Herpes Neonatal: Importancia Diagnóstica y Terapéutica

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NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

THE OHIO STATE UNIVERSITY

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NEONATAL HSV: OUTCOME*

Disease Classification	% Mortality		% Morbidity*
	No Therapy	ACV	ACV
SEM	0	0	0-2
CNS	50	6	70
Disseminated	85	30	20

* Psychomotor retardation, spastic quadriplegia, blindness, learning disability

*Corey and Wald (CASG), NEJM, 2009

NEONATAL HSV MORTALITY

Lopez-Medina, Cantey et al. PAS 2012

- Retrospective study: 2001-2011 of 50 infants with neonatal HSV disease:
  - 26% mortality (13 infants)
  - 85% of mothers had no past history of HSV infection; none received antiviral therapy
  - 0-22 d; 10 DISS, 3 CNS; 7 HSV-2, 3 HSV-1, 1 both
  - 38% (n=5) had fever at presentation
  - 23% (n=3) diagnosed at autopsy
  - 54% (n=7), acyclovir >48 hrs after presentation

NEONATAL HSV: ISSUES

- Acyclovir dose (60 mg/kg/day): empiric?
- Duration of therapy (minimum):
  - SEM: 14 days
  - Disseminated, CNS: 21 d
- PCR: CSF (diagnosis, end of therapy) / blood
- Improved serologic assays (IgG)
- Exposed newborn: prophylaxis?
- Acyclovir suppression: pregnancy; neonate following SEM/CNS disease

HIGH DOSE ACYCLOVIR

Kimberlin (CASG) et al. *Pediatrics* 2001

- 60 mg/kg/day x 21 days
- 66 infants (HD) vs 107 (SD: 30 mg/kg; historical controls)
- Mortality rate (24 months):
  - DISS: 31% (HD) vs 61% (SD)*
  - CNS: 6% (HD) vs 19% (SD)
- Morbidity (normal dev at 12 months):
  - DISS: 83% (HD) vs 60% (SD)
  - CNS: 31% (HD) vs 29% (SD)
  - Logistic regression: HD rx infants 6.6 times as likely to have nl dev at 12 months

ACYCLOVIR: WHEN TO START?

- No established standard:
  - All sepsis evaluations?
  - Fever in all neonates < 14 or 21 days of age?
  - Targeted:
    - Clinical/lab signs of HSV
    - Sepsis-like picture (including hypothermia); “sicker”; CSF pleocytosis (mononuclear) outside of enteroviral season

ACYCLOVIR: WHEN TO START?

- Shah et al. *Pediatrics* 2011:
  - Multicenter, retrospective cohort study from 2003-2009
  - 1086 neonates with HSV infection from discharge database of 41 children's hospitals
  - Mortality:
    - Early acyclovir therapy (within 1 day of admission): 6.6%
    - Delayed (>1 day and ≤7 days after admission): 9.5% (adjusted OR 2.6; 95% CI:1.4-5.1)

NEONATAL HSV: EVALUATION

- History (maternal, infant); physical exam
- Culture (or PCR):
  - Lesion
  - Mucosal surfaces: conjunctiva, throat/NP, rectum
- CSF: HSV PCR, indices
- Brain MRI, EEG
- Eye exam, ?hearing evaluation
- Blood HSV PCR

BLOOD HSV PCR

Cantey JB et al. *J Pediatrics*. 2012;161:357

- Retrospective review of all positive blood PCR tests performed; 2005-2010 at Dallas, Columbus
- 294 infants <42 days of age: 21 (7%) positive
  - 24% SEM; 24% CNS; 52% DISS
  - 52% HSV-2; 33% mortality (all DISS)
- Blood HSV PCR was the first (n=4) or only (n=2) positive diagnostic test for 29% of infants (4, DISS, 2 CNS –none had cutaneous lesions)
- No false-positive tests; follow-up testing?

HSV TRANSMISSION: RISK FACTORS

- Primary vs. Recurrent Maternal Infection

	Genital HSV Infection	
	Primary	Recurrent
Overall risk	33- 50%	0.3- 5%
Viral shedding site	Cervix	Labia
Viral shedding duration	3 wks	2- 5 days
Quantity of virus shed	Large	Small
Neutralizing antibody	Absent	Present

- Prematurity, PROM (>4 hrs), skin laceration, scalp electrode

MANAGEMENT OF NEWBORN EXPOSED TO HSV AT DELIVERY

- Infant SX: culture; treat; contact precautions
- Infant asymptomatic:
  - Culture (?PCR; 24 – 36 hrs of age): throat, conjunctivae, and rectum
  - Blood PCR
  - ?Acyclovir prophylaxis:
    - Dependent on maternal infection (primary/recurrent - HSV 1 and 2 antibody tests using glycoprotein G-based type specific IgG assays) and newborn risk factors

MATERNAL ANTIVIRAL PROPHYLAXIS

Cochrane Database Syst Rev 2008 (Hollier and Wendel)

- Majority of women with genital HSV have a recurrence during pregnancy
- 40% of those with 1st episode during pregnancy will have recurrence at delivery
- 7 randomized trials (n=1249):
  - Acyclovir vs. placebo or no treatment (5 trials)
  - Valacyclovir vs. placebo (2 trials)

MATERNAL ANTIVIRAL PROPHYLAXIS

Cochrane Database Syst Rev 2008 (Hollier and Wendel)

- Antiviral prophylaxis reduces viral shedding (RR 0.14, 95% CI 0.05-0.39) and recurrences at delivery (RR 0.28, 95% CI 0.18-0.43), and reduces the need for c-section for genital herpes (RR 0.3, 95% CI 0.20-0.45).
- Insufficient evidence on reduction of incidence of neonatal herpes
- No cases of symptomatic neonatal herpes

NEONATAL HSV FOLLOWING MATERNAL ANTIVIRAL PROPHYLAXIS

Pinninti et al. *J Pediatr* 2012

- 8 infants: 2005-2009
- 6 mothers: 1st HSV episode during pregnancy
- 7 perinatal (5 mothers received prophylaxis until delivery): 5, SEM (2, surface cx positive); 2, CNS
- 1 congenital (DISS)
- 7 infants diagnosed by 8 d of age; 1, 27 d (CNS)
- 2, HSV-2; 2, HSV-1; 2, not typed; 2, PCR only
- 1, HSV-2 resistant to acyclovir (skin vesicles and keratitis), mother had received valganciclovir

ACYCLOVIR SUPPRESSION: INFANTS

Kimberlin and CASG. NEJM 2011

- Phase III, double-blind, placebo-controlled studies (2): HSV CNS and SEM from 1997-2008
- BW $\geq$ 800 g, age $\leq$28 d; culture confirmation of HSV (SEM) or positive PCR (CSF, UAB)
- After IV acyclovir, infants randomized to oral acyclovir (300 mg/m^2/d TID) or placebo for 6 mo
- Cutaneous recurrences treated with open-label acyclovir; after a 2nd skin recurrence, blinded study drug discontinued and open-label acyclovir allowed

ACYCLOVIR SUPPRESSION: INFANTS

Kimberlin and CASG. NEJM 2011

- Primary endpoint:
  - Neurodevelopmental outcome at 12 months of age (Bayley-II)
- 74 infants enrolled:
  - 45 CNS (8 DISS): 19 institutions
    - 23 HSV-2; 7 HSV-1
  - 29 SEM: 12 institutions
    - 13 HSV-2; 10 HSV-1

ACYCLOVIR SUPPRESSION: INFANTS

Kimberlin and CASG. NEJM 2011

- 45 CNS infants: 87% completed 6 months of blinded therapy or reached endpoint of 2 cutaneous recurrences; 62% had Bayley exam
  - Acyclovir group had significantly higher mean MDI at 1 yr (88 vs. 68, p=0.046); PDI same
- 29 SEM infants: 90% completed 6 months of blinded therapy or reached study endpoint; 52% had Bayley performed
  - No difference in MDI or PDI at 1 year (MDI: 92 vs. 85)

ACYCLOVIR SUPPRESSION: INFANTS

Kimberlin and CASG. NEJM 2011

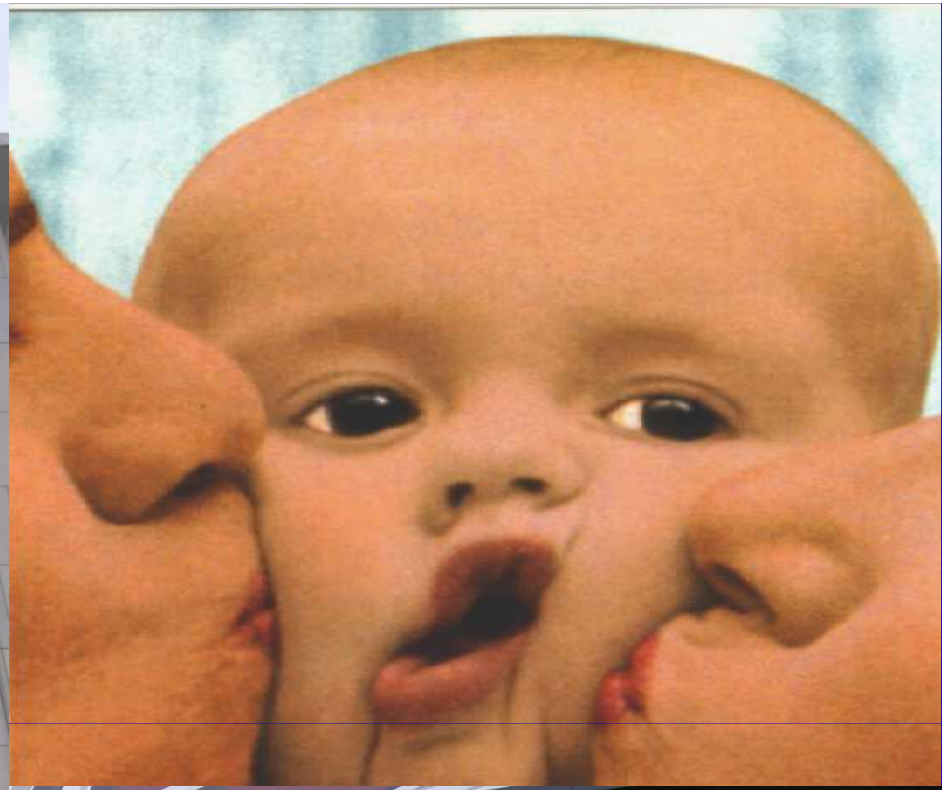
- Among all infants who discontinued study medication because they had 2 skin recurrences:
  - Median time infants received study drug was 2.5 months longer in the acyclovir group than among those assigned to placebo (p=0.009)
- 3 CNS infants had recurrence of CNS disease during the 12 months after enrollment:
  - 2, placebo; 1, acyclovir (28 wk preterm)
- Neutropenia (<500): not significant (p=0.09)
  - 25%, 20% (acyclovir) vs. 5%, 7% (placebo)

FUTURE ISSUES

- Is longer suppression (> 6 months) better?
- Optimal dose of acyclovir for suppression?
- Added therapy?
  - "HSV-immune globulin"
  - Anti-inflammatory agents (e.g. steroids)
- Combination antiviral therapy? CMX-001?
- Maternal screening? Vaccine!

Gracias!


YANKEE STADIUM

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