The Clinical Spectrum of Herpes Simplex Viremia

Richard A. Zuckerman
Section of Infectious Disease and International Health, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

(See the article by Berrington et al, on pages 1295–1301.)

The vast majority of herpes simplex virus (HSV) infections in adults are relatively benign in their clinical manifestations. However, this ubiquitous virus clearly produces a diverse spectrum of disease. Although mucocutaneous HSV infection and reactivation can be associated with more generalized symptoms, the presence of viremia had previously been considered a rare occurrence. In the mid-1900s, HSV was isolated from the blood of an immunocompetent child with herpetic rhinitis [1], signaling the possibility of more widespread infection in clinically benign disease. Subsequently, though, sensitive HSV culture techniques were unable to identify viremia in immunocompetent pediatric patients with clinical HSV infection [2]; studies of blood cultures for HSV in immunocompetent adults have not been published. More recently, highly sensitive polymerase chain reaction (PCR) assays have altered our understanding of the natural history of HSV infection. HSV DNA has been found in the blood in 34% of children with primary gingivostomatitis [3], in 24% of adults with primary genital herpes [4], and in 20% of persons with reactivation herpes labialis [5]. Patients with PCR evidence of viremia have been shown to have a higher rate of systemic symptoms and meningeal signs than those without such evidence [4], consistent with the probability that PCR detection in the blood correlates with viral dissemination. HSV viremia has been reported most often in patients with some identifiable form of immunocompromise (eg, transplant recipients, neonates, and pregnant women), although there is a paucity of prospective data on the incidence of viremia. In light of this information, it is evident that primary HSV infection and reactivation may frequently expand beyond the mucocutaneous surface in immunocompetent and immunocompromised individuals.

Despite this high frequency of primary and reactivation HSV disease with concomitant HSV DNA detectable in blood by PCR, severe disseminated clinical disease due to HSV infection appears to be relatively rare. Although we do not know the true incidence of severe disseminated HSV disease, clinical experience suggests that it is a rare occurrence. Why the disconnect? Several factors could explain the phenomenon. First, it could be that detection of DNA by PCR, although a more sensitive marker for HSV detection than culture [6], is too sensitive in this setting and overestimates the amount of productive virus that would be capable of causing active disease at another site. In this scenario, the level of virus may be lower than required to produce disease, as has been demonstrated in animal studies [7]. Second, the majority of circulating virus may be nonproductive [8]. Third, viral characteristics, such as tissue tropism or virulence factors, that predispose to more severe disease could be present in a minority of viruses, although there is little empirical evidence of this in vivo. Finally, host genetic and immunologic characteristics likely also play an important role in susceptibility to HSV [9]. Given the rarity of severe disseminated clinical HSV disease, it is possible that each of these factors may play a role.

How can clinically significant disseminated HSV disease be diagnosed early? Current strategies have relied largely on clinical features (eg, typical mucocutaneous lesions in an at-risk host with a systemic disease syndrome) followed by virologic and histological testing. DNA PCR testing of blood adds a sensitive diagnostic test to our armamentarium, but there is a critical need to clarify the appropriate setting in which to order the test as well as how to interpret a positive result. No systematic review of the clinical manifestations and outcomes in adult hospitalized patients with HSV viremia detected by DNA PCR has been published to date. In this issue of Clinical Infectious Diseases, Berrington et al [10] endeavor to fill this void in our knowledge base.

In their study, the authors reviewed 951 PCR test results for clinically directed samples from a single referral institution with...
3 hospitals over a period of nearly 5 years. After accounting for a series of technical, ethical, and design criteria, they identified 13 patients with complete and reviewable records from among 19 adult patients with PCR evidence of HSV viremia. A number of important findings arose from their efforts. First, PCR-detected HSV viremia occurs in both patients with and those without identified concomitant illnesses. This indicates that HSV viremia can occur with primary disease and with reactivation, as suggested by serologic testing that was performed for a subset of these patients. The finding of viremia in a population with other diagnoses makes clinical sense, because herpes classically reactivates in the setting of other acute medical illnesses. Unfortunately, because of the retrospective design of the study, we do not know the relative frequency of this phenomenon. Also important is that the study was conducted during a time when the majority of HSV-seropositive and highly immunocompromised transplant recipients were probably receiving some form of suppressive or prophylactic antiviral therapy [11, 12], further limiting our ability to draw conclusions about the epidemiology and natural history of HSV viremia from the data presented.

