CLINICAL PRACTICE GUIDELINE: Emergency Department

Herpetic Corneal Infections

Disclaimer: This Clinical Practice Guideline ('CPG') was written for use in The Royal Victorian Eye and Ear Hospital Emergency Department. It should be used under the guidance of an Ophthalmology or ENT registrar. If clinical advice is required, please contact the Eye and Ear Admitting Officer for assistance: EYE: +61 3 9929 8033; ENT: +61 3 9929 8032. Links to internal Eye and Ear documents cannot be accessed from the website CPG.

See also: Microbial Keratitis, Herpes Zoster Ophthalmicus

Description:

Herpes Simplex Virus (HSV) is typically a unilateral disease that can affect all layers of the eye. HSV may manifest as blepharitis, follicular conjunctivitis, keratitis, keratouveitis or more rarely, retinitis and optic neuritis. A history of cold sores elsewhere may or may not be present.

Please note that this CPG is a guideline only. Evidence is lacking for some treatment options for herpetic eye diseases, and clinical judgment remains important.

Red Flags:

- HSV keratitis can appear similar to other eye conditions – Herpes zoster, Acanthamoeba, topical medication toxicity, healing abrasions
- Topical steroids can significantly worsen epithelial disease
- Stromal disease in the presence of an epithelial defect runs the risk of corneal perforation
- Think of HSV in a patient with uveitis and raised intraocular pressure (IOP)

How to Assess:

History:

- Symptoms: redness, pain, photophobia, blurred vision
- May be a history of topical steroid use
- Past history:
  - Previous HSV infections (skin, eye etc.)
  - Treatments used in the past e.g. antivirals Systemic symptoms

Examination:

<u>Eyelid and conjunctival disease</u>

- Vesicles on skin, lid margin, or bulbar conjunctiva
- Unilateral blepharoconjunctivitis or follicular conjunctivitis
- Palpable pre-auricular lymph node

Corneal epithelial disease (due to actively replicating viral particles)

- Test corneal sensation prior to instillation of local anaesthetic
- Dendritic lesions – dichotomous branching with terminal bulbs; unifocal or multifocal
- Geographic lesions – sharply demarcated corneal ulcers with scalloped margins

Stromal disease (usually due to immune response to non-replicating viral particles)

- Test corneal sensation prior to instillation of local anaesthetic
- Immune stromal keratitis
    - Focal, multifocal, or diffuse stromal opacities +/- mild anterior chamber reaction
    - No epithelial defect
    - Possible partial or complete immune ring
    - Called interstitial keratitis if accompanied by deep corneal vessels. May have lipid deposition.
- Necrotising stromal keratitis
    - Corneal opacity in presence of an epithelial defect and stromal thinning
    - Difficult to distinguish from other forms of microbial keratitis
    - May lead to corneal perforation
    - Frequently a significant anterior uveitis, and/or trabeculitis leading to raised IOP

Endothelial Disease

- Disciform keratitis
    - Localised endothelial dysfunction causing disc-shaped area of corneal oedema
    - Minimal inflammation of stroma
    - Usually has focal keratic precipitates (KPs) underlying the oedema

Iridocyclitis

- Granulomatous uveitis or non granulomatous uveitis may accompany necrotising stromal keratitis (herpetic keratouveitis) or occur independently of corneal disease
- Often associated with high IOP caused by trabeculitis
- May have segmental iris atrophy or synechiae from previous episodes

Investigations:

- Viral swab for HSV in all patients unless previous swab was positive. Gently wipe the cotton tip across the surface of an epithelial defect or, in the absence of epithelial disease sample the tear film from the inferior fornix.

Acute Management:

- HSV epithelial keratitis (live virus) should be treated with antiviral medication but not with steroids.
- HSV stromal, endothelial, or uveitic disease (little if any live virus) requires steroids and consideration of antiviral prophylaxis.

Epithelial Disease

- Send off viral PCR swab
- Gently debride epithelium with a cotton tip and prescribe topical antiviral (aciclovir eye ointment 5 times per day for 10 days), or for at least 3 days after epithelial healing
- Oral antivirals (e.g. valaciclovir 500mg orally 3 times per day for 2 weeks) may be considered, although generally not necessary and not covered by Pharmaceutical Benefits Scheme (PBS) for this indication.
- Avoid topical steroids.

Stromal disease without epithelial defect

- Send off viral PCR swab (although result may be negative in the absence of an epithelial defect)
- Topical prednisolone acetate 1%/phenylephrine eye drops (Prednefrin Forte®) 2 hourly by day.
- Antiviral cover to reduce risk of reactivation of epithelial disease: valaciclovir 500mg once daily OR topical aciclovir eye ointment 5 times per day.
- Topical prednisolone acetate 1%/phenylephrine eye drops (Prednefrin Forte®) can be tapered every 1-2 weeks according to clinical improvement. Some clinicians elect to taper topical aciclovir concurrently.
- Prophylactic antiviral should continue until steroid dose is less than the equivalent of prednisolone acetate 1% one drop per day.

