Interesting and Important Pediatric Cases

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• No disclosures / conflicts of interest

Overview

Case 1
Case: 13 yo w/ fever, sore throat, neck swelling

- 13 yo previously healthy girl seen in urgent care with sore throat 5 days ago, re-presents with fever, neck swelling, and pleuritic chest pain
  - Rapid strep and throat culture negative
  - Current exam: febrile, unilateral neck swelling/pain, peritonsillar fullness w/out exudate, tachypneic, bilateral crackles
  - Labs:
    - WBC 7.5 (5.3 N), plts 64K
    - ESR 62, CRP 54
    - BUN/Cr 36/1.2
    - AST 240, ALT 350
  - Micro: rapid flu and viral panel neg
  - CXR: multiple bilateral airspace opacities; small R effusion
  - Admitted: received ceftriaxone, azithromycin → hypotension, respiratory distress → vancomycin added, transferred to PICU

Lemierre’s Syndrome: Epidemiology

- Decreasing in incidence in antibiotic era
  - 1955: 269 cases
  - 1956: 148 cases
  - 1958-1972: 0 cases
  - 1974-1986: 36 cases (35 with tonsillitis/peritonsilar abscess)
- 14 cases at one children’s hospital (Wisconsin) between 1995-2002
- Typical age 15-27 (range 7-38)
- 60% male

Lemierre’s Syndrome: Features

- Septic thrombophlebitis, usually preceded by pharyngitis, and usually associated with tonsillar/peritonsillar involvement
  - Pathophysiology: direct extension from oropharynx to adjacent structures
- Other possible antecedent conditions:
  - Dental infection
  - Mononucleosis
  - Prior catheter insertion

Lemierre’s Syndrome
Resurgence of a Forgotten Disease

- Characterized by Andre Lemierre (1936) based on 36 cases:
  “To anyone instructed as to the nature of these septicaemias it becomes relatively easy to make a diagnosis on the simple clinical findings, the appearance and repetition several days after the onset of a sore throat, of severe pyretical attacks with an initial rigor and still more certainly the occurrence of pulmonary infarcts and arthritic manifestations make a syndrome that is so characteristic that mistake is almost impossible.”

Lemierre A. Lancet 1936; 1:701-703


Golpe, Postgrad Med, 1999
Lemierre’s Syndrome: Features

- Presenting symptom: **sore throat (33%) > neck mass (23%), neck pain (20%) > others (bone/joint pain, ear pain/otitis, dental pain, orbital pain, GI symptoms)**

- **Pharyngitis to Thrombophlebitis ≤ 1 week**
  - Usually jugular, IVC; rarely portal vein, dural, pelvic vein

- **Metastatic sites**
  - **Pulmonary (97%):** bilateral, usually nodular infiltrates; pleural effusion, empyema, lung abscess, cavitiation
  - **Musculoskeletal:** septic arthritis (16%), osteomyelitis (3%)
  - **Derm:** skin/soft tissue infection (16%)
  - **GI:** Commonly LFTs, rarely liver/splenic abscess
  - **Neuro:** meningitis (3%)
  - **Renal:** infarct (rare)


CT head/neck: peritonsillar abscess

CT head/neck: internal jugular vein thrombus

CT chest: pulmonary septic emboli
Lemierre’s Syndrome: Microbiology

- Usually normal oropharyngeal flora
  - *Fusobacterium necrophorum****
  - *Fusobacterium nucleatum*
  - *Eikenella corroden*
  - *Porphyromonas asaccharolytica*
  - *Streptococcus spp* (S. pyogenes)
  - *Peptostreptococcus spp*
  - *Bacteroides spp*
  - MSSA, MRSA
  - Rare catheter associated pathogens

Lemierre’s Syndrome: Treatment

- Empiric therapy:
  - Beta-lactamase resistant beta-lactam
    - e.g. amp/sulbactam, pip/tazo, tic/clav
  - Carbapenem (e.g. meropenem)
    - Also flagyl, cefoxitin, clindamycin
  - Macrolides (e.g. azithro) do NOT treat *Fusobacterium*
  - Vanco if specific concern for staph, or if central catheter present
  - Duration 4 weeks, minimum 2 weeks IV

