What’s new with HSV?

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Personal/Professional Financial Relationships with Industry

<table>
<thead>
<tr>
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<th>Company Name(s)</th>
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<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers**</td>
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<td>Board of Directors or officer</td>
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<tr>
<td>Royalties from Emory or from external entity</td>
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<td>Industry funds to Emory for my research</td>
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<td>Other</td>
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**Does not include stock in publicly-traded companies in retirement funds and other pooled investment accounts managed by others.
Objectives

- Describe the changing epidemiology of HSV and neonatal HSV
- Describe the clinical manifestations and workup of neonatal HSV
- Describe the recent papers that have changed aspects of management
HSV Epidemiology

- HSV seroprevalence has fallen (NHANES data):
  - 1999-2004
    - 58% seroprevalence HSV-1, 17% seroprevalence HSV-2
  - 2005-2014
    - 54% seroprevalance HSV-1, 16% seroprevalence HSV-2
    - Largest decline HSV-1 was in 14-19 year age groups
- HSV-1 is now the predominant cause of genital HSV
  - Up to 80% in some populations
Neonatal HSV and Maternal History

What percentage of infants with neonatal HSV disease are born to mothers with no known history of HSV infection?

- 10%
- 30%
- 65%
- 80%
HSV Epidemiology in Pregnancy

- 20-30% of pregnant women are seropositive for HSV-2
- 75% of women with prior history of genital HSV will have a recurrence during pregnancy
- HSV seronegative women have a 4% chance of getting HSV-1 or 2 during pregnancy
- HSV-1 positive women have a 2% chance of getting HSV-2 during pregnancy
- In up to 80% of cases of neonatal HSV there is no known maternal history of genital HSV
Neonatal Transmission Risk Class

<table>
<thead>
<tr>
<th>Maternal Infection Classification</th>
<th>PCR/Culture Result</th>
<th>Maternal Serology</th>
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<tbody>
<tr>
<td>First episode, primary</td>
<td>Positive HSV 1 or 2</td>
<td>Negative HSV 1 and 2</td>
</tr>
<tr>
<td>First episode, non-primary</td>
<td>Positive HSV 1</td>
<td>Positive HSV 2 only</td>
</tr>
<tr>
<td></td>
<td>Positive HSV 2</td>
<td>Positive HSV1 only</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Positive HSV 1</td>
<td>Positive HSV 1</td>
</tr>
<tr>
<td></td>
<td>Positive HSV 2</td>
<td>Positive HSV 2</td>
</tr>
</tbody>
</table>

Assume first episode if PCR, culture, or serology results not available.
Risk of Transmission

What is the risk of transmission to a neonate with maternal primary HSV and lesions present at vaginal delivery with no intervention?

- 30-60%
- < 1%
- 70-80%
- 10-20%
Infant Risk of Transmission

- First episode primary: 57%
- First episode non-primary: 25%
- Recurrent HSV: 2%

Other perinatal risk factors:
  - Vaginal delivery
  - Broken skin barrier (e.g. scalp electrode)
  - HSV-1 vs HSV-2 infection
Neonatal HSV Clinical Features

- Mode of acquisition:
  - In utero (5%)
  - Peripartum (85%)
  - Postpartum (10%)

- In utero usually manifests with severe chronic skin findings, severe neurologic findings, ocular findings at birth.

- No clinical difference between peripartum and postpartum infections
Peri/Post Natal Acquisition

Three clinical manifestations of disease:

- SEM (Skin, Eye, Mouth): 45%
- CNS: 30%
- Disseminated 25%
Peri/Post Natal Acquisition

- SEM/Disseminated typically present early 9-11 days average
- CNS typically presents late 16-17 days average
- Nearly all neonatal HSV will present by 5 weeks of age

- Up to 75% of those with SEM alone will develop CNS or disseminated disease without therapy
- 2/3 disseminated also have CNS disease
- 1/3 of CNS disease does not have skin lesions
Prevention

- Delivery by C-section for active lesions even if ruptured membranes
  - PROM for HSV is 4 hours
- Women with recurrent disease but no lesions should deliver vaginally
- ACOG recommends women with active recurrent HSV receive suppressive antiviral therapy starting 36 weeks
  - Has not been studied yet to show definitively it prevents disease
  - Misses the largest group of neonates with HSV – those born to mothers with no history (80%)
- New guidelines on management of asymptomatic babies exposed to maternal genital lesions:
Guidance on Management of Asymptomatic Neonates Born to Women With Active Genital Herpes Lesions
David W. Kimberlin, Jill Baley, COMMITTEE ON INFECTIOUS DISEASES and COMMITTEE ON FETUS AND NEWBORN
*Pediatrics* 2013;131;e635; originally published online January 28, 2013;
DOI: 10.1542/peds.2012-3216

