Pediatric Potpourri: What do we now?
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Disclosure

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Four-day-old Girl

- Admitted on 3/19/2003 after being seen in clinic for well baby visit
- Erythematous papules in the perineal area
- Afebrile, eating OK
- No known ill contacts
- ROS negative for irritability, URI symptoms, vomiting, diarrhea, seizures

Four Day Old Girl

- Born at 37 weeks 2 days gestation by uncomplicated vaginal delivery
- Birthweight 6 pounds 8 ounces
- Mom denied history of genital herpes
Admission PE

- Temp 97.7° axillary, HR 135, RR 62, Oxygen saturation 99% on room air
- 3 erythematous vesicopustular lesions of the perineum

What to do?

Hospital Course

- Viral cultures obtained from the lesion, vagina, eye (bulbar conjunctiva), mouth and rectum
- CSF (traumatic tap done 3/19)
- RBC 82,000, WBC 84 (50% seg, 38% lymph, 6% mono, 6% eos)
- protein 106, glucose 40
- HSV PCR reported as negative on 3/20
- AST and ALT normal
- Empiric acyclovir started

On 3/20 eye culture reported as positive for HSV by shell vial test
- Other cultures negative
- HSV PCR on blood sent on 3/22
Management of Neonates Born to Women with Active HSV

- DOI: 10.1542/peds.2012-3216
- [http://pediatrics.aappublications.org/content/131/2/e635.full.html](http://pediatrics.aappublications.org/content/131/2/e635.full.html)

Terminology of HSV Infection & Disease

- First-episode primary genital infection
  - when an individual with no HSV-1 or HSV-2 antibody acquires either virus in the genital tract
- First-episode nonprimary infection
  - person with pre-existing HSV-1 antibody acquires HSV-2 genital infection (or vice versa)
- Recurrent infection
  - viral reactivation from latency and subsequent antegrade translocation back to skin and mucosal surfaces

Maternal HSV Classification^a^

<table>
<thead>
<tr>
<th>PCR/Culture From Genital Lesion</th>
<th>Maternal IgG Antibody Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented first-episode primary infection</td>
<td>Positive, either virus</td>
</tr>
</tbody>
</table>
| Documented first-episode nonprimary infection | 1. Positive for HSV-1  
2. Positive for HSV-2 | 1. Positive for HSV-2 and negative for HSV-1  
2. Positive for HSV-1 and negative for HSV-2 |
| Assume first-episode (primary or nonprimary) infection | 1. Positive for HSV-1 or HSV-2  
2. Negative OR not available^b^ | 1. Not available  
2. Negative for HSV-1 and/or HSV-2 OR not available |
| Recurrent infection | 1. Positive for HSV-1  
2. Positive for HSV-2 | 1. Positive for HSV-1  
2. Positive for HSV-2 |

^a^For women without a clinical history of genital herpes
^b^Strongly suspicious lesion

Terminology of HSV Infection & Disease

- Genital HSV infection can be either clinically apparent (eg, genital lesions) or inapparent (asymptomatic, or subclinical)
- Neonatal infection
  - occurs when viral replication has been established, but the virus is not causing disease
- Neonatal disease
  - viral replication produces clinical signs of illness (eg, skin lesions, encephalitis, hepatitis)
- Once an infant is infected with HSV, progression to disease is virtually certain

*Pediatrics*, February 2013, Volume 131:e635-e643
Risk of Maternal Infection During Pregnancy

- Recurrent infections are the most common form of genital HSV during pregnancy
- ~10% of HSV-2 seronegative women have an HSV-2 seropositive sexual partner and thus are at risk of primary HSV-2 infection
- Approximately one-fifth to one-third of women of childbearing age are seronegative for both HSV-1 and HSV-2
- Among discordant couples, the chance that a woman will acquire either virus during pregnancy is estimated to be 3.7%

For women who are already seropositive for HSV-1, the estimated chance of HSV-2 acquisition during pregnancy is 1.7%

Approximately two-thirds of women who acquire genital herpes during pregnancy remain asymptomatic consistent with the finding that 60%-80% of women who deliver an HSV-infected infant have an unapparent HSV infection at the time of delivery and have no prior history of genital herpes nor a sexual partner reporting a history of genital herpes

Neonatal HSV Infection

- Acquired during 1 of 3 distinct times
  - intrauterine (in utero) - 5%
  - intrapartum (perinatal) - 85%
  - postpartum (postnatal) - 10%
  - maternal or non-maternal

Risk of Neonatal HSV Infection

- Five factors
  1. Type of maternal infection (primary vs. recurrent
  2. Maternal HSV antibody status
  3. Duration of rupture of membranes
  4. Integrity of mucocutaneous barriers (eg, scalp electrodes)
  5. Mode of delivery (cesarean vs. vaginal)
Risk of Neonatal HSV Infection

- Infants born to mothers who have first episode of HSV infection near term and are shedding virus at delivery are at much greater risk compared to mothers with recurrent genital herpes
- 57% of infants delivered to women with first episode primary genital HSV developed disease
- compared to 25% for infants delivered to women with first-episode nonprimary infection and 2% of infants delivered to women with recurrent HSV disease