Lemierre’s Syndrome: Treatment

- Surgery
  - Recommended for ongoing sepsis, lack of response to antibiotics
    - Catheter removal
    - Drainage of source (e.g. peritonsillar abscess, empyema)
  - Anticoagulation: controversial
    - Generally done if extension of thrombus on therapy
    - Balance between risk of emboli and hemorrhage

Lemierre’s Syndrome: Diagnosis

- Clinical suspicion
  - Oropharyngeal infection
  - Persistent fever
  - Neck swelling/pain
  - Symptoms of metastatic disease/septic emboli
    - (e.g. respiratory symptoms, bone/joint pain)
  - Microbiologic data (anaerobic throat/blood cultures)
  - Imaging: CT neck with contrast, ultrasound, MRI, conventional venography

### Lemierre’s vs. Streptococcal Pharyngitis

| Hypothetical Cohort of 1,000,000 patients with pharyngitis, 15-24 years old |
|---------------------------------|------------------------|
| Outcomes, by type of pharyngitis | Events per 1,000,000 patients (%) |
| **Group A Streptococcus** | 100,000 (10%) |
| Acute rheumatic fever | 50 |
| Complex acute rheumatic fever | 5 |
| Death | 1 |
| **Fusobacterium necrophorum** | 100,000 (10%) |
| The Lemierre syndrome | 250 |
| Long-term disability | 20 |
| Death | 11 |

### ??? Proposed (by others) Guidelines

- Possibly apply to adolescents and young adults
- Treat empirically if at least 3 of the following:
  - Fever
  - Tonsillar exudates
  - Swollen, tender cervical LAD
  - Lack of cough
- Consider change in diagnostics (e.g. anaerobic cultures)
- Empiric treatment with PCN, cephalosporins, clindamycin if allergic
  - No macrolides
- Close follow-up for evolution of symptoms
  - BUT- we don’t know whether early antibiotics prevent Lemierre’s

### (my) Recommended Approach

- Usual criteria for group A strep diagnosis and treatment
  - Treat only with microbiologic confirmation
- Use PCN / amox or cephalosporin (or clinda) over macrolides
- If not improved 3-5 days, consider:
  - Mononucleosis: EBV, CMV, acute HIV
  - Peritonsillar/retropharyngeal abscess
  - Lemierre’s, especially if neck swelling/pain (red flag!)
    - Careful exam for evidence of metastatic infection (lungs, neuro exam, bones/joints)
    - Consider anaerobic throat culture
    - Start amox/clav or clindamycin and monitor closely
    - If ill-appearing, aerobic and anaerobic blood cultures, and admit → CT head/neck/chest, IV antibiotics

### Sidenote: How can I talk a parent out of unnecessary abx?

- **Antibiotic resistance**
- **Obesity**: OR for being overweight at 3 years was 1.22 (p<0.05) if exposed to antibiotics within 6 months of life (Trasande, 2012)
- **Inflammatory bowel disease**: 84% relative risk increase if antibiotic-exposed (Kronman, 2011)
- **Allergies**: OR 1.59 (95% CI: 1.10, 2.28) for developing allergies by 6 yo, if exposed to antibiotics in first 6 months of life (Murk, 2011)
- **Asthma**: OR 1.52 (95% CI 1.30-1.77) for developing asthma between 3-18 yo, if received antibiotics in the first year of life (Risnes, 2010)
- **Antibiotic-associated diarrhea**: in 5-25% (Walk, 2008) (→ rash)
  - C.difficile
  - AOM: diarrhea in ~50% of antibiotic-treated patients vs. ~35% in untreated (Lieberthal, 2013)
- **Drug reactions**: allergy/anaphylaxis, SJ/TEN, erythema multiforme, fixed drug eruption, drug-induced hypersensitivity syndrome/DRESS (drug reaction, eosinophilia, and systemic symptoms)
Case 2

