Viral keratitis

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**Typical presentation**

77 year old man
4 weeks right eye red and painful.
POH Nil
PMHx: HTN, osteoporosis, obesity

VAR HM, VAL 6/6-3
IOP R 15, L 8

Microbial keratitis
2.5 x 3.5mm defect, infiltrate 3.5 x 6.5mm
Empirical Treatment

Topical ofloxacin 1/24 D+N
Oral ACV 400 mg 5x/day

Corneal swabs Bacillus sp.
HSV 1 detected on PCR
Oral acyclovir in acute disease

HEDS (Herpetic Eye Disease Study)

Topical antiviral (1% trifluridine) all patients
Additional topical steroid reduced persistence and progression of stromal disease

No additional benefit from addition of oral acyclovir

BUT role for oral acyclovir to reduce epithelial toxicity

Herpes Eye Disease Study
Which topical anti-viral?

Topical best for epithelial reactivation, not effective versus latent disease (in ganglion)

Acyclovir 3% (Zovirax)
Trifluridine 1% (Viroptic)
Gancyclovir gel 0.15% (Virgan)

Cochrane review (2010)

Oral acyclovir alone as effective as topical
Trifluridine and acyclovir are more effective than idoxuridine and vidarabine
Gancyclovir as effective as acyclovir.
While not improving outcome addition of interferon may speed epithelial healing
Epithelial debridement is improved with addition of anti viral
Acute exacerbation of herpetic stromal keratitis
Exclude bacterial co-infection
Topical steroids
Topical acyclovir

Neurotropic keratitis prone to delayed epithelialisation
Risk of progressive thinning and perforation
Minimise epithelial toxicity

Consider preservative free drops
Consider oral acyclovir 400mg 5x/day

Consider tarsorrhaphy or BTXA ptosis
Prophylaxis to prevent recurrence

Acyclovir 400mg BD

(HEDS 1998)
337 patients with a history of stromal keratitis
the cumulative probability of recurrent stromal keratitis was:
14% in the acyclovir group
28% in the placebo group (P=0.005)

After acyclovir was stopped recurrence rate returns to normal level - benefit not sustained
No acute rebound effect in rate of HSV in 6 months post

Herpetic Eye Disease Study Group. Acyclovir for the prevention of herpes simplex virus eye disease.
Corneal perforation

Exclude bacterial/fungal co-infection

Small perforation <2mm
apply cyanoacrylate glue
Bandage contact lens

Delay penetrating keratoplasty by 6 months if possible

Oral Valtrex 500mg 3x day initially
Management post glue

Bandage contact lens- change monthly

Minimise steroids, no antibiotics

Oral Valtrex 500mg daily

Delay penetrating keratoplasty by 6 months if possible

Grafts do better in quiet eye

Graft survival at 5 years
  • Herpetic perforation/active infection 54%
  • Inactive herpetic scar 77%

(ACGR 2012)
Acyclovir after penetrating keratoplasty for herpetic keratitis

68 patients with HSK underwent PK
Oral acyclovir 400mg twice daily or placebo for 6 months
Results
• 3 cases in acyclovir group
• 9 cases in placebo group
Oral acyclovir is effective in preventing HSV recurrences after PK

52 patients post PK for HSV
Systemic more effective than topical in preventing recurrence of herpetic keratitis
Recurrence rates: topical group 55% systemic group 19%

Suggest at least 12 months of treatment
• Consider longer if still requiring steroids

Ophthalmology 2003;110:1916-1919 van Rooij et al
Acyclovir or Valacyclovir?

**Acyclovir**
Dosage 400mg bd ($28 for 200mg x90)
In vitro studies have shown that acyclovir preferentially affects cells that have been infected by HSV, and, unlike other antivirals, acyclovir has relatively little effect on normal, uninfected cells.

**Safe and well tolerated**
The drug is excreted primarily by the kidney; therefore, smaller doses may be required in patients with decreased kidney function (*Lietman 1982*).
- Can cause obstructive nephropathy
- GFR abnormal, reversible tubular toxicity
- Dosage adjustment for renal impairment

**Valacyclovir** ($22 for 30 days)
Oral valacyclovir, the acyclovir prodrug, is known to increase the bioavailability of acyclovir three to five times

**Dosage 500mg daily**
**Toxicity mild**
Neurotoxicity has been reported among elderly and renally impaired patients (*Asahi 2009*).

