Herpes Simplex Eye Infections

Overview\[1\]
There are two types of herpes simplex virus (HSV) which are capable of causing an acute viral infection characterised by clusters of vesicles. HSV-1 mainly causes infection above the waist (characteristically the face, lips and eyes) and is spread by saliva. HSV-2 generally gives rise to sexually transmitted infection (genital herpes) and is spread by direct genital contact via infected secretions. Occasionally, the latter can give rise to ocular infection either venereally or at birth (ophthalmia neonatorum) during a vaginal delivery.

Primary herpes simplex eye infections usually occur in childhood (rarely before 6 months old) and adolescence. It may manifest itself as a vesicular ulcerative blepharitis or a follicular conjunctivitis but up to 99% of cases are subclinical. The most common site of this infection is the skin and mucous membranes supplied by the trigeminal nerve (95% of cases). After the acute infection, the virus will remain in the cell body of the trigeminal nerve until a trigger factor reactivates it, so giving rise to secondary infection.

Herpes simplex eye infections\[1\]
Herpes simplex can infect the eye at one or more levels:
- **Lids and surrounding skin** - seen as blepharitis and dermatitis respectively.
- **Conjunctiva** - characterised by conjunctivitis.
- **Cornea** - keratitis. This is inflammation of one or more of the three corneal layers:
  - **Epithelial** keratitis is the most common ocular manifestation, occurring in up to 80% of cases. It is characterised by dendritic ulcers.
  - The **stroma** and **endothelium** can also be affected. Stromal infection may be non-necrotising (disciform keratitis) or, more rarely, necrotising (and may be associated with severe complications, including perforation). Keratitis can lead to scarring and visual disturbance or, in severe cases, visual loss. Indeed, it is the most common infective cause of blindness due to corneal disease in high-income countries.
- **Uveal tract** - uveitis: patients have usually had severe corneal disease.
- **Retina** - retinitis: this is rare and may be seen in neonates with severe systemic disease.

Epidemiology
- **Annual incidence**: new cases 13 per 100,000, and recurrent infection 18 per 100,000.\[2\]
- Overall prevalence of ocular herpes simplex: 150 per 100,000.
- Male:female = 1:1. Peak initial presentation age: 37 years (average).
- Outbreaks tend to occur in the winter and early summer.\[3\]

Presentation\[1\]
Primary HSV infection
Ubiquitous disease with no apparent risk factors other than contact with an infected individual or an infected mother in the case of ophthalmia neonatorum.

**Symptoms**
- Usually occurs in children aged 6 months to 5 years. Over 90% are subclinical.
- May have generalised symptoms of a viral illness (upper respiratory tract infection, mild fever, malaise).
- May experience photophobia.
- In immunocompromised individuals and neonates: may become generalised and life-threatening. Neonatal infection is rare but has a high mortality rate.\[4\]

**Examination**
- Unilateral clear skin vesicles on erythematous base (lids, periorbital area), which eventually crust over.
- Acute unilateral follicular conjunctivitis.
- There may be associated punctate keratitis.
- Preauricular lymphadenopathy.
- May have secondary nasolacrimal duct obstruction.

Secondary (recurrent) HSV
Trigger factors
These may include:

- Stress (emotional or physical).
- Sunlight (or any ultraviolet (UV) light).
- Fever or illness.
- Trauma (including surgical).
- Menstruation.
- Cold wind.
- Use of contact lenses.
- Immunosuppression.
- Trigeminal nerve manipulation.
- Topical latanoprost treatment (for glaucoma).

Symptoms

- Unilateral in about 88% of cases. (Immunosuppression: more likely to be bilateral.)
- Red eye.
- Pain.
- Photophobia.
- Epiphora (tearing).
- History of previous episodes.
- May complain of blurred vision.

Examination

- Assess visual acuity.
- Examine lids and conjunctiva for evidence of inflammation. Involvement here is less common in secondary infection although conjunctival injection (red eye) is almost universal. There may be erosions around the lid margin with the presence of small vesicles or pustules.
- Observe cornea: any opacities or haziness? This may suggest stromal involvement.
- Test corneal sensation (twist the corner of a clean, dry tissue paper to a point and gently touch the corneal surface: this should elicit brisk blepharospasm and some sort of negative comment from the patient) - this can be reduced in epithelial disease.
- Stain the cornea and look for evidence of ulcers by staining with fluorescein. Corneal ulcers in HSV infection:
  - **Dendritic** - most common: linear branching lesions with terminal bulbs.
  - **Geographic** - as with dendritic but the linear component widens, giving rise to amoeboid appearance.
  - **Marginal** - ulcer at the edge of cornea: stromal involvement more likely.
  - **Corneal vesicles** - only apparent on slit-lamp examination: epithelial vesicles corresponding to skin lesions (eventually coalesce to give rise to the above ulcers).
- There may be associated uveitis which is characterised by limbal injection (redness around the rim of the cornea) and there may be an irregularly shaped pupil owing to posterior synechiae.
- Assess for evidence of tender preauricular lymphadenopathy, systemic illness and, in infants with confirmed ophthalmia neonatorum, assessment of the mother (± sexual partners) for evidence of HSV-2 infection is necessary.

Neonatal ocular HSV
This serious condition usually results in conjunctivitis, epithelial or stromal keratitis, cataracts, iridocyclitis, chorioretinitis and optic neuritis. Referral is mandatory for a full assessment and for further management.

Differential diagnosis

- Herpes zoster ophthalmicus (think of this in the elderly patient).
- Conditions causing epithelial defects (notably abrasions, recurrent corneal erosion, acanthamoeba keratitis, and keratitis of other aetiology).
- Contact lens-related problems.
- Other corneal conditions such as corneal graft rejection, or toxic keratopathies secondary to topical medication.
- Conditions causing conjunctivitis.
- Other conditions causing red eye.
- Orbital cellulitis.