Drug-induced hypersensitivity / DRESS

- Case 1: 16 yo girl with “septic shock”
  - Medications: 4 weeks prior to admission switched from doxycycline to minocycline for acne
  - 11 days prior to admission: pruritis without rash → in 2 days involved entire body, “dark all over” with “goose-bump” rash
  - Patient self-increased minocycline dose because of the rash
  - Associated symptoms: symmetric facial swelling (neck, tongue, lips, cheeks), fever, rigors, myalgias, decreased appetite, cervical adenopathy. No sore throat or neck pain.
  - Outpatient: Flu/RSV neg, GAS probe neg
  - Continued minocycline throughout
  - In ED: treated for allergic reaction; CT neck showed ?parotitis
  - Fedirle to 105 (rectal) with hypotension → PICU

- Case 2
  - Teenage boy on trimethoprim/sulfa x 3 weeks for cellulitis
  - Facial swelling, periorbital edema, vomiting/diarrhea, high fever (104-105), rash (arm → torso + 4 extremities), scleral injection
  - WBC 13.7 (9% PMNs, 17% lymph, 35% atypical lymph, 10% eos)
  - AST 530, ALT 1391, lipase normal
  - Discontinued drug, admitted for r/o sepsis, home and improving

Punch biopsy:
- Overall... pattern favors hypersensitivity/drug reaction... infiltrate of lymphocytes, plasma cells, neutrophils, and eosinophils...
**Symptoms**
- Fever
- Malaise
- Diffuse lymphadenopathy
- Rash
  - morbilliform \(\rightarrow\) erythrodermic
  - scarring, papules, bullae, purpura
  - often mucous membrane involvement
- Hepatitis
- Symmetric facial edema (50%)
- Other: arthralgias, pancreatitis, myocandidis

**Drug-induced hypersensitivity / DRESS**

**Characteristics in 124 Probable/Definite Cases of DRESS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age, mean +/- SD</th>
<th>Male</th>
<th>Liver involvement</th>
<th>Lung involvement</th>
<th>Eosinophils &gt; 0.7 x 10^9/L</th>
<th>Fever &gt; 38.5</th>
<th>Eosinophils</th>
<th>Lymphadenopathy</th>
<th>Atypical lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean +/- SD</td>
<td>40 +/- 21</td>
<td>50%</td>
<td>90%</td>
<td>7%</td>
<td>82%</td>
<td>71%</td>
<td>68%</td>
<td>65%</td>
<td>95%</td>
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<tr>
<td>Male</td>
<td>50%</td>
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<td>Onset (wks), mean +/- SD</td>
<td>4.1 +/- 2.2</td>
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<td>Resolution (wks), mean +/- SD</td>
<td>7.3 +/- 10.6</td>
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**Epidemiology**
- M = F
- Estimated incidence: 1/1000 – 1/10,000 drug exposures

**Pathophysiology:** interaction with herpesviruses?

**Culprits:**
- Antiepileptics (esp carbamazepine), allopurinol > sulfonamides, minocycline, vanco, amox/clav, dapsone, flagyl, antiretrovirals, NSAIDs, ACE-inhibitors, beta blockers, antidepressants
- Onset usually within 2-6 weeks of starting the drug
- later than most skin reactions (e.g. SJS within 28 days)

**Potentially life-threatening**

**Treatment:** stop the drug; sometimes corticosteroids

**Differential diagnosis**
- Serum sickness
- Toxic shock
- Viral hepatitis
- Sepsis
- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Autoimmune (e.g. Still's disease, lupus)
- Systemic vasculitis (e.g. Kawasaki disease)

**Bottom line:** think of this in your patients on medications, including antibiotics
- Can be mild, and can resolve with stopping the drug, but can become severe if exposure continues
- Labs: CBC w/diff (eos, atypical lymphs); LFTs; Cr, lipase
- Skin biopsy helpful

