Shedding Patterns of Genital Herpes Simplex Virus Infections
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Genital herpes simplex virus (HSV) infections are among the most common sexually transmitted infections encountered by humans and, in 2018, were estimated to occur in approximately 27% of US adults.1 There is no cure for HSV infection; consequently, infection can be transmitted from individual to individual, most often because of asymptomatic viral shedding. Thus, the reservoir of individuals infected with HSV continues to increase.

For the most part, knowledge about genital HSV infections is predicated on studies of infections caused by HSV-2. However, over the past 2 decades, HSV-1 has been recognized as an increasing cause of genital infections and accounts for an estimated greater than 50% of new infections among some subpopulations, such as college students and heterosexual women.2-4

Differences in the shedding patterns, clinical manifestations, and management between genital herpes caused by HSV-1 and HSV-2 are poorly described. Although currently available serology can determine the overall prevalence of HSV-2 infections, commercially available serological tests for HSV-1 perform relatively poorly,5 and no serologic test has been developed to distinguish individuals who have genital HSV-1 infection from those with oropharyngeal HSV-1 infection. Thus, the true prevalence of and optimal management strategies for HSV-1 genital infection are lacking.

Until now, knowledge of the natural history of genital HSV-1 infections has been limited to observational studies with small numbers of patients. In this issue of JAMA, Johnston and colleagues begin to address this knowledge gap by providing data to inform clinical care and highlighting persistent research questions through a prospective cohort study of volunteers with first-episode genital HSV-1 infection.6

Between 2013 and 2018, a total of 82 individuals (median age, 26 years; 54 [65.8%] women) with first-episode infection were recruited to the study, including 42 with primary (seronegative) infection and 22 with initial genital infection (preexisting antibodies to HSV-1). HSV was detected from the genital tract of 53 individuals (64.6%) and from the mouth of 24 individuals (29.2%). All study participants were HIV and HSV-2 seronegative. Of note, 18 participants (22%) who were initially enrolled withdrew from participation during follow-up or were lost to follow-up.

Regardless, and despite the relatively small study population (n = 82), this report represents the largest cohort of individuals with first-episode infection and the 2 years of intense follow-up supplemented by polymerase chain reaction (PCR) testing for detection of asymptomatic HSV DNA shedding provide important insights for clinicians. Shedding frequency was determined at 2 and 11 months after enrollment by PCR testing of anogenital swabs collected daily for 30 days. Participants with evidence of viral shedding at 11 months were followed up for up to 2 years. Oropharyngeal swabs assessed shedding from the mouth as well.

In this study cohort, genital HSV-1 shedding was relatively common soon after infection but decreased relatively rapidly, from 12.1% (detected on 275 of 2264 days) at the 2-month assessment period to 7.1% (detected on 122 of 1719 days) at the 11-month assessment period. Most shedding occurred in the absence of symptoms. Shedding from the mouth was significantly lower, with HSV detected on 88 of 2223 days (3.9%). Shedding was considerably higher among individuals with primary infection (17.2%) compared with those with nonprimary infection (6.9%). Long-term shedding was uncommon. Shedding, and thus transmission risk, decrease rapidly during the first year after infection. However, HSV shedding still occurs and therefore viral transmission can still occur, particularly because shedding occurs predominantly in the absence of symptoms. Further, symptomatic recurrences were much less likely following initial genital HSV-1 than reported for HSV-2 infections. Taken together, these data appear to validate the sense that risk for genital transmission of HSV-1 may decline rapidly following initial infection, but it is not zero.

Shedding of HSV-1 from the mouth was constant at about 3% at each interval. Unreported studies of shedding of HSV-1 from the oropharynx performed both in dental clinics and in nursing populations indicate an overall shedding rate of approximately 1% based on culture and not the more sensitive method of PCR.7 Thus, this rate of oral shedding may be higher than that in previous prospective studies that used culture could detect and raises the point that the mouth is a source of HSV-1 for transmission with oral-genital sex.

To put these data in perspective, shedding with HSV-2 is significantly greater and associated with a higher percentage of symptoms, although asymptomatic shedding is common and unpredictable with HSV-1 as well, particularly in the months soon after acquisition of infection. However, seroprevalence of HSV-2 infection is decreasing in the US.8 As such, these data from Johnston et al6 can guide clinicians in patient counseling and recommendations for the use of suppressive antiviral therapy. For example, in the absence of better readily available serological tests, suppressive therapy might be offered to those with initial HSV-1 infections to reduce the probability of transmission.8

Although the study by Johnston et al6 did not include pregnant individuals, the findings also may have implications for management of HSV-1 in pregnancy. HSV is a common cause...
of neonatal infection, and there appears to be no distinction in the severity of resultant disease when the newborn is infected with either HSV-1 or HSV-2. Specifically, pregnant people who experience primary infection during the third trimester of gestation are likely to transmit infection to their newborn, irrespective of virus type. The resulting disease in the neonate can be localized to the skin, eyes, and mouth, particularly if the infection is nonprimary. However, with primary infection during pregnancy, disease in the newborn is far more severe and can result in encephalitis or multiorgan dissemination. In a study based on Medicaid claims data, the incidence of neonatal HSV disease increased from 3.4 per 10,000 births in 2009 to 5.3 per 10,000 births in 2015, suggesting the importance of distinguishing primary from nonprimary infection in pregnancy and a role for antiviral prophylaxis for people diagnosed with initial genital HSV late in pregnancy to decrease the probability of transmission to the newborn, irrespective of viral type.

The study by Johnston et al in this issue of JAMA adds new information about genital HSV-1 infections and should help guide patient education and public health recommendations. At the same time, the study indicates a need for continued development of better tools for diagnosis of genital HSV-1, especially improved serological tests.

For clinicians, these data emphasize the importance of determining the HSV viral type in persons presenting with initial episodes of genital herpes to accurately counsel patients regarding risk of clinical recurrence, the likelihood of asymptomatic shedding of virus and hence transmission, and antiviral prophylaxis. At present, PCR testing, and not serological testing, is the best tool for determination of viral type.

For investigators, this study should stimulate further investigation into host defense against HSV and, in particular, improved serological tests for HSV-1 given the demonstrable prognostic value of differentiating primary from nonprimary initial genital HSV infection.

ARTICLE INFORMATION

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