Prevention and management of perinatal Herpes Simplex Virus infections

Idaho Perinatal Project
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Disclosures
• Nothing to disclose

Objectives
• Understand the epidemiology and risks for perinatal transmission of HSV
• Understand the management of HSV-exposed infants
• Understand the diagnosis and short and long-term management of neonatal HSV disease
5 day-old infant presented to the ED because her parents thought she was breathing fast. In the ED she had a temp of 100.6, RR 52, O2sat 60%.

A r/o sepsis work-up was initiated and she was started on ampicillin, gentamicin and acyclovir.

AST 5398, ALT 1363, plts 72k
Bacterial cultures – negative
HSV FA from the nasopharynx - positive
HSV plasma PCR – 2,600,000 copies/ml HSV-2

Quickly progressed to high frequency ventilation. NICU stay complicated by E. coli sepsis requiring ECMO and CRRT.

Ultimately discharged after an 8 week hospital stay.

**Epidemiology of maternal HSV**

- HSV infection is common in adults
- Most infections are asymptomatic
- Most women who are infected don't know they are
- Women aged 15-30 are most at risk of acquiring HSV
HSV seroprevalence adults - NHANES - 1999-2010

- 15.7% HSV-2 seroprevalence 2005-2010
  - no significant change from 1999-2004
- 54% HSV-1 seroprevalence 2005-2010
  - ↓ 7% from 1999-2004

Bradley et al. JID 2014

NHANES n>11,000

Figure 1. Herpes simplex virus type 1 seroprevalence by age and time period.

JID Bradley et al 2014

Figure 2. Herpes simplex virus type 2 seroprevalence by age and time period.

JID Bradley et al 2014
HSV seroprevalence in pregnancy

- Chart survey >15,000 delivering at the Univ Wash Med Center 1989-2010
- 9% seropositive HSV-2 only
- 15% seropositive HSV-1 and 2
- 53% seropositive HSV-1 only
- 23% seronegative for both
- Decrease in seroprevalence of HSV-2 by 4.8%/yr

Delaney et al. JAMA 2014;312:746

Rate of acquisition of HSV

- 3438 women ages 18-30 initially seronegative for HSV followed for 20 months (Control arm of the HERPEVAC trial)
  - HSV-1 acquisition: 127 (3.7%) - 2.5 / 100 person-years
    - 74% asymptomatic
  - HSV-2 acquisition: 56 (1.6%) - 1.1 /100 person-years
    - 63% asymptomatic
    - 84% of recognized disease was genital

Bernstein et al. CID 2013;56:344

Incidence of neonatal HSV disease

- 5 – 3 / 10,000 live births in U.S.
- ~23,000 births/yr in Idaho – 1 -7/year
- ~80% of infants with neonatal HSV infection are born to women without a history or clinical evidence of HSV infection
Risk of maternal to infant HSV transmission

Points
- Women acquiring HSV late in pregnancy are most at risk for transmitting to their infants
- Most infected infants are born to women with clinically inapparent infection at delivery
- Decreasing infant exposure to the virus is protective

Risk of transmission
- Type of maternal infection (genital culture positive at delivery)
  - Recurrent: 1-3%
  - 1st episode (non-primary): 25-30%
  - 1st episode (primary): 40-45%

Brown et al. JAMA 2003, 289:203
Risk factors for transmission

- HSV shedding at delivery
  - 5% of infants infected if women were culture positive (OR 346)
- Caesarean delivery
  - 1.2% vs 7.7% (OR 0.14)
- HSV-1 vs HSV-2 (OR 17)
- Invasive monitoring (OR 7)
- Prematurity
- Maternal age < 21 years

Brown et al. JAMA 2003, 289:203

Prevention of perinatal HSV transmission

- No recommendation for HSV serologic testing during pregnancy
- If couples are known to be discordant for HSV (pregnant woman positive and partner negative):
  - Condom use during first two trimesters
  - Abstinence during the third trimester—including oral-genital if partner is HSV-1 positive

Prevention
Prevention

- Acyclovir or valacyclovir
  - Starting at 36 weeks for women with recurrent disease during pregnancy
    - Reduces risk of recurrence at delivery by ~75%
    - Reduces rate of caesarean by ~40%
    - Reduces rate of HSV detection by PCR or culture at delivery by 90%
  - No study has been sufficiently powered to demonstrate reduction in infant infection

Hollier LM, Wendel GD. Cochrane Database of Systematic Reviews 2008, Issue 1

Prevention

- Acyclovir or valacyclovir
  - ACOG recommends offering suppressive acyclovir to women with a history of genital HSV starting at 36 weeks.
  - Not completely protective – cases of neonatal HSV when the mother was taking acyclovir prophylaxis have been reported