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**Case 3**
4/26/13

Case: 2 yo w/ fever, hip pain

• 2 year-old otherwise healthy boy with 6 days of fever, fussiness presents to urgent care/ED
  – Limp → refusal to bear weight
  – Difficult diaper changes

• Differential diagnosis
  – Trauma (accidental or non-accidental)
  – Slipped capital femoral epiphysis (SCFE)
  – Legg-Calve-Perthes disease
  – Malignancy
  – Juvenile idiopathic arthritis
  – Septic arthritis, osteomyelitis
  – Transient synovitis (formerly toxic synovitis)

Transplant Synovitis vs. Septic Arthritis

• Transient synovitis
  – Most common cause of non-traumatic hip pain in kids
    • Most unilateral; 5% bilateral
  – Typical age: 3-8 years; more likely in boys (2:1 M)
  – Symptoms: pain, limited range of motion, antalgic gait, non-toxic, fever often absent
  – Unclear cause – often a preceding URI
  – Treatment: supportive (NSAIDs)
  – Natural history: gradual resolution in 1-4 weeks

• Septic arthritis
  – Any age, neonates and up; pathogens vary by age group
  – Symptoms: pain, very limited range of motion, refusal to weight-bear, fever, ill-appearing
  – Long-term joint dysfunction in 10-25%

Hip pain: Distinguishing between Transient Synovitis and Septic Arthritis

Kocher criteria

1. fever >38.5 (oral)
2. non-weight bearing
3. ESR > 40 mm/hr
4. WBC > 12K

Kocher Criteria

<table>
<thead>
<tr>
<th>No. of Predictors</th>
<th>Transient Synovitis (N=48)</th>
<th>Septic Arthritis (N=42)</th>
<th>Predicted Probability of Septic Arthritis (genital)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10 (21.1%)</td>
<td>0 (0%)</td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>17 (34.7%)</td>
<td>1 (2.4%)</td>
<td>3.8</td>
</tr>
<tr>
<td>2</td>
<td>18 (37.5%)</td>
<td>2 (4.8%)</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>4 (8.2%)</td>
<td>4 (9.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>35 (80.5%)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

TABLE V. Distribution of Number of Multivariate Predictions and Associated Algorithms for the Predicted Probability of Septic Arthritis

Kocher Criteria – modified (CRP added)

<table>
<thead>
<tr>
<th>No. of Predictors</th>
<th>Probability of Septic Arthritis Based on Number of Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(T &gt; 38.5, non-weight bearing, ESR &gt; 40, WBC &gt; 12K, CRP &gt; 2 mg/dL, 20 mg/L)</td>
</tr>
<tr>
<td>0</td>
<td>Notes</td>
</tr>
<tr>
<td>1</td>
<td>Kocher, 1999 0%</td>
</tr>
<tr>
<td>2</td>
<td>Kocher, 2004 2%</td>
</tr>
<tr>
<td>3</td>
<td>Kocher, 2005 5%</td>
</tr>
<tr>
<td>4</td>
<td>Kocher, 2006 10%</td>
</tr>
<tr>
<td>5</td>
<td>Kocher, 2007 15%</td>
</tr>
</tbody>
</table>

Notes

Transient Synovitis vs. Septic Arthritis

- Bottom line: use the Kocher criteria, but interpret with caution
  - CRP particularly useful if NEGATIVE:
    - Levine et al, 2003: if CRP < 1 mg/dL, 13% probability of SA
    - Caird et al, 2006: if CRP < 2 mg/dL, 15% probability of SA
  - When unsure – get the sono, call ortho, tap the joint

Case: 2 yo w/ fever, hip pain
Back to our patient:
- CBC 18>12.2<1050 (51% PMN, 43% lymph, 0 bands)
- ESR 100 (ref 0-20 mm/hr)
- CRP 0.6 (ref <0.5 mg/dL)
  Kocher criteria: 4 present >60% probability of SA
- UA negative
- Urine and blood cultures sent (neg)
- Bilateral hip x-ray: no fracture or dislocation, no lytic or blastic lesions, no definite joint space asymmetry
- Bilateral hip ultrasound: small L hip effusion
- Arthrocentesis: 58,000 WBCs (97% PMNs)