Investigations

Most cases will be confirmed clinically and do not require further investigation following ophthalmological review. However, if there is doubt over the diagnosis, corneal or skin scrapings can be taken and a viral swab may be performed (after de-roofing the corneal vesicles). Polymerase chain reaction (PCR) can identify minute quantities of herpes simplex viral DNA in tissue samples and tears. Real-time PCR may be a useful technique for rapid diagnosis of ocular HSV infection, particularly in the identification of aciclovir-resistant keratitis.

High-resolution optical coherence tomography (OCT) may be a useful imaging tool in the future diagnosis of HSV keratitis.
Management\[1, 8\]

**General principles**

Patients suspected of having a herpes simplex infection of the eye should be referred on the same day to the local ophthalmology team.

Diagnosis is made on slit-lamp examination and misdiagnosis or inappropriate treatment can lead to serious (sometimes sight-threatening) sequelae.

- Have a high index of suspicion - and refer if in doubt!
- The absence of a dendritic ulcer does not preclude a diagnosis of corneal herpes simplex and should not inhibit referral if the clinical picture is otherwise suspicious.
- Steroid therapy should never be initiated in the primary care setting.
- If ophthalmia neonatorum is suspected, referral is all the more urgent. This is a notifiable disease and the mother ± sexual partners may need screening for other sexually transmitted infections.
- Treatment should only be initiated in primary care in exceptional circumstances - eg, in recurrent herpes simplex infection as part of a shared care arrangement with a specialist.

All patients suspected of HSV infection should discontinue contact lens wear until 24 hours after complete resolution of symptoms.

**Treatment**

- **Uncomplicated blepharitis and conjunctivitis** - symptomatic management: the use of warm saline compresses with a topical drying agent (such as 70% alcohol) may provide some symptomatic relief. Antibacterial ointment may prevent secondary infection of the lesions but its use is not widespread. Use of antiviral ointment is equivocal with conflicting evidence as to its efficacy in reducing keratitis.
- **Epithelial keratitis** - topical antiviral treatment is the norm - eg, aciclovir five times a day until at least three days after complete healing. Alternatives include famciclovir or oral antivirals (which have the benefit of not being toxic to the corneal epithelium), depending on the type of keratitis. Other treatment regimes have used (or added) alfa/beta interferons topically with good results. Debridement of dendritic ulcers may be carried out in allergic or noncompliant patients but there are few studies comparing this with antiviral treatments and so, at the moment, its effectiveness compared with these treatments is not really known.\[9\]
- **Stromal keratitis: disciform** - these patients will be very carefully treated with a combination of topical steroids and antiviral agents. Adjunctive medication including cycloplegics, topical antibiotics and anti-glaucomatous drugs may also be used.
- **Stromal keratitis: necrotic** - similar to disciform keratitis but steroid therapy will only be added cautiously once the overlying epithelial defect has healed.
- **Uveitis/retinitis** - these patients have usually got severe stromal disease which is treated as above. Systemic antivirals may also be used. These patients will often be managed as inpatients.
- **Penetrating keratoplasty (corneal graft)** - this may be carried out after the acute infection has subsided but where a sight-threatening scar remains. The role of this procedure in managing this disease is decreasing as primary management of the acute phase has improved considerably over the period of a few decades.\[10\] The risk of recurrence can be reduced with the use of systemic aciclovir and the risk of graft rejection is reduced by mycophenolate mofetil.\[11\]
- Deep anterior lamellar keratoplasty is a partial-thickness graft that preserves the endothelial layer, reducing the risk of graft rejection.\[12\]

**Complications**

- Adverse reaction to aciclovir: topical aciclovir needs to be applied frequently and can give rise to significant local irritation. Oral aciclovir comes with a long list of possible side-effects, including gastrointestinal disturbances, dermatological problems, headache, fatigue and a myriad of rare but more serious side-effects.
- Recurrence: 20% by two years, 40% by five years and 67% by seven years, with increasing risk after each episode.
- Corneal scarring and visual impairment.
- Secondary bacterial or fungal infection.
- One study found that HSV keratitis resulted in significant impairment in corneal sensitivity to mechanical forces and heat in some patients.\[13\]
- Other more rare complications: corneal perforation, secondary glaucoma, systemic disease in the immunocompromised individual.

**Prognosis**\[1, 8\]

- Eyelid lesions and conjunctival disease alone tend to resolve over two weeks.
- Corneal epithelial disease - 50% of active lesions heal spontaneously but 95% heal with topical antiviral agents (of these, about two thirds of the eyes heal within a week and 90% by two weeks).\[9\] 90% of eyes treated with a combination of antivirals and interferons heal within a week.\[9\] Medication can be tapered after two weeks. The outlook is generally good for these patients.
- Stromal disease - more likely to develop scarring and decrease in visual acuity: 90% remain 6/12 or better but 3% drop to 6/30 or less.
Prophylaxis

Patients with multiple episodes of epithelial or stromal disease may be considered for prophylactic oral antivirals (such as aciclovir 400 mg twice daily for a year). This has been shown to reduce incidence of recurrence of the disease during this time if this is not their first episode of HSV activation. There is also some limited evidence suggesting that oral aciclovir may help reduce the recurrence rate (and graft rejection rate) in corneal transplant patients.

Further reading & references

1. Herpes simplex - ocular; NICE CKS, September 2012 (UK access only)
3. Simple Keratitis; Family Practice Notebook
8. Barker N; Ocular Herpes Simplex, Clinical Evidence, 2008

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