

Herpes simplex keratitis: Keeping it simple(x)

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Disclosures

- ❖ No financial / conflict of interest disclosures

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Epidemiology

- ❖ Eight known human herpes viruses
- ❖ Herpes simplex I (oral-facial-ocular), II (genital)
- ❖ Can cross infect
- ❖ Herpes viruses 6 & 7 (roseola infantum) and herpes virus 8 (Kaposi sarcoma and lymphoma)
- ❖ Varicella-Zoster, CMV, Epstein-Barr



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Epidemiology

- ❖ Man is the only host
- ❖ DNA Virus
- ❖ HSK is a leading cause of corneal blindness worldwide
- ❖ Around 21 total new & recurrent cases of HSK per 100,000 people per year (US)

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Epidemiology

- ❖ 80-90% of the population in US over the age of 15 has antibodies to HSV
- ❖ Passive immunity up to 6 months old (neonatal infection still possible)
- ❖ Most have primary exposure by age 5: only 5-10% clinical
- ❖ Spread by close personal contact
- ❖ 70% of trigeminal ganglia on autopsy harbor HSV

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Epidemiology

- ❖ After primary exposure, the virus lays dormant in neural ganglia (carried by axonal flow) including the trigeminal and sacral ganglia



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Triggers for reactivation



- ❖ Dormant virus particles can be reactivated by various triggers
- ❖ These include stress, UV light (sun), trauma, fever, menstruation, some eye drops like prostaglandins and beta blockers, excimer laser treatment

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Triggers

- ❖ Original primary infection of trigeminal ganglion more commonly associated with gingivostomatitis (cold sore) than ocular disease
- ❖ Recurrence can then be either oral or ocular

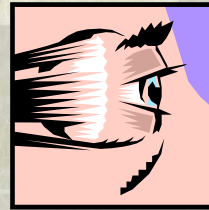
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Ocular findings

- ❖ There are several ocular findings associated with HSV infection. Some are more commonly seen in primary cases, others in cases of reactivation.
- ❖ Lid vesicles with edema
- ❖ Conjunctivitis (follicular)
- ❖ Canaliculitis
- ❖ Epithelial lesions (dendritic, punctate, geographic)
- ❖ Stromal infiltrative disease (disciform, etc.)
- ❖ Endothelial inflammatory disease

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Ocular findings



- ❖ Neurotrophic keratitis
- ❖ Uveitis
- ❖ Iris atrophy
- ❖ Acute retinal necrosis

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Primary infection

- ❖ Lid lesions with edema, follicular conjunctivitis, and corneal epithelial lesions are commonly seen with primary infection. Most often blepharoconjunctivitis
- ❖ Corneal stromal disease is very rare in these instances as is iritis or endothelial disease
- ❖ Approximately 10% of cases can be bilateral.....usually in patients with atopic disease

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Primary infection

- ❖ The initial ocular symptoms in adult patients usually are the result of recurrence in cases where the primary infection was asymptomatic (or at a very young age)
- ❖ Ocular symptoms in children or adolescents may represent primary infection

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Primary infection

- ❖ Epithelial lesions may be in the form of a dendrite or may be fine punctate lesions which then go on to coalesce into dendrites
- ❖ Geographic ulcers very rare in primary disease
- ❖ Dendrite formation follows a very similar course in both primary and recurrent disease

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Primary infection

- ❖ Clinical symptoms occur 1-2 weeks after contact and are accompanied by fever, malaise, etc.
- ❖ Lid lesions are small, ulcerated vesicles often seen on lid margins. Can be hidden by lashes
- ❖ Fluorescein staining can help detect/outline them

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Primary infection

- ❖ Conjunctivitis is usually follicular with injection and chemosis
- ❖ Epithelial dendrites take on the traditional branching pattern with fluorescein staining of the center and rose bengal / lissamine green staining of the edges and terminal end bulbs

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Lid lesions and conjunctivitis



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Primary infection

- ❖ Possibly corneal hypesthesia (takes time)
- ❖ Limbal dendrites are often more refractory to treatment than central dendrites



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Secondary/recurrent infection

- ❖ Reactivation can lead to several ocular complications
- ❖ Epithelial disease mimics that seen in primary infection with the exception that geographic or "megaherpetic" lesions are possible
- ❖ Infected epithelial cells can release VEGF leading to corneal neovascularization

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Secondary/recurrent infection

- ❖ Stromal inflammatory disease is common in secondary cases including disciform keratitis. Necrotizing more rare
- ❖ Stromal disease is an inflammatory reaction and is the main cause of scarring related vision loss.....may not represent replicating virus
- ❖ CD4 T cell mediated inflammation