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/131/2/e635.full.html
AAP Neonatal HSV Exposure Pathway - 2013

- Provides guidance for neonates exposed to mothers with VISIBLE GENITAL LESIONS concerning for HSV
- Full pathway requires ability to do rapid, type specific antibody on mother at time of delivery
- Full pathway requires rapid ability to do HSV PCR and cultures
- Ability to match maternal antibody and vaginal culture types
- Primarily consensus based
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?

no

Send maternal type specific serology for HSV-1 and HSV-2 antibodies, 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
- CSF cell count, chemistries, and HSV PCR
- Serum ALT
Start IV acyclovir at 60 mg/kg/day in 3 divided doses

Determine Maternal HSV Infection Classification (Table 2)

First-Episode Primary or First-Episode Nonprimary

Recurrent Infection

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

Neonatal PCRs or viral cultures positive

Go to Fig 3.

Stop acyclovir. Educate family for signs and symptoms of neonatal HSV disease and follow closely §

Go to Fig 3.

yes

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

Neonatal surface cultures negative, AND blood and surface PCRs negative

Go to Fig 3.

Neonatal surface cultures positive, OR blood or surface PCRs positive

Obtain CSF for cell count, chemistries, and HSV PCR. Send serum ALT. Start IV acyclovir at 60 mg/kg/day in 3 divided doses.

Educate family on signs and symptoms of neonatal HSV disease and follow closely §

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* This algorithm should be applied only in facilities where access to PCR and type-specific serologic testing is readily available and turnaround time for test results is appropriately short. In situations where this is not possible, the approach detailed in the algorithm will have limited, and perhaps no, applicability.

§ Evaluation and treatment is indicated prior to 24 hours of age if the infant develops signs and symptoms of neonatal HSV disease. In addition, immediate evaluation and treatment may be considered if:

- There is prolonged rupture of membranes (>4-6 hours)
- The infant is premature (≤37 weeks gestation)

† Conjunctiva, mouth, nares, rectum and scalp electrode site, if present.

‡ HSV blood PCR is not utilized for assignment of disease classification.

§ Discharge after 48 hours of negative HSV cultures (and negative PCRs) is acceptable if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital until HSV cultures are finalized as negative or are negative for 96 hours after being set up in cell culture, whichever is shorter.
Asymptomatic neonate following vaginal or cesarean delivery to mother with visible genital lesions that are characteristic of HSV

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Lesions at delivery, no known history

- Send maternal type specific serology for HSV-1 and HSV-2 antibodies, 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
- CSF cell count, chemistries, and HSV PCR
- Serum ALT

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Determine Maternal HSV Infection Classification (Table 2)

First-Episode Primary or First-Episode Nonprimary
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  - Go to Fig 3.

Recurrent Infection
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  - Go to Fig 3.

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Lesions at delivery, (+) prior history

yes

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

Neonatal surface cultures negative, AND blood and surface PCRs negative

Obtain CSF for cell count, chemistries, and HSV PCR. Send serum ALT. Start IV acyclovir at 60 mg/kg/day in 3 divided doses.

Educate family on signs and symptoms of neonatal HSV disease and follow closely§

Neonatal surface cultures positive, OR blood or surface PCRs positive

Go to Fig 3.

“§” denotes infant must stay in house until most/all results known
Exposure Treatment (Fig 3)

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

Treatment of Infection and Proven Disease
- Treat with intravenous acyclovir at 60 mg/kg/DAY in 3 divided daily doses for 14 days (SEM) or 21 days (CNS or disseminated)
- Additional evaluation may be indicated

Preemptive Therapy of Infection but No Proven Disease
- Treat with intravenous acyclovir at 60 mg/kg/DAY in 3 divided daily doses for 10 days

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

Positive
- Continue intravenous acyclovir for 7 days more

Negative
- D/C intravenous acyclovir after 21 day treatment course

* Serum ALT values in neonates may be elevated due to noninfectious causes (delivery-related perfusion, etc). For this algorithm, ALT values more than 2 times the upper limit of normal may be considered suggestive of neonatal disseminated HSV disease for HSV-exposed neonates.

