

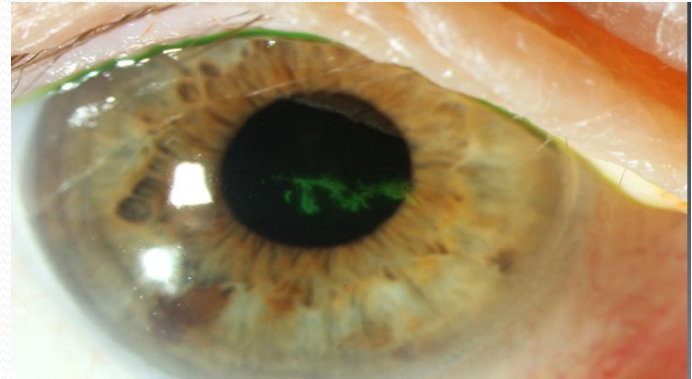
Oral Medications in Eyecare: Antivirals, Antifungals, Anti-allergenics

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Topics

- Herpes Zoster
 - Herpes Simplex
 - Fungal Infections
 - Allergies
-
- Rapid fire cases



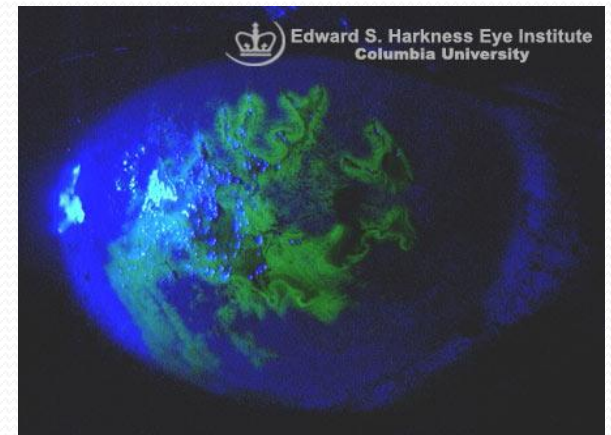
Antivirals: Goals



- Review Herpes Zoster and Herpes Simplex and the use of oral antiviral medications to treat these conditions.
- Discuss the indications and side effects of these medications.
- Present interesting cases which discuss appropriate treatment and management.
- Topical medication treatment options will be included when indicated.

Which antivirals can we use in NY?

- Valacyclovir and Acyclovir
- Limited to treatment of 7 days
- This course will discuss extended use of antivirals beyond the NY State Bill.



Orals in Herpetic Eye Disease

- Valacyclovir (Valtrex)
- Acyclovir (Zovirax)
- Famciclovir (Famvir) *This is not in our bill*

Other medications you will encounter when your patient is treated for post herpetic neuralgia:

- Neurontin
- Lyrica
- Tricyclic antidepressants- amitriptyline, nortriptyline

Oral Antiviral Drugs

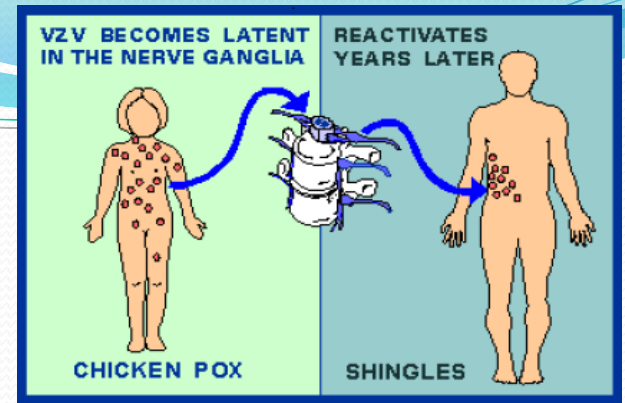
- Zovirax (acyclovir)
 - 200 mg capsule
 - 400 mg pill
 - 800 mg pill
- Valtrex (valacyclovir)
 - 500 mg
 - 1000 mg
- Famvir (famciclovir)
 - 125 mg
 - 250 mg
 - 500 mg



What's the Deal with Herpes Viruses?

- Are a leading cause of human viral disease.....
second to flu, cold viruses,....COVID might equal the flu now...
- About 130 Herpes viruses have been identified
8 infect humans
5 infect the eye:
HSV-1, HSV-2, Varicella Zoster, Epstein Bar, Cytomegalovirus
- What about seropositivity?
Nearly 100% by age 60 but only 1% will develop ocular manifestations in their lifetime.

Herpes Zoster: What is it?



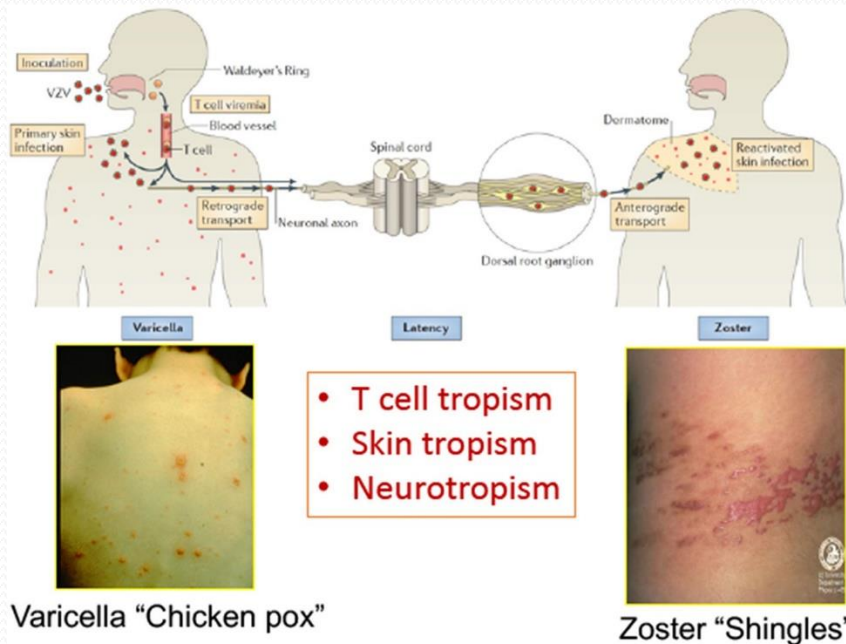
- Also known as “shingles”, is caused by the reactivation of the varicella zoster virus (VZV), the same virus that causes varicella (chickenpox).
- Approximately 99.5% of people born in the United States who are 40 years of age and older have had varicella.
- Only people who were previously infected with VZV (through natural infection that caused varicella or varicella vaccination) can develop shingles.
- Once the primary infection resolves, the virus remains dormant in the dorsal root ganglia.
- VZV can reactive later in a person’s life and cause a painful, maculopapular rash: herpes zoster.

Herpes Zoster

- There are an estimated one million cases of herpes zoster in the United States annually.
- **A person's risk for herpes zoster increases sharply after 50 years of age roughly doubling in each decade after.**
- Most people typically have only one episode of herpes zoster in their lifetime, however second and third episodes are possible.

Basics HZV

- Varicella zoster virus infects the human host when virus particles reach mucosal epithelial sites of entry.
- Local replication is followed by spread to tonsils and other regional lymphoid tissues, where VZV gains access to T cells.
- Infected T cells then deliver the virus to cutaneous sites of replication.
- VZV establishes latency in sensory ganglia after transport to neuronal nuclei along neuronal axons.
- Reactivation from latency enables a second phase of replication to occur in the skin, which typically causes lesions in the dermatome that is innervated by the affected sensory ganglion.



Location in Latent State Herpes Viruses

Virus	Primary Infection	Usual Site of Latency	Recurrent Infection	Route of Transmission
HSV-1	Gingivostomatitis ¹	Cranial sensory ganglia	Herpes labialis, ^{2,3} encephalitis, keratitis	Via respiratory secretions and saliva
HSV-2	Herpes genitalis, perinatal disseminated disease	Lumbar or sacral sensory ganglia	Herpes genitalis ^{2,3}	Sexual contact, perinatal infection
VZV	Varicella	Cranial or thoracic sensory ganglia	Zoster ²	Via respiratory secretions
EBV	Infectious mononucleosis ¹	B lymphocytes	Asymptomatic shedding ^{3,4}	Via respiratory secretions and saliva
CMV	Congenital infection (in utero), mononucleosis ¹	Monocytes	Asymptomatic shedding ²	Intrauterine infection, transfusions, sexual contact, via secretions (e.g., saliva and urine)
HHV-8 ⁵	Uncertain ⁶	Uncertain	Kaposi's sarcoma	Sexual or organ transplantation

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HHV-8 = human herpesvirus 8; HSV = herpes simplex virus; VZV = varicella-zoster virus.

¹Primary infection is often asymptomatic.

²In immunocompromised patients, dissemination of virus can cause life-threatening disease.

³Asymptomatic shedding also occurs.

⁴Latent EBV infection predisposes to B-cell lymphomas.

⁵Also known as Kaposi's sarcoma-associated herpesvirus.

⁶A mononucleosis-like syndrome has been described. Kaposi's sarcoma itself also can result from a primary infection.

Why does Zoster reactivate?

