Respiratory Herpesvirus Infections*
An Overview

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Human herpesviruses can cause acute and recurrent disease. The seven pathogenic human herpesviruses include the following: herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpesviruses 6 (HHV-6) and 7 (HHV-7). These large DNA viruses can produce either a chronic or latent infection and can be reactivated by various internal or external triggers. Herpes simplex virus-1, HSV-2, and VZV induce a lifelong latent state within nervous tissue, whereas EBV, CMV, HHV-6, and HHV-7 are latent within the lymphocyte subpopulation.

Typically, primary infections with HSV-1, HSV-2, and VZV involve the skin. Cytomegalovirus and EBV cause a characteristic mononucleosis-type syndrome. Asymptomatic infection with each herpesvirus is quite common. Following recovery from the primary infection, a latent state develops. Reactivation of virus may occur at regular intervals, as with HSV-2, or many years following the initial infection, as with VZV. With reactivation, virus replication can lead to either minor or major pathologic changes in local tissues. Lower respiratory tract involvement by herpesviruses has been demonstrated after primary infection and following reactivation. Clinically significant infections have been described in both immunocompetent and immunocompromised hosts. Involvement of the lung by HSV-1, HSV-2, EBV, and CMV has been demonstrated predominantly in the immunocompromised host. The review papers in this supplement provide us with current knowledge of herpesvirus reactivation in the lower respiratory tract of critically ill patients.

In a review of varicella-zoster pneumonia, Feldman describes the epidemiology, clinical findings, and possible treatment for this infection. Varicella pneumonia does occur in otherwise healthy adults but more commonly develops in patients receiving corticosteroids, in patients receiving transplants, and in children with malignancy. Pregnant and postpartum women also have an increased risk. An overall mortality rate of 40 percent has been reported for varicella pneumonia. Bacterial superinfection is common following VZV pneumonia, and long-term sequelae in terms of lung dysfunction are well defined. Treatment with intravenous acyclovir has been employed with apparent success; however, there is little information on the benefit of oral acyclovir in this clinical situation. One noncontrolled study has demonstrated benefit for prophylactic oral acyclovir during the second and third weeks of varicella exposure. Whether the use of the soon-to-be-licensed live-attenuated varicella vaccine will reduce the incidence of VZV pneumonia is still to be determined.

Involvement of the lower respiratory tract by HSV was first reported in 1970 by Nash and Foley. Over the past 25 years, several studies have documented the epidemiology and clinical presentation of HSV infection of the lung and lower airways. The role of HSV infections in burn patients is catalogued by Hayden and colleagues. Burn-wound infections with HSV have been found in the face and neck areas, predominantly in male subjects and in children less than 10 years of age. These infections are usually HSV-1, represent reactivation of latent virus, and occur 1 to 3 weeks after the initial burn. Although there are no controlled studies, clinical response has been reported with intravenous acyclovir. Klainer’s retrospective review of 14 patients after surgery who had HSV lower respiratory tract infection documents bronchospasm in 60 percent. In Schuller’s review of 42 patients, HSV lower respiratory tract infection was associated with ventilated patients and failure to wean. Those patients designated “immunocompetent” by Schuller were older or likely to be chronic smokers and on the ventilator for longer time periods. Treatment with acyclovir did not appear to affect outcome, and mortality was greater than 50 percent for the total group.

Tuxen reported HSV isolation in patients with adult respiratory distress syndrome (ARDS). A pro-
spective, controlled study failed to demonstrate any clinical benefit of acyclovir prophylaxis in a similar group of patients with ARDS. The percentage of HSV-positive clinical specimens appeared to correlate with the severity of the illness, a finding also supported by Schuller. Overall, the risk of pulmonary invasion by HSV has been reported to be low, even following recovery of virus.

Cytomegalovirus has been recovered from the lower respiratory tract in ventilated patients, but the role of this virus in causing pneumonia or respiratory failure is difficult to document. Clinically inapparent infection is probably most common; fever and leukocytosis are rare. No treatment studies are available for CMV pulmonary involvement except following bone marrow transplantation.

These papers suggest that many important questions still need to be addressed concerning lower respiratory tract infections due to herpesviruses. What is the pathogenesis of HSV infection in the lower respiratory tract? How can one differentiate colonization rates or asymptomatic virus shedding from infection and disease? What is the risk of nosocomial infection and potential spread to health-care personnel? Who should receive specific antiviral therapy or prophylaxis?

From these reviews, we have learned that the pathogenesis of HSV pulmonary involvement is not completely understood. Hematogenous spread could occur but is unlikely to, since visceral involvement is rarely found in autopsies from patients with HSV lung pathology. Contiguous spread or aspiration of HSV is probably more likely. The importance of local trauma and/or immunosuppression for reactivation of HSV has been discussed and supported by animal studies. Quantitative lower respiratory tract viral cultures might differentiate "colonization" from infection and should be studied. Surveillance viral cultures in ventilator patients could be used to document possible transmission of virus to health-care personnel or to other patients. This would solidify our knowledge of the potential for nosocomial spread with these herpesviruses. Although the published studies of acyclovir treatment have demonstrated the antiviral effect in lower respiratory tract herpesvirus infections, clinical benefit has been difficult to prove. Only after answering these questions will we be able to address whether targeted treatment would be beneficial in specific subgroups. The papers in this supplement provide a point of departure for future research.

REFERENCES