Neonatal Herpes Simplex Virus Infection: Presentation, Treatment, and Prevention

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University of Alabama at Birmingham

Disclosures

• I have no actual or potential conflict of interest in relation to this program
• I participate as one of dozens of sites for clinical trials conducted by GSK, Cellex, and Cubist. All funds from these efforts go to my university and not to me.
• I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation

Learning Objectives

• Understand the natural history of neonatal HSV disease, including disease classification.
• Understand the appropriate work-up of a neonate with suspected HSV.
• Know the current therapy of neonatal HSV disease.
• Know prognostic factors for morbidity and mortality.

Incidence of Neonatal HSV Infection

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>Rate of neonatal HSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>7 Census Regions (ICD9)</td>
<td>1 in 1,300</td>
</tr>
<tr>
<td>USA</td>
<td>Seattle, WA</td>
<td>1 in 2,300</td>
</tr>
<tr>
<td>USA</td>
<td>Birmingham, AL</td>
<td>1 in 2,750</td>
</tr>
<tr>
<td>UK</td>
<td>National voluntary reporting</td>
<td>1 in 60-70,000</td>
</tr>
<tr>
<td>Switzerland</td>
<td>National</td>
<td>1 in 62,500</td>
</tr>
<tr>
<td>Netherlands</td>
<td>National</td>
<td>1 in 35,000</td>
</tr>
<tr>
<td>Australia</td>
<td>National</td>
<td>1 in 30,000</td>
</tr>
<tr>
<td>Norway</td>
<td>National (CNS only)</td>
<td>1 in 25,000</td>
</tr>
<tr>
<td>Sweden</td>
<td>Stockholm</td>
<td>1 in 15,000</td>
</tr>
<tr>
<td>Japan</td>
<td>National</td>
<td>1 in 14-20,000</td>
</tr>
</tbody>
</table>

Neonatal HSV Acquisition

<table>
<thead>
<tr>
<th>Route of Infection</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>in utero</td>
<td>5</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>85</td>
</tr>
<tr>
<td>Postpartum</td>
<td>10</td>
</tr>
</tbody>
</table>

Intrapartum and Postpartum HSV Infection

• Disseminated disease ~ 25%
  – DIC
  – Pneumonia
  – Hemorrhage
  – CNS involvement (60% to 75%)
• Encephalitis (CNS disease) ~ 30%
  – Seizures
  – Lethargy
  – Irritability
  – Poor feeding
  – Temperature instability
• Skin, eyes, and/or mouth (SEM disease) ~ 45%
Neonatal HSV Disease

Signs and Symptoms Prior to Study Enrollment

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin Vesicles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of Patients</td>
<td>83%</td>
<td>63%</td>
<td>58%</td>
</tr>
<tr>
<td>Duration of symptoms*</td>
<td>3.8 ± 0.5</td>
<td>6.1 ± 1.0</td>
<td>3.7 ± 0.6</td>
</tr>
<tr>
<td><strong>Lethargy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of Patients</td>
<td>19%</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td>Duration of symptoms*</td>
<td>3.5 ± 0.7</td>
<td>4.6 ± 0.7</td>
<td>3.4 ± 0.7</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of Patients</td>
<td>17%</td>
<td>44%</td>
<td>56%</td>
</tr>
<tr>
<td>Duration of symptoms*</td>
<td>4.6 ± 1.5</td>
<td>3.1 ± 0.4</td>
<td>4.6 ± 0.6</td>
</tr>
<tr>
<td><strong>Seizure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of Patients</td>
<td>2%</td>
<td>53%</td>
<td>22%</td>
</tr>
<tr>
<td>Duration of symptoms*</td>
<td>7.8</td>
<td>2.9 ± 0.5</td>
<td>2.3 ± 0.7</td>
</tr>
</tbody>
</table>

*Days ± SE

Pediatrics 2001;108:223-229

Changes in Characteristics by Extent of Disease

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Premature</strong></td>
<td>43%</td>
<td>20%</td>
<td>27%</td>
<td>36%</td>
<td>28%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Enrollment Age</strong></td>
<td>11.2 ± 0.9</td>
<td>12.0 ± 2.2</td>
<td>15.2 ± 1.3</td>
<td>19.7 ± 1.6</td>
<td>10.1 ± 1.1</td>
<td>11.4 ± 0.8</td>
</tr>
<tr>
<td>(days ± SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time between first</strong></td>
<td>5.9 ± 0.7</td>
<td>5.7 ± 1.3</td>
<td>6.6 ± 0.8</td>
<td>7.4 ± 1.3</td>
<td>5.3 ± 0.7</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>HSV and enrollment</td>
<td>(days ± SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pediatrics 2001;108:223-229

Factors That Influence Transmission

- Type of maternal infection
- Transplacental antibody
- Fetal scalp monitor
- Duration of rupture of membranes
- Mode of delivery