Clinical Manifestations

- Intrapartum or postpartum infection
  - Disseminated
  - CNS
  - Skin, eyes, mouth (SEM)

Disseminated

- Disease involving multiple organs
  - lung, liver, adrenal glands, skin, eye, and/or brain (60%)
- Typically presents at first to second week of life
- Serum ALT >2 times upper limit of normal
- HSV PCR of blood
  - not utilized for assignment of disease classification
- 21 days of IV acyclovir
  - 60 mg/kg/day divided every 8 hours

CNS

- CSF PCR
  - should be repeated prior to completing therapy
- Generally presents at second to third week of life
- Overall half of all infants with neonatal HSV disease will have CNS involvement
- CNS disease or disseminated disease with CNS involvement
- 21 days of IV acyclovir
SEM Only

- Culture of skin lesions (scraping), conjunctivae, mouth, nasopharynx, and rectum
- Antigen assay (DFA) and PCR can be done in addition to culture but do not replace culture
- Overall 70% of infants with neonatal HSV disease will have characteristic vesicular lesions
- SEM disease 83%, CNS disease 63%, disseminated disease 58%
- 14 days of IV acyclovir
Asymptomatic neonate following vaginal or cesarean delivery to mother with visible genital lesions that are characteristic of HSV.

Obstetric provider obtains swab of lesion for HSV PCR assay and culture.

Type all positive results.

Maternal history of genital HSV preceding pregnancy?

Send maternal type specific antibody, if assays are available at the delivery hospital.

At ~24 hours of age obtain from the neonate:

• HSV surface cultures* (and PCRs if desired)
• HSV blood PCR

If infant remains asymptomatic, do not start acyclovir.

No

Yes

At ~24 hours of age obtain from the neonate:

• HSV surface cultures (and PCRs if desired)
• HSV blood PCR
• CSF cell, chemistries, and HSV PCR
• Serum ALT

Start IV acyclovir.

If infant remains asymptomatic, do not start acyclovir.

No

Yes

Negative Maternal History of Genital Infection Preceding Pregnancy

Neonatal virology studies negative (PCRs negative; viral cultures negative at 48-72 hours).

Positive Maternal History of Genital Infection Preceding Pregnancy

Neonatal surface cultures negative, AND blood and surface PCRs negative

Neonatal surface cultures positive, OR blood and surface PCRs positive

Obtain CSF for cell count, chemistries, and HSV PCR. Obtain serum ALT.

Start IV acyclovir.

If infant remains asymptomatic, CSF indices not indicative of infection, CSF and blood PCR negative, and normal serum ALT

No

Yes

Treatment of Infection and Proven Disease

Treat with IV acyclovir 60 mg/kg/day in 3 divided doses for 14 days (SEM) or 21 days (CNS or disseminated)

Preemptive Treatment of Infection but No Proven Disease

Treat with IV acyclovir 60 mg/kg/day in 3 divided doses for 10 days

Repeat CSF HSV PCR near end of 21 day course of treatment

Positive

Negative

Continue IV acyclovir for 7 days more

D/C IV acyclovir after 21 day course
Suppressive Acyclovir After Neonatal Herpes


Infants with CNS involvement (CNS disease alone or disseminated disease with CNS involvement) or SEM were randomized to receive either placebo or acyclovir after completing IV acyclovir

- Acyclovir 300 mg/m² BSA/dose orally three times per day for 6 months

Infants surviving neonatal HSV disease with CNS involvement had improved neurodevelopmental outcomes

- Trend towards neutropenia in those receiving acyclovir but the neutropenia resolved in all patients
- No associated complications
2012 Red Book

- "Use of oral acyclovir suppressive therapy for the 6 months following treatment of acute neonatal HSV disease has been shown to improve neurodevelopmental outcomes in infants with HSV CNS disease and to prevent skin recurrences in infants with any disease classification of neonatal HSV."
- "Absolute neutrophil counts should be assessed at 2 and 4 weeks after initiating suppressive therapy and then monthly during the treatment period."

28-month-old Girl

- Seen in clinic Feb 2011 for evaluation of recurrent fever
- Beginning 3-4 months ago she developed regularly recurring episodes of fever
  - Fever lasts 5-6 days
  - Recurs approximately every 3 weeks
  - Episodes are accompanied by oral ulcers

28-month-old Girl

- When seen during the episodes no apparent focus of infection
- She is well in between the episodes
- ROS negative for rash, arthritis, arthralgias, vomiting diarrhea, cough, weight loss

Prior evaluation

- Febrile episode in December
- Normal urinalysis
- Hemoglobin 10.3, platelet count 281,000
- WBC 8.2 with 50% neutrophils, 3% bands, 30% lymphs, 13% monocytes, 4% eosinophils
- EBV serology negative
Past Medical History

- No hospitalizations
- PET at age one year
- Immunizations up to date
- Does attend daycare

Physical Exam

- Temp 98.0, Wt 50th percentile, Ht 75th percentile
- Exam normal

Diagnosis?