Hollier LM, Wendel GD. Cochrane Database of Systematic Reviews 2008, Issue 1

Prevention of neonatal HSV

- Cesarean section
  - Women with active lesions at time of delivery
  - Women with prodromal symptoms
  - Protection with C-section not complete: ~10% of infected infants born by C-section in a large case series
  - Avoidance of invasive perinatal procedures in women with known HSV
    - AROM, Fetal scalp monitoring, forceps, etc.
Diagnosis of genital HSV disease

- Viral culture – sensitivity is lower for recurrent infections
- PCR – more sensitive, but not always available
- Serology – FDA approved type-specific antibody tests for HSV-1 and HSV-2 IgG are available

Management of the HSV-exposed infant

- Women in labor with visible genital lesions consistent with HSV should have the lesions swabbed for HSV culture and PCR. Positive tests should be typed.
- Maternal antibody status should be determined

AAP guidance

- Asymptomatic infant born to a woman with lesions at delivery and a previous history of genital HSV
  - Swabs for HSV culture (+/- PCR) should be obtained from the nasopharynx, conjunctiva, mouth, rectum and site of fetal scalp electrode (if applicable) – about 24 hours after delivery
  - Obtain blood for HSV DNA PCR
  - If cultures are negative for 48 hours and PCR is negative, infant can be discharged with close follow-up

AAP guidance

- Asymptomatic infant born to a woman with lesions at delivery and no previous history of genital HSV
  - Send maternal type-specific serology
  - Swabs for HSV culture (+/- PCR) should be obtained from the nasopharynx, conjunctiva, mouth, rectum and site of fetal scalp electrode (if applicable) – about 24 hours after delivery
  - Obtain blood for HSV DNA PCR
  - Get CSF cell count, chemistries and HSV PCR
  - Serum ALT
  - Start acyclovir 60mg/kg/day div q 8 hours

AAP guidance

- If maternal recurrent infection is documented
  - Viral isolate and maternal serology match
  - And PCRs and cultures are negative at 48-72 hours
  - Discontinue the acyclovir, educate the family about signs and symptoms of HSV disease and monitor
AAP guidance
- If mother is determined to have either primary disease or first-episode nonprimary disease
  - Viral isolate and maternal serology don't match
  - And PCRs and cultures are negative at 48-72 hours
  - And CSF parameters are normal and ALT (<2xULN)
  - And infant remains asymptomatic
  - Treat with acyclovir pre-emptively for 10 days

AAP guidance
- If mother is determined to have either primary disease or first-episode nonprimary disease
  - Viral isolate and maternal serology don't match
  - Any of the infant testing is positive for HSV
  - Treat for neonatal HSV disease

Timing of Transmission
- 5% in utero
  - If <20 weeks can result in spontaneous abortion, hydranencephaly, chorioretinitis, etc.
- 85% intra-partum
  - Via conjunctiva, nasopharynx, skin or trauma (e.g. fetal scalp monitor)
- 10% post-partum
  - Exposure to caregiver with herpetic whitlow, orolabial or breast lesions
Women with primary HSV gingivostomatitis during pregnancy

- Case series from Seattle Children's Hospital found 7 neonates whose mother's had had primary HSV-1 gingivostomatitis during pregnancy
  - 2 in first trimester and 5 in the third trimester
  - 3 infants with SEM, 2 with CNS disease and 2 with disseminated disease
  - One infant with disseminated disease died


Presentation of neonatal HSV

Clinical Manifestations

- **Skin, Eye, Mouth (SEM) disease (30-40%)**
  - No CNS or other organ involvement
- **Central Nervous System (CNS) disease (34%)**
  - +/- SEM, but no other organ involvement
- **Disseminated disease (20-30%)**
  - Can include CNS

Neonatal HSV disease

- Rarely asymptomatic
- 68% with skin lesions at time of presentation
- 39% with fever
- 38% with lethargy
- 27% with seizures
- 19% with conjunctivitis
- 13% pneumonia

*Kimberlin et al. Pediatr 2001;108:223*

Age at onset of symptoms

- Time of disease onset in affected infants
  - <24 hours – 9%
  - 1-5 days – 30%
  - >5 days – 60%
- Disease onset varies with type of disease
  - Disseminated disease (mean 11 days)
  - Skin, eye, mouth (means 11 days)
  - CNS disease (17 days)

*Kimberlin et al. Pediatr 2001;108:223*

SCH experience (1993-2012)

- 63 infants
- Age at diagnosis
  - Disseminated disease 7 (4-15)
  - SEM 9 (2-19)
  - CNS 17 (5-34)
SEM Disease

- Presents ~10 days of life
- Well except vesicles and/or keratoconjunctivitis (can be subtle)
- 75% presenting as SEM go on to CNS or disseminated disease if untreated
- Outcome good if treated

Neonatal HSV

Color atlas and synopsis of clinical dermatology Ed. Fitzpatrick et al. Pg 799

www.med.cmu.ac.th/.../ic-5-neonatal-HSV/case.htm
CNS Disease

- Later onset (3rd week of life) – but can present early
- Often present with seizure, lethargy, irritability, poor feeding, temperature instability
- Neurologic sequelae
  - Cognitive impairment
  - Spastic quadriparesis
  - Microcephaly
  - Blindness
  - 30-40% without skin lesions

