Australian Paediatric Surveillance Unit
STUDY PROTOCOL

Updated 2017

Neonatal and Young 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[1,2]. Death or handicap is almost inevitable without antiviral therapy after disseminated or central nervous system (CNS) neonatal HSV disease[1,2]. Early diagnosis and the prompt commencement of systemic antiviral therapy with acyclovir are vital for a favourable outcome[3-5]. Neonatal HSV infection is most commonly acquired during delivery following primary maternal genital HSV infection[6], 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[7].

We completed 15 years of active surveillance study through the APSU, and published the spectrum of ***neonatal*** HSV disease in Australia from 1997 to 2011[3]. Key findings were that the incidence and mode of presentation of neonatal HSV infection has remained relatively steady in Australia over this period but the survival of infants improved. Implementation of international guidelines which recommend larger doses of antiviral (parenteral acyclovir) therapy for longer duration[2] to limit progression of disseminated neonatal HSV disease are thought the likely explanation. The published study also highlighted important epidemiological changes in the condition. HSV-1 is now the major serotype causing neonatal HSV disease in Australia, and importantly, adolescent mothers (i.e. ≤ 20 years of age) are more likely to transmit genital HSV-1 infection to their newborns than adult mothers.

Further study of this rare but clinically important condition is needed to address knowledge gaps and confirm previous trends. Firstly, the efficacy of high dose antiviral therapy for neonatal HSV is not possible to evaluate in a randomized clinical trial due to the rarity of the condition[3]. Ongoing surveillance is needed to determine if the observed improvement in short term survival in 2011 is sustained, and associated with the improved 12 months outcomes. Although the overall reported incidence of neonatal HSV has remained stable over the last 18 years, we have observed recent state based differences that suggest some Australian centres may be observing an increase in the condition that would warrant public health action. This trend coincides with recent observations of increased reported incidence of neonatal HSV, particularly in the UK[4.]. Molecular tests (PCR) supplemented by neuroimaging are now the standard method of diagnosis of neonatal HSV, resulting either enhanced detection or increased reporting of asymptomatic infection. Our current protocol does not include this population. This data needs to be captured to better inform vertical transmission risks and postnatal management of this subgroup.

Infants surviving neonatal HSV CNS disease have been reported to have improved CNS outcomes when they receive suppressive oral aciclovir for 6 months (300 mg/m^2 BSA/ dose = 10 mg/kg/dose, three times daily) after completion of their parenteral therapy[2], 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. Ongoing surveillance is needed to determine the uptake and efficacy of suppressive antiviral therapy for neonatal HSV infection.

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 3 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 3 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 3 months of age (regardless of gestation) seen in the last month with laboratory confirmation of HSV infection, and with *either* clinical evidence of HSV infection *or* laboratory confirmation of maternal perinatal HSV infection in an asymptomatic infant.

Laboratory confirmation is by detection of HSV by PCR in a surface swab**, respiratory specimen and/or sterile site (CSF or blood) (or by virus isolation), or by immunofluorescence

Clinical evidence of neonatal HSV infection is one or more of: typical herpetic lesions of the skin, eye or mouth; evidence of disseminated infection (bleeding, bruising or coagulopathy, jaundice or elevated serum bilirubin, hepatosplenomegaly or elevated liver transaminases), pneumonitis (respiratory distress or chest radiograph) or encephalitis (lethargy, seizures, apnoeas or abnormalities on neuroimaging or EEG).

Laboratory evidence of maternal perinatal HSV infection will be by detection of HSV in maternal genital swab and /or mother seroconverted to HSV or IgM positive in pregnancy or early postnatal period.

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 :

If active lesions at delivery: HSV type specific genital swab for **HSV PCR (and typing) and/or ***viral culture +/- immunofluorescence (IF). 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 for detection of HSV. Please contact Prof Cheryl Jones through the APSU on xxx if you have any other questions about this study.

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

***Viral culture and IF are now rarely performed. If requested by your laboratory, place a spot on slide and air dry for IF, then place swab in viral medium

INVESTIGATORS

Principal Investigator: Prof. Cheryl Jones, The Children's Hospital at Westmead, Westmead, NSW and The University of Sydney,
A/ Prof. Yvonne Zurynski, The Australian Paediatric Surveillance Unit and The University of Sydney,
Dr Suzy Teutsch, The University of Sydney, The Children's Hospital at Westmead NSW

Advisory group

A/ Prof. Christopher Blyth, Princess Margaret Hospital, Perth
A. Prof. Clare Nourse, Mater Children's Hospital, Queensland
A/ Prof. Pamela Palasanthiran, Sydney Children's Hospital, Randwick
Prof. Bill Rawlinson, SESLHD Randwick and UNSW,
Dr. Tom Connell, Royal Children's Hospital Melbourne and Monash Medical Centre, Victoria
Dr Celia Cooper, Women and Childrens Hospital, Adelaide SA

REFERENCES

1. Kimberlin DW, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics 2001; 108: 230-8.
2. D Kimberlin et al. Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes.N Engl J Med 2011;365:1284-92.
3. Jones CA, Raynes Greenow C, Isaacs D, on behalf of APSU HSV study team and contributors. Population-based surveillance of neonatal HSV infection in Australia (1997-2011). Clin Infect Dis. 2014 15;59:525-31.
4. Batra D, Davies P, Manktelow BN, Smith C. The incidence and presentation of neonatal herpes in a single UK tertiary centre, 2006-2013. Arch Dis Child 2014; 0: 1-6. doi:10. 1136/archdischild-2013-305335.