Osteomyelitis and septic arthritis in children:
anatomical considerations
- Septic arthritis usually hematogenous in children
- Osteo \rightarrow septic arthritis common
- Septic arthritis \rightarrow osteomyelitis unlikely

Case: 2 yo w/ septic arthritis of hip
- Management:
  - Admit, ortho consult (or transfer to facility with ortho)
- Who needs surgical drainage for SA?
  - Hip: always \rightarrow risk of avascular necrosis of femoral head
  - Other joints: not necessarily
    - May require \( \geq 1 \) aspiration if reaccumulates
- Next steps in management – IMPORTANT
  - Adjunctive therapy to improve outcomes in pediatric septic arthritis:
    STEROIDS!!! (give before antibiotics)
**Why try this?**
- Residual joint dysfunction in 10-25% of children with septic arthritis
- Cytokine levels in joints correlate with severity of inflammation
- Animal data show decreased inflammation and arthritis in H. influenzae (rabbits) and S. aureus (mice)
- Analogous to use of steroids in meningitis → blunt the inflammatory response triggered by administering antibiotics

**Do the data support this?**
- Yes: 2 double-blind RCTs

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**Steroids for Hematogenous Septic Arthritis**

**UCSF PROTOCOL**

1. Obtain baseline CBC with diff, blood culture, ESR and CRP
2. Obtain joint aspiration **BEFORE** giving steroids and antibiotics**
3. Administer IV dexamethasone **BEFORE** administering IV antibiotics
   - Ideally 30 minutes prior; may also be given concurrently, or up to 2 hours after antibiotics
   - Dose: IV dexamethasone 0.15 mg/kg/dose IV q6 hours x 4 days
4. Administer IV antibiotics

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**Table: Comparison of Studies**

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<th>Population</th>
<th>Intervention</th>
<th>Antibiotics</th>
<th>Follow-up</th>
<th>Pathogens</th>
<th>Outcomes in steroid group (primary/secondary)</th>
<th>Reasons to remember this</th>
</tr>
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<tbody>
<tr>
<td>Odoo, Ped ID 2003</td>
<td>100 children 6 mo - 12 yr Groups comparable</td>
<td>Dexamethasone 0.6 mg/kg/day divided q 4 days</td>
<td>Uniform emetic antibiotics, by age</td>
<td>End of treatment, 6 mo, 12 mo</td>
<td>Identified in 90%</td>
<td>Less residual dysfunction (p&lt;0.001)</td>
<td>Many providers do not know about these studies</td>
</tr>
<tr>
<td>Harel, J Ped Ortho 2011</td>
<td>49 children 6 mo -13 years Groups comparable</td>
<td>Dexamethasone 0.6 mg/kg/day divided q4 days</td>
<td>Uniform emetic antibiotics (cefuroxime)</td>
<td>End of treatment, 2 mo, 6 mo, 12 mo</td>
<td>Identified in 35%</td>
<td>Faster resolution of fever (p&lt;0.05)</td>
<td>Urgent care / ED providers have the opportunity to bring steroids into the equation</td>
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Kawasaki Disease (KD): Background

- Vasculitis that typically occurs in healthy children
  - 25% of untreated children develop coronary artery abnormalities
  - KD is the common cause of acquired heart disease in developed world

- Most commonly ages 6 months – 5 years
  - Japanese: KD in 1% by 5 years of age

- Cause unknown → ?infectious agent
  - Winter/spring predominance in temperate climates
  - Apparent “outbreaks” with wavelike spread

- Probably a combination of exposure to an infectious agent in predisposed individuals

Case: Is this Kawasaki Disease?