Risk of Transmission

Type of Maternal Infection

Adapted from:
JAMA 2003;289:203-209

Risk of Transmission

Type of Maternal Infection

Adapted from:
JAMA 2003;289:203-209

First episode genital HSV (n=23) (19%)
1º HSV-1 (n=3) (13%)
1º HSV-2 (n=4) (17%)
Infant with HSV (n=1)
Infant with HSV (n=1)
57%

Adapted from:
JAMA 2003;289:203-209

Women delivered (n=58,288)
Cultured within 48 hrs (n=39,949) (69%)
Subclinical shedding (n=128) (0.3%)
Serologies available (n=121) (95%)

First episode genital HSV (n=23) (19%)
1º HSV-1 (n=3) (13%)
1º HSV-2 (n=4) (17%)
Infant with HSV (n=1)
Infant with HSV (n=1)
57%
## Risk of Transmission

### Type of Maternal Infection

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Number of Women (n=58,288)</th>
<th>Cultured within 48 hrs (n=39,949) (69%)</th>
<th>Subclinical shedding (n=128) (0.3%)</th>
<th>Serologies available (n=121) (95%)</th>
<th>First episode genital HSV (n=23) (19%)</th>
<th>1º HSV-1 (n=3) (13%)</th>
<th>Non-1º HSV-1 (n=1) (4%)</th>
<th>Non-1º HSV-2 (n=15) (65%)</th>
<th>1º HSV-2 (n=4) (17%)</th>
<th>HSV-1 (n=8) (8%)</th>
<th>HSV-2 (n=90) (92%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women delivered</td>
<td>n=58,288</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Neonate with HSV

- 25%
- 20%
- 5%
- 2%

Adapted from: JAMA 2003;289:203-209

## Diagnosis of Neonatal HSV

- **Surface cultures**
  - Swabs of mouth, nasopharynx, conjunctivae, rectum
- **Culture of skin vesicle**
- **Specimens from blood (urine and stool removed from list of sites)**
- **CSF for PCR (+ culture)**
- **DFA staining of vesicle scrapings**
- **PCR of blood may be of benefit in diagnosis (in addition to standard work-up)**


## Neonates Delivered to Women with Active Genital HSV Lesions

- **Obtain HSV cultures at 12-24 hours of life**
- **If mother has first-episode genital infection, some experts recommend empiric parenteral acyclovir treatment**
  - Can begin after HSV cultures are obtained at 12-24 hours of life
  - Can begin at birth (still obtain HSV cultures prior to starting antiviral therapy)
- **Most experts would not empirically treat neonates born to women with active recurrent genital HSV lesions with acyclovir**
- **First-episode clinical infections are not always primary infections**


## HSV Culture Follow-up

- **If the neonate’s HSV cultures obtained at 12-24 hours of life subsequently grow, HSV infection is confirmed and the baby should then be evaluated for HSV disease (including LP, ALT)**
  - No evidence of HSV disease: empiric treatment x 10d
  - Evidence of HSV disease: treatment x 14-21 days


## Neonates Delivered to Women with History of Genital Herpes

- **Observe for signs of infection (e.g., vesicular lesions of the skin, respiratory distress, seizures, or signs of sepsis)**
- **Should not obtain surface cultures for HSV at 12-24 hours of life**
- **Should not receive empiric parenteral acyclovir**
- **Educate parents about the signs and symptoms of neonatal HSV infection during the first 6 weeks of life**

Vesicular Eruptions in the Neonate
Differential Diagnosis

<table>
<thead>
<tr>
<th>Infectious Etiologies</th>
<th>Noninfectious Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV</td>
<td>Neonatal lupus</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Erythema toxicum</td>
</tr>
<tr>
<td>Psudomonas</td>
<td>Pustular melanosis</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>Miliaria</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Urticaria pigmentosa</td>
</tr>
<tr>
<td>Candida</td>
<td>Bullous necrolysis</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>Dermatitis herpetiformes</td>
</tr>
<tr>
<td>VZV</td>
<td>Necrotic bullae</td>
</tr>
<tr>
<td>CMV</td>
<td>Acropustulosis</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Neonatal bullous dermatitis</td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>Langerhans cell histiocytosis</td>
</tr>
</tbody>
</table>

Clin Perinatol 1997;24:129-150

Mortality Among Infants with Disseminated Disease

Pediatrics 2001;108:230-238

Mortality Among Infants with CNS Disease

Pediatrics 2001;108:230-238
Development of Abnormal Laboratory Values On Therapy

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>45 mg/kg/d</th>
<th>60 mg/kg/d</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500-1,000/mm³</td>
<td>1/4 (25%)</td>
<td>5/29 (17%)</td>
<td>6/33 (18%)</td>
</tr>
<tr>
<td>&lt; 500/mm³</td>
<td>0/4 (0%)</td>
<td>1/29 (3%)</td>
<td>1/33 (3%)</td>
</tr>
</tbody>
</table>

* 1 CNS
† 3 CNS, 2 SEM

Neonatal Morbidity Among Survivors With Known Outcomes After 12 Months

CASG Phase III Neonatal Suppression Studies

- Immediate suppression (randomized to active drug) vs.
- Deferred suppression (randomized to placebo but moved to open-label suppression following the second cutaneous recurrence)