High prevalence of acyclovir resistant corneal HSV-1 has been reported in immunocompetent patients with HSV keratitis (*Duan 2008*).
Paediatric use

Paediatric HSK has a high rate of misdiagnosis, stromal involvement, recurrence and vision loss

Acyclovir is safe and well tolerated
Reduced dosage

Effective in treating active epithelial keratitis
Useful in prophylaxis in children prone to recurrent epithelial disease
Used as prophylaxis for children treated with steroids for immune stromal disease

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment Dose Thrice Daily</th>
<th>Prophylactic Dose Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (up to 18 mos)</td>
<td>100mg(2.5ml)</td>
<td>100mg(2.5ml)</td>
</tr>
<tr>
<td>Toddlers (18 mos–3 yrs)</td>
<td>200mg(5ml)</td>
<td>200mg(5ml)</td>
</tr>
<tr>
<td>Young children (3–5 yrs)</td>
<td>300mg(7.5ml)</td>
<td>300mg(7.5ml)</td>
</tr>
<tr>
<td>Older children (6 yrs and older)</td>
<td>400mg(10ml)</td>
<td>400mg(10ml)</td>
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Ophthalmology Liu et al

A.  
B.  
C.  
D.  

The Royal Victorian Eye & Ear Hospital  
THE UNIVERSITY OF MELBOURNE  
CENTRE FOR EYE RESEARCH AUSTRALIA
Vaccination

Inactivated HSV 1 vaccine (Lupidon 1)

Number and duration of HSV-1 recurrences reduced (20 patients)
No statistical difference

No increase in peripheral blood HSV-1 specific CD8 cells

(Trial of HSV-2 vaccine found to be ineffective)

Cornea 1999;18(1):47-51
Oral acyclovir in herpetic keratitis

Effective for treatment if topical contraindicated
Useful for prophylaxis in recurrent disease

Essential post graft

Preferred treatment in children (reduced dosage)

Long term safety high

Beware development of resistance
**Herpes zoster ophthalmicus**

Prodrome includes two to three days of generalized malaise with fever and headache, with signs of hyperesthesia, pain, burning sensation, or itching, with associated erythema and edema.

- A macular rash appears, which is first papular and becomes vesicular within twelve to twenty-four hours. There is erythema and edema at the base of some vesicles.
- tender lymphadenopathy
- two to three weeks the acute phase subsides
- post-herpetic neuralgia common.
HZO Ocular involvement
Conjunctiva/ Sclera

Follicular conjunctivitis
Occasional vesicular eruptions

Scleral involvement usually late
• Diffuse or nodular scleritis
HZO Corneal involvement

Early

- generally self-limited, include
- punctate epithelial keratitis
- pseudodendritic keratitis

These are usually present within the first week of the disease, and varicella zoster virus has been cultured from these lesions

- Mucous plaque keratitis (PCR negative)
- Anterior stromal keratitis often first 3 weeks, associated anterior uveitis

Late

- Disciform keratitis 3-4 months after acute zoster
- Neurotrophic keratitis represents loss of corneal sensation with resultant corneal epithelial break-down and ulceration.

40% have some anterior uveitis
HZO Management

Systemic treatment of acute HZO
- Oral acyclovir 400mg 5 times a day for 10 days (Valtrex 1000mg tds)
- more rapid resolution of signs and symptoms, especially if such treatment is given within the first 72 hours of the skin eruption.
- Prophylaxis against ocular involvement helps 67% vs 40%
- Reduction of severity in post herpetic neuralgia

Local treatment
- Little evidence of benefit for topical antiviral for epithelial disease
- Stromal disease inflammatory responds to topical steroids, no benefit in anti viral prophylaxis
- May require prolonged course of treatment
HZO Neurotrophic keratitis