- Age
- Immunosuppressive medical conditions and medications: HIV, chemotherapy, malignancies and chronic corticosteroid use
- Psychological/emotional stress: immune function and susceptibility to infection may be affected by this type of stress

HZV: Dermatitis

- Manifestations:

- Painful vesicular dermatitis localized to a dermatome supplied by a spinal or cranial sensory ganglion
 - Pustules 3-4 days
 - Dry and crusting lesions 10-12 days
 - Can result in scarring (local ischemia secondary to local vasculitis)
- Prodrome: fever and malaise with possible erythema and hyperesthesia in the affected dermatome
- Most common dermatomes: T3-L3, and V

****Pain prior to the onset of the rash is very common and often misdiagnosed****

- Post Herpetic Neuralgia in affected dermatome: weeks-years

Dermatomes Reactivation

Herpes Zoster Rash Follows a Dermatomal Distribution^{1,2}

Dermatomes served by the
TRIGEMINAL NERVE
(Vth Cranial Nerve)

**Ophthalmic
Branch**

**Maxillary
Branch**

**Mandibular
Branch**

**Greater
Occipital
Nerve**
(branch
from
spinal
nerve C2)

spinal nerves
C2 and C3

Trigeminal ~13%

Cervical ~14%

Thoracic ~50%

Lumbar ~13%



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*Homeopathy*360
You think, We Link...



wikipedia



Ramsay Hunt Syndrome Type 2

- **Aka: Herpes Zoster Oticus**
- Symptoms: hearing loss and vertigo
- Involvement of the vestibulocochlear nerve
- Associated with erythematous vesicular rash of the skin of the ear canal or auricle



3 phases of clinical manifestations

- Pre-eruptive phase (pre-herpetic neuralgia)
- Acute eruptive phase
- Chronic phase (Post Herpetic Neuralgia- PHN)

1st Phase: Pre-eruptive Phase

- Sensory phenomena along 1 or more skin dermatomes, lasting 1-10 days (average, 48 hours)
- Phenomena can be noted as: burning pain, itching, pins and needles, tingling or numbness

*****May show to us first as a masquerade syndrome**

- Malaise, myalgia, headache, photophobia, and possible fever

2nd Phase: Acute Eruptive

- Patchy erythema
- Vesicles develop
- Typically unilateral, stopping abruptly at the midline of the limit of sensory coverage of the involved dermatome
- Regional lymphadenopathy



2nd Phase: continued

- Vesicles initially are blister like and clear but eventually cloud, rupture, crust, and involute
- Usually, no scarring when lesions resolve
 - Scarring can occur if deeper epidermal and dermal layers have been compromised
- The pain experienced can be severe
- Zoster Sine Herpete: Severe pain without a vesicular eruption

Resolution

- 10-15 days
- Complete healing of lesions may take up to a month
- Anti viral therapy can reduce the severity and duration of herpes zoster if started **within 72 hours** of the appearance of the characteristic rash
- Early detection and treatment is important

3rd Phase: Post Herpetic Neuralgia

- Persistent pain lasting 30 or more days after all lesions have crusted, pain can be severe and incapacitating
- Ranges from mild short-term itch to long lasting debilitating pain
 - Burning, shooting, sharp, throbbing, tender
- Pain usually is confined to the area of original dermatome involvement
- Pain can persist for weeks, months, or years
- PHN is observed more frequently after cases of Herpes Zoster Ophthalmicus and in instances of upper-body dermatome involvement

Systemic Complications of HZV

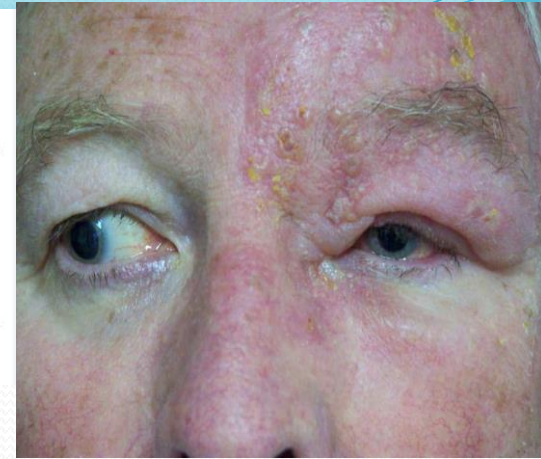
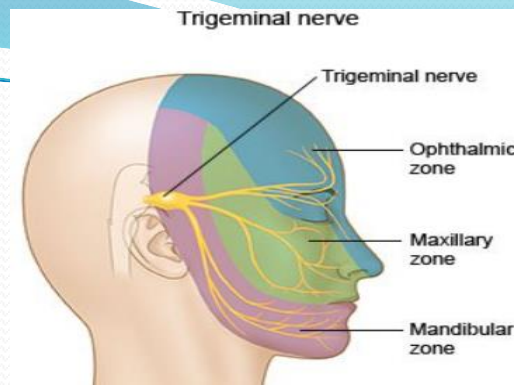
Complication	Manifestations	Site of VZV Reactivation
Aseptic meningitis	Headache, meningismus	Cranial nerve V
Bacterial superinfection	Streptococcus, staphylococcus cellulitis	Any sensory ganglia
Bell's palsy	Unilateral facial paralysis	Cranial nerve VII
Eye involvement (herpes zoster ophthalmicus)	Keratitis, episcleritis, iritis, conjunctivitis, uveitis, acute retinal necrosis, optic neuritis, acute glaucoma	Cranial nerve II, III, or V (ophthalmic [V1] branch)
Hearing impairment	Deafness	Cranial nerve VIII
Motor neuropathy	Weakness, diaphragmatic paralysis, neurogenic bladder	Any sensory ganglia
Postherpetic neuralgia	Pain persisting after the rash has resolved	Any sensory ganglia
Ramsay Hunt syndrome	Ear pain and vesicles in the canal, numbness of anterior tongue, facial paralysis	Cranial nerve VII geniculate ganglia, with spread to cranial nerve VIII
Transverse myelitis	Paraparesis, sensory loss, sphincter impairment	Vertebral ganglia
Vasculopathy (encephalitis)	Vasculitis of cerebral arteries, confusion, seizures, TIAs, stroke	Cranial nerve V

* TIA denotes transient ischemic attack, and VZV varicella–zoster virus.

Is Herpes Zoster contagious?

- People with active lesions caused by herpes zoster can spread VZV to susceptible people (via direct contact)
- The lesions are infectious until they dry and crust over
- People who have not had chickenpox and never received chickenpox vaccine can get infected with VZV from someone with herpes zoster
- **Why is it important to tell your employer about pregnancy and immunocompromise as a doctor?**

HZ Ophthalmicus



- Occurs along the dermatome of the ophthalmic division of the trigeminal nerve (5th Cranial Nerve)
- Function is to provide sensory innervation to the face, divided into 3 main branches: V₁ ophthalmic, V₂ maxillary, V₃ mandibular
- The ophthalmic division: frontal, lacrimal, and nasociliary branches
- HZO represents up to 25% of all cases of HZ

HZO: Hutchinson's sign

- The nasociliary branch innervates the globe
- Classically, involvement of the tip or side of the nose is considered to be a clinical predictor of ocular involvement
- 1/3 of patients without the sign develop ocular manifestations



HZO

- Infection & inflammation can affect any adnexal, ocular, or orbital structure
 - Secondary bacterial infection
 - Eyelid scarring, notching, loss of cilia, trichiasis , cicatricial entropion
 - Scarring and occlusion of puncta and canaliculi
 - Episcleritis or scleritis
 - Keratitis
 - Uveitis
 - Pupil anomalies
 - Glaucoma
 - Occlusive arteritis
 - Acute retinal necrosis
 - Cranial nerve palsies (III, IV, VI)
 - Optic neuropathy

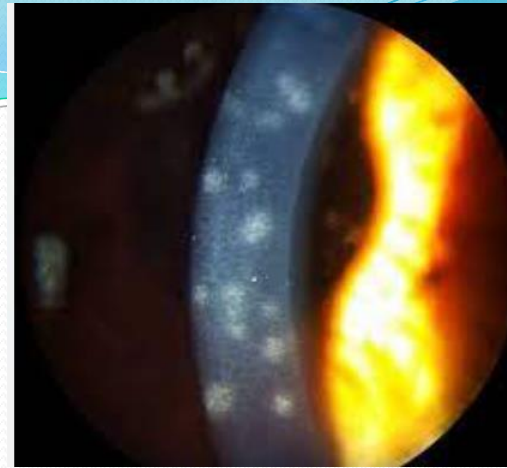


Specific Anterior Segment Findings

- Blepharitis, eyelid edema
- Conjunctivitis
- Keratitis: punctate, pseudo-dendritic, stromal, endotheliitis
- Scleritis, episcleritis
- Uveitis, hypopyon, trabeculitis
- Anterior and posterior synechia, patchy sector iris atrophy
- High or low IOP
- Long term sequelae:
- Severe dry eye
- Lid and corneal scarring
- Neurotrophic keratitis
- Recurrent or smoldering uveitis

HZO: Keratitis

- Punctate epithelial erosions
- Dendritic like epithelial keratitis
- Elevated non-infectious mucoid plaques
- Nummular subepithelial/ant stromal infiltrates
 - Fine granular subepithelial deposits surrounded by a halo of stromal haze
- Stromal keratitis
- Disciform edema
- Neovascularization
- Serpiginous ulceration
- Neurotrophic keratitis- decreased corneal sensation



Corneal sensitivity



- Herpetic infection, simplex or zoster, is a leading cause of neurotrophic keratitis.
- A herpetic infection can lead to impaired corneal nerve function leading to reduced corneal sensation

Testing:

Cornea sensation should be tested prior to the instillation of anesthetic drops

- Can test five locations: four quadrants and center.
- Can also test sensation directly over the lesion
- **We don't test enough !**

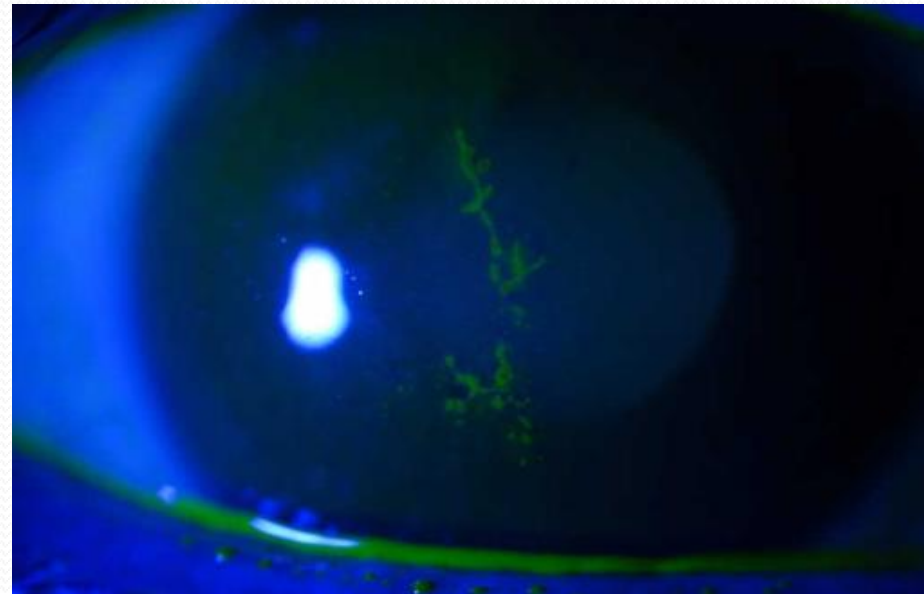
How do we test?

