

Neonatal *and* infant HSV disease in Australia

Cheryl Jones, on behalf of APSU HSV investigators and
contributors to the APSU

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THE UNIVERSITY OF
SYDNEY

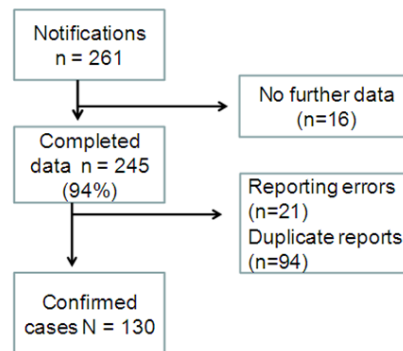
Overview Neonatal HSV

- * Incidence, Presentation, Baby and maternal details
- * Vertical transmission of HSV
- * Risk Factors
- * Investigations
- * Treatment Prevention



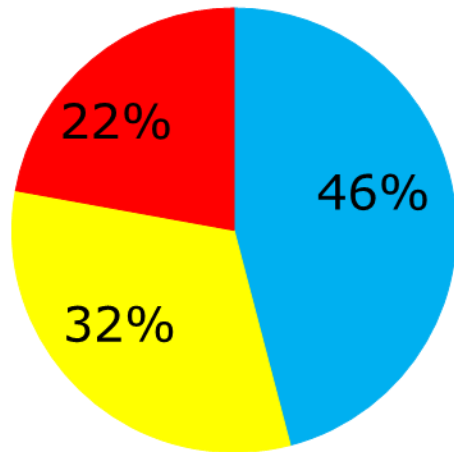
Incidence presentation and maternal details

Neonatal HSV cases Australia 1997-2011



Reported incidence: 3.25 per 100,000 live births

Neonatal HSV in Australia 1997-2011



■ Skin, Eye, Mouth

■ Disseminated infection

■ CNS



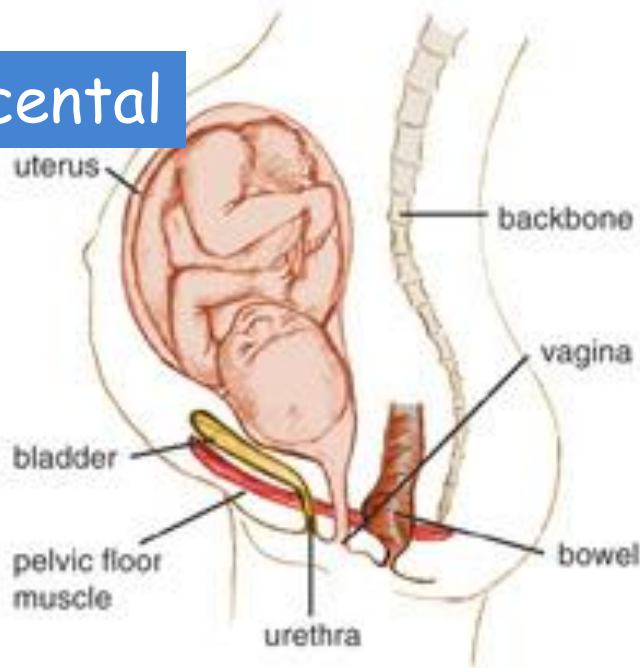


Vertical Transmission HSV

Mode of Vertical Transmission HSV

1. During pregnancy 5%

Transplacental



Ascending

2. During delivery 85%

3. Postnally 10-15%
Close contact with mother

Questions & Answers



Breast milk

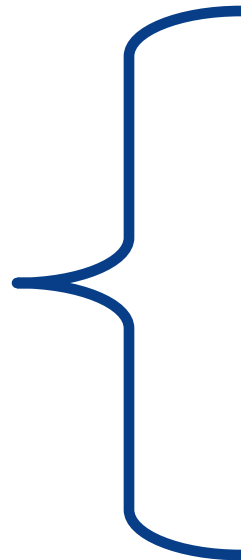


Vertical Transmission of HSV

Most genital HSV infections are
asymptomatic
(Primary or Recurrent)



PERINATAL
85%

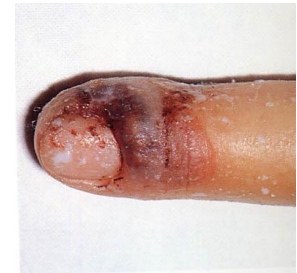
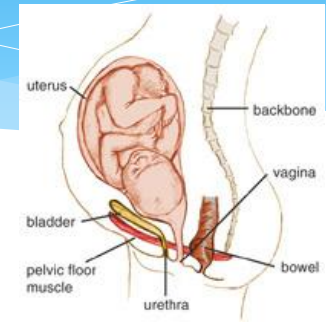


