

A PRIMER ON HERPES SIMPLEX KERATITIS



Are you ready to manage patients with this common disease?

BY ALISON BOZUNG, OD, FAAO

Herpes simplex virus (HSV) belongs to a small subfamily of viruses, Herpesviridae. HSV is a double-stranded DNA virus that has approximately 90% seropositivity in people over age 60 years in the United States.¹ Once contracted, HSV exhibits retrograde movement from the end organ toward sensory ganglia, where it remains dormant or in a state of nonreplication for variable periods of time.

One aspect that makes HSV challenging to treat is its propensity to recur. The Herpetic Eye Disease Study Group found that the recurrence rate of keratitis was approximately 32%

over 18 months.² Studies have shown varying recurrence rates, however, ranging between 9.6% and 27% at 1 year, 27% and 36% at 5 years, and approximately 63% at 20 years.^{3,4}

When managing a patient with HSV keratitis, determining the level of tissue involvement is of paramount importance. Genetic differences in viral DNA may cause some HSV strains to generate more aggressive stromal disease, whereas other strains more commonly manifest with epithelial dendrites.^{5,6} Moreover, multiple HSV substrains have been found in the same host, signifying a broad spectrum of disease.

This article reviews three forms of HSV keratitis and discusses long-term management.

EPITHELIAL KERATITIS

Three Types

HSV keratitis affecting the corneal epithelium can be described as dendritic, geographic, or marginal.

Dendritic ulcers form from epithelial vesicles that have coalesced. They appear as branching, tree-like disruptions with swollen borders containing live virus. The elevated borders may stain with rose bengal, whereas the bed of the ulcer will stain with fluorescein (Figure 1).

Once a dendrite widens to lose its branching appearance, it is called a *geographic ulcer*. These ulcers possess scalloped edges but demonstrate staining patterns similar to those of dendrites. Both dendritic and geographic ulcers may be associated with subadjacent stromal haze in the “foot-print” of the ulcerated area (Figure 2).

Marginal ulcers are a clinically underrecognized manifestation of HSV. They present with a perilimbal epithelial defect, an underlying infiltrate, superficial neovascularization, and pronounced adjacent limbal injection. Staphylococcal-associated marginal infiltrates, on the other

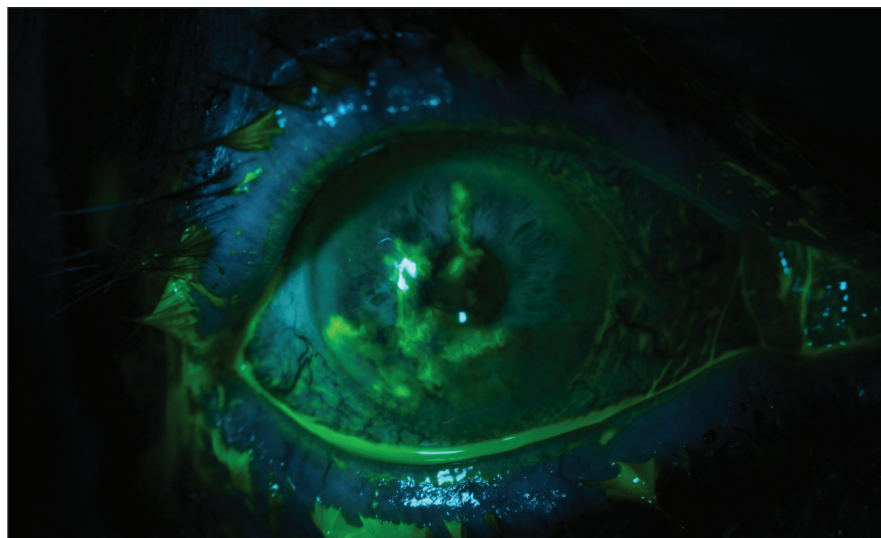


Figure 1. Multiple HSV epithelial dendrites stained with fluorescein.