- Fine wisp of a cotton-tip applicator
- Dental floss (non- flavored)
- Cochet-Bonnet Esthesiometer
 - Contains a thin, retractable, nylon filament that extends up to 6 cm in length
 - The longer the filament, the more flexible it is, indicating that more corneal sensation is present
 - Check superior, temporal, inferior, nasal, central

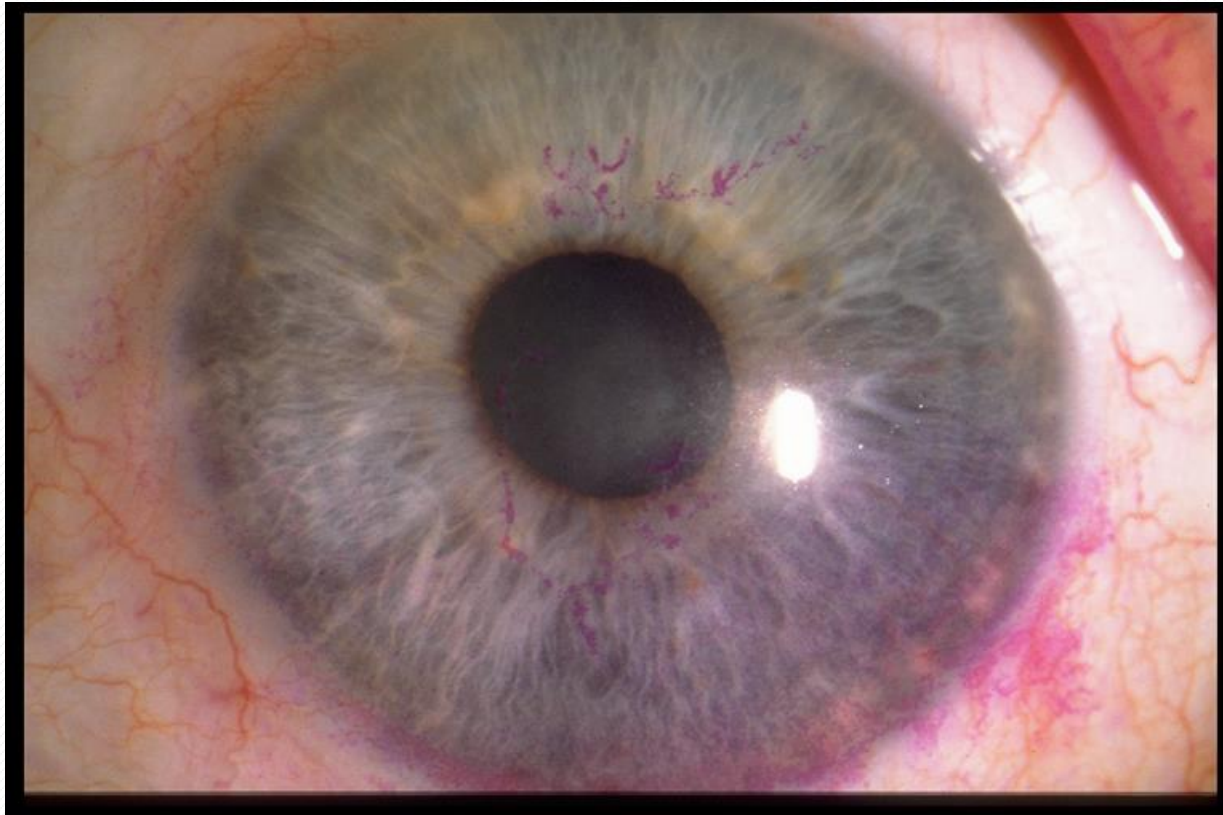


Back to HZV keratitis: “Pseudo” Dendrite

- Swollen epithelial cells in a dendritic pattern
 - “Stuck on” appearance
 - No central ulceration
 - No end bulbs
 - Minimal staining
-
- How does it compare to an HSV dendrite?

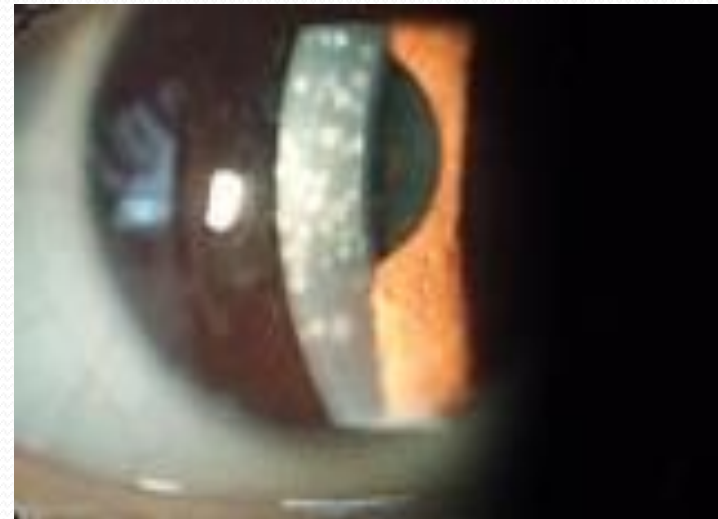
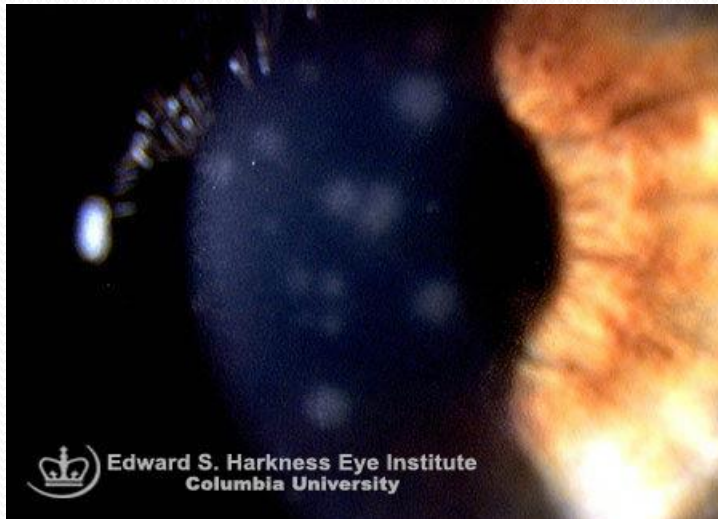


HZV Mucous Plaques: appear grayish, stuck-on, stain with RB



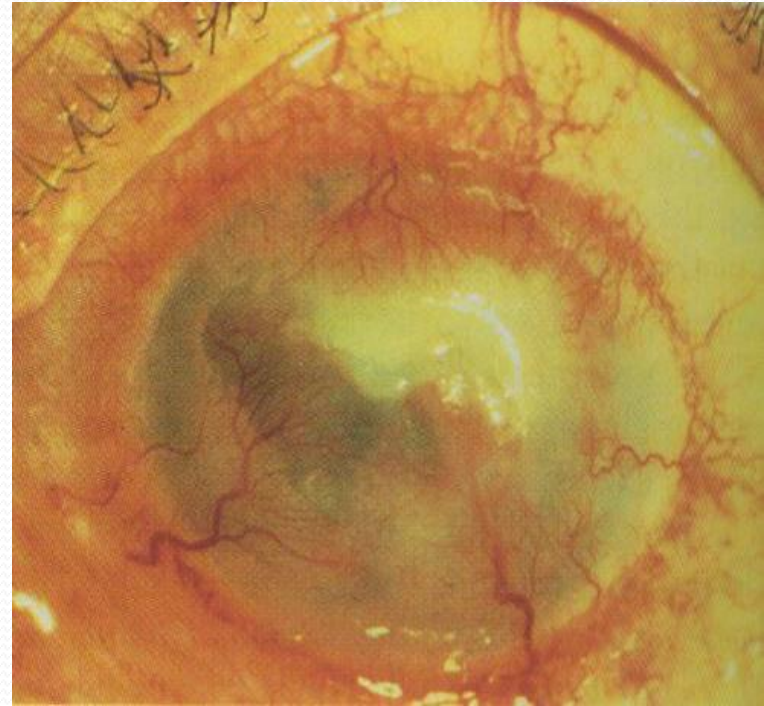
Anterior Stromal: Nummular keratitis

- Coin like opacities, found also in other viral keratitis
- The lesions underlie areas of previous epithelial keratitis
- Represent an immune-mediated stromal reaction to viral antigens