- Don’t leave! This can happen in adults, too
  - 2010, Gomard-Mennesson et al: another case series found an additional 27 cases

- For adults – a zebra, but important to know about

- For kids – not a zebra, though we think about it a lot more than we diagnose it

- Easy to recognize when classic
  - More often get questions about “incomplete” Kawasaki – how to recognize, diagnose, and monitor

Classic Kawasaki Manifestations

“CRASH and Burn”

5 days fever
Plus 4 out of 5:
1. Conjunctivitis
2. Rash
3. Adenopathy (cervical)
4. Strawberry tongue (lips/oral cavity changes)
5. Hands/feet (changes in extremities)

* Manifestations often not present simultaneously → role for watchful waiting

Used with permission: Maen Housset, 2011
Kawasaki Disease: Treatment

- **IVIG**
  - 2 g/kg given over 10-12 hours
  - Ideally given within 10 days
  - 10% with continued fever → usually respond to 2nd dose IVIG
  - 80-100 mg/kg/day divided q6
    - Drop to 3-5 mg/kg/day after 2 weeks
    - Continued for 6-8 weeks until ECHO rules out coronary artery problems
- **High dose aspirin**
  * IVIG + aspirin → 5% risk of CAD (25% if untreated)
- **Steroids**
  - Not first line therapy: no benefit
  - Possible role in refractory cases

**Case: Is this Kawasaki?**

4 year-old boy with high fever (104) x 5 days, plus:

- Red, cracked lips
- Rash on arms/legs/cheeks
- Eye redness
- Abdominal pain
- Rhinorrhea
- Cough
- Overall well-appearing; not irritable

<table>
<thead>
<tr>
<th>Favors Kawasaki</th>
<th>Does not favor Kawasaki</th>
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### Case: Is this Kawasaki?

- **4 year-old boy with high fever (104) x 5 days, plus:**
  - Labs reassuring: ESR and CRP elevated but CBC, albumin, ALT, UA normal
  - Red, cracked lips
  - Rash on arms/legs/cheeks
  - Eye redness
  - Abdominal pain
  - Rhinorrhea
  - Cough
  - Overall well-appearing; not irritable

Favors Kawasaki

**Does not favor Kawasaki**

#### Important points:
- Infants at high risk for bad outcomes
  - Get labs if 7 days of fever, even without other KD symptoms
  - Can diagnose before 5 days of fever if 4 or more classic criteria present
  - Use the AHA algorithm; watchful waiting and repeating labs may be appropriate
  - Very elevated platelets should increase your suspicion for KD
  - Characteristics very suggestive of KD – look carefully:
    - Limbic-sparing conjunctivitis
    - Perineal desquamation
    - Lack of exudative pharyngitis, hand-foot-mouth, etc…
  - Pitfalls:
    - Antibiotics for cervical adenitis → mouth changes → presumed drug rxn
    - Sterile pyuria as culture negative (or pre-treated) UTI
    - Aseptic/viral meningitis because of fever, rash, CSF pleocytosis

#### Differential diagnosis – ID:
- Measles
- Other viral infections:
  - EBV, adenovirus, enterovirus (e.g. Coxsackie)
- Leprosy
- Rickettsial disease (e.g. Rocky Mountain spotted fever)
- Scarlet fever
- Staphylococcal scalded skin syndrome
- Toxic shock
- Bacterial cervical lymphadenitis

#### Differential diagnosis – non-ID:
- Drug hypersensitivity reactions (e.g. DRESS!)
- Stevens-Johnson syndrome
- Systemic onset JIA
- Mercury hypersensitivity reaction (acrodynia)

#### Evaluation of Suspected Incomplete Kawasaki Disease (KD):

- **Newburger et al, Kawasaki Guidelines, Pediatrics 2004**
Case: Is this Kawasaki?

“Kawasaki disease should be considered in the differential diagnosis of every child with a fever of at least several days’ duration, rash, and nonpurulent conjunctivitis, especially in children < 1 year old and in adolescents, in whom the diagnosis is frequently missed.”