CONDITION: HERPES SIMPLEX KERATITIS

Description

Herpes simplex infection is very common but usually remains latent. Primary infection usually occurs in childhood and spreads via droplets or direct inoculation. Initial infection is usually subclinical or associated with mild fever, upper respiratory tract symptoms and malaise. Mild blepharitis or follicular conjunctivitis can also develop at this time, but treatment is often not required (Salmon, 2020). Most cases of herpes simplex virus are caused by HSV-1. 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. Patients who are immune-supressed or immunodeficient are at higher risk of severe disease.

Significance

Herpes simplex keratitis is the leading cause of corneal opacification and one of the leading causes of corneal blindness in developed countries (Farooq & Shukla, 2012).

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 to 2 per 1000 (Liesegang *et.al.,* 1989).

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 an ophthalmologist is warranted if severe or central epithelial involvement, or in cases of stromal or disciform keratitis. 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 blurred vision, 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. Subepithelial haze is common. If the infectious ulcer enlarges then this linear shape is lost and a geographic ulcer forms. Corneal sensation is generally reduced. The corneal findings may be accompanied by an anterior chamber reaction, which is usually mild.

2. **Stromal disease:** This condition is rarer, and is characterized by necrotic, grey/white, corneal stromal infiltration which may progress to stromal scarring, vascularisation and deposition of lipid. Keratic precipitates, uveitis and raised intraocular pressure (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 keratic precipitates underlying the area of corneal oedema. IOP may be elevated. Corneal sensation is reduced.

4. **Neurotrophic keratitis:** This is not a specific type of herpes simplex keratitis but can occur in herpes simplex keratitis, due to corneal anaesthesia (partial or complete loss of corneal sensation). This may initially start as a non-healing or recurrent epithelial defect, and can progress to stromal involvement with ulceration, corneal melt and corneal perforation.

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

1. **Topical Treatment**

    a. **Epithelial Disease:** Topical antiviral agents, most commonly acyclovir (aciclovir) 3% eye ointment administered five times daily (1 cm into the inferior fornix) for 10 days, are prescribed to inhibit viral replication within infected cells. Topical corticosteroids are

absolutely contraindicated in cases of herpes simplex keratitis with epithelial-only involvement as this may lead to the formation of a geographic ulcer.

Ganciclovir is another topical antiviral treatment (available as 0.15% gel) that is also used five times per day to treat epithelial herpes simplex keratitis. However, in New Zealand topical ganciclovir is a Section 29 medication, and supply of these medications is restricted to registered medical practitioners. Therefore, even though therapeutically qualified optometrists are considered authorised prescribers in New Zealand, they are not able to prescribe this medication.

b. **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 corticosteroids (Knickelbein *et.al.,* 2009) 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 (Wilhelmus *et.al.,* 2009). Stromal disease is difficult to resolve, may permanently reduce vision, and is best managed by referral to an ophthalmologist.

c. **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.

d. **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.

Adverse effects of topical treatment

The most common adverse effects of topical acyclovir are mild stinging or irritation after instillation. Hypersensitivity reactions are very rare. Patients should not wear contact lenses for the duration of treatment. Drug-related congenital abnormalities have not been reported to be associated with use of acyclovir during pregnancy, and the medication is generally considered to be safe during pregnancy and breast-feeding.

The adverse effects of corticosteroids, including the development of cataract and raised intraocular pressure are well documented and have been covered in other sections. One possible adverse effect of topical corticosteroids is the reactivation of herpes simplex keratitis (McGhee *et.al.,* 2002). Patients receiving corticosteroid treatment for herpes simplex keratitis with stromal or endothelial involvement will also have antiviral cover.

a. **Oral Treatment**

Randomised controlled trials have shown long-term suppressive therapy with oral acyclovir reduces the rate of recurrent epithelial and stromal keratitis by around 50% (Group HEDS,

1998) (Group HEDS, 2000). 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 (Group HEDS, 2000) or of a rebound effect. Oral acyclovir (aciclovir) 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 (Barron *et.al.,* 1994).[9]

Another randomised (although unmasked) clinical trial in 52 patients with history of recurrent ocular HSV found that the recurrence rate in patients treated with oral acyclovir (400 mg twice daily) was the same (23.1%) as the rate observed in patients treated with oral valacyclovir (500 mg once daily) for 12 months (Miserocchi, 2007). Serious adverse events were not noted in either group.

Famciclovir (250 mg twice daily) has also been suggested as a prophylactic treatment for recurrent ocular HSV, but the medication is not funded or approved for this use in New Zealand.

b. **Review**

Patients with epithelial disease should be reviewed after 3 to 7 days, with the expectation that dendritic lesions should be healed within a week. Treatment is continued for approximately three days after the epithelium has healed.

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 teratrogenic 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.

Precautions for valacyclovir are similar to those listed for acyclovir above.

Adverse effects:

The most commonly-reported adverse effects reported for both acyclovir and valacyclovir 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

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Please note: 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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