

Herpes simplex virus (HSV) is a common cause of recurrent mucocutaneous and, less often, visceral infection. Foscarnet and cidofovir act by inhibiting the viral polymerase independent of the viral thymidine kinase, while continuous infusion acyclovir relies on the limited amount of 2'-deoxythymidine triphosphate (dTMP) in the cell. Hammond et al [7]. Acyclovir's antiviral activity hinges on initial phosphorylation by the HSV viral thymidine kinase enzyme; cellular kinases then phosphorylate the drug further and acyclovir-triphosphate then interferes with viral replication by inhibiting the viral polymerase. Typically immunocompromised patients who develop acyclovir-resistant or refractory HSV infection have had previous repeated or prolonged exposure to acyclovir or other similar antiviral nucleoside analogues for prophylaxis or treatment of HSV [6]. Acyclovir-resistant HSV infection is a rare clinical problem typically seen in the immunocompromised population, where it can cause painful protracted mucocutaneous disease associated with significant morbidity and mortality [3–5]. The need for frequent intravenous delivery and hydration, coupled with the electrolyte monitoring and repletion requirements of foscarnet, typically require hospitalization for initiation, which can be prolonged for some individuals. Thus, resistance is typically mediated through alterations in the viral thymidine kinase, but can also be mediated through alterations in the viral polymerase that can confer cross-resistance to other antiviral therapies. In contrast, as novel immunosuppressive therapies for the management of hematologic malignancy grow, patients with hematologic malignancy remain a large at-risk population with substantial exposure to prophylactic anti-HSV antivirals. Acyclovir, a nucleoside analogue developed >40 years ago for the treatment of HSV and other herpesviruses, and the closely related prodrug valacyclovir, have been the mainstay of treatment and prevention of HSV infection and recurrence. Systemic treatment options for acyclovir-resistant HSV infection are limited and include intravenous foscarnet, intravenous cidofovir, and high-dose or continuous infusion acyclovir [7, 8]. Last, continuous infusion acyclovir is infrequently chosen for treatment of acyclovir-resistant HSV, and requires careful monitoring given the potential for acyclovir to cause crystal nephropathy in patients who are not adequately hydrated. To avoid the toxicities and other burdens of systemic therapy, compounded topical cidofovir and intralesional cidofovir are sometimes used for treatment of localized disease, though limited data suggest the topical approach alone may result in complete resolution as infrequently as 30% of the time [12]. A case series derived from a phase 2 study of this drug for treatment of mucocutaneous acyclovir-resistant HSV infection in immunocompromised patients showed that the drug was well tolerated, and 19 of 23 participants (83%) had complete resolution of HSV lesions by 28 days [15]. All 3 systemic treatment options are associated with significant toxicities and require careful monitoring.