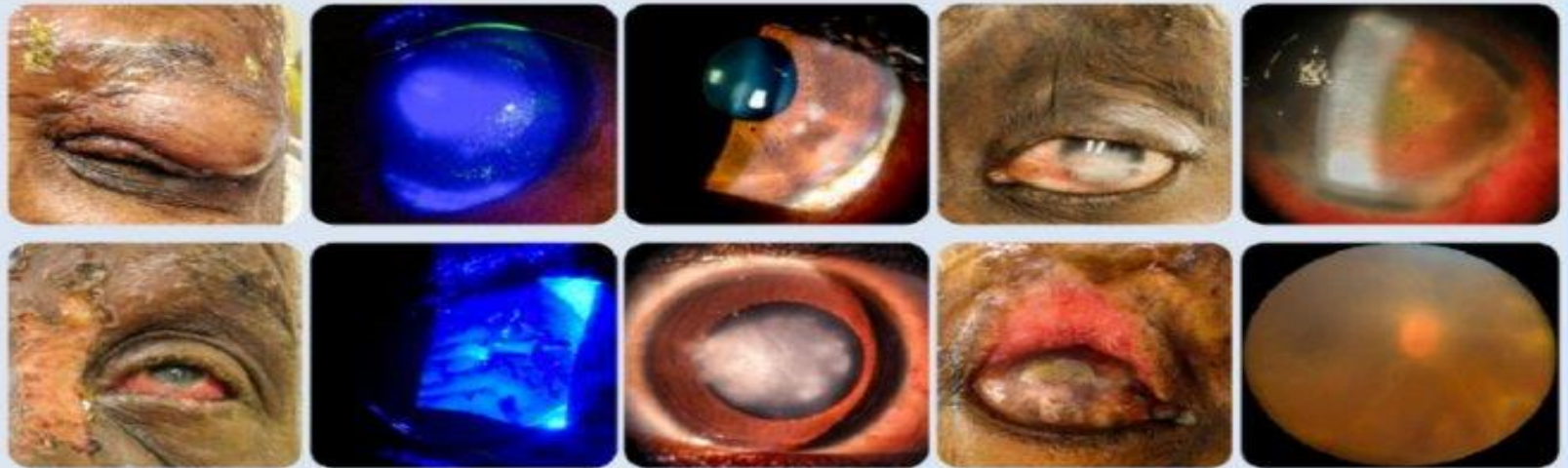
HZO Stromal Keratitis

- Stromal inflammation
 - Vascularization
 - Corneal opacification
 - Bullous Keratopathy
 - Lipid keratopathy
 - Corneal thinning
 - Irregular astigmatism
 - Sterile corneal ulceration and perforation



Hold on...it's not just anterior segment disease

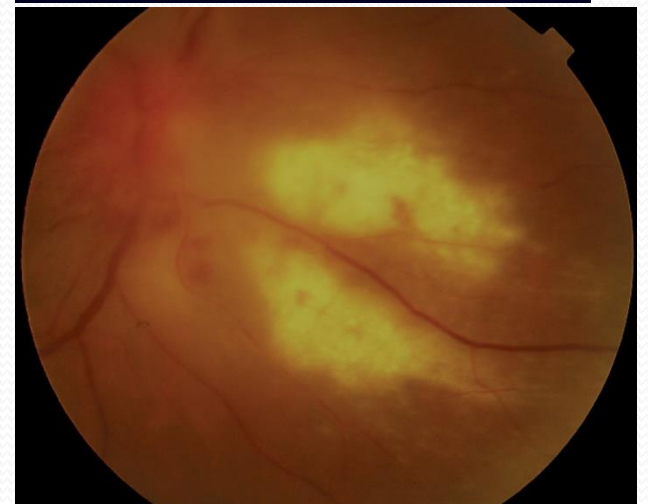
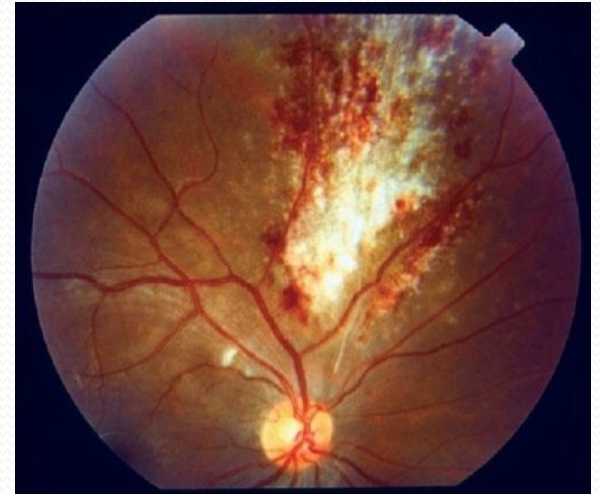
- Dilate your patients!!



Clinical stage	Eye lid and conjunctival involvement Early corneal involvement Corneal involvement Late corneal complications and eyelid deformities Anterior and posterior segment involvement
Clinical signs	Cutaneous macular rash and vesicles with oedema of the superior eyelid Cutaneous macular rash and vesicles and blepharoconjunctivitis Punctate epithelial keratitis: multiple focal swollen corneal surface epithelial cells (Pseudo)dendritic keratitis: elevated plaques of swollen epithelial cells that form a branching pattern Nummular keratitis: multiple fine infiltrates immediately beneath corneal surface Stromal keratitis: deep stromal inflammation with lipid infiltrates Eye lid scarring and neurotrophic keratopathy: generalised corneal epithelial erosions with or without ulceration, calcareous plaque formation, and corneal neovascularisation Severe upper eyelid scarring and corneal opacification due to neurotrophic keratopathy Anterior keratouveitis: localized stromal oedema, keratic precipitates, cells and flare in the anterior chamber, and posterior synechiae Necrotizing retinitis: vitreous inflammation, necrotizing retinitis, and occlusive vasculitis

Evaluation and Management of Herpes Zoster Ophthalmicus

Atypical presentations of Herpes Viruses in posterior segment HSV, HZV, CMV



Retinitis and Choroiditis

- Viral retinitis and choroiditis constitute ocular emergencies.
- Need A/C Tap or Vitreous Tap for confirmation of diagnosis by retina.
- Patients are empirically treated with intravitreal antivirals and IV (inpatient) or outpatient with double Zoster oral dose.

How to manage HZO

- Oral antivirals
- PF Lubricants
- Topical antibiotics
- Topical antivirals?
- Topical steroids
- Cycloplegics
- IOP management

HZO Treatment: Orals

- Oral Acyclovir 800mg 5x / day for 7-10 days
- Oral Valacyclovir 1g TID for 7-10 days
- Oral Famciclovir 500mg TID for 7 -10 days

Oral Anti-Viral Medication Adults

Drug	Mechanism of Action	Bioavailability	Dosing	Side Effects
Acyclovir	Acyclovir interferes with DNA synthesis inhibiting viral replication	10-30% gets absorbed Short $\frac{1}{2}$ life *Metabolized in kidneys	Simplex: 400 mg 5x/day Zoster: 800 mg 5x/day	Overall very safe Nausea, vomiting, headaches, dizziness, confusion
Valacyclovir	Acyclovir pro-drug Equivalent to acyclovir but better for pain management	95% converted to acyclovir* Better bioavailability and longer $\frac{1}{2}$ life	Simplex: 500 mg TID Zoster: 1 g TID	Same as acyclovir
Famciclovir	Inhibits DNA chain elongation It is metabolized to penciclovir where it is active 10-20x as long as acyclovir	Superior to acyclovir*	Simplex: 250 mg TID Zoster: 500 mg TID	Same as acyclovir

Antivirals for NY ODs

Maximum 7 day prescription

Must refer within 3 days of diagnosis

(iii) the following antiviral agents used for herpes zoster ophthalmicus; provided an optometrist shall use or prescribe in maximum, one seven-day prescription; provided, however, if a patient is diagnosed with herpes zoster ophthalmicus and has not already been examined by a primary care physician or other appropriate physician for such viral condition, an optometrist shall refer the patient to a licensed primary care physician, licensed physician specializing in diseases of the eye, or other appropriate physician within three days of such diagnosis:

(1) valacyclovir; and

(2) acyclovir.

Oral Antivirals: What do they do?

Disrupt viral DNA Synthesis in infected host cells while leaving uninfected DNA host cells alone.

- **Start within 72 hours** of onset of skin lesions
 - Reduces viral shedding
 - Decreases systemic dissemination of virus
 - Accelerates lesion resolution
 - Ameliorates the incidence and severity of most common ocular complications: dendritic keratitis, stromal keratitis, and uveitis
 - Reduced severity and duration of acute neuralgia
 - May reduce duration but not severity of post herpetic neuralgia



Antiviral Side Effects

- Generally, well tolerated
- Category B pregnancy and lactation
- GI disturbances*
- Nausea *
- Vomiting
- Abdominal pain
- Headache
- Dizziness
- Precaution in renal impairment
 - Adjust dosage* co-manage with PCP
 - If your patient has renal impairment suggest contacting primary care doctor regarding renal dose
 - Checking BUN and Creatinine is suggested

HZO Treatment Options

With oral antiviral in place:

- Cutaneous lesions
 - Moist compresses
 - Topical antibiotics (avoid secondary infection)
 - Epithelial lesions:
 - SPK: PF lubrication, antibiotic ointment
 - Corneal pseudo-dendrite ? Should we add antiviral drops...no real benefit
 - Stromal, endothelial keratitis and uveitis: topical corticosteroids and cycloplegics
 - Neurotrophic ulcerations
 - PF art tears
 - Bandage contact lenses
 - Amniotic membranes
 - Autologous serum
 - Oxervate
 - Surgical considerations for significant ulcerations: tarsorrhaphy, conjunctival flap, PK
- 



Follow-up

- Ocular involvement present: Every one to seven days depending on clinical circumstances (what you are treating).
- Patients without ocular involvement: follow closely.
Eye involvement may be delayed*
- Be aware of potential relapses in old..... old ... or immunocompromised (HIV, Cancer).... Steroid taper may cause relapse.

Post-herpetic neuralgia (PHN)

- PHN occurs in up to 30% of patients with HZO
- Treatment options:
 - Capsaicin 0.25% cream BID
 - Topical lidocaine patch
 - Neurontin (gabapentin)
 - Lyrica (pregabalin)
 - Tricyclic antidepressants (amitriptyline)
 - Oxycodone

What's new? What about vaccines?