Disseminated Disease

- Onset 7-10 days of age
- Initial symptoms may be subtle
- May present with CNS symptoms, lethargy, fever, respiratory distress, jaundice, DIC, shock
- Lung, liver, adrenals and/or brain involvement
- ~40% without skin lesions
Diagnosis

- Early diagnosis and treatment greatly decrease morbidity and mortality
- Must have high level of suspicion (17-39% have no lesions, symptoms non-specific)
- 60-80% of women who transmit HSV to their neonate have no known history of genital infection
- Those with a previous history, even with active recurrence, would be at LESS risk than 1st episode without lesions

Work-up of infant with suspected HSV infection

- CBC, LFTs, coag’s, BUN/creatinine
- CXR if respiratory symptoms
- Swabs of conjunctiva, oropharynx and lesions for viral FA and culture
- Rectal swab for viral culture
- Blood for HSV PCR
- CSF cell count/chemistry and HSV culture and PCR
Who should get an HSV w/u?

- Infant < 4 wks with lesions, seizures, hepatitis, DIC, pneumonia, conjunctivitis, CSF pleocytosis
- Infant with symptoms of sepsis with bacterial Cx negative at 48 hours without improvement
- Despite advances, mean duration of symptoms before diagnosis and treatment is still >5 days in the U.S.

Sensitivity of HSV DNA PCR and cultures - SCH cohort

<table>
<thead>
<tr>
<th></th>
<th>SEM n=26</th>
<th>CNS n=18</th>
<th>DIS n=19</th>
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<tbody>
<tr>
<td>Plasma PCR positive</td>
<td>14/18 (78%)</td>
<td>7/11 (64%)</td>
<td>18/18 (100%)</td>
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<td>CSF PCR positive</td>
<td>2/24 (8%)</td>
<td>13/18 (72%)</td>
<td>9/14 (64%)</td>
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<td>Surface cultures positive</td>
<td>24/25 (96%)</td>
<td>9/18 (50%)</td>
<td>45/61 (74%)</td>
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Treatment of neonatal HSV
Treatment

- Start therapy empirically while awaiting tests
- High dose (60mg/kg/day IV Q8h) for 21 days or 14 days if limited to SEM
  - Decreased mortality from 61% with 10mg/kg to 31% for disseminated disease
  - 19% to 6% for CNS disease

Kimberlin Peds 2001108:230

Treatment, cont’d

- Ensure adequate hydration status
- Monitor renal function and CBC, ANC
- Confirm CSF normal, and negative by HSV PCR before discontinuation of therapy
- For eye involvement, topical antiviral therapy in addition to IV and Ophtho consult
  - 1-2% trifluridine
  - 0.1% iododeoxyuridine, or
  - 3% vidarabine

Outcome
Predictors of Poor Outcome

- Extent of infection:
  - disseminated > CNS > SEM
- Disseminated disease:
  - Lethargy at presentation
  - AST > 10x normal
- CNS disease:
  - Seizures on presentation

Morbidity and Mortality After 12 Months of Age by Viral Type

- Trend toward higher mortality with type 1
- Intact survival worse with type 2


SCH cohort

- 63 infants
  - All but 2 treated with high-dose acyclovir
- Outcome
  - SEM - 0% mortality 0% neurologic deficits
  - CNS - 0% mortality 65% neurologic deficits
  - DIS - 32% mortality 17% neurologic deficits
HSV plasma viral level and outcome

- HSV-1
- HSV-2
- HSV-1 died
- HSV-2 died

**Log10 HSV DNA in plasma**

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<th>Log10 HSV DNA</th>
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**T1/2 = 1.51d**

Plasma viral load decline on treatment

- Ti/2 = 1.51d

**Log10 HSV DNA in CSF**

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<th>Log10 HSV DNA</th>
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- HSV-1
- HSV-2
- HSV-1 died
- HSV-2 died
Acyclovir suppression

Skin recurrences after primary infection are common ->>50%

Frequent skin recurrences is associated with worse neurologic outcome

Oral acyclovir can prevent skin recurrences

Acyclovir for suppression of recurrences

- 45 infants with CNS and 29 with SEM disease randomized to 6 months oral ACV vs placebo
- 28 CNS and 15 SEM had Bayley ND exams at 12 months
- CNS infants on acyclovir had higher Bayley scores at 12 months (p=0.049)
- Both groups had fewer cutaneous recurrences

Kimberlin et al. NEJM 2011;365:1284-92
Acyclovir suppression recommendations

- Recommend – following treated CNS disease
- Acyclovir dosing – 300 mg/m²/dose q 8 hours
- Monitor CBC monthly – neutropenia common
- Consider following SEM disease
- Advantages
  - Fewer medical evaluations for recurrent disease
  - Less difficulty with child care, etc

References

Questions?