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Recurrent infection

- ❖ Mild iritis is often seen
- ❖ Sectoral iris atrophy accompanied by iritis / trabeculitis and an increase in IOP can be seen even in the absence of corneal disease. Can present as Posner-Schlossman syndrome (glaucomatocyclitic crisis)
- ❖ Up to 80% of such cases caused by HSV, 20% by VZV. CMV also a cause
- ❖ Endotheliitis (with or without trabeculitis)

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Recurrent infection

- ❖ Tear production is often reduced
- ❖ Due to decreased corneal sensitivity and inhibited feedback mechanism



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Recurrent infection

- ❖ This loss of sensory feedback can lead to neurotrophic corneal lesions (HS kills nerves)
- ❖ This is the breakdown of the corneal epithelium without trauma, infection, or severe desiccation
- ❖ Early signs include punctate RB / LG staining
- ❖ Severe cases lead to persistent, non-healing epithelial defects with ulceration

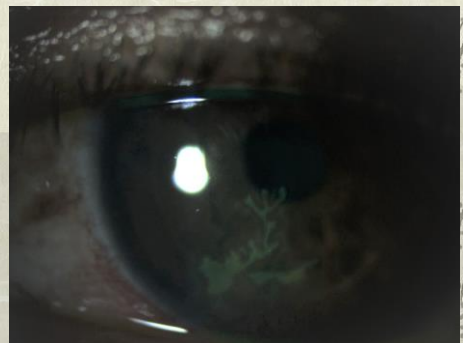
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Recurrent infection

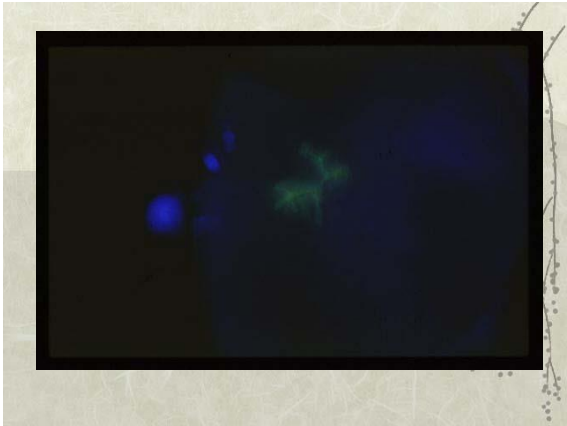
- ❖ Cases of reactivation can include stromal disease alone, epithelial disease alone, or the two in conjunction with one another
- ❖ The other associated findings can be present with or without corneal involvement