**Stage 1**
Rose Bengal staining of the inferior palpebral conjunctiva
Decreased tear breakup time
Increased mucous viscosity
Punctate epithelial fluorescein staining

**Stage 2**
Epithelial defect - Usually oval and in the superior cornea
Edges may become smooth and rolled
Stromal swelling with folds in the Descemet membrane

**Stage 3**
Stromal lysis/melting
May result in perforation
Neurotrophic keratitis

- Topical lubrication with preservative-free artificial tears, gels, and ointments
- Chloromycetin ointment for epithelial defects
- Discontinuation of any topical ocular therapies with preservatives, especially those that can decrease corneal sensitivity (eg, timolol, betaxolol, sulfacetamide, diclofenac, ketorolac) or
- Punctal occlusion may need to be considered.

Other therapies used
- Consider scleral contact lenses
- Consider 20% autologous topical serum
- Topical RGTA® (Cacicol20®; OTR3, Paris, France), a matrix agent mimicking heparan sulfate,
- Cx43 inhibitor (Nexagon)
- Recombinant human nerve growth factor (rhNGF) eye drops (Oxervate)
Recombinant Human Nerve Growth Factor
Oxervate (Dompe)

- Phase 2 Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis.

- rhNGF group 55% complete epithelial healing versus 19% controls at 4 weeks
- More than 96% of patients who healed after controlled rhNGF treatment remained recurrence free during follow-up.
- Treatment with rhNGF was well tolerated; adverse effects were mostly local, mild, and transient.

Bonnini et al Ophthalmology 2018 Apr 10
Management of neurotrophic keratitis

Surgical care may be necessary in stage 2 or 3 neurotrophic keratopathy.
- Protect the epithelium by lid closure (BOTOX ptosis or lateral tarsorrhaphy)
- Close a persistent epithelial defect
- Repair a deep ulceration

Inpatient care
- Patients with stage 3 neurotrophic keratopathy may be hospitalized for daily follow-up care until significant improvement is seen.

Monitoring

Deterrence
- Avoid topical corticosteroids - These may increase collagenase activity and stromal melting
- Avoid topical NSAIDs
- AVOID PRESERVATIVES
Zoster Vaccine

Vaccine the key to preventing HZO

The zoster vaccine (ZV) is safe and effective in reducing the burden of illness, severity of PHN, and incidence of HZ.

Centers for Disease Control and Prevention recommended for persons aged 60 years and above

Food and Drug Administration approved for those aged 50 and older.

It is most effective in preventing HZ in recipients in their 50s.

In Australia the shingles vaccine, Zostavax®, has been approved to be placed on the National Immunisation Program (NIP), to be provided free of charge from 1 November 2016 to people aged 70 years.

But those in their 50s, 60s, and 80s will continue to have to fork out $200 or more for a dose of the Zostavax vaccine.
Adenoviral EKC
Clinical signs and symptoms

EKC is predominantly a unilateral condition initially, but can become bilateral in up to 70% of cases.
• symptoms are “pink eye” or “red eye”, excessive tearing, foreign body sensation, and photophobia.
• ocular or periorbital pain
• decreased visual acuity.
• recent history of an eye examination, an affected family member, or an occupational exposure.
• preceded by flu-like symptoms such as fever, malaise, myalgia, respiratory symptoms, nausea and vomiting, and diarrhea.

The ocular signs are predominantly bulbar conjunctival redness, chemosis, tarsal follicular reaction, petechiae, or even subconjunctival hemorrhage.
Adenoviral EKC
Highly contagious

The modes of transmission are mainly through hand to eye contact, ocular secretions, respiratory droplets, and contact with ophthalmic care providers and their medical instruments.
• biphasic disease that begins with an infective phase that is then followed by an inflammatory phase, which tends to begin 7-10 days after the initial infection as the virus continues to shed.
• The patient remains infectious for up to 2-3 weeks.
Viral conjunctivitis

Involvement of the entire ocular surface, including both the conjunctival and corneal epithelia.
• In severe cases, there may be formation of pseudomembranes and symblephara
• multifocal subepithelial infiltrates that can reduce vision for years.
Adeno EKC Management

Adenoviral conjunctivitis is a self-limited disease that usually exhibits complete resolution within 3 weeks

**Acute disease**
- Conservative treatments, including artificial lubricants and cool packs, can provide efficient symptomatic relief without any adverse effects.
- Topical antibiotics are used to treat or prevent bacterial superinfection.
- Topical antihistamine and vasoconstrictors also reduce discomfort and disease duration in spite of the risk of local toxicity.
- The use of topical steroids is controversial. Topical steroids are frequently given in the acute phase, although this only has a transient alleviating effect. The disease and infection durations could be prolonged (increased viral replication and shedding).

**Prevention of spread**

**Complications**
Adenoviral EKC

Complications

- **Pseudomembranes**, sheets of fibrin-rich exudate lacking blood or lymphatic vessels adhered to the upper and lower tarsal conjunctiva. May benefit from surgical debridement
- multifocal **subepithelial infiltrates** present in 50% of cases. Respond to steroids
Adeno EKC New treatments

- **Topical interferon b** reduces the length of disease and prevents corneal complications in some studies.
- Povidone-iodine is a broad-spectrum antiseptic agent highly effective against free adenovirus, but less effective against intracellular adenoviral particles in infected cells in vitro.
- **Combination of topical povidone-iodine and dexamethasone** decreases the secretion of virus and reduces disease progression. (Shire)
  - Topical steroids relieve symptoms, and povidone-iodine kills the virus in tears, thus reducing the risk of disease spread.

**Anti viral**

- Virustatic agents such as trifluridine, vidarabine, and ganciclovir are only mildly effective against adenovirus
  - Topical ganciclovir decreases adenovirus load experimentally although it lacks efficacy in the treatment of conjunctivitis in clinical trials.
- Topical cidofovir has significant antiviral activity against adenovirus in vitro and in animal models.
  - Topical administration of cidofovir significantly reduced adenovirus viral titers and shortened the duration of shedding and also provides prophylaxis against adenovirus exposure but clinical studies disappointing.
  - Cidofovir can lower the frequency of severe corneal opacities.
- **Ranpirnase (Okogen)** has a potent anti-adenoviral effect and is more efficacious than cidofovir treatment in animal models. Clinical trial commencing soon.
CMV keratitis
Clinical manifestations

- Corneal endotheliitis with coin-shaped lesion or linear KPs similar to the rejection line.
- Corneal endotheliitis with localised corneal oedema with KPs associated with two of the following signs:
  - recurrent/chronic anterior uveitis
  - ocular hypertension/secondary glaucoma
  - corneal endothelial cell loss.
- Mean patient age was 66.9±10.9 years (85 males (80.2%), 21 females (19.8%)).
- Patients were commonly diagnosed with anterior uveitis and ocular hypertension prior to confirmation of CMV endotheliitis. 
Cytomegalovirus (CMV) corneal endotheliitis.

Coin shaped lesions
Linear KP (cf rejection line)
Localised corneal oedema

CMV keratitis diagnostic tap

Viral examination by PCR of aqueous humour

Positive for CMV DNA, but negative for HSV DNA and VZV DNA

Treatment of CMV keratitis

Anti CMV therapy

Systemic ganciclovir or valganciclovir
Topical administration of ganciclovir
Intracameral ganciclovir

2/3 good response
1/3 partial response

Prior to first DSAEK: decompensated cornea secondary to hypertensive uveitis and visual acuity of 1/60. The first DSAEK was not covered with valganciclovir treatment and failed 10 months after the surgery.

3 months after the second DSAEK with a positive CMV aqueous tap and subsequent oral valganciclovir treatment. BCVA was 6/24 and endothelial cell count of 1153 cells/mm².
Summary of viral keratitis

- Herpetic keratitis responds well to topical acyclovir
- Oral Valtrex useful for prophylaxis against recurrence, in grafts and perforations, complex cases
- Herpes zoster ophthalmicus commonly leads to corneal complications
- Neurotrophic keratitis key is to avoid preservatives and consider lid protection early
- Adenoviral conjunctivitis responds poorly to anti virals
- Consider CMV keratitis for recurrent endothelial graft failure, unresponsive to acyclovir