A second important issue raised by the study of Berrington and colleagues is the finding of high mortality in patients with detectable HSV DNA in the blood. As the authors acknowledge, the retrospective nature of the study precludes any extrapolation about causality. Although the results of HSV DNA testing changed the clinical management for all of these patients (all were given acyclovir), it is not clear if the outcomes were altered. On the other hand, it would seem highly probable that earlier intervention could have changed the outcome of death in some patients; 5 of 8 patients without an apparent alternative diagnosis to explain their illness had HSV isolated from other visceral organs or body cavities, indicating a high burden of disease by the time of diagnosis. As for the patients with other diagnoses, it is unclear what role HSV reactivation played in their disease. If HSV was not the primary cause of death, could it contribute to the severity of other illnesses either directly or indirectly? Precedent suggests that this is possible. HSV infection has been shown to be disease modifying in patients also infected with human immunodeficiency virus, being associated with increased acquisition and transmission [13]. Furthermore, HSV suppression has been associated with reduced human immunodeficiency virus load [14], decreased mortality [15], and delayed CD4 cell count decline [16]. The direct and indirect effects of HSV coinfection have not been well evaluated in other disease states.

Our ability to prevent adverse clinical outcomes of HSV disease must rely on our ability to either diagnose and treat disease early or to prevent it altogether (reactivation and primary infection). Future studies will need to define the true incidence and clinical significance of HSV viremia detected by PCR in various populations; however, defining the clinical significance will be a difficult task, because any longitudinal study in an at-risk population will ethically need to include therapy for all patients with viremia. Thus, we will likely never truly know the natural history of this process through prospective study. Previous research suggests that the majority of immunocompetent adults with HSV DNA detected in the blood will do well [3–5]; thus, clinicians will need to exercise caution to avoid overuse of PCR testing and overinterpretation of the results until more definitive studies are conducted. Validated assays are currently not widely available, further limiting the utility of testing in most settings. With regard to prevention, many of our most highly compromised patients already benefit from prophylactic antivirals during their periods of highest risk. With newer, more potent immunosuppressive and immunomodulatory agents being used to treat various cancers and immune-mediated disease, it may be time to consider expanding our use of prophylactic therapy to other compromised individuals (many of the patients described by Berrington and colleagues fit this category). Finally, prevention of primary HSV infection is achievable. Although a vaccine may not be available for some time, we know that we can effectively prevent sexual transmission of HSV by means of a nucleoside inhibitor (valacyclovir) [17], and it may be prudent to consider performing HSV serological analysis for patients at highest risk (eg, pregnant and immunocompromised patients) and to recommend preventive antivirals to seropositive partners of seronegative patients. Further study, including evaluation of the social, emotional, financial, personal, and population effects of such a strategy, will need to be considered.

In summary, the study by Berrington and colleagues is particularly important because of its capacity to draw attention to the changing role played by molecular testing for HSV in ill adult patients. It also comes at a time when we should be reflecting on the benefits of expanding our HSV screening and prevention efforts. More research will be required before practical testing and treatment guidelines can be proposed.

Acknowledgments
Potential conflicts of interest. R.A.Z.: no conflicts.

References
5. Brice SL, Stockert SS, Jester JD, Huff JC, Bunker JD, Weston WL. Detection of herpes simplex virus DNA in the peripheral blood dur-
16. Herpes medication does not reduce risk of HIV transmission from individuals with HIV and genital herpes but demonstrates modest reduction in HIV disease progression and leads to new important insights about HIV transmission, UW-led international study finds. University of Washington Press Release, 8 May 2009.