



## Condition: Herpes Simplex Keratitis

### Description:

Herpes simplex infection is very common but usually remains latent. When the virus is reactivated it travels along the trigeminal nerve to cause local infection (peri-oral & cornea). Patients with herpetic eye infection risk recurrent eye disease throughout their lives, with potential progressive irreversible scarring at each recurrence.

### Significance:

Herpes simplex keratitis is the leading cause of corneal opacification and one of the leading causes of blindness in the Western world.<sup>1</sup>

### Incidence:

Up to 90% of adults have antibodies to HSV-1 indicating previous exposure to the virus. Whereas the incidence of ocular infection with HSV is only 1-2 per 1000.<sup>2</sup>

### Management category:

Optometric management to resolution if epithelial involvement only; but urgent referral if epithelium not healed within 7 days or at any time deterioration is noted. Urgent referral to ophthalmologist if severe, central or stromal involvement. Optometric prescription of oral antiviral agents for the prevention of recurrences should be under the direction of an ophthalmologist due to the significant risk of vision loss in recurrent herpetic disease.

### Signs and symptoms:

Symptoms of herpes simplex keratitis include photophobia, foreign body sensation, lacrimation and redness. Herpes simplex keratitis remains primarily a clinical diagnosis based on the characteristic findings of corneal lesions, but the presentation with recurrences can be quite variable.

1. Epithelial disease: Dendritic ulcers are the most common presentation of HSV keratitis. These appear as a linear branching ulcer with terminal end bulbs and



central ulceration through to the level of Bowman's membrane. If the infectious ulcer enlarges then this linear shape is lost and a geographic ulcer forms.

2. Stromal disease: This is characterized by necrotic, grey/white, corneal stromal infiltration which may progress to stromal scarring. Keratic precipitates, uveitis and raised IOP may also occur in conjunction with stromal keratitis.
3. Disciform keratitis: represents an immunological reaction to viral antigens. This presents as a central (or paracentral) area of affected endothelium and oedematous, thickened stroma with folds in Descemet's membrane and is associated with a mild uveitis and fine keratic precipitates underlying the area of corneal oedema.

Diagnostic evaluation includes positive fluorescein staining of the dendritic lesions, positive lissamine green staining of the epithelium adjacent to the dendritic lesion, and positive polymerase chain reaction (PCR) for HSV-1. Because HSV is often recurrent, and its presentation can be variable, obtaining a corneal sample for PCR confirmation of HSV during an early epithelial presentation can be very useful.

### **Differential diagnoses:**

- Corneal abrasion (pseudo-dendrite)
- Acanthamoeba keratitis (pseudo-dendrite)
- Herpes Zoster Ophthalmicus (pseudo-dendrite)
- Bacterial keratitis
- Fungal keratitis
- Contact lens complications
- Recurrent epithelial erosion

### **Management:**

#### *Topical Treatment*

Epithelial Disease: Topical antiviral agents, most commonly acyclovir 3% eye ointment administered five times daily for 10 days, are prescribed to inhibit viral replication within infected cells.

Stromal Disease: Inflammation of the corneal stroma may accompany epithelial disease or may occur independently. The mainstay of treatment for stromal keratitis/keratouveitis is topical antiviral cover with or without the judicious use of topical low potency



corticosteroids.<sup>3</sup> The HEDS group have shown that the use of topical corticosteroid use shortens the duration of HSV stromal keratitis and reduces the persistence and progression of stromal keratitis.<sup>4</sup> Stromal disease is difficult to resolve, may permanently reduce vision, and is best managed by referral to an ophthalmologist.

*Disciform keratitis:* This is managed with cycloplegia and long-term, low dose, topical steroid therapy. Topical antiviral cover should also be employed to avoid steroid-related reactivation of HSV epithelial keratitis. As this condition is potentially sight-threatening it is best managed by an ophthalmologist/corneal specialist. Treatment for this condition may be ongoing for several months to years.

*Neurotrophic keratitis:* Because of decreased corneal sensitivity, a neurotrophic ulcer can develop. All suspected cases of neurotrophic keratitis should be referred to a corneal specialist for further evaluation since chronic non-healing epithelial defects may develop, with the risk of scarring or secondary bacterial infection.