† If evidence of CNS disease at beginning of therapy.
Summary of Exposure Recs (Exposure to active lesions)

- If history uncertain or primary, full neonatal workup is indicated including:
  - HSV cultures +/- PCRs
  - HSV blood PCR
  - CSF with HSV PCR
  - Serum ALT
  - Infant will receive 10 days of IV acyclovir unless maternal type specific serology and culture/PCR indicates recurrent maternal infection

- If history of recurrent disease, infant must get HSV surface cultures +/- PCR and blood PCR
  - Infant must stay in hospital pending some lab results
  - If any test is positive do full workup and treat for minimum 10 days
Issues with this Protocol

△ Most hospitals will not have rapid, type-specific antibody available
  △ Must be matched to PCR or culture from maternal genital tract
  △ Must default to unknown or high risk status if you can’t test
    △ Many “first time” lesions are really recurrent – this places many infants into a high risk group unnecessarily

△ Not evidence based:
  △ No legitimate reference to support 10 days of preemptive therapy
  △ No reference to support utility of CSF in asymptomatic 1 day old

△ Veers from our prior recommendations:
  △ Exposed low risk babies now must stay until all cultures and blood PCR resulted
  △ All unknown/high risk infants will default to getting 10 days of IV acyclovir in hospital whether they have any positive studies themselves or not
Evaluation of Suspected Neonatal HSV

- HSV surface cultures
  - Skin vesicle
  - Mouth, NP, conjunctivae, anus 12-24 hours after birth

- HSV skin PCR
  - Can do on vesicle, also other sites
  - More sensitive than culture
  - Rapid – same day turn around in some centers

- HSV PCR on CSF
- HSV PCR on blood
- Serum ALT
  - Done as part of fever pathway at CHOA on all newborns < 14 days old
  - If > 2x normal all HSV workup then initiated
Plasma and Cerebrospinal Fluid Herpes Simplex Virus Levels at Diagnosis and Outcome of Neonatal Infection

Ann J. Melvin, MD, MPH^1, Kathleen M. Mohan, ARNP^1, Joshua T. Schiffer, MD, MPH^2,3, Linda M. Drolette, BS^4, Amalia Magaret, PhD^3,5, Lawrence Corey, MD^3,5, and Anna Wald, MD, MPH^2,3,4,5

Objective To evaluate the utility of quantitative herpes simplex virus (HSV) polymerase chain reaction (PCR) levels for prognosis and management of neonatal HSV disease.

Study design Clinical and virologic data were abstracted by medical record review from neonatal HSV cases treated at Seattle Children’s Hospital between 1993 and 2012. HSV PCR results from plasma (n = 47), cerebrospinal fluid (n = 56), or both (n = 40) at the time of diagnosis were available from 63 infants; 26 with skin-eye-mouth (SEM), 18 with central nervous system (CNS), and 19 with disseminated (DIS) disease.

Results Plasma HSV PCR was positive in 78% of the infants with SEM, 64% with CNS and 100% with DIS disease. Mean plasma viral level was 2.8 log_{10} copies/mL in SEM, 2.2 log_{10} copies/mL in CNS, and 7.2 log_{10} copies/mL in DIS infants. The HSV levels were higher among infants who died compared with surviving infants, 8.1 log_{10} copies/mL (range 7.7–8.6) vs 3.8 log_{10} copies/mL (range 0.0–8.6), P = .001, however, level of HSV DNA in the cerebrospinal fluid or in plasma did not correlate with neurologic outcome. Dynamics of HSV clearance from plasma during high-dose acyclovir treatment showed single-phase exponential decay with a median viral half-life of 1.26 days (range: 0.8–1.51).

Conclusions Plasma HSV levels correlate with clinical presentation of neonatal HSV disease and mortality, but not neurologic outcome. (J Pediatr 2015; ■: ■ - ■).
Plasma and CSF HSV PCR Diagnostics