- Mean age of onset of HZV is now 52
 - CDC recommends healthy adults 50 and over
 - **SHINGRIX**- has replaced ZOSTAVAX[®] (live vaccine, 50% effective, 1 dose, decrease efficacy after 4-5 years)
 - Shingrix contains an inactivated form of the varicella-zoster virus (recombinant vaccine)
 - Provides strong protection against shingles & post herpetic neuralgia
 - 90+ % effective 2 doses: IM 2-6 months apart
 - Efficacy good 7-8 years
- * We should be advocates*

Possible ways you will be involved in HZO

- **Diagnosis-** you are the first person to diagnose Herpes Zoster * presentation or symptoms may be subtle*
- **Consultation-** primary care doctor sends to you to evaluate a patient who has already started treatment

Clinical Case 1

- 50 year old asian male
- Referred by a dermatologist same day for corneal evaluation due to Shingles
- Had tingling and pain along left forehead a week ago
- Skin lesions appeared a couple of days ago
- No pertinent medical hx
- Currently using Chinese herbal ointment over lesions
- **Anything else you want to ask?**

Additional information

- Eye is red but no pain, no photophobia, good vision
- Pt reports tremendous stress recently
- Never reports never had the chicken pox
- Not sure if he had vaccine as a child
- Photo shows: vesicular rash on forehead respecting the vertical midline

Findings

- Va cc: OD 20/20 OS 20/20
- PERRL- APD
- EOMS full
- SLE: LUL swelling with vesicles on UL
- Cornea: cl, (-) Fl (-) FL or RB staining
- Conj: Grade 2+ diffuse injection
- AC: D & Q
- Iris: flat, clear

Findings

- Tap: 16
- Dilation:
- No vitritis
- Healthy ONH, mac clear, normal vasculature
- Retinal periphery clear

What would you do?

- How would you treat the patient?
- Patient education?

How do we treat?

- Pt given Valtrex 1 gram TID and triamcinolone ung TID by dermatology
- Do we need to Rx anything else?
- When to see pt back?
- Triamcinolone (corticosteroid cream used for eczema, dermatitis, allergies, rash)

Treatment Options

- Oral corticosteroid in combination with anti-viral may reduce acute pain of herpes zoster.
- The use of corticosteroids for the treatment of HZO is controversial.
- However, we are not licensed in NY State to prescribe oral steroids.
 - Another reason to co-manage.

Back to our Patient....

- He did not show for his f/u
- Wife reported he seemed confused, and memory was deteriorating and was admitted to hospital
- +Photophobia and bothered by loud sounds
- No fever, HA, nausea, vomiting, no chest pain, palpitations, shortness of breath, abdominal pain, diarrhea, urinary symptoms

Hospital Results & Diagnosis

- Lumbar Puncture: CSF: Glucose 73
- Protein 62
- Lymphocytes 87
- HSV-1 and HSV-2 PCR was negative
- Negative blood and CSF cultures
- Negative HCV, HBV, HIV, PPD
- MRI: inflammation of meninges
- **Aseptic Meningitis**
- **Tx: IV acyclovir x 14 days**
- **On hospital discharge, pt's mental status returned to baseline**

Aseptic Meningitis

- Characterized by serous inflammation of meninges
- Clinical manifestations vary, with headache and fever
- Other neurologic complications: associated with HZ:
 - Cerebellar ataxia
 - Encephalitis
 - Transverse myelitis
 - Guillain-Barré syndrome

Moral

- Make sure co-manage with PCP.
- HZO is typically a benign course, but complications can be serious.

Clinical Case 2

- 75 yo Caucasian F with acute unilateral eye pain OS , redness, and photophobia. Otherwise, healthy.
- Visual Acuity
- OD 20/20 OS 20/70
- IOP 14/25 mm HG



Source: Uddawa RB, Smith HA, Pearson FX, Chaudry HS. The Color Atlas of Family Medicine, Second Edition. www.accessmedicine.com Copyright © Elsevier Health Sciences Company, Inc. All rights reserved.

Exam

	OD	OS
Lids/Lashes	Normal	Erythema
Conjunctiva	White and Quiet	2+ injection
Cornea	Clear	Small and medium KPs, some pigmented diffusely, 1+ edema with DME, no dendrite
A/C	Deep and Quiet	2+ cell (wbc's) 1+ flare
Iris	Round, reactive	Few TIDs
Lens	1+ NS	1+ NS
Vitreous	Clear	Clear

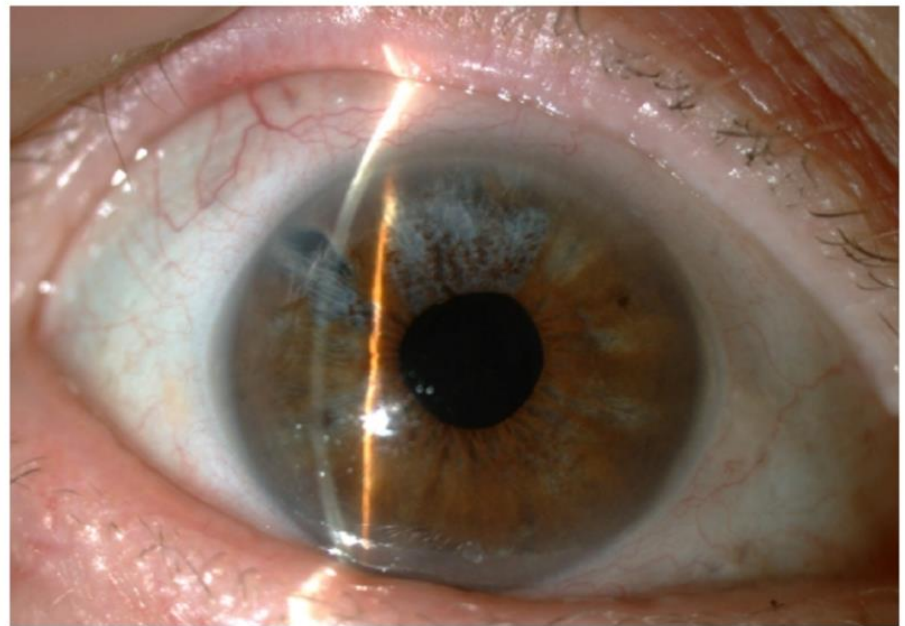
Case Continued

- Differential Diagnosis:
- Herpetic (CMV, HZV, HSV)
- FHI (Fuchs)
- HLA-B27 associated
- Post surgical or trauma

By the way.....Zoster rash on face respecting vertical midline

DIAGNOSIS : HERPES ZOSTER OPHTHALMICUS (HZO)

- Keratouveitis
- Classic findings in herpetic anterior uveitis
- High IOP
- Iris Atrophy
 - Varies in size shape and location
- Decreased corneal sensation
- KPs
- Recurrent iritis in one eye



Lab workup

- Associated with vesicular rash V₁ distribution?
- NONE!
- Caveat: young patients with HZV- check HIV
- You must dilate this patient

Summary: Management for HZO

- Oral antivirals :
 - Acyclovir (Zovirax) 800 mg 5x /day OR
 - Valacyclovir (Valtrex) 1000 mg TID for 7-10 days
 - First 72 hours most effective.
- If pseudodendrite present, no need to add a topical antiviral, oral antiviral is sufficient.
- Topical steroids based on degree of anterior chamber inflammation and corneal edema.

Herpes Zoster Eye Disease Study (ZEDS)

- NYU sponsored- ongoing August 23, 2017- estimated January 15, 2024
- Drug: Masked Placebo
- Drug: Masked Oral Valacyclovir
- Objective : to determine whether prolonged suppressive oral antiviral treatment with valacyclovir reduces complications of Herpes Zoster Ophthalmicus (HZO) thereby improving clinical outcomes.

Goals of ZEDS

- The primary aim:
 - Test the hypothesis that suppressive antiviral treatment for 12 months with oral valacyclovir 1000 mg daily reduces the rate of new or worsening dendriform epithelial keratitis, stromal keratitis, endothelial keratitis or iritis compared to placebo, at 12 months as the primary endpoint, and at 18 months
 - Including 6 months of follow-up after treatment, as a secondary endpoint, in patients with HZO who have had an episode of one of these disease manifestations during the year prior to enrollment.
- The second aim:

Test the hypothesis that suppressive treatment for 12 months with oral valacyclovir 1000 mg daily reduces the severity and duration of postherpetic neuralgia (PHN), compared to placebo.