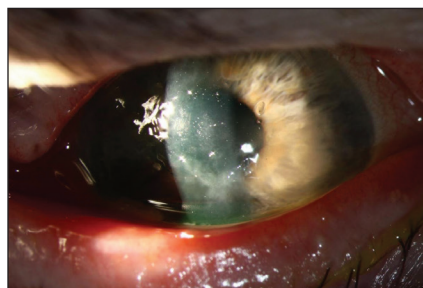


Figure 2. Anterior stromal haze underlying an area of epithelial ulceration.

hand, start as an infiltrate with or without an overlying epithelial defect and form in locations where the eyelids juxtapose the limbus. These infiltrates are associated with blepharitis.

Treatment

Epithelial HSV keratitis responds well to topical antiviral therapy such as with trifluridine (Viroptic, Monarch Pharmaceuticals), acyclovir (Avaclyr, Fera Pharmaceuticals), or ganciclovir (Zirgan, Bausch + Lomb). Oral antivirals may also be used as primary therapy, especially when the cost of topical medications is prohibitive. Topical corticosteroids should be avoided in patients with primary epithelial keratitis because these drugs may exacerbate the disease course. Topical antibiotics are recommended when an epithelial defect is present to prevent bacterial co-infection.



Figure 3. Stromal haze and interstitial neovascularization.

STROMAL KERATITIS

Stromal involvement in HSV may be primary or secondary. With primary involvement, it is thought that the virus migrates into stromal

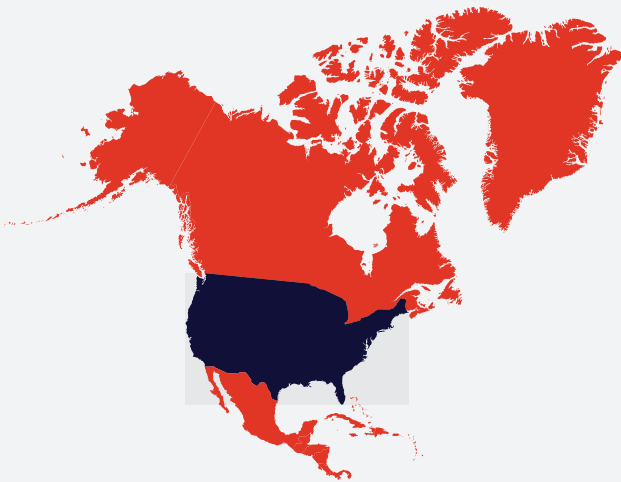
keratocytes, where it replicates and affects the cell's outward antigenicity, leading to a host inflammatory response. Viral antigens may also exist in the extracellular matrix and directly provoke an immune-mediated response.⁷ Secondary stromal involvement in HSV occurs when edema or inflammation is instigated by epithelial or endothelial infection.

Primary stromal HSV is often referred to as *interstitial keratitis*. It accounts for approximately 20% to 48% of recurrent HSV keratitis.⁷ Clinically, primary stromal HSV presents with haze, edema, and deep fronds of stromal neovascularization (Figure 3). It lacks epithelial defects or keratic precipitates. During a flare, two processes must be addressed—the virus and the host immune response. Aggressive topical corticosteroids are necessary to manage the inflammation. These agents should be tapered over a period of at least 10 weeks. Although either topical or oral antivirals may be used to address the virus, the currently preferred practice is to use oral antivirals.⁸

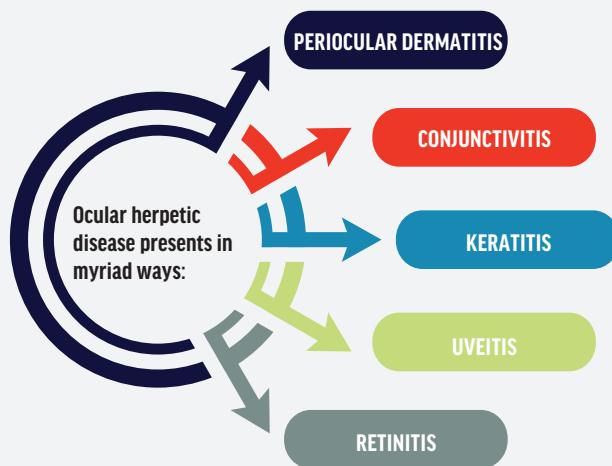
Occasionally, primary stromal HSV is termed *necrotizing stromal keratitis*. This rare but severe form often mimics severe microbial ulcers and can result in corneal perforation. High-dose oral antivirals and topical corticosteroids are the mainstays of treatment. Unfortunately, even with

AT A GLANCE

- ▶ In the management of patients with herpes simplex virus (HSV) keratitis, determining the level of tissue involvement is important because genetic differences in viral DNA may cause some strains of HSV to generate more aggressive stromal disease, whereas other strains more commonly manifest with epithelial dendrites.
- ▶ HSV keratitis affecting the corneal epithelium can be described as dendritic, geographic, or marginal.
- ▶ Management of the ophthalmic complications of HSV depends on the level of corneal involvement.



In the United States, the incidence of new ophthalmic HSV is estimated at 11.8 per 100,000 person years.¹



HSV may present bilaterally in up to 10% of individuals, and it is more likely to develop in children and individuals with atopy or immunosuppression.²

1. Young RC, Hodge DO, Liesegang TJ, Baratz KH. Incidence, recurrence, and outcomes of herpes simplex virus eye disease in Olmsted County, Minnesota, 1976-2007: the effect of oral antiviral prophylaxis. *Arch Ophthalmol*. 2010;128(9):1178-1183.
2. Hogan MJ, Kimura SJ, Thygeson P. Observations on herpetic keratitis and keratoconjunctivitis. *AMA Arch Ophthalmol*. 1956;56(3):375-388.

timely and aggressive management, patients are often left with significant corneal scarring.

ENDOTHELIAL KERATITIS

Herpetic endotheliitis results in stromal edema from endothelial dysregulation, keratic precipitates, and anterior chamber cell. IOP may be elevated due to concurrent trabeculitis. Stromal infiltrates and neovascularization are notably absent. Early in the disease course, corneal swelling may be diffuse, but it is often worse centrally and may prevent adequate visualization of keratic precipitates and anterior chamber cell. HSV endotheliitis

falls into three main classifications: disciform (Figure 4), diffuse, and linear. Differentiation depends on the distribution of keratic precipitates and stromal edema, although all three forms are treated in a similar manner.

Typically, HSV endotheliitis responds well to oral antivirals and topical corticosteroids. Suspected cases of HSV-related anterior uveitis are managed similarly. When IOP is elevated, aqueous suppressants should be prescribed.

LONG-TERM MANAGEMENT

Treating the ophthalmic complications of HSV can be challenging.

Management depends on the level of corneal involvement. In the acute phase, the focus of treatment is to limit duration and prevent serious tissue damage. Once the acute phase has passed, the goal of treatment shifts to preventing recurrence and managing the sequelae of the disease, such as corneal scarring, neovascularization, and neurotrophic keratopathy.

Prophylactic oral antivirals, which reduce recurrence rates by nearly 50%, should be considered for individuals with a history of recurrent HSV keratitis or keratoplasty.^{2,9} Those who have persistent low-grade stromal inflammation or neovascularization

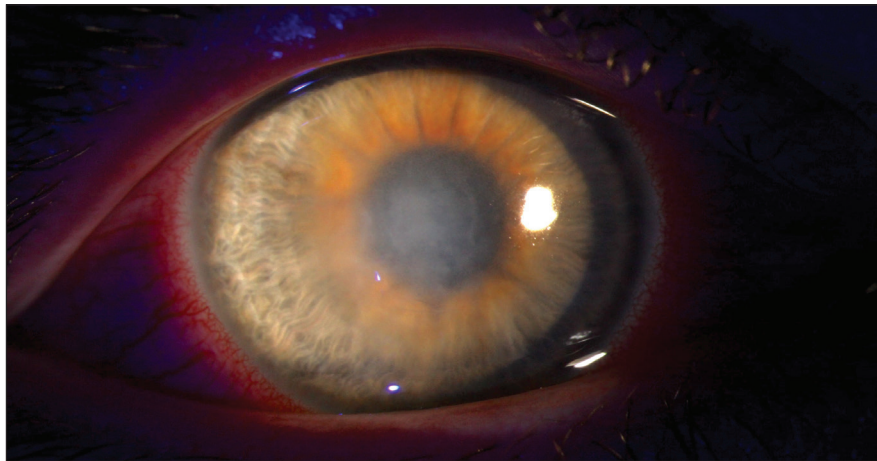


Figure 4. Central stromal edema resulting from HSV disciform endotheliitis.

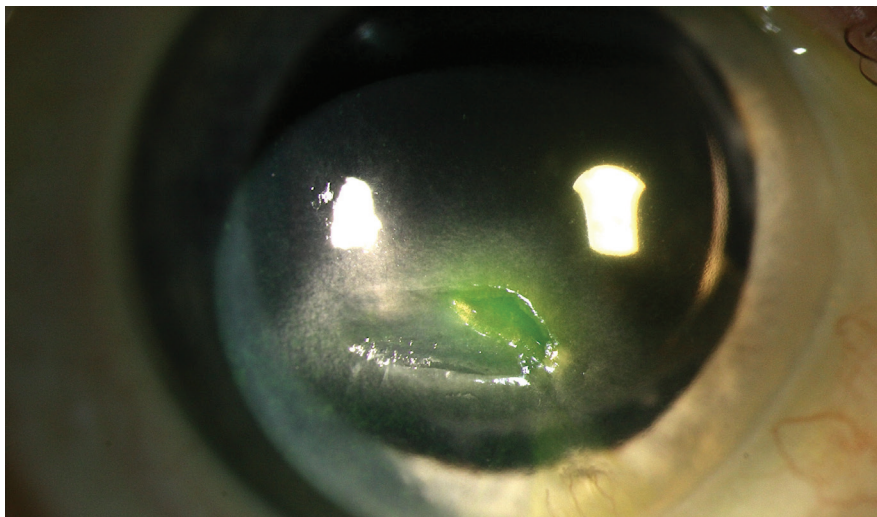


Figure 5. Sterile corneal ulceration caused by HSV-related neurotrophic keratopathy.

can benefit from prophylactic oral antivirals and low-dose topical corticosteroids to suppress their local immune reaction against viral antigens. Side effects such as elevated IOP and cataract development must be discussed with these patients and managed concurrently.

Herpetic keratitis can lead to severe scarring. In developed nations, it is the most common infectious cause of corneal blindness,¹⁰ and the disease is a frequent indication for penetrating or deep anterior lamellar keratoplasty. Corneal neovascularization can be problematic in these patients because the intrastromal vessels increase immunogenicity of the graft, elevating the risk of repeat keratoplasty.¹¹

Perhaps one of the most common¹² and difficult sequelae to manage is neurotrophic keratitis. Hallmarks of this process are poor epithelial healing, a lack of corneal sensation, and reduced tear production. Neurotrophic corneas are therefore prone to epithelial erosions, ulceration (Figure 5), and, ultimately, perforation. Based on the degree of severity, treatment strategies vary. Conservative measures include frequent instillation of preservative-free lubrication drops, placement of a bandage or scleral contact lens, and administration of autologous serum eye drops. More aggressive measures include partial tarsorrhaphy or corneal transplantation in the event of perforation.

Fortunately, a novel therapy for neurotrophic keratopathy became available in 2018, when the FDA approved the first drug specifically indicated for treating neurotrophic keratitis. Cenegermin (Oxervate, Dompé Farmaceutici) is a recombinant human nerve growth factor. Other topical biologics are currently under investigation, and novel surgical techniques are being explored. In corneal neurotization, for example, a sensory nerve is harvested, attached to the supraorbital or supratrochlear nerve, and then inserted near the neurotrophic eye's limbus. To read more about interventions that address the underlying cause of the insensate cornea, visit: bit.ly/CRST0319cornea.

BE PREPARED

All eye care specialists can expect to encounter patients with HSV keratitis. Astute clinical judgement can help practitioners to effectively manage both the acute and long-term sequelae of this disease. ■

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ALISON BOZUNG, OD, FFAO

- Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami
- alisonbozung@gmail.com
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