Periodic Fever Syndrome

- Recurrent bouts of fever without any definitive infection
- Most commonly PFAPA
  - periodic fever, aphthous stomatitis, pharyngitis, and lymphadenitis (typically cervical)
- Cyclic neutropenia, Hyperimmunoglobulinemia D (HIDS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Familial Mediterranean Fever
  - genetic mutations identified
PFAPA Diagnosis

- Clinical
  - Regularly recurring episodes of fever usually with an early age of onset
  - At least one symptom being aphthous stomatitis, pharyngitis, or lymphadenitis
  - Asymptomatic intervals between episodes
  - Normal growth and development
  - CBC to exclude cyclic neutropenia
  - Genetic testing available for HIDS, TRAPS, FMF

Clinical Characteristics

<table>
<thead>
<tr>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>2.8 years</td>
</tr>
<tr>
<td>Duration of Episode</td>
<td>4.8 days</td>
</tr>
<tr>
<td>Symptom Free Interval</td>
<td>28.2 days</td>
</tr>
<tr>
<td>Max Temp</td>
<td>40.5°C</td>
</tr>
<tr>
<td>Total Duration of PFAPA</td>
<td>6.3 years</td>
</tr>
</tbody>
</table>

Wurster VM et al, J Pediatr 2011;159:958-64

PFAPA Therapy

- 84% said glucocorticoids were very effective
- generally given once at the onset of the episode
- 24% of patients who received cimetidine had very effective results

Wurster VM et al, J Pediatr 2011;159:958-64

Tonsillectomy for PFAPA

- Randomized, controlled trial
- 26 children with at least 5 PFAPA episodes were randomized to tonsillectomy (N=14) or follow up alone (N=12)
- Six months after randomization all 14 children in the tonsillectomy group and 6/12 children in the control group were free of symptoms
- P<.001
3-year-old Boy

- Onset of left knee pain on 6 Jan 2013
- Went to ED 7 Jan and splinted
  - afebrile, no swelling, x-ray normal
- Saw Ortho 8 Jan and cast placed
- Had increasing pain
- Developed fever on 10 Jan

3-year-old Boy

- Admitted 11 Jan
- Cast removed and noted to have left knee swelling and was warm to touch
- I&D done with irrigation
  - Gram stain with Gram pos cocci resembling Staph
- Started empiric IV vancomycin

Hospital Course

- Blood and left knee synovial fluid cultures grew MRSA so vancomycin was continued
- Patient had some improvement but continued to have intermittent fever and pain
- PICC placed 14 Jan
- Repeat blood culture no growth
- Rifampin added on 16 Jan

MRI 16 Jan

- Heterogeneous bone marrow signal with marked edema on the proximal tibia extending into the epiphysis and metaphysis
- Popliteal abscess
- Joint effusion
Hospital Course
- Went back to the OR on 18 Jan for drainage and irrigation
- Vancomycin antibiotic beads placed
- Culture grew MRSA
- One temp to 100.4 on 19 Jan and then afebrile
- Discharged on IV vancomycin as a continuous infusion and po rifampin on 22 Jan

Outpatient Course
- Random vancomycin level 19.9 mcg/ml
- C-reactive protein back to normal on 14 Feb
  - 3.2 mg/L
- D/Ced vancomycin on 18 Feb and started po TMP/SMX to complete a total of 8 weeks treatment

Osteomyelitis in Children
- Most cases arise hematogenously
- Metaphysis of the long bones
  - femur, tibia, humerus
- Preceding blunt trauma to the site is common, but the role of trauma in the pathogenesis is not clear
  - Small hematomas may permit bacterial seeding after transient bacteremia

Microbiology
- *Staphylococcus aureus* is by far the most common pathogen
  - MSSA or MRSA
- Group A Strep, Pneumococcus, and *Kingella kingae*
- Group B Strep and Gram negative enterics in newborns
- Salmonella in Sickle Cell disease
- *Pseudomonas aeruginosa* is particularly associated with puncture wounds of the calcaneus, metatarsal, and tarsal bones
**Diagnosis**
- MRI is the most sensitive modality for detecting acute osteomyelitis
- bone marrow edema
- also helpful for diagnosing pyomyositis
- helps plan the optimal surgical management
- C-reactive protein and ESR can be helpful to guide response to therapy

**Initial Empiric Therapy**
- IV vancomycin
- emergence of MRSA
- ~30% of *S. aureus* locally are resistant to clindamycin

**Therapy**
- Treat for 4-8 weeks
- Can do sequential parenteral-oral therapy
- C-reactive protein normal prior to stopping antibiotics

**MRSA**
- Infectious Diseases Society of America (IDSA) Practice Guideline (www.idsociety.org)
- http://www.idsociety.org/Organism/#MRSA
MRSA Bone & Joint Infections

- Surgical debridement and drainage of associated soft tissue abscesses
- For septic arthritis drainage or debridement of the joint space should always be performed
- Treat 8 weeks for osteomyelitis, 3-4 weeks for septic arthritis
- Some experts recommend adding rifampin
- If bacteremic add rifampin after clearance of bacteremia

Liu C et al, Clin Infect Dis 2011;52:3-38

Questions

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