

# Management of Herpes Simplex Virus Infections and Ulcers

Antiviral drugs, topical corticosteroids, and keratoplasty are options for management of HSV infection and related manifestations.

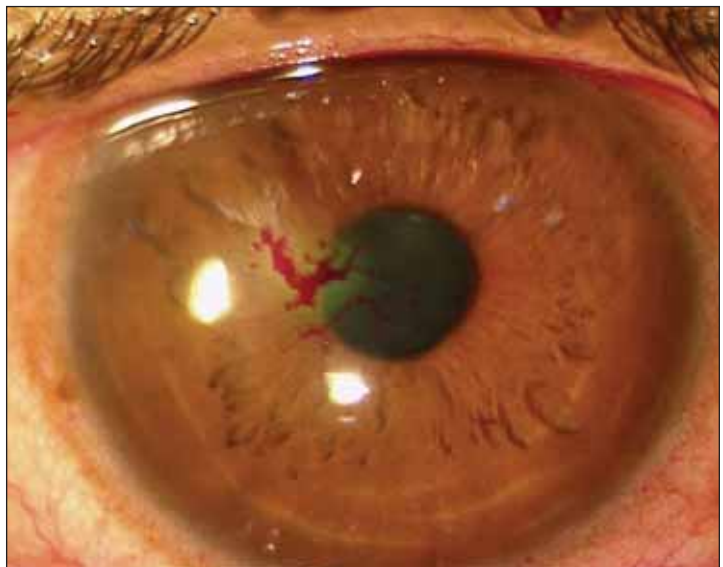
**BY VISHAL JHANJI, MD; AND RASIK B. VAJPAYEE, MS, FRCS(Edin), FRANZCO**

Ocular infection with herpes simplex virus (HSV) is a leading cause of ocular morbidity and vision loss.<sup>1</sup> HSV is ubiquitous, and there is a high prevalence of ocular herpes among the general population.<sup>2,3</sup> The incidence of ocular HSV has been reported to be 21 per 100,000, and the prevalence of a history of an HSV incident 150 per 100,000.<sup>3</sup> In the United States, an estimated 400,000 people are affected, with 20,000 new cases per year, and the reported incidence ranges from 4.1 to 20.7 cases per 100,000 patient years.<sup>4</sup>

Most patients with ocular HSV infections experience acute epithelial keratitis, which is treatable with a range of antiviral drugs. However, around 20% of patients who have had acute epithelial keratitis develop herpetic stromal keratitis (HSK), a chronic, vision-impairing lesion. Most of these cases are a consequence of reactivation of latent virus in the trigeminal ganglion.<sup>4</sup> Clinical manifestations of herpetic eye disease are primarily blepharoconjunctivitis or, more commonly, recurrent disease involving the corneal stroma. This article reviews the presentation of and treatment options for manifestation of ocular HSV infection.

## PRIMARY HSV BLEPHAROCONJUNCTIVITIS

HSV is a double-stranded DNA virus with two serotypes. HSV1 shows airborne transmission and classically causes infections of the eyes, face, and trunk; HSV2 is sexually transmitted and usually causes genital herpes. Clinical appearances of HSV infection are determined by the direct pathologic effect of the virus and the host response. Most people come in contact with the virus during the first



**Figure 1. Slit-lamp photograph showing a dendritic ulcer in an eye with herpes simplex infection.**

decade of life. Primary ocular infection is usually blepharoconjunctivitis, occasionally with corneal involvement in the form of punctate superficial keratitis. Following this, the virus ascends the sensory nerve axon to reside in latency in the trigeminal ganglion. Viral reactivation, replication, and retrograde migration to the cornea result in recurrent keratitis, which may be epithelial, stromal, endothelial (discoid), or neurotrophic. Potential intraocular involvement includes anterior uveitis, retinal vasculitis, and retinitis.

## RECURRENT HERPETIC EYE DISEASE

Patients with recurrent herpes have both cellular and humoral immunity against the virus. The disease may

present as any one or a combination of the following: blepharoconjunctivitis, episcleritis, scleritis, dendritic keratitis, metaherpetic ulceration, viral necrotizing keratitis, interstitial keratitis, and limbal vasculitis.

**Dendritic keratitis.** Dendritic keratitis is the most common form of recurrent herpetic eye disease. The infected corneal epithelial cells exhibit a cytopathic effect that spreads from cell to cell, exhibiting a dendritiform response over the corneal surface (Figure 1). During the course of infection, some of these cells are shed from the corneal surface, exposing the Bowman membrane. This gives rise to a dendritic ulcer. When the ocular milieu favors viral replication (eg, during use of corticosteroids), the virus spreads in all directions instead of linearly from cell to cell. As these cells are shed, the underlying denuded area forms a large, amoeboid geographic ulcer with dendritic advancing edges. The base of the ulcer stains with fluorescein and the ulcer margin stains with rose bengal. Corneal sensations are reduced in approximately 70% of patients.<sup>5</sup>

Diagnosis can usually be made on clinical examination, but when there is diagnostic uncertainty investigation is recommended with conjunctival and corneal swabs (viral transport medium) for culture, polymerase chain reaction (PCR), and enzyme-linked immunosorbent assay.