Now to: Herpes Simplex Virus

- Approximately 400,000 to 500,000 people affected by ocular HSV in USA
- 48,000 active cases of HSV eye disease annually
 - 20,000 new cases
 - 28,000 recurrent cases

HSV keratitis: Leading cause of corneal blindness in the US -HSV-1 (65%)



Global Ocular HSV



- 1 million new cases
- 9 million recurrent episodes
- 1 million people visually disabled worldwide
- Avg 4 visits for first episode/ 6 visits for recurrent episodes
- Estimate 58 million days of work are lost treating ocular HSV worldwide (444K US)
- Mean time of resolution
 - 17.6 days first episode
 - 28.4 days recurrent episodes

HSV 1 vs. HSV 2



- Spread by direct contact of skin or mucous membranes with infectious secretions (saliva or genital)
- 50%-90% of adults have Ab to HSV-1
- HSV-1: orofacial, ocular
- HSV-2: sexually transmitted: genital *(may have HSV-2 in eye via contact with infected secretions or via the birth canal)

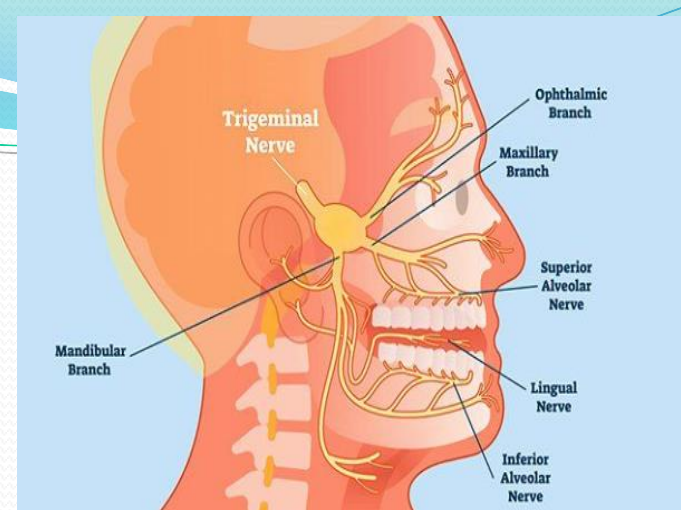


HSV Laboratory Evaluation

- Diagnosis: primarily clinical
- Lab evaluation:
 - Serologic tests for neutralizing or complement-fixing immunoglobulins may show a rising Ab titer during primary infection, but of are no assistance for recurrent disease
 - The absence of Ab may be helpful, as opposed to the presence of such Ab, to rule out disease



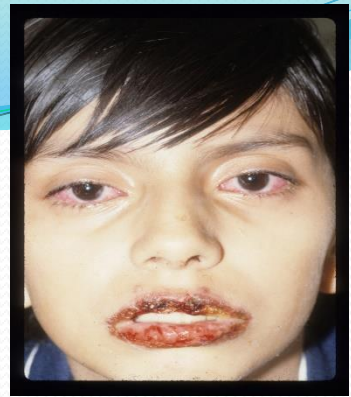
Primary Infection



- Typically, primary herpes is pediatric
- Spread by direct contact or secretions
- Initially, the virus enters the eye and travels to the trigeminal ganglion, where it replicates and becomes latent.
- When it later travels to the cornea, HSV causes episodic ocular disease, but it remains in the trigeminal ganglion for life.



HSV: Primary Outbreak



- **The primary outbreak is typically mild or subclinical (90% of people are asymptomatic), and goes unrecognized**
 - **Fever, lymphadenopathy, manifests as nonspecific upper respiratory tract infection**
- **Primary HSV -1 occurs most commonly on skin and mucosal surfaces innervated by cranial nerve V**

Primary HSV: Ocular

- Mainly manifests as blepharitis, conjunctivitis, less commonly, keratitis, 90% unilateral
- Pre-auricular lymphadenopathy
- Cutaneous vesicles on eyelid skin or margin
- Unilateral blepharoconjunctivitis
- Follicular conjunctivitis
- Epithelial keratitis
 - Scattered punctate epithelial lesions
 - Epithelial dendrites
- Stromal keratitis develops in <10% of patients with primary infection



HSV Blepharoconjunctivitis

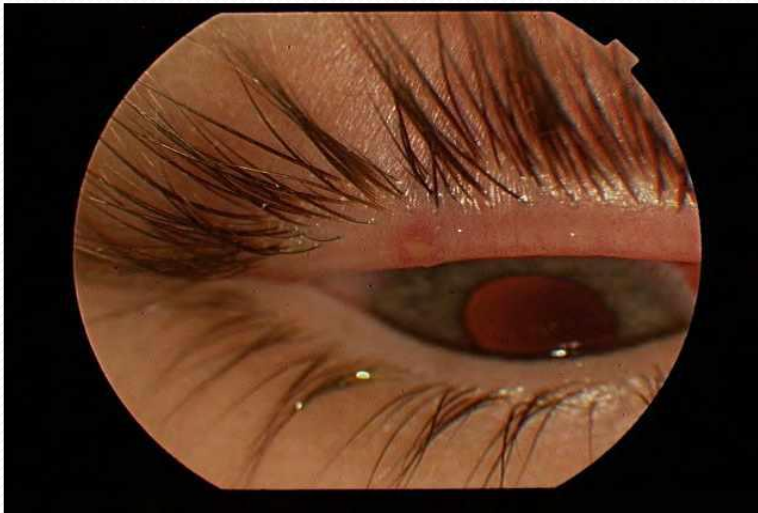
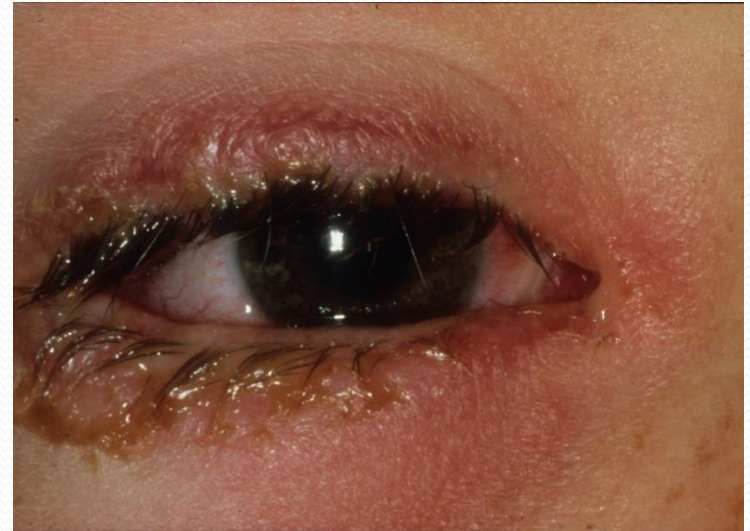
- Blepharoconjunctivitis:

- Vesicular / pustular / ulcerative lesions in periocular area
- Can have associated conjunctivitis



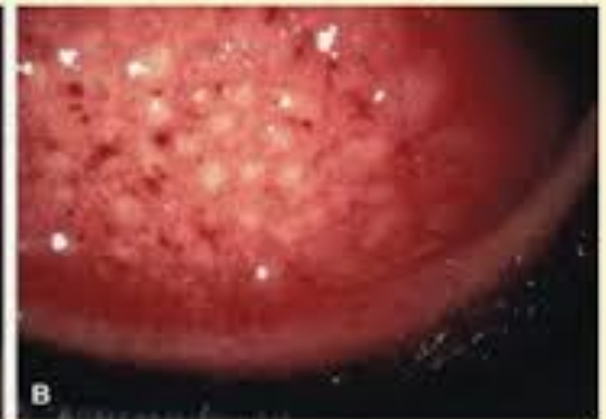
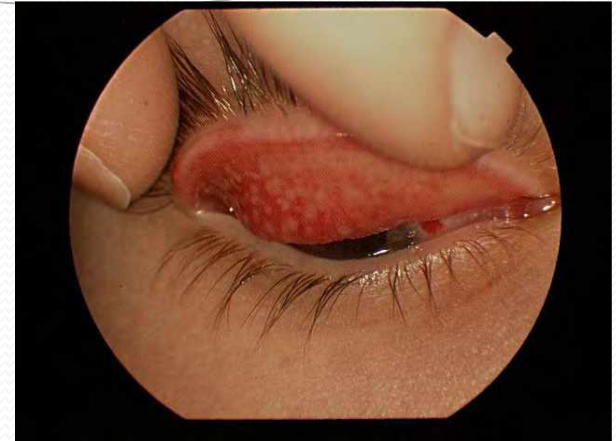
Ocular HSV: Blepharconjunctivitis

- Erythematous lid vesicles can rupture to form ulcers
- Can be painful



HSV

- Conjunctivitis
 - Follicular
 - Unilateral typically
 - May have preauricular node
 - Can form membranes



Is it HSV or Pink Eye?



- We may mistake a primary HSV infection for “pink eye”
- Typical conjunctivitis caused by viruses such as adenovirus, tend to be bilateral
- HSV is usually unilateral
- Consider pediatric HSV when a patient has unilateral recurrent disease

Primary HSV: Specific treatment: Blepharoconjunctivitis

- Typically self limiting, however treating can reduce severity, duration and possible spread
- Skin, outside lid lesions tx options:
 - Antibiotic ointment BID-QID
 - Ganciclovir 0.15% gel
- Blepharoconjunctivitis tx options:
 - Topical or oral antivirals 7-10 days
 - Trifluridine 1% gtts
 - Ganciclovir 0.15% gel 5 x day
- When to see pt back?
- Monitor in 2-3 days, then 1 week, then another week



What about reactivation?

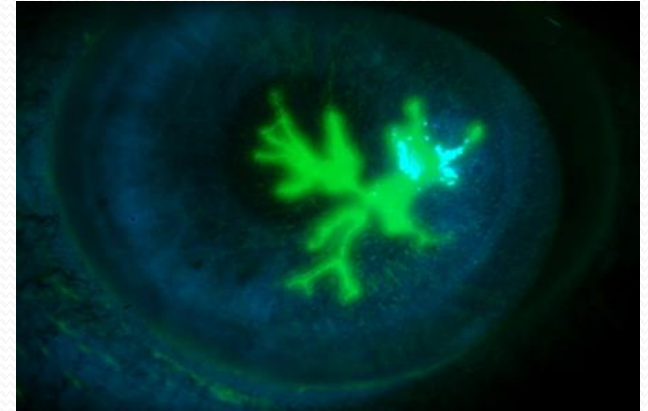
After primary infection, the virus becomes latent in the trigeminal ganglion or **cornea**

- Most clinical ocular infections are manifestations of virus reactivation
- The majority of cases are unilateral, with recurrences affecting the same eye.
- Bilateral disease (not necessarily concurrent) occurs in 1-12% of cases and is more common in patients with atopy or other immune issues

Triggers:

- Stress*, UV radiation, hormonal changes, fevers, corneal trauma, surgery
- Lesions are more common in the immunocompromised (i.e. recent organ transplant or HIV patients)
- Psychological stress, although commonly mentioned, wasn't found to be a trigger by the Herpetic Eye Disease Study

HSV: How does it affect the eye in reactivation?