Bayley Mental Score at 12 Months

<table>
<thead>
<tr>
<th></th>
<th>CASG 103 (CNS Involvement Study)</th>
<th>CASG 104 (SEM Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acyclovir N=16</td>
<td>Placebo N=12</td>
</tr>
<tr>
<td></td>
<td>Acyclovir N=8</td>
<td>Placebo N=7</td>
</tr>
<tr>
<td>Mean</td>
<td>88.24†</td>
<td>86.12†</td>
</tr>
<tr>
<td>Adjusted Mean</td>
<td>88.24†</td>
<td>86.12†</td>
</tr>
<tr>
<td>P-value by ANCOVA*</td>
<td>0.046</td>
<td>0.263</td>
</tr>
</tbody>
</table>

* Adjusted for covariates at baseline which were unbalanced between treatment groups:
† Head circumference at birth, birth weight, enrollment weight
‡ Enrollment weight

48th IDSA Annual Meeting, Vancouver, BC, October 22, 2010; Abstract #2977
When Should You Start Acyclovir in a Neonate?

- Caviness et al.
  - 10 cases from ~ 10,000 admissions over 5 years
  - Rash, lethargy, respiratory distress, or ↑ transaminases present in all 10
  - Abnormal CSF indices with PMN predominance can make bacterial meningitis more likely
  - Abnormal CSF indices with mono predominance does not make neonatal HSV more likely
  - Enteroviral meningitis 20-times more likely than HSV CNS disease in febrile neonate with CSF pleocytosis during enteroviral season
  - SBI 23-times more likely than neonatal HSV

J Pediatr 2008;153:164-169

When Should You Start Acyclovir in a Neonate?

- Kimberlin editorial
  - Do not routinely use amp, gent, and acyclovir for r/o sepsis
  - Work-up for neonatal HSV and begin IV acyclovir for:
    - Skin vesicles
    - Seizures
    - Marked ↑ in transaminases
    - Sepsis-like picture (including hypothermia)
    - Infant more ill appearing than would be expected in clinician’s judgment
    - ± CSF pleocytosis with mononuclear cell predominance outside of enteroviral season


Management of asymptomatic neonates born to women with active genital herpes lesions

DRAFT COID/COFN

Statement

Asymptomatic neonates born to women with active genital herpes lesions

- Obstetrician obtains swab of lesion for HSV culture and PCR
- Type all positives
- Maternal history of prior genital HSV?
- Send maternal type specific serology
- At ~24 hours of age* obtain:
  - HSV surface culture (and PCR if desired)
  - HSV Blood culture and/or PCR HSV†
  - CSF cell count, chemistries, and HSV PCR
  - Serum ALT
- Start IV acyclovir at 60mg/kg/day in three divided doses

DRAFT COID/COFN

Classification of Maternal HSV Genital Infection

Statement

<table>
<thead>
<tr>
<th>PCR/Culture</th>
<th>HSV-1 and HSV-2 IgG/Ab Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive, either virus</td>
<td>Both negative</td>
</tr>
<tr>
<td>Positive for HSV-1</td>
<td>Positive for HSV-2</td>
</tr>
<tr>
<td>Positive for HSV-2</td>
<td>Positive for HSV-1</td>
</tr>
<tr>
<td>Negative or not available</td>
<td>Positive for HSV-1 or HSV-2 if available</td>
</tr>
<tr>
<td>Negative or not available</td>
<td>Positive for HSV-1, HSV-2, or not available</td>
</tr>
</tbody>
</table>

* Immediate evaluation and treatment may be considered if:
- Prolonged rupture of membranes
- Prematurity

§ Follow closely for signs and symptoms of neonatal HSV disease and educate family on its recognition.
Management of asymptomatic neonates born to women with active genital herpes lesions

**DRAFT COID/COFN**

**Statement**

- Asymptomatic neonate delivered vaginally or by cesarean section to mother with active genital HSV
- Obstetrician obtains swab of lesion for HSV culture and PCR
- Type all positives
- Maternal history of prior genital HSV?
- Send maternal type specific serology

At ~24 hours of age:

- HSV surface culture (and PCR if desired)
- HSV blood culture and/or PCR
- If infant remains asymptomatic, do not start acyclovir

At ~24 hours of age:

- HSV surface culture (and PCR if desired)
- HSV Blood culture and/or PCR
- HSV†
- CSF cell count, chemistries, and HSV PCR
- Serum ALT

Start IV acyclovir at 60mg/kg/day in three divided doses

PCR or culture (surface or blood) are positive

- Educate family on signs and symptoms of neonatal HSV disease
- Follow closely

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

Go to Treatment Algorithm

- **No**
- **Yes**

- Immediate evaluation and treatment may be considered if:
  - prolonged rupture of membranes
  - prematurity

- For this algorithm, ALT values more than two-times the upper limit of normal may be considered suggestive of neonatal disseminated HSV disease for HSV-exposed neonates

Go to Treatment Algorithm

**PCRs negative and cultures (surface and blood) negative at 48-72 hours**

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

**Go to Treatment Algorithm**