**Stromal keratitis.** Stromal keratitis may occur with or without epithelial ulceration. Stromal inflammation in HSV keratitis is thought to be due to a combination of HSV-specific T-cell activation by viral antigens, cytokine-mediated T-cell activation, and autoimmunity due to components of HSV binding to host autoantigens.<sup>6</sup> This can occur in the form of irregular, patchy, or disciform keratitis, the last being most prominent. Disciform keratitis manifests with a disc of inflammatory edema and corneal stromal infiltrates. The disciform area may be central or eccentric (Figure 2). Disciform keratitis probably results from viral antigen hypersensitivity rather than reactivation of the virus.

Clinical presentation includes painless decrease in visual acuity, central or paracentral disc of corneal edema, folds in Descemet membrane, mild anterior chamber activity, fine keratic precipitates, and ring of Wessely (stromal halo of precipitated viral antigen and/or host antibody). There may also be associated increase in intraocular pressure.

Occasionally, epithelial ulcers do not completely heal or are accompanied by recurrent epithelial breakdown. This trophic keratopathy is secondary to impaired corneal innervation and tear film instability. Clinically, trophic ulcers have gray, thickened borders of heaped-up epithelium. Longstanding metaherpetic ulcers carry a high risk of corneal stromal melting.

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## DIAGNOSIS

Clinical examination is one of the most important diagnostic aids in eyes with suspected herpetic infections, but HSV can masquerade as other ophthalmic inflammatory conditions. In eyes with unexplained postoperative inflammation, HSV may present without any typical signs.<sup>7-9</sup> Clinical suspicion is therefore important, particularly in cases that do not respond to conventional antimicrobial or antiinflammatory therapy.

Microscopic examination of Giemsa-stained smears may reveal typical eosinophilic viral inclusion bodies in the nuclei, although not invariably. Other stains used are Wright, hematoxylin-eosin, and Papanicolaou methylene blue. Swabbing the ulcerated areas and immediately inoculating into tissue culture results in a viral isolation rate of approximately 70%.<sup>10</sup>

Additional tests include immunomorphologic methods of evaluating scrapings from vesicles, such as immunofluorescent electron microscopy, immunoperoxidase staining, radioimmunoassay, agar gel immunodiffusion, and DNA probes. Real-time PCR assay is increasingly being used for the diagnosis of ocular herpes infection. PCR is a technique for amplifying short regions of DNA between regions of known sequences. The use of PCR for the diagnosis of HSV is reported to be equally specific as, and possibly more sensitive than, cell cultures.<sup>11</sup> PCR-based techniques have been successfully employed on various clinical samples including tear film, corneal epithelium, and corneal buttons.

## MANAGEMENT

**Epithelial keratitis.** In the presence of corneal ulceration, gentle debridement of the ulcer is performed with a sterile cotton-tipped applicator followed by topical

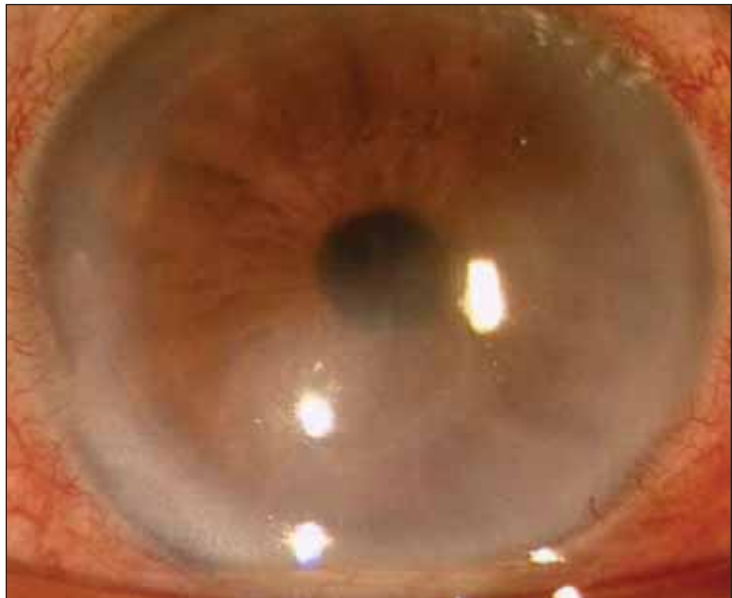


Figure 2. Slit-lamp photograph of disciform herpetic keratitis.

antiviral drugs for 14 to 21 days. Topical antiviral drugs are effective in dendritic and geographic ulcers, in which active viral replication remains the basic pathogenesis of the corneal lesion.

Topical antivirals currently in use include trifluridine 1% (dosed eight times per day), acyclovir 3% (dosed five times per day initially and then gradually tapered but continued for at least 3 days after complete healing), and ganciclovir 0.15% gel (dosed five times per day). Oral antivirals can be prescribed for patients unable or unwilling to use topical medication. The Herpetic Eye Disease Study (HEDS) showed that treatment of patients with epithelial keratitis using oral acyclovir does not reduce the rate of stromal disease or iritis.<sup>12</sup>

**Stromal keratitis.** The aim of treatment of herpetic stromal keratitis is to suppress the inflammatory response. This can be achieved with topical corticosteroids. However, corticosteroids should be used cautiously under the effective cover of antiviral treatment. Topical acyclovir 3% (dosed five times per day) is given initially. Systemic acyclovir (dosed initially 400 mg five times per day then reduced to a prophylactic dose of 400 mg two times per day) is preferred, especially in eyes with associated atopic keratoconjunctivitis, ocular surface disease, or frequent recurrences. Topical steroids are deferred until the epithelium is intact. Prednisolone 0.1% to 1.0% should be prescribed for use four to six times per day, then slowly tapered down in frequency and strength. A useful rule of thumb to follow in tapering steroids is the 50% reduction technique, meaning each dosage reduction is never more than half of the current level of

### TAKE-HOME MESSAGE

- Blepharconjunctivitis is a common primary ocular infection.
- Corneal epithelial cells infected with dendritic keratitis exhibit a cytopathic effect that spreads from cell to cell.
- Disciform keratitis manifests with a disc of inflammatory edema and corneal stromal infiltrates.
- HSV can masquerade as other ophthalmic inflammatory conditions.
- Real-time PCR assay can be used to diagnose ocular herpes.
- When tapering steroids, use the 50% reduction technique.



therapy. Less severe disease warrants starting steroid therapy at levels well below 1.0%.

**Oral antiviral therapy.** Available oral antiviral drugs include acyclovir, famciclovir, and valacyclovir. Oral therapy with or without topical antiviral therapy may be indicated in patients with primary HSK or recurrent epithelial dendritic or geographic keratitis, patients who are unable or unwilling to use topical treatment, and immunosuppressed patients. In some patients with immunosuppression, intravenous acyclovir may be required (5 mg/kg of body weight every 8 hours for at least 3 to 6 days before switching to oral acyclovir). Long-term oral antiviral treatment is needed in patients with HSV infection who have undergone keratoplasty.<sup>13</sup>

**Surgery.** Herpetic keratitis may be associated with corneal melting and perforation. Corneal gluing with cyanoacrylate tissue adhesive may be a viable option in eyes with perforations less than 2 mm in diameter. However, recent evidence shows that results of corneal gluing in herpetic corneal perforations are suboptimal.<sup>14</sup>

In eyes with significant corneal scarring secondary to herpetic keratitis, penetrating keratoplasty (PKP) is the primary surgical option for visual rehabilitation. Factors associated with good outcomes in these cases include surgery on an uninfamed eye, absence of deep neovascularization, and use of fine sutures and high doses of topical steroids immediately after surgery.<sup>15</sup> Cohen et al<sup>16</sup> reported a high overall success rate (80%) in 107 patients with HSV infection who underwent corneal grafting. Seven patients with active disease in this series at the time of surgery had a lower overall success rate. Ficker et al<sup>17</sup> reported increased success in grafting inflamed eyes with the use of prophylactic antivirals and corticosteroids.

A number of studies have reported significant efficacy in protecting grafts from recurrent HSV disease with the use of prophylactic acyclovir.<sup>13,18-20</sup> The generally recommended dosage is 400 mg acyclovir by mouth twice daily for 12 to 18 months after corneal transplantation. Ghosh et al<sup>13</sup> reported that oral acyclovir is more effective than topical acyclovir in prevention of recurrent HSV infection after PKP.

## CONCLUSION

Herpetic eye disease is a commonly encountered cause of ocular morbidity and vision loss. Clinical examination for classic signs of HSV infection is a useful diagnostic modality. In some instances, HSV has unusual clinical manifestations, particularly in cases with unexplained ocular inflammation after ocular surgery. A high index of suspicion and good microbiologic support are necessary for diagnosis and management of ocular her-

pes in such patients. Treatment with antiviral drugs is effective in most cases, and judicious use of topical corticosteroids is required in selected cases. Surgery in the form of keratoplasty is associated with good outcomes in uninfamed eyes; however, long-term prophylaxis with oral antivirals is advocated. ■

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