- Keratitis: epithelial (punctate, dendritic, amoeboid, geographic ulcers), stromal, disciform, endotheliitis
- Trabeculitis and iridocyclitis
- **Epithelial disease is usually caused by actively replicating virus.**
- **Stromal disease typically caused by immunologic mechanisms.**
- **Making the distinction is important because the treatments are different!**

HSV: Epithelial Keratitis: “Tree branching ulcers”

Ocular irritation, redness, photophobia, watering, blurred vision

Keratitis: central desquamation results in a dendrite

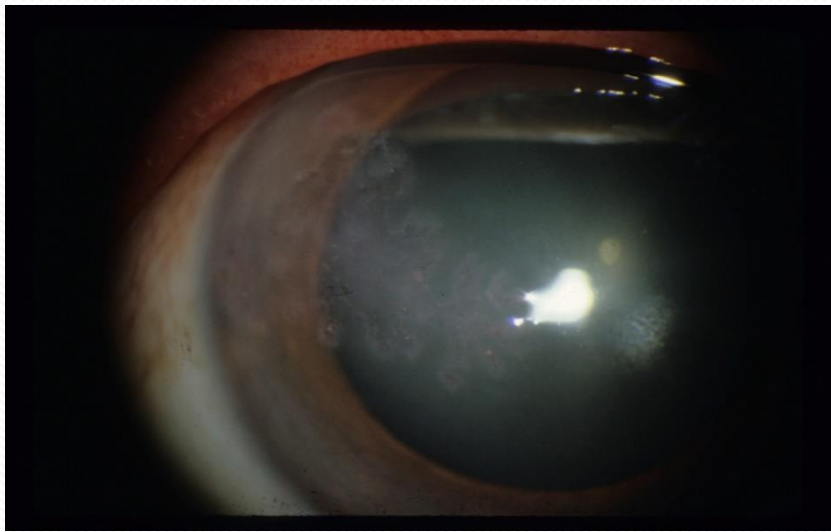
- Swollen opaque epithelial cells arranged in a coarse punctate or stellate pattern

With central ulceration and terminal end bulbs

- Dendrite can be central or peripheral
- Edges of ulcer (terminal end bulbs) stain with Rose Bengal or lissamine green, base stains with Fluorescein
- **Corneal sensation is reduced***
- Test corneal sensitivity prior to anesthetic



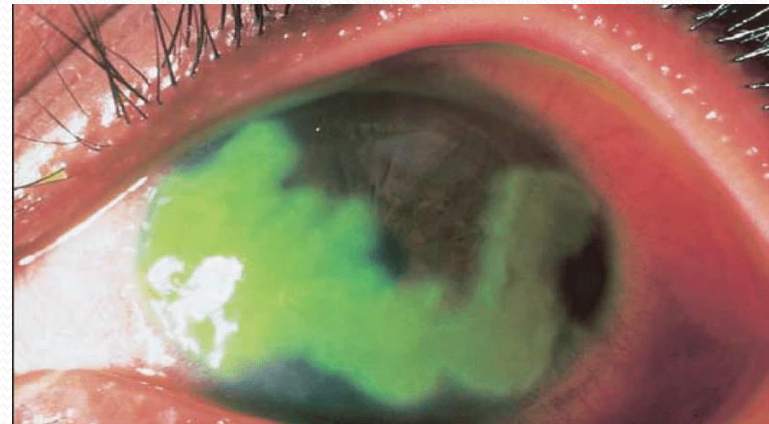
HSVK: many forms



Ameboid



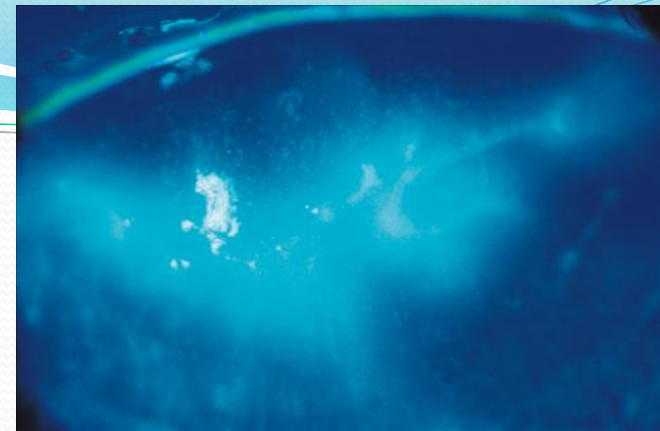
Geographic



HSV Keratitis: Trouble Making the Diagnosis?

- If diagnosis is unclear: can consider initially observe for a day or two with PF art tears and/or antibiotic cover.
- Natural history of untreated epithelial keratitis is to resolve over 7-14 days.
- Dendriform Keratitis: should consider other differentials.

Epithelial HSV Differential Diagnosis



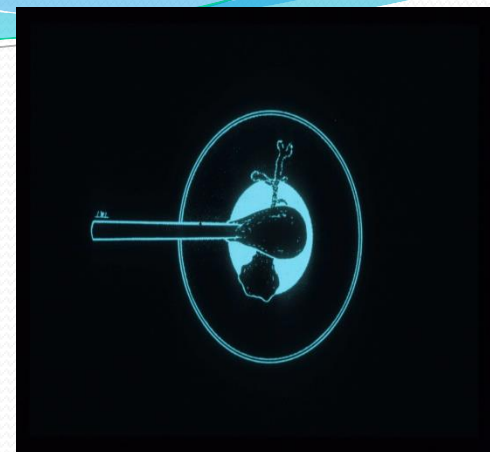
- Herpes Zoster virus
 - Adenovirus, EBV
 - Epithelial regeneration line
 - Neurotrophic keratopathy (post herpetic, diabetes)
 - Soft contact lens wear related keratitis
 - Topical medications (medicamentosa)
 - Acanthamoeba
 - Thygeson's superficial punctate keratitis (atypical)
 - Limbal stem cell deficiency
 - Epithelial basement membrane dystrophy
 - Whorl like keratopathy from medications
-
- Dendriform lesions in CL user without prior HSV - consider Acanthamoeba keratitis: +pain

Acanthamoeba

- Ubiquitous protozoa in freshwater and soil
- Resistant to killing by freezing, desiccation, and chlorine
- Exist as mobile trophozoites or dormant cysts
- Laboratory diagnosis:
 - Scrapings or corneal biopsy
 - Giemsa, PAS, calcofluor white, acridine orange stains
 - Culture: Non-nutrient blood agar plate with *E. coli* overlay
buffered charcoal yeast extract agar
 - Confocal Microscopy – identifies cyst forms

HSV: epithelial - Treatment

- Consider debridement
- **Topical OR oral treatment, not both**
- Topical antiviral therapy
 - 1% Trifluridine (Viroptic) Q2H, generic avail
 - For first few days until epi healed (up to 7 days) then 4-5 x day
 - Max 9 x day, max 21 days
 - Viroptic toxic to cornea
- Topical Ganciclovir 0.15% ophthalmic gel (Zirgan), no generic
- 5 x day x 5 days (until epi healed), then TID up to 7 days
- Consider cycloplegics if pain, photophobia, AC rxn
 - Cyclopentolate 1%
 - Homatropine 5%
- **No steroids!**



Toxic Effects of Topical Antivirals

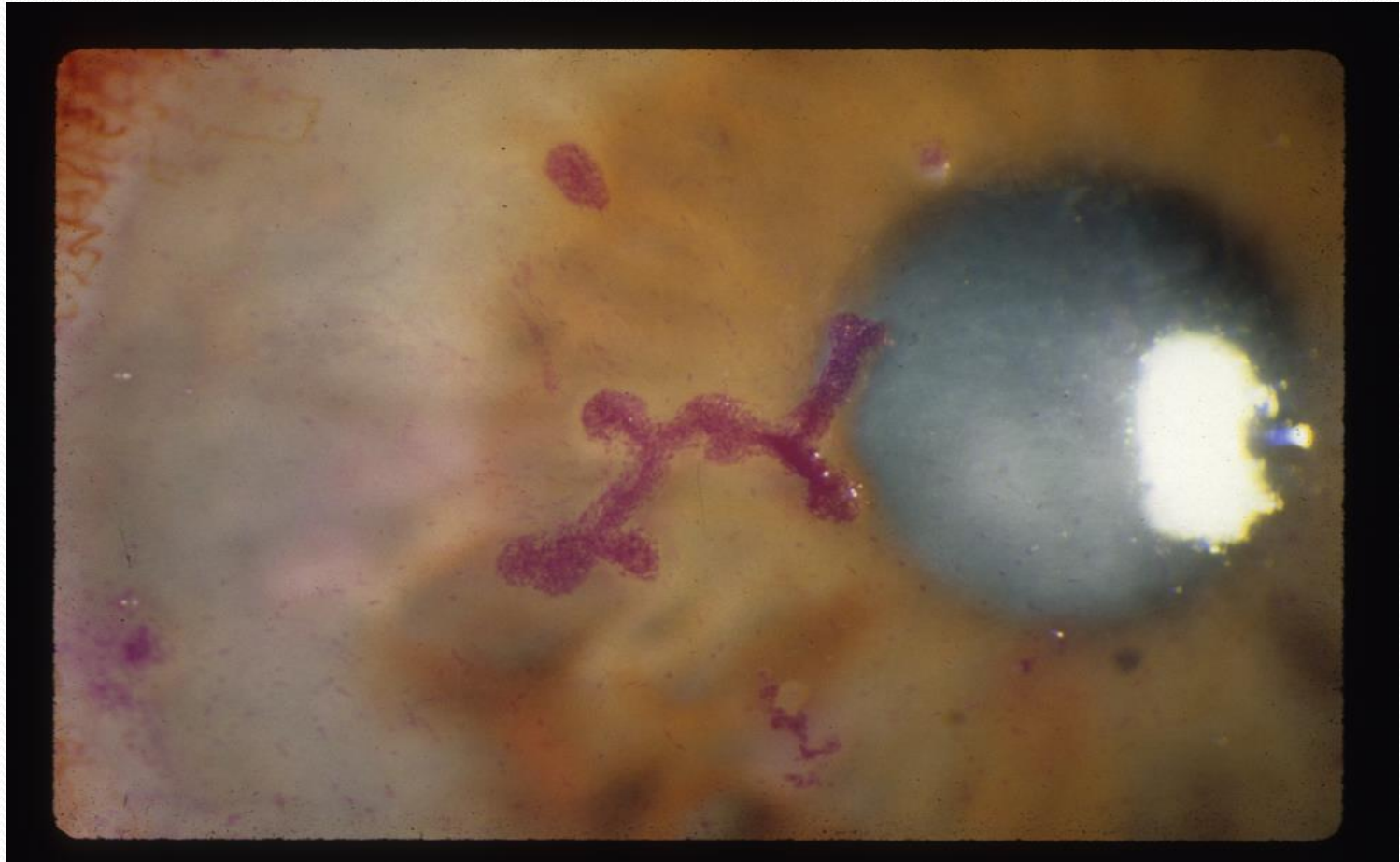
- Follicular Conjunctivitis
- Cicatricial Conjunctivitis
- Epithelial toxicity
- Punctal stenosis
- Contact dermatitis



