

## Neonatal and Infant Herpes Simplex Virus (HSV) Infection

### BACKGROUND

Neonatal herpes simplex virus (HSV) infection is a rare, but important condition that presents with disease localised to the skin, eye and/or mouth, encephalitis or a highly lethal disseminated infection associated with shock, DIC and bleeding<sup>1,2</sup>. Death or handicap is almost inevitable without antiviral therapy after disseminated or central nervous system (CNS) neonatal HSV disease<sup>1,2</sup>. Early diagnosis and the prompt commencement of systemic antiviral therapy with acyclovir are vital for a favourable outcome<sup>3-5</sup>. Neonatal HSV infection is most commonly acquired during delivery following primary maternal genital HSV infection<sup>6</sup>, or it can be acquired after birth from an infected caregiver. Rarely, neonatal HSV disease presents after intrauterine infection with a triad of neurological, eye and skin signs at birth<sup>7</sup>.

We have just completed 13 years of active surveillance study through the APSU, which has documented the spectrum of **neonatal** HSV disease in Australia from 1997 to 2009. While the incidence and mode of presentation of neonatal HSV infection remained relatively steady over this period, the survival of infants improved<sup>9</sup>. One possible explanation for this observation is that international guidelines have recommended larger doses of antiviral (parenteral acyclovir) therapy for longer duration<sup>10</sup> to limit progression of neonatal HSV disease in disseminated infection and to reduce the likelihood of early neurological recurrence. The efficacy of this intervention is not possible to evaluate in a randomized clinical trial due to the rarity of the condition<sup>5</sup>. The past national study has documented the uptake of this changed management since 2003<sup>8,9</sup>. Thus, the observed improvement in short term survival may in part be due to the increased antiviral dose, however longer follow up and improved morbidity data are required to support this notion.

The method of diagnosis of neonatal HSV has also changed over the 13 year period, with the more frequent use of PCR over virus isolation. It also highlighted important epidemiological changes of the condition. HSV-1 is now the major serotype causing neonatal HSV disease in Australia, and importantly, adolescent mothers (i.e.  $\leq 20$  years of age) are more likely to transmit genital HSV-1 infection to their newborns than adult mothers. Differences in the mortality and morbidity between the two HSV serotypes have been reported<sup>10</sup>, further supporting ongoing surveillance to determine the consequences of this change, and whether earlier detection leads to earlier commencement of antiviral therapy, thus leading to enhanced survival in recent years.

Although highly informative, the past surveillance study design did not provide an opportunity to characterise morbidity in survivors or to document the frequency or management of early viral recurrences, or of presentations of HSV infection in infancy beyond the first four weeks of life. Ad hoc clinical observations suggest that infants experience frequent skin HSV recurrences in infancy and research has shown that the heightened susceptibility of newborn infants to HSV infection extends beyond the neonatal period for 6 months or more. Infants surviving neonatal HSV CNS disease have been reported to have improved CNS outcomes when they receive suppressive oral aciclovir for 6 months ( $300 \text{ mg/m}^2 \text{ BSA/ dose} = 10 \text{ mg/kg/dose}$ , three times daily) after completion of their parenteral therapy<sup>9</sup>, and this is now routinely recommended. However, there is a paucity of data on both the initial presentation of recurrences and outcome of HSV in infancy beyond the neonatal period to inform management.

Thus important trends and significant knowledge gaps in the epidemiology, management and outcome of HSV infection in the newborn period have emerged from the past surveillance study that require follow up. In view of this, our objectives here are to use the APSU national prospective surveillance mechanism to better define the incidence of HSV infection in infants less than 12 months of age in Australia, and to document management of initial and recurrent infections and outcome. This new knowledge will better inform clinical practice guidelines, and provide indirect evidence of efficacy of management and diagnostic changes.

### STUDY OBJECTIVES

1. To estimate the incidence and to describe the demographics, presentation, diagnosis and management of acute HSV infection in infants less than 12 months of age in Australia.
2. To determine the acute and prophylactic management of these infections.
3. To describe the outcome at discharge from hospital and at 12 months *after* diagnosis.
4. To describe the relationship between infant and maternal risk factors for neonatal HSV infection and adverse outcomes for the infant after infection.

## CASE DEFINITION and REPORTING INSTRUCTIONS

Please report any neonate or infant aged less than 12 months of age (regardless of gestation) seen in the last month with clinical evidence of HSV infection\* AND confirmed by any one or more of the following:

- HSV isolated from surface swab of the baby or HSV DNA detected in surface swab or blood by PCR
- HSV DNA detected in the CSF, in association with CSF pleocytosis or other evidence of HSV encephalitis (neuroimaging, EEG)
- mother seroconverted to HSV or IgM positive in pregnancy or early postnatal period
- HSV isolated from mother around delivery and baby has typical clinical manifestations.

\*Clinical manifestations may be localised (herpetic lesions of the skin, eye or mouth) or disseminated to include many organ systems including encephalitis, pneumonitis, shock or hepatitis (manifested by coagulopathy, jaundice, hepatosplenomegaly) or signs of encephalitis alone.

### FOLLOW UP OF NOTIFICATIONS

Clinicians notifying a case of neonatal or infant herpes simplex virus infection will be requested to complete a brief questionnaire at presentation, and at 12 months after diagnosis of the infection.

### RECOMMENDED INVESTIGATION OF SUSPECTED NEONATAL HSV INFECTION\*

#### Baby:

1. Swab(s) from nose, throat and/or eye (or nasopharyngeal aspirate). Send for \*\*HSV PCR (and typing) and/or \*\*\*viral culture +/- immunofluorescence (IF).
2. Swab(s) from Vesicle (de-roof vesicle, swab fluid and base) for PCR\* and/or viral culture +/- immunofluorescence.
3. CSF for HSV culture and PCR (and typing)
4. Blood for HSV PCR (and typing)
5. If clinically indicated: evidence of HSV dissemination (CXR, liver function tests, platelet and coagulation screen)
6. PM specimens: any tissue for viral culture for \*PCR and/or \*viral culture +/- immunofluorescence (IF)
7. If CSF examination delayed, CSF from baby for HSV serology can be undertaken transport media. Send swab on ice to laboratory for immediate processing.

**Mother:** Serum for type specific serology HSV (1 and 2), IgM and IgG, at diagnosis, 2 weeks, 6 weeks.

\*Please seek advice from your local microbiology laboratory for the preferred specimen collection of viral culture. If your local laboratories are unable to perform these investigations please contact Prof Cheryl Jones on 02 9845 3382 or 02 9845 0000 or [cheryl.jones@health.nsw.gov.au](mailto:cheryl.jones@health.nsw.gov.au) to arrange for investigations to be performed in Sydney or if you have any other questions about this study.

\*\*Swabs for PCR are generally not placed in transport media.

\*\*\*For viral culture and IF, place a spot on slide and air dry for IF, then place remainder on swab in viral

### INVESTIGATORS

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