### *Oral Treatment*

Randomized controlled trials have shown long-term suppressive therapy with oral acyclovir reduces the rate of recurrent epithelial and stromal keratitis by around 50%.<sup>5, 6</sup> The use of oral acyclovir had the most benefit for patients who had a history of stromal keratitis as this type of HSV keratitis has been most strongly associated with loss of visual acuity. Once treatment is stopped there is no evidence of ongoing benefit<sup>6</sup> or of a rebound effect. Oral acyclovir is typically prescribed as a prophylactic dose of 400mg twice daily for 6-12 months or longer.

The HEDS study group found that there was no statistically or clinically beneficial effect of oral acyclovir in treating **active** HSV stromal keratitis in patients receiving topical corticosteroid and topical antiviral therapy at the same time.<sup>7</sup>

### *Review*

Patients with epithelial disease should be reviewed after 3-7 days, with the expectation that dendritic lesions should be healed within a week.



### **Referral criteria:**

- Epithelial cases refractory to standard topical therapy
- Stromal keratitis
- Disciform keratitis
- Neurotrophic keratitis
- In patients where multiple recurrences occur, especially in the setting of a corneal opacity which may progress, oral prophylaxis may be required.

### **Warnings and precautions:**

Oral acyclovir is eliminated by renal clearance and its dose should be modified for patients with renal impairment. All elderly patients are likely to have some degree of renal impairment and the need for dose reduction must be considered for this group of patients. Consultation with the patient's General Practitioner is therefore recommended for elderly patients and those with potentially compromised renal function.

Acyclovir has been associated with reversible encephalopathic changes and should be used with caution in patients with neurological abnormalities.

Systemic dosing in rabbits, mice and rats did not produce embryotoxic to teratogenic effects. There have been no human birth defects associated with acyclovir use, however, its use should only be considered when potential benefits outweigh the risks. Caution is advised in breast-feeding mothers as acyclovir has been detected in breast milk following oral administration.

### *Side effects*

The most common side effects reported are: headache, dizziness, nausea, vomiting, diarrhoea and abdominal pain. Patients may also report pain, fever, pruritus, rashes and photo-sensitivity.

For a full list of side effects see:

<http://www.medsafe.govt.nz/profs/datasheet/z/zoviraxtab.pdf>



### **Informed consent:**

As with all healthcare interventions, the therapeutic optometrist is responsible for ensuring that the patient has been advised of the possible benefits and risks associated with the prescription medication, in order that the patient can make an informed decision and provide consent to the treatment plan.

### **References:**

1. Farooq AV, Shukla D. Herpes simplex epithelial and stromal keratitis: an epidemiologic update. *Survey of Ophthalmology* 2012;**57**(5):448-62.
2. Liesegang TJ, Melton LJ, 3rd, Daly PJ, et al. Epidemiology of ocular herpes simplex. Incidence in Rochester, Minn, 1950 through 1982. *Archives of Ophthalmology* 1989;**107**(8):1155-9.
3. Knickelbein JE, Hendricks RL, Charukamnoetkanok P. Management of herpes simplex virus stromal keratitis: an evidence-based review. *Survey of Ophthalmology* 2009;**54**(2):226-34.
4. Wilhelmus KR, Gee L, Hauck WW, et al. Herpetic Eye Disease Study. A controlled trial of topical corticosteroids for herpes simplex stromal keratitis. *Ophthalmology* 1994;**101**(12):1883-95; discussion 95-6.
5. Wilhelmus KR, Beck RW, Moke PS, et al. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. *New England Journal of Medicine* 1998;**339**(5):300-06.
6. Group HEDS. Oral acyclovir for herpes simplex virus eye disease: effect on prevention of epithelial keratitis and stromal keratitis. *Archives of Ophthalmology* 2000;**118**(8):1030.
7. Barron BA, Gee L, Hauck WW, et al. Herpetic Eye Disease Study. A controlled trial of oral acyclovir for herpes simplex stromal keratitis. *Ophthalmology* 1994;**101**(12):1871-82.

*These guideline documents are not exhaustive and should be considered 'living' documents that will be added to over time. Conditions outside those described in these guidelines may be deemed out of scope for independent optometric management and require referral to a medical practitioner. If in doubt, please check with the Board for advice.*

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