Take Note:

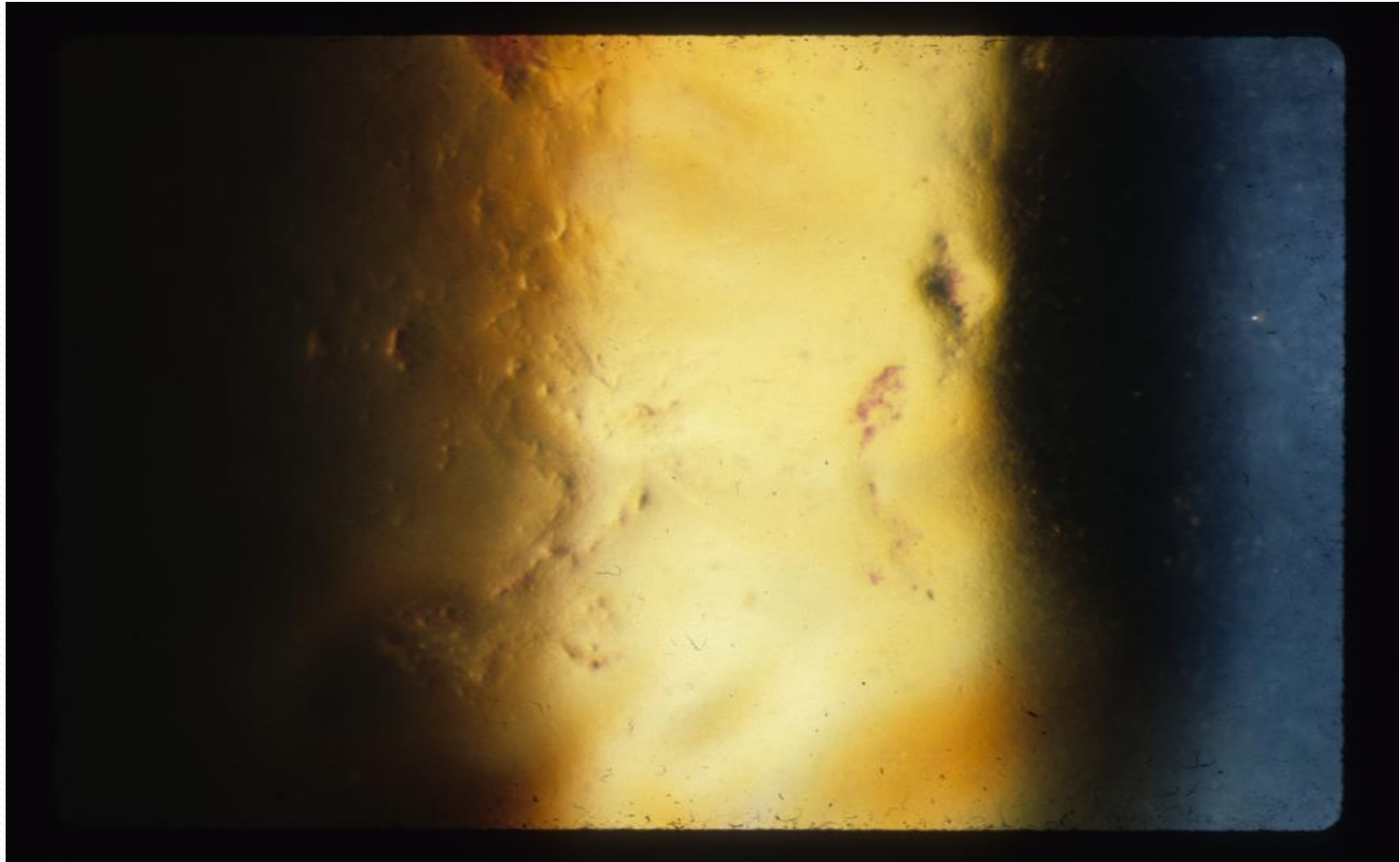
- Most dendritic lesions are cured in less than two weeks.
- If it's past two weeks:
 - The virus may be resistant to your treatment
 - It's not herpetic
 - OR you are dealing with corneal toxicity which can look herpetic keratitis !

Debridement



Pre-Debridement

Post Debridement



Post-Debridement

Orals in HSV keratitis

- Oral antivirals
 - Decreases duration of viral shedding and decreases time to healing
 - Consider especially if:
 - Significant keratitis
 - Compliance is an issue with drops
 - Immunocompromised patient
 - Acyclovir 400 mg 5x/day
 - Valacyclovir 500 mg BID-TID
 - Famciclovir 250 mg BID-TID
-
- Good ocular penetration, reduces corneal toxicity of topical meds, may be easier to use than topical
 - Some add topical antibiotic cover with oral antiviral



Summary: Oral Acyclovir for HSV Keratitis

- Has been reported to be as effective as topical antivirals for infectious epithelial keratitis with the added advantage of no ocular toxicity.
- The use of systemic acyclovir may be preferred over topical agents for patients:
 - with preexisting ocular surface disease who are at high risk for toxicity from topical meds,
 - who are immunocompromised
 - pediatric patients
- May prescribe both oral and topical antiviral agents for immunocompromised pts.

Dosing? Adults

Drug	Mechanism of Action	Bioavailability	Dosing	Side Effects
Acyclovir	Acyclovir interferes with DNA synthesis inhibiting viral replication	10-30% gets absorbed Short $\frac{1}{2}$ life *Metabolized in kidneys	Simplex: 400 mg 5x/day Zoster: 800 mg 5x/day	Overall very safe Nausea, vomiting, headaches, dizziness, confusion
Valacyclovir	Acyclovir pro-drug Equivalent to acyclovir but better for pain management	95% converted to acyclovir* Better bioavailability and longer $\frac{1}{2}$ life	Simplex: 500 mg TID Zoster: 1 g TID	Same as acyclovir
Famciclovir	Inhibits DNA chain elongation It is metabolized to penciclovir where it is active 10-20x as long as acyclovir	Superior to acyclovir*	Simplex: 250 mg TID Zoster: 500 mg TID	Same as acyclovir

Dosing of Acyclovir in children

AGE	Treatment dosing TID	Prophylactic dose BID
Infants up to 18 months	100 mg (2.5ml)	100 mg (2.5ml)
Toddlers (18 mo.-3 years)	200 mg (5ml)	200 mg (5 ml)
Young children (3-5 years)	300 mg (7.5 ml)	300 mg (7.5 ml)
Older children (6 and older)	400 mg (10 ml)	400 mg (10 ml)

Evidence Based Medicine

- Before we move on to more details about HSV treatment...
- Let's review some evidence...
 - HEDS I & HEDS II



The Herpetic Eye Disease Study: HEDS

- Multi-armed set of five randomized, placebo-controlled trials designed to determine best treatments and prophylaxis for HSV keratitis and one epidemiologic study that investigated risk factors.
- Focused on the use of oral acyclovir to prevent HSV epithelial and stromal keratitis and provides valuable epidemiologic data, particularly with regard to recurrence rates.
- HEDS multi-center randomized trial enrolled 703 patients with at least one episode of ocular HSV in the previous 12 months and no disease activity within the previous 30 days.
- Patients received either 400 mg of acyclovir twice daily or placebo. Regardless of symptoms, ocular exams were performed at 1, 3, 6, 9, and 12 months after the start of treatment.

HEDS I

Objectives:

- Efficacy of topical corticosteroids with topical trifluridine in treating simplex stromal keratitis.
- Efficacy of oral acyclovir with topical trifluridine and topical steroid in simplex stromal keratitis
- Efficacy of oral acyclovir with topical trifluridine and topical steroids in simplex iridocyclitis.

Results:

- **Stromal keratitis**
 - Topical steroids with topical trifluridine provided faster resolution than trifluridine alone. A delay in steroid treatment not critical visual acuity outcome.
 - No benefit to adding oral acyclovir to topical steroid and topical trifluridine.
- **Uveitis**
 - Stopped prematurely due to recruitment difficulties.
 - Data suggests there is a benefit of adding oral acyclovir to prophylactic treatment regimen of topical steroids and trifluridine

HEDS II HERPETIC EYE DISEASE STUDY

ACYCLOVIR PREVENTION TRIAL

Objectives:

- Evaluate whether early treatment oral acyclovir in simplex epithelial keratitis prevents progression to stromal keratitis or iridocyclitis.
- Evaluate efficacy of low –dose oral acyclovir in preventing herpetic recurrences in patients with previous episodes of herpetic eye disease.

Results:

- Adding oral acyclovir to trifluridine does not prevent patients from developing stromal keratitis or uveitis.
- Risk of these patients developing stromal keratitis or uveitis is quite low with trifluridine treatment alone.
- Oral acyclovir (400 mg BID x 1 year) reