evaluate & Treat
  - PCN IM x 1

- Maternal treatment:
  - None, OR
  - Unconfirmed OR
  - 4 wk or less before delivery, OR
  - Non-penicillin drug, OR
  - Maternal evidence of reinflection/relapse (fourfold increase or greater increase in maternal titer)

- Adequate maternal treatment before pregnancy with stable low titer (serofast), AND infant examination normal, proceed with evaluation.

- Diagnosed: Infants
  - Infants with RPR/VDRL fourfold or greater than maternal RPR/VDRL test
  - Infants with no RPR/VDRL test

- Infants with no RPR/VDRL test
  - Infants with negative maternal RPR/VDRL test

- Infants with positive maternal RPR/VDRL test
  - Infants with negative maternal RPR/VDRL test

- Infants with positive maternal RPR/VDRL test
  - Infants with negative maternal RPR/VDRL test

- Infants with positive maternal RPR/VDRL test
  - Infants with negative maternal RPR/VDRL test

- Infants with positive maternal RPR/VDRL test
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  - Infants with negative maternal RPR/VDRL test

- Infants with positive maternal RPR/VDRL test
  - Infants with negative maternal RPR/VDRL test
Adequate Maternal Treatment

- Documented IM benzathine PCN > 4 wks prior to delivery
- No evidence of reinfection/relapse (rising titers or < 4 fold dec. in titer)

Inadequate Maternal Treatment

- None
- Inadequate
  - Medication other than benzathine PCN
  - Wrong dose
- Not documented (or unavailable)
- < 4 wks prior to delivery

Neonatal Therapy

1. Aqueous PCN G 50,000 u/kg IV BID x 7 days and TID x 3 days (10 days total)
   or
   Procaine PCN G 50,000 u/Kg IM once daily x 10 days
2. Procaine PCN G 50,000 u/Kg IM x 1

• If you have gone through the schematic, and still have questions, then and only then call ID
  1 (800) DCO-NRAD

Syphilis Plush Doll $5.95
MURINE TYPHUS

Murine Typhus

- Also known as:
  - “Endemic typhus”
  - or
  - “Flea borne typhus”

Etiology: *Rickettsia typhi*

- Do not confuse with:
  1. **Louse-borne (epidemic or sylvatic) typhus** is caused by *Rickettsia prowazekii*
     - Common in crowded conditions where lice are easily spread between people
  2. **Scrub typhus** caused by *Orientia tsutsugamushi* (mite-borne)
     - *Tsutsuga = illness*
     - *Mushi = insect*

Epidemiology of Murine Typhus

- The rat flea (*Xenopsylla cheopis*) is the primary vector though other fleas have been implicated
- **Rats, opossums, cats and dogs** can be infected and serve as reservoirs
• Flea feces containing the *Rickettsia* may be rubbed into a break in the skin or mucous membrane resulting in infection

• It is also possible to become infected by inhalation of flea feces

• Worldwide distribution
• U.S. distribution
  – South Texas
    • ≤9%–14% of children in Nueces County have antibodies reactive to *R. typhi* (Purcell, et al.)
  – South California
  – Gulf coast
  – Hawaii
• Predominately from April to October
• Incubation period is 6-14 days

<table>
<thead>
<tr>
<th>Table 1. Signs and Symptoms Recorded for Pediatric Patients Diagnosed as Having Murine Typhus in South Texas</th>
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</thead>
<tbody>
<tr>
<td><strong>Sign or Symptom</strong></td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Fever and headache or rash</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Fever, headache, and rash</td>
</tr>
<tr>
<td>Fever only</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
<tr>
<td>Anorexia</td>
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<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Cough</td>
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</table>

Whiteford et al.

<table>
<thead>
<tr>
<th>Table 2. Cutaneous Findings in 94 Pediatric Patients With Murine Typhus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic of Rash</strong></td>
</tr>
<tr>
<td>Rash present*</td>
</tr>
<tr>
<td>Macular</td>
</tr>
<tr>
<td>Maculopapular</td>
</tr>
<tr>
<td>Erythematous</td>
</tr>
<tr>
<td>Petechial and macular</td>
</tr>
<tr>
<td>Papular</td>
</tr>
<tr>
<td>Petechial</td>
</tr>
</tbody>
</table>

Whiteford et al.
Diagnosis

- Typically diagnosis is based on clinical signs and symptoms
  - Typically patients do not recall a fleabite**
  - They often do recall contact with associated mammal populations**
- Indirect IFA, Latex agglutination, enzyme immunoassay
  - These may be useful to confirm diagnosis retrospectively

Treatment

- Doxycycline **
  - > 45 Kg – 100 mg BID
  - <45 Kg – 2.2 mg/Kg BID
  - Typically 5-10 days (until 3 days after defervescence and after evidence of clinical improvement
- Alternatives: chloramphenicol, fluoroquinolones

Mortality

- Mortality is 1-4% (especially elderly or immunocompromised persons)
- Compare that to epidemic typhus where mortality rates as high as 60% have been documented

Reminder:

- PPD is the material injected (purified protein derivative) for a TST
- TST (tuberculin skin test) is the name of the test
What defines a Positive TST?

- It depends on circumstances!
- Why did you place a TST?
  - Clinical signs/symptoms?
  - High risk based on your screening questionnaire?
  - Known, significant exposure

Interpreting TST

- Situation 1 -- ≥ 15 mm
- Situation 2 -- ≥ 10 mm
- Situation 3 -- ≥ 5 mm

Situation 1 -- (TST ≥ 15 mm)

- > 4 years old with no risk factors

Situation 2 -- (TST ≥10mm)

- Child at increased risk of disseminated disease
  - < 4 y/o
  - Children with certain medical conditions
    - Hodgkin disease
    - Lymphoma
    - DM
    - CRF
    - Malnutrition
  - Child with increased exposure risk
    - Born in high prevalence region
    - Exposure to high risk adult
    - Travel to high prevalence region

Situation 2

- A 7 y/o patient who was born in Guatemala, and has an 11 mm TST. She had a BCG vaccine in infancy.

Situation 3 -- (≥ 5mm)

- Children in close contact with known/suspected contagious people with TB
- Children suspected to have TB disease
  - CXR findings
  - Clinical evidence
- Children receiving immunosuppressive therapy (including suppressive doses of corticosteroids) or immunosuppressive conditions (e.g. HIV)
Situation 3

• A 5 year old whose father is a heroin user and was incarcerated.

False positive TST

• Infection with non-tuberculosis mycobacteria
• Previous BCG vaccination
• Incorrect method of TST administration
  – e.g. Subcutaneous injection
• Incorrect interpretation of reaction
• Incorrect bottle of antigen used

False negative TST

• Cutaneous anergy
• Recent TB infection (within 8-10 weeks of exposure)
• Very old TB infection (many years)
• Very young age (<6 months old)
• Recent live-virus vaccination (e.g., measles and smallpox)
• Overwhelming TB disease
• Some viral illnesses (e.g., measles and chicken pox)
• Incorrect method of TST administration
• Incorrect interpretation of reaction

TB Diagnosis

• TST (tuberculin skin test)
• Interferon Gamma Release Assay (LGRA)
• Culture (sputum, gastric aspirates, bronchial washings, pleural fluid, CSF, urine, biopsy specimen)

Reminders

• Measure induration – not erythema
• Read test at 48-72 hrs
• Perform a physical exam and CXR before you call ID for advice
Case (Situation 3 revisited)

“I am seeing a 5 year old whose father is a heroin user and was incarcerated. The child has a 6 mm TST.”

The physical examination and CXR are normal.

LTBI

- In this case, do not try to obtain sputum by gastric aspirates, sputum samples or bronchoscopy
  - With no infiltrate you will not obtain an organism!

Meds for LTBI

- Recommended
  - Isoniazid 10-20 mg/Kg once daily x 9 months (max dose 300 mg)

- Alternative
  - Isoniazid 20-40 mg/Kg twice weekly x 9 months (max dose 900 mg)
  - Rifampin 10-20 mg/Kg daily x 6 months

Not LTBI

- If the CXR or physical examination note abnormalities c/w TB then the therapy will be 3-4 medications 6-12 months (occasionally longer) depending on the situation.

Other

- Gamma Interferon Release Assay (e.g. Quantiferon TB gold)
  - 3 mycobacterial proteins (ESAT-6, CFP-10, and TB 7.7) stimulate the patient’s T-cells \textit{in vitro} to release interferon-gamma, which is then measured using ELISA technology.
**Gamma Interferon Release Assay**

- **Advantages**
  - Only one visit needed
  - No reader bias
  - No interference by prior BCG
  - No booster phenomenon

- **Disadvantages**
  - Must be processed in lab within 12 hours
  - Requires phlebotomy
  - Not useful in children < 5 y/o
  - False positive results can occur with M. sulgai, M. kansasii, M. marinum

**Fever of Unknown Origin**

- **FUO** was initially defined as
  - (1) temperatures of >38.3°C (>101°F) on several occasions;
  - (2) duration >3 weeks;
  - (3) failure to reach a diagnosis despite 1 week of inpatient investigation

**Practical Definition of FUO in Children**

- Fever >101°F (38.3°C) of at least 8 days, when no diagnosis is apparent after initial outpatient or hospital evaluation

This requires a careful Hx, PE & initial laboratory assessment.

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1. Lorin and Feigin in Textbook of Pediatric Infectious Diseases; Feigin and Cherry 1998
**It’s not an FUO just because you don’t know what it is!**

**Fever Without Localizing Signs (FWLS)**
- The duration does not yet meet the criteria for FUO (< 8 days)
- or the w/u is not yet complete

**Practical Tips**
- Fever ≠ Infection
- Antibiotics ≠ Antipyretics
- Significant Infections will usually declare themselves in a short time
- Most common viral infections resolve in 5-7 days

- Fever for a few days every week or month is not typical for infections – Periodic fevers often have an immunologic (genetic) origin

**FUO--What to Do**
- Take a thorough history, including:
  - Has fever been truly documented?
  - “100 and 4” (100.4° or 104°?)
  - What type of thermometer (if any)?
    - Axillary, oral, rectal?
  - Thorough Physical examination

**FUO-Basic Workup**
- CBC
- UA
- Liver enzymes
- Chemistry
- ESR or CRP ?
- PPD
- CXR ?
- Blood cultures
- Urine culture
- Throat culture
- Stool culture
- CSF cultures (cell count & chemistry)
- Serologic tests based on known exposures; travel history, etc.
Pediatrics Grand Rounds  
17 August 2012  

University of Texas Health Science Center at San Antonio

• If the appropriate length of time has passed and fever persists
  &
• Preliminary tests are not revealing
  &
• The patient remains without localizing signs

Diagnosis of FUO is reasonable

<table>
<thead>
<tr>
<th>Etiology</th>
<th>McClung (1972) %</th>
<th>Steele et al. (1992) %</th>
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<tbody>
<tr>
<td>Infection</td>
<td>29</td>
<td>20</td>
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<tr>
<td>Bacterial/Fungal</td>
<td>28</td>
<td>11</td>
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<tr>
<td>Viral</td>
<td>1</td>
<td>9</td>
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<td>Collagen Vascular Disease</td>
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<td>JRA</td>
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<tr>
<td>No Etiology</td>
<td>41</td>
<td>67</td>
</tr>
</tbody>
</table>

• With improving diagnostic methods, fewer people with infectious diseases are initially classified as FUOs and fewer with FUOs are proving ultimately to have infectious etiologies

The End

LIVE...

...like somebody left the gate open