Stromal disease with epithelial defect

- Perform a corneal scrape to exclude microbial keratitis.
- Initiate treatment with oral valaciclovir 500mg TDS for 7-10 days OR topical aciclovir 3% 5 x per day, and topical fluoroquinolone, e.g. ofloxacin 0.3% eye drops hourly, day and night for microbial keratitis until confirmation of negative bacterial and fungal scrape. Review daily and modify treatment according to laboratory results and clinical response.
- Topical prednisolone acetate 1%/phenylephrine eye drops (Prednefrin Forte®) BD initially, and then increase to QID on confirmation of negative bacterial and fungal scrape.
- Corneal perforation should be referred immediately to the Corneal Fellow.

Endothelial disease

- Send off viral PCR swab (although result may be negative in the absence of an epithelial defect)
- Topical prednisolone acetate 1%/phenylephrine eye drops (Prednefrin Forte®) QID to 2 hourly by day (depending on severity).
- Oral antivirals (e.g. valaciclovir 500mg orally 3 times per day for 2 weeks and then reduce to prophylactic dose)
- Topical prednisolone acetate 1%/phenylephrine eye drops (Prednefrin Forte®) can be tapered every 1-2 weeks according to clinical improvement.
- Prophylactic antiviral should continue until steroid dose is less than the equivalent of prednisolone acetate 1% one drop per day.

Iridocyclitis

- In the absence of necrotising disease, treatment is as per uveitis, with addition of IOP lowering medications as indicated.
- Prophylactic topical aciclovir 5 x per day, OR oral valaciclovir (500mg 3 times per day) should be considered
- In the presence of concurrent epithelial disease, the epithelial disease should be treated first, prior to considering the addition of topical steroids (usually at least 72 hours later).

Special considerations

- Pregnancy:

  As all 3 oral anti-viral agents are category B3 agents, topical antiviral would be preferred.

- Paediatric:

  Epithelial disease

  - Topical aciclovir 5 x per day for 14 days (or for at least 3 days after healing) – whichever is shorter
  - Oral antivirals may be considered if unable to administer topical aciclovir

- Systemic treatment:

  - Indicated for stromal disease, skin involvement, systemic disease, immunocompromised
  - 3 months – 12 years: Oral aciclovir 10mg/kg (max 400mg) 5 x per day for 5-7 days
  - > 12 yo: Oral aciclovir 10mg/kg (max 400mg) 5 x per day for 5-7 days, or valaciclovir 500mg BD for 5 days

- Elderly patients >65 years old
    - Systemic aciclovir and valaciclovir can increase risk of central nervous system (CNS) reactions (hallucinations, confusion, encephalopathy) and risk of acute renal failure.
    - Renal function should be checked and monitored when commencing oral antivirals in the elderly. Famciclovir may be the preferred agent in the elderly population if CNS reactions occur, although it is not on the hospital formulary.

Follow up:

Epithelial disease, stromal disease, or endothelial disease:

- Review after 7 – 10 days

Necrotising Stromal Disease

- Consider admission or daily outpatient review.
- Steroid eye drops should be tapered very slowly over 8-12 weeks and may need to continue indefinitely, depending on the degree of clinical improvement.
- Continue treatment dose of valaciclovir (500mg oral 3 x per day) for 7 days and then reduce to prophylactic dose (500mg oral daily) until steroid drops are once daily or less. If using topical aciclovir, some clinicians elect to taper this after 7 days.

Long term management

- Prophylactic valaciclovir 500mg orally daily is useful in patients who have a history of multiple recurrences, those who have scarring close to the visual axis, those who are using topical corticosteroids for stromal disease or those who are immunocompromised. Consider ceasing after 12 months.

Discharge instructions:

- Education regarding the risk of recurrence, the need to present early and to report history of HSV.
- Education regarding dangers of self-medicating with topical steroid drops in the absence of specialist examination.

Evidence Table

Author(s)	Title	Source	Level of Evidence (I – VII)
Barron BA, Gee L, Hauck WW, et al.	Herpetic Eye Disease Study. A controlled trial of oral aciclovir for herpes simplex stromal keratitis.	Ophthalmology. 1994;101:1871-1882.	II
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;101:1883–1895; discussion 1895–1896.	II
	External Disease and Cornea. Basic and Clinical Science Course, Section 8.	American Academy of Ophthalmology. 2011-2012.	VII

The Hierarchy of Evidence

The Hierarchy of evidence is based on summaries from the National Health and Medical Research Council (2009), the Oxford Centre for Evidence-based Medicine Levels of Evidence (2011) and Melynk and Fineout-Overholt (2011).

I) Evidence obtained from a systematic review of all relevant randomised control trials.
II) Evidence obtained from at least one well designed randomised control trial.
III) Evidence obtained from well-designed controlled trials without randomisation.
IV) Evidence obtained from well-designed cohort studies, case control studies, interrupted time series with a control group, historically controlled studies, interrupted time series without a control group or with case series.
V) Evidence obtained from systematic reviews of descriptive and qualitative studies.
VI) Evidence obtained from single descriptive and qualitative studies.
VII) Expert opinion from clinician, authorities and/or reports of expert committees or based on physiology.

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