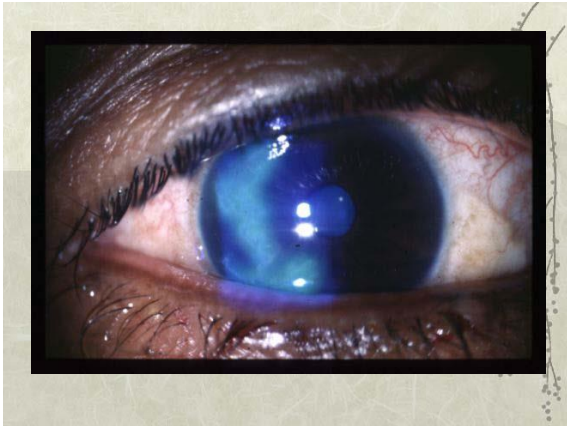
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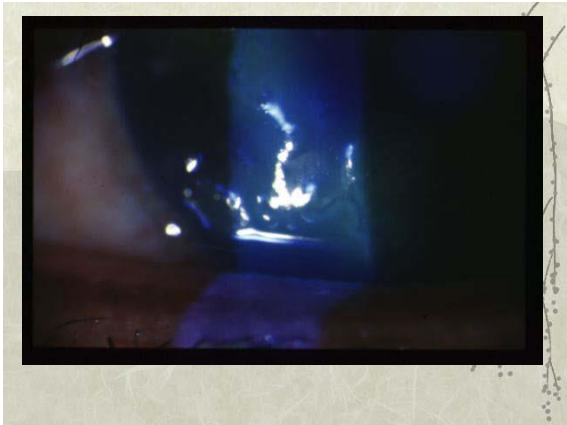
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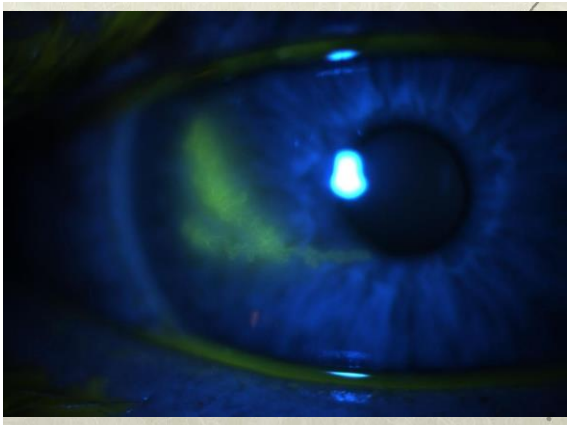
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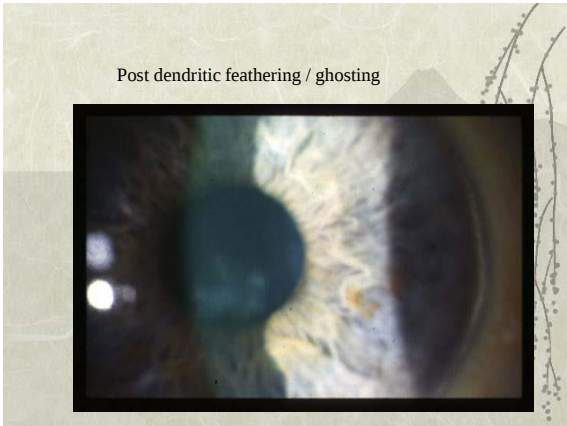
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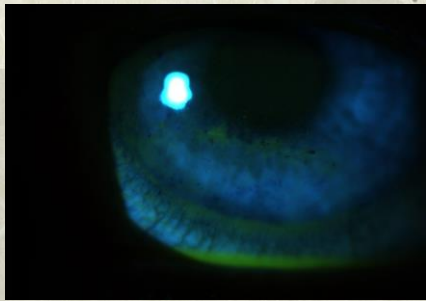
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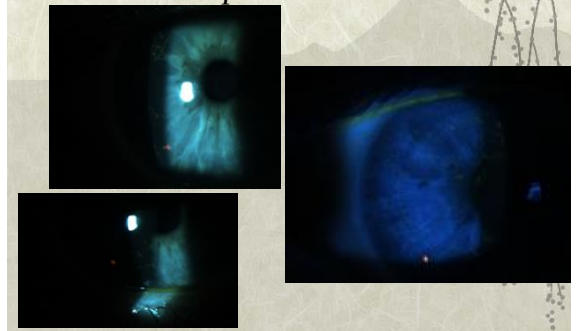
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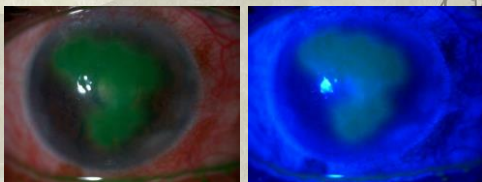
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Exposure pseudodendrite

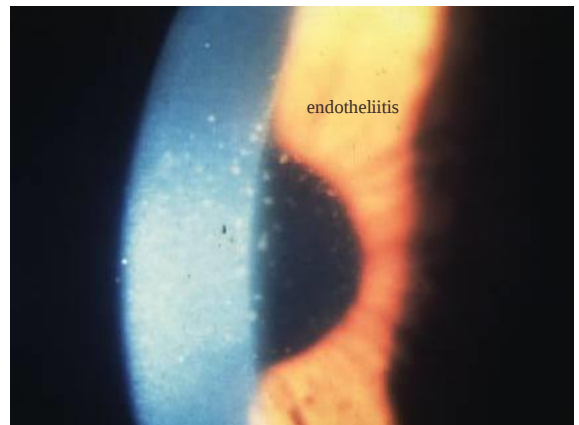
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Zoster pseudodendrites

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Geographic HSK

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endotheliitis

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endotheliitis

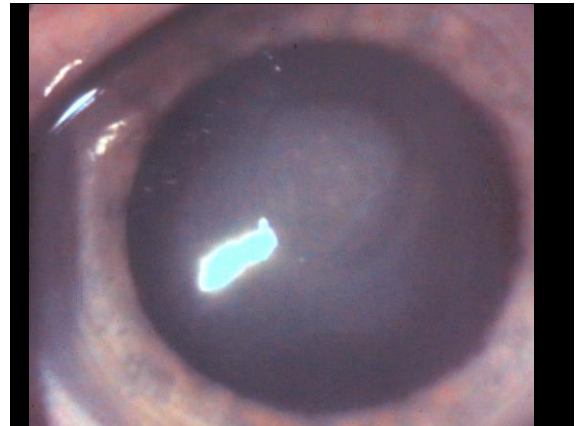
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endotheliitis

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endotheliitis

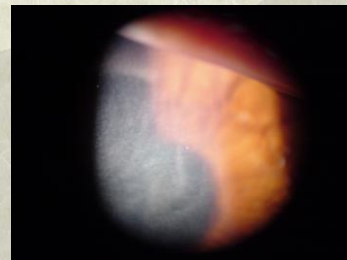
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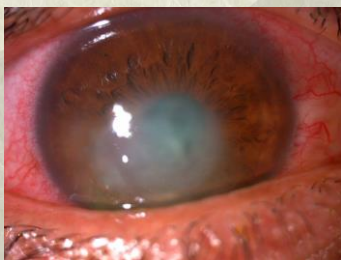
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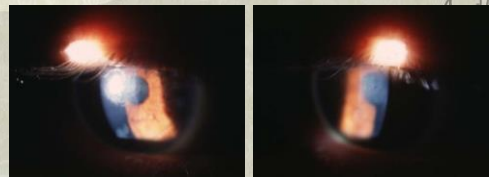
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Disciform stromal keratitis

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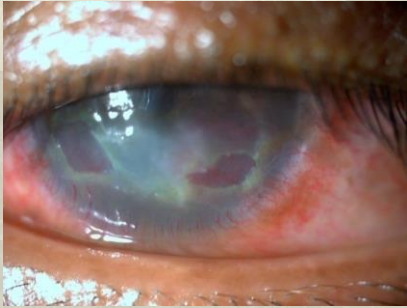
Disciform stromal keratitis

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Stromal keratitis

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Stromal keratitis from Zoster



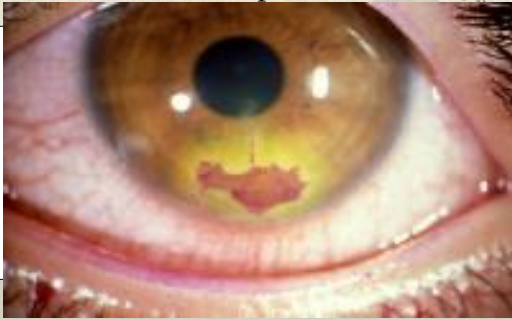
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Neurotrophic Ulcer



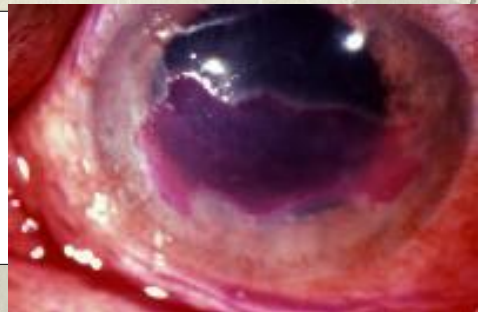
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Neurotrophic ulcer



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Neurotrophic Ulcer



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Treatment of ocular disease



- ❖ Lid lesions and conjunctivitis can often be managed palliatively. Cool compresses and artificial tears helpful and oral agents can be used (typically Acyclovir or Valtrex)

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Treatment

- ❖ Epithelial lesions respond extremely well to topical antiviral therapy. Typically, Viroptic or Zirgan
- ❖ Viroptic is extremely effective against HSV but very toxic to the cornea. Also, very expensive, even generic.

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Treatment

- ❖ Viroptic is utilized Q 2-3h with an ideal maximum of around nine drops per day (toxicity). Once epithelium heals, decrease to QID for about 1 more week
- ❖ Medicamentosa is very common with secondary PEK
- ❖ Alternate with preservative free tears

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Treatment

- ❖ Zirgan is a gel forming drop. May also be effective against adenovirus and is effective against Zoster dendrites.
- ❖ Prolonged contact time, so dosing is less: 5 times per day until the epithelium is intact, then TID for several more days. Also very expensive.
- ❖ Avaclyr 3% Acyclovir ointment. Fera pharmaceuticals. FDA approved in Summer of 2019 but never went to market. Zirgan dosing
- ❖ Older agents that are no longer readily available include IDU (Idoxuridine) and Vira-A (vidaribine) ointment

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Treatment

- ❖ A viable alternative to topical therapy is the use of oral antiviral agents
- ❖ Can be very effective, but may take longer
- ❖ Very, very cost effective if using Acyclovir. Dosing can be 800mg TID (or 400 mg 5 X day). Cost of around \$30.
- ❖ Also available in 200mg pills on most \$4 / \$10 plans. Can run in to issues with supply (need 12 pills per day, and can only fill at that price once per month). Only single daily pill approved

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Oral agents-Simplex dosing

- ❖ **Acyclovir** (200,400,800) : 800mg TID or 400 mg 5 x day
- ❖ Also available in a pediatric suspension
- ❖ **Famvir** (125,250,500) : 500mg TID
- ❖ **Valtrex** (500,1000) : 500 mg TID. (It is a pro-drug of Acyclovir, so more bioavailability)



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Oral antiviral agents

- ❖ Only contraindication is kidney disease
- ❖ Can be toxic in patients with kidney issues
- ❖ In elderly patients with kidney disease, Acyclovir can cause visual hallucinations and "death delusions"

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Oral agents

- ❖ L-Lysine prophylaxis with 500mg daily. Also comes in a 1000 mg / day tablet as well
- ❖ Amino acid
- ❖ Works for cold sores, so....

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Treatment

- ❖ Steroids hasten the progression of and worsen epithelial disease. Can be used for provocative testing if followed very closely
- ❖ However, they are often critical in the management of stromal lesions to prevent scarring

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Treatment

- ❖ Treat stromal inflammation aggressively with topical steroids while concomitantly utilizing oral antiviral therapy

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Treatment

- ❖ Topical steroids also indicated for iritis, trabeculitis, and endothelitis.
- ❖ Many patients with recurrent stromal disease require chronic low dose topical steroids (one drop per day or one drop every other day) to prevent flare ups
- ❖ Need to stay on oral antivirals as well (acyclovir 400mg PO BID or Valtrex 500 QD). Even so, can still get dendrites

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Treatment

- ❖ Neurotrophic keratitis is managed based upon its level of severity
- ❖ Mild cases can be handled with copious lubrication and/or punctal occlusion
- ❖ More severe cases may require a bandage CL or an amniotic membrane.
- ❖ Oxervate
- ❖ In extreme cases resistant to other therapy, possibly tarsorrhaphy or corneal neurotization surgery

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Oxervate .002%

- ❖ Completely unique agent to treat neurotrophic keratitis
- ❖ Dompe pharmaceuticals out of Italy
- ❖ Exactly mimics nerve growth factor proteins
- ❖ Dosed 6 X day for 8 weeks

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Oxervate .002%

- ❖ Retail price of \$12,000 per 8-week supply, but many company programs to help with cost if insurance denies coverage
- ❖ Available only through Accredo specialty mail order pharmacy
- ❖ Can take a long time to obtain approval / denial

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Herpetic Eye Disease Study

- ❖ Originally undertaken to evaluate the usefulness of oral acyclovir in stromal HSV disease
- ❖ Looked at over 700 patients from 1992-1996 with various manifestations of ocular HSV infection

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H.E.D.S. - findings

- ❖ Several interesting findings:
- ❖ Epithelial disease alone did not make future recurrences much more likely, but stromal disease definitely did
- ❖ Stromal disease was 8-10 times more likely over an 18-month study period in those with previous stromal episodes. More episodes = more risk

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H.E.D.S. - findings

- ❖ 400 mg of oral Acyclovir twice per day for one year resulted in a 45% decrease in the rate of recurrence for all forms of ocular complications
- ❖ Over the six months after discontinuation, there was no rebound increase but no continued benefit.....so you have to keep taking it
- ❖ Could there be a role for Cyclosporin A and similar drugs, given the CD4 T cell mediated inflammation?

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Another study

- ❖ Olmstead County, Minnesota (394 patients)
- ❖ Those NOT taking prophylactic antivirals were.....
- ❖ 9.4 X more likely to have epithelial recurrence
- ❖ 8.4 X more likely to have stromal rec.
- ❖ 34.5 X more likely to have lid / conj. rec.

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Prophylaxis

- ❖ So.....
- ❖ At least discuss prophylaxis for all patients with stromal disease and patients with multiple attacks of epithelial disease
- ❖ Acyclovir 400mg PO BID or Valtrex 500 QD
- ❖ Very safe, caution in severe kidney disease, monitor creatine and BUN levels

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Prophylaxis

- But.....
- ❖ Significant issue with resistance to prophylactic drug over time. Must consider this very carefully
- ❖ 30% of bone marrow transplant patients have acyclovir resistance

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