- Quantitative plasma (47), CSF (56) or both (40) PCRs on 63 infants 1993-2012
  - Clinical classifications:
    - 26 SEM, 18 CNS, 19 disseminated
  - HSV PCR quant levels statistically higher in those who died versus those who survived
  - HSV levels did not correlate with neurologic outcome
  - Median viral half-life on high dose ACV was 1.26 days (0.8-1.51)
- Keep in mind our PCRs are not quantitative at Emory & CHOA
Plasma and CSF HSV PCR Diagnostics - Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>SEM, N=26</th>
<th>CNS, N=18</th>
<th>DIS, N=19</th>
<th>Total, N=63</th>
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<tbody>
<tr>
<td>Plasma PCR +</td>
<td>14/18 (78)</td>
<td>7/11 (64)</td>
<td>18/18 (100)</td>
<td>39/47 (83)</td>
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<tr>
<td>CSF PCR +</td>
<td>2/24 (8)</td>
<td>13/18 (72)</td>
<td>9/14 (64)</td>
<td>24/56 (43)</td>
</tr>
<tr>
<td>Surface Cx +</td>
<td>24/25 (96)</td>
<td>9/18 (50)</td>
<td>12/18 (67)</td>
<td>45/61 (74)</td>
</tr>
</tbody>
</table>

- Of note plasma PCR is very sensitive – and will pick up patients with only SEM
- Classification into SEM/DIS should be based on cumulative clinical findings not just PCR results
- All CSF positive cases should be treated as CNS disease regardless of other findings
Outcome

- Classic morbidity/mortality:
  - Disseminated disease 85% mortality if untreated, 50% permanent neuro deficits in survivors
  - CNS disease 50% mortality, 33% permanent neuro sequelae if untreated

- With treatment (high dose acyclovir):
  - Disseminated disease 29% mortality, 17% permanent neuro deficits in survivors
  - CNS disease 4% mortality, still 31% permanent neuro sequelae
You are treating an infant for neonatal HSV encephalitis. The IV comes out at day 14 of therapy. Your best treatment option is:

- Switch to oral acyclovir 300 mg/m2/dose PO TID
- Discontinue therapy
- Replace IV, restart IV acyclovir 20 mg/kg/dose IV q8h
- Switch to oral valganciclovir 7.5 mg/kg/dose PO BID
Treatment

- Acyclovir 20 mg/kg/dose IV q8h for all neonatal HSV
- Still no oral options
- Treat 14 days for SEM, minimum 21 days disseminated and CNS
- CNS disease requires repeat LP at end of therapy to document HSV PCR clearance
  - If not clear, therapy is continued until negative
- All infants now continued on suppressive therapy for 6 months following treatment:
  - 300 mg/m2/dose TID x 6 months
  - Mildly better neurodevelopmental outcomes
  - Less skin recurrences
  - Check ANC 2 weeks, 4 weeks, then monthly on therapy
Neonatal HSV Chronic Suppression

Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes

David W. Kimberlin, M.D., Richard J. Whitley, M.D., Wen Wan, Ph.D., Dwight A. Powell, M.D., Gregory Storch, M.D., Amina Ahmed, M.D., April Palmer, M.D., Pablo J. Sánchez, M.D., Richard F. Jacobs, M.D., John S. Bradley, M.D., Joan L. Robinson, M.D., Mark Shelton, M.D., Penelope H. Dennehy, M.D., Charles Leach, M.D., Mобeen Rathore, M.D., Nazha Abughali, M.D., Peter Wright, M.D., Lisa M. Frenkel, M.D., Rebecca C. Brady, M.D., Russell Van Dyke, M.D., Leonard B. Weiner, M.D., Judith Guzman-Cottrill, D.O., Carol A. McCarthy, M.D., Jill Griffin, R.N., Penelope Jester, R.N., M.P.H., Misty Parker, M.D., Fred D. Lakeman, Ph.D., Huichien Kuo, M.S., Choo Hyung Lee, M.S., and Gretchen A. Cloud, M.S., for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group
Neonatal HSV Chronic Suppression

- 74 infants enrolled
  - 45 CNS disease, 29 skin eye, mouth
  - Only 28/45 with CNS disease evaluated for neurodevelopmental outcomes at 12 months of age using Bayley Scales
    - Scores higher (88.24 vs 68.12, p=0.046) in those randomized to acyclovir vs placebo
Conclusions:

- Most infants with neonatal HSV are born to mothers with no known history of HSV
- Evaluation for neonatal HSV should include samples from all potential sites
- PCR can supplement culture and is more sensitive – preferred for lesions
- Pathway for neonatal HSV delivery exposures has changed dramatically – need to become familiar with pathway
- All infants with neonatal HSV should be placed on chronic suppressive acyclovir for 6 months after treatment course
References:

► Kimberlin DW, Baley J; Committee on infectious diseases; Committee on fetus and newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics. 2013 Feb;131(2):e635-46.