70%

No knowledge of
genital HSV
disease

Mode of Neonatal HSV Transmission Australia 1997-2011

- * Intrauterine 3%
- * Perinatal ~49%
Maternal genital HSV disease
- * Postnatal- 20%
- * Unknown/Not reported- 26%





Risk Factors for Vertical Transmission Neonatal HSV

Risk factors for Vertical transmission

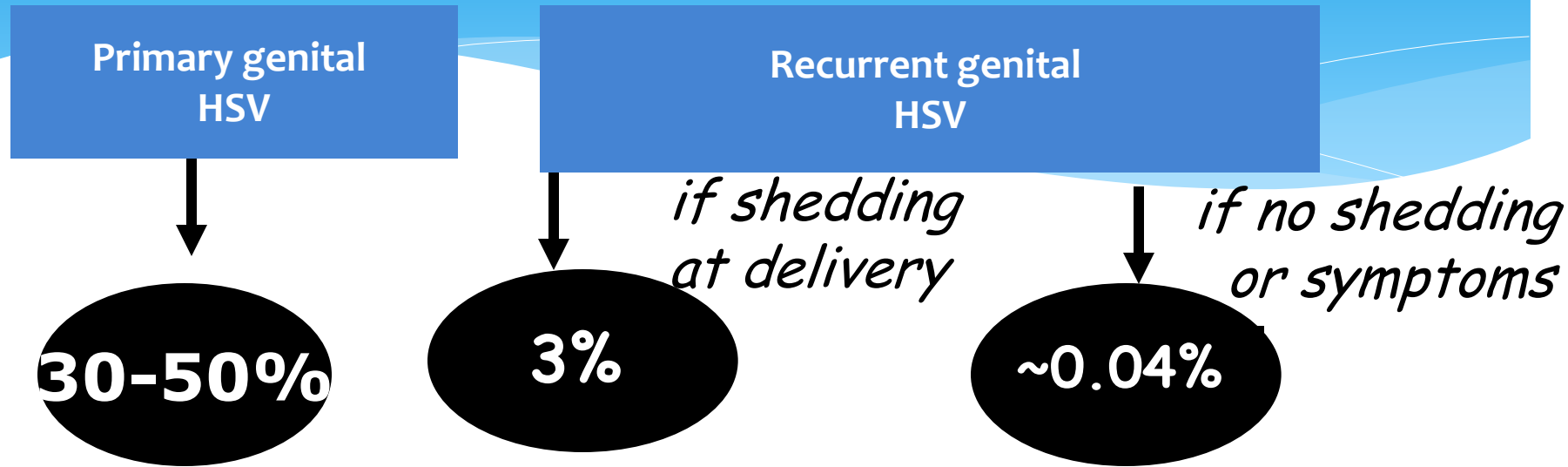
- * Primary genital HSV disease : esp. late pregnancy
- * HSV Serodiscordant partner
- * Invasive Obstetric Procedures
 - * Fetal scalp electrodes
 - * Artificial ROM
 - * Assisted delivery:ventouse/forceps
- * Low maternal neutralising antibody levels to HSV
- * Route of delivery: vaginal > c.section
- * HSV serotype (HSV-1 > HSV-2)
- * ? HIV co-infection

OR 6.8

Brown et al, 2003

Maternal HSV

Risk of vertical transmission



Brown et al, 1991

Risk of transmission greatest if HSV seroconversion has not occurred prior to onset of labour *Brown et al, 1997*

If virus present in genital tract, Caesarean section reduces risk of transmission to newborn OR 0.14 (0.02 - 1.08) *Brown et al, JAMA 2003*

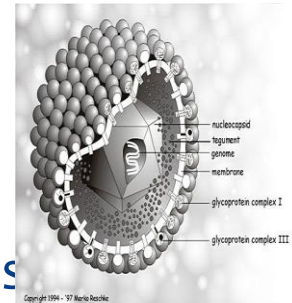
HIV co-infection in pregnancy and vertical transmission of HSV?

HSV on HIV infection/ MTC transmission?

- * Vertical transmission HIV 2-3 increased in HSV-2 seropositive mothers, Thai study *Bollen 2008*
- * Not increased in US study *Chen 2008*

HIV on HSV vertical transmission?

- * Not been fully defined.
- * Prevalence of HSV-2 shedding in late pregnancy increases HIV positive: 12.1% vs 1.7%
- * Risk of HSV reactivation in African HIV-positive women is greater than in HIV-negative women, and the in pregnancy (8% vs 1–2%).
Hitti: 1997,



Serotype dependant risk of vertical transmission: Genital HSV -1 vs HSV-2

Type HSV	No. neo HSV / Total	OR (95% CI)	P value	Adjusted OR*
HSV-1	5/16 (33%)	OR 16.5 (4.1-65)	<0.001	59.3 (6.7-525)
HSV-2	5/186 (2.7%)			

*** Adjusted for new infection**

Brown et al, JAMA 2003

SEROPREVALENCE OF HSV IN AUSTRALIA

4000 randomly sampled sera (Ausdiab study)

		HSV-2	HSV-1
* Age	25-34	10.2%	67%
	35-44	15.5%	75%
* Sex	male	8.4%	71%
	female	15.6%	80%
* Geography	city	14.4%	74-79%
	rural	8.7%	79%
* Total		12.8%	75.7%

HSV-1 genital infection in Australia

- * **Compared anogenital specimens HSV-1 positive NSW Virol ref lab:**
- * ↑ HSV-13% 1980 to 41% in 2001.
- * Female sex and age under 25 were associated with a greater proportion of HSV-1 isolates in both time periods.

Haddow et al 2006



Treatment, Outcome Neonatal HSV

Neonatal HSV- Investigations Rx

- * Isolation/ Detection of HSV from infant samples e.g. skin lesion, nose, throat, conjunctiva swab
- * skin lesion: indirect IF (rapid)
- * CSF exam
 - * - haemorrhagic encephalitis
 - * HSV DNA PCR
 - * Culture ; better yield in newborn cf adults
- * CNS imaging; blood tests
 - * Blood: FBC, LFTs, coags,
- * Infant serology: little role to play



Neonatal HSV CSF examination Australia 1997-2011

Investigation			
CSF cell count (No. /mm ³), n=93	White cell count	Mean Median Min, Max >14/mm ³	7595 0 0, 1800 n = 33 (38%)
	Red cell count	Mean Median Min, Max >165/mm ³	19,741 82 0, 1,000,000 n = 41 (35%)
CSF HSV DNA PCR, n=96		Positive	36 (37.5%)
		Positive with normal CSF WCC	12
CSF HSV IgG, n=4		Positive	1 (25%)

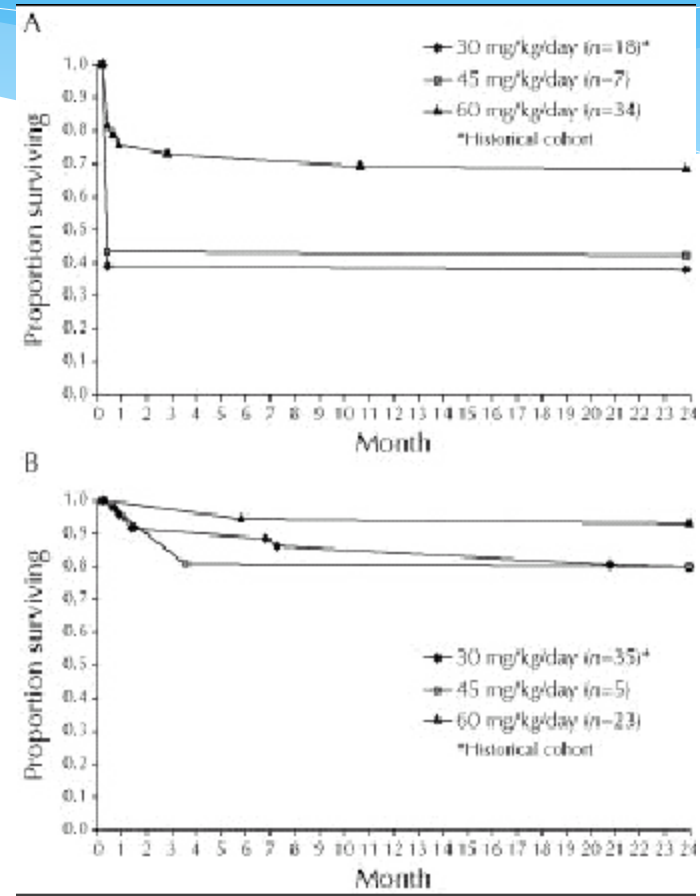
^a Corrected for elevated red cell count where applicable

Recommended Antiviral Rx Neonatal HSV Disease

* Aciclovir 20mg/kg/dose
given 8th hourly

21 days if encephalitis/
disseminated
infection or LP not
performed

14 days for disease
localised to skin, eye
or mouth



Neonatal HSV infection

Management of recurrences

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes

David W. Kimberlin, M.D., Richard J. Whitley, M.D., Wen Wan, Ph.D.,

N Engl J Med 2011;365:1284-92

- * 74 infants: 45 CNS, 29 SEM
- * Oral aciclovir 300mg/m²/dose tds for 6 mo post rx
- * Better neurodevelopment after CNS disease
 - * 60% vs 31% normal or mild impairment by Bayley
- * Trend to neutropenia (0.09)
- * NB - Small nos. esp HSV-1 CNS

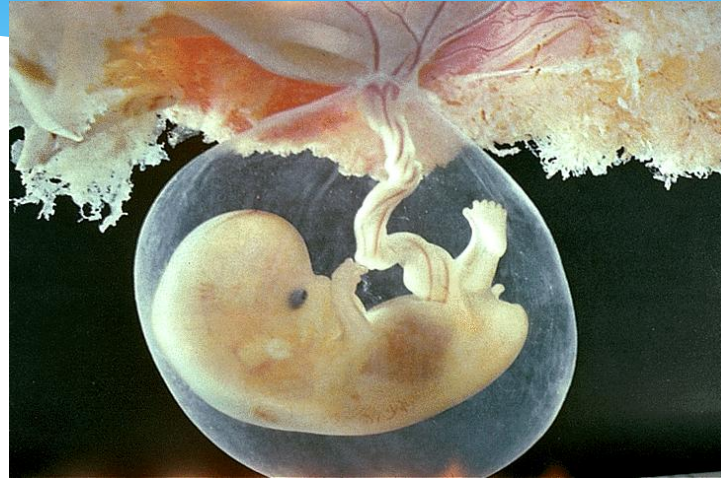
Table 2. Demographic and Clinical Characteristics of Infants with and without 12-Month Bayley Scales of Infant Development Assessments.^a

Characteristic	CASG 103 (CNS) Study			CASG 104 (Skin, Eye, and Mouth) Study		
	Bayley Assessment (N=28)	No Bayley Assessment (N=17)	P Value	Bayley Assessment (N=15)	No Bayley Assessment (N=14)	P Value
Gestational age — wk			0.17			0.69
Median	39.5	38		38	39	
Range	28–41	25–40		27–41	27–40	
HSV type — no./total no. (%) [†]			0.03			0.003
I	7/19 (37)	0/11		2/13 (15)	8/10 (80)	
II	12/19 (63)	11/11 (100)		11/13 (85)	2/10 (20)	
White-cell count in cerebrospinal fluid at presentation — cells/mm ³			0.98			0.48
Median	65	71		6	5	
Range	1–58,080	0–1216		0–20	2–33	
HSV DNA in cerebrospinal fluid at presentation — no./total no. (%) [‡]			0.16			0.22
Positive	19/28 (68)	15/17 (88)		0/15	0/12	
Negative	9/28 (32)	2/17 (12)		15/15 (100)	12/12 (100)	
Evidence of HSV disease on MRI — no./total no. (%)	13/23 (57)	7/13 (54)	1.00	0	0	—
Abnormal EEG — no./total no. (%)	14/19 (74)	6/12 (50)	0.26	NA	NA	



Prevention of Vertical transmission of HSV

Strategies to prevent neonatal HSV infection



- Pre/antenatal strategies to prevent maternal (genital) HSV infection
- Antenatal strategies to prevent transmission to the newborn
- Postnatal strategies to prevent infection of the newborns/ disease

Antiviral therapy during pregnancy

- * Used in two ways
 - * Rx severe/disseminated disease/
 - * Prevent recurrence in third trimester in primary genital infection or frequent symptomatic past infection

- * Balance potential risk to fetus with potential benefits of Rx

Neonatal Herpes Disease following Maternal Antenatal Antiviral Therapy

- * Multicenter case series
- * J Pediatr 2012: 161;134-138.e3
- * 8 infants -neonatal HSV disease following maternal antiviral suppressive therapy during pregnancy
 - * 6 mothers -first episode of genital HSV
 - * 2 mothers prior Hx of genital HSV with no outbreak
 - * Perinatal transmission in 7/8 infants
 - * Intrauterine transmission 1/8
- * Suppressive therapy does not prevent neonatal HSV disease, which can have an atypical clinical presentation and drug resistance

Conclusions

- * Although uncommon, neonatal HSV disease continues to cause significant mortality despite available therapies and sensitive diagnostic techniques in Australia.
- * HSV-1 is the major serotype causing neonatal HSV disease in Australia.
- * Still need rapid bedside test to guide empiric management of this rare, but devastating condition
- * Further evidence of importance of active surveillance for rare diseases
- * Paucity of evidence to guide Mx exposed asymptomatic infant and HSV in infancy beyond the neonatal period

Neonatal and Infant HSV study

From 2012 on

To determine epidemiology ,management outcomes of acute HSV infection in infants **less than 12 months** of age in Australia

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