Neonatal Herpes Simplex Virus Infection

Epidemiology and Treatment

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KEYWORDS

• Herpes simplex virus • Genital herpes • Pregnancy • Mother-to-child transmission
• Neonatal herpes • Polymerase chain reaction • Antiviral therapy

KEY POINTS

- Both herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) can cause genital infections, although in recent years HSV-1 has become the predominant cause of genital herpes.
- Despite the relatively high HSV-1 and HSV-2 seroprevalence rates, neonatal HSV infection remains rare.
- Recurrent HSV genital lesions pose a lower risk for transmission to exposed infants than primary HSV genital lesions.
- Neonatal HSV infection is categorized as skin, eye, and/or mouth (SEM), disseminated, or central nervous system (CNS) disease; these categories are predictive of morbidity and mortality.
- Efforts to prevent vertical transmission and use of appropriate antiviral therapy are necessary to help reduce neonatal HSV disease burden.

INTRODUCTION

HSV genital infections are common in adolescents and adults worldwide. Although less common, HSV infections that are transmitted from pregnant women to their infants can cause substantial morbidity and mortality in the infants. There are 2 distinct types of HSV, HSV-1 and HSV-2, both of which can be responsible for neonatal disease. Advances in diagnostic capabilities and antiviral treatment options have led to improved clinical outcomes in infected infants, but significant morbidity and mortality remain in infants with invasive HSV disease, particularly those with CNS (morbidity) or disseminated (mortality) involvement. This review offers a description of the pathogen

Disclosures: None.

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Clin Perinatol 42 (2015) 47–59
http://dx.doi.org/10.1016/j.clp.2014.10.005 **perinatology.theclinics.com**
0095-5108/15/$ – see front matter

and the epidemiology of maternal and neonatal infection, as well as an overview of clinical features associated with mother-to-child transmission (MTCT), methods of preventing transmission, and, finally, current treatment considerations for neonatal HSV infections.

DESCRIPTION OF THE PATHOGEN

HSV-1 and HSV-2 are members of the alpha herpes virus subfamily of the family Herpesviridae. HSV virions consist of a core containing a single linear, double-stranded DNA molecule approximately 152 kilo base pairs in length; an icosahedral capsid made up of 162 capsomeres surrounded by an amorphous, tightly adherent tegument; and a lipid bilayer envelope containing viral glycoprotein spikes surrounding the capsid-tegument complex. These glycoprotein spikes mediate attachment and entry into host cells and are responsible for evoking the host response.[1]

HSV DNA consists of 2 covalently linked components, designated simply as long (L) and short (S), each consisting of unique regions (U_L and U_S) flanked by inverted repeats.[2] The genomes of HSV-1 and HSV-2 share approximately 50% homology, resulting in significant cross-reactivity between antigenically related glycoproteins of both HSV types.[3] Type-specific glycoproteins, such as glycoprotein G, do occur (gG-1 and gG-2 for HSV-1 and HSV-2, respectively), allowing for differentiation of the 2 virus types via antigen-specific antibody response. HSV type differentiation can also be achieved by restriction endonuclease fingerprinting and DNA sequencing.[4,5]

HSV infection is characterized by short reproductive cycles, host cell destruction during active replication, and the virus' ability to establish lifelong latency in sensory neural ganglia.[6] Within an HSV-infected cell, key steps in viral replication include cell surface attachment, entry of the viral genome into the nucleus, transcription, DNA synthesis, capsid assembly, DNA packaging, and envelopment as new virions pass through the trans-Golgi network.

EPIDEMIOLOGY

Humans are the only known natural reservoir of HSV, and seroprevalence studies indicate that HSV-1 and HSV-2 infections are common worldwide, in both developed and undeveloped countries.[7] Acquisition of HSV results in lifelong infection, with periodic clinical or subclinical viral reactivation. Prevalence of HSV antibodies increases with age, although earlier acquisition of infection is seen with HSV-1 as compared to HSV-2, and in people of lower socioeconomic status for both HSV-1 and HSV-2.[8,9] More than 90% of adults have acquired HSV-1 infection by their fifth decade of life, although only a minority develop clinically apparent disease at the time of acquisition.[10]

Previous studies indicated an increasing seroprevalence of HSV-2 in developed countries,[11,12] but more recent seroepidemiologic studies performed as a part of the National Health and Nutrition Examination Surveys (NHANES) have indicated otherwise. Specifically, while the seroprevalences of HSV-1 and HSV-2 in the United States were approximately 58% and 17%, respectively, in persons aged 14 to 49 years during the period 1999 to 2004, a follow-up study from 2005 to 2010 showed that HSV-1 seroprevalence had decreased to 54%, whereas HSV-2 seroprevalence had not significantly changed (nearly 16%).[13,14] Further analysis of HSV-1 seroprevalence within this larger study population shows that the largest decline in HSV-1 seropositivity occurred in the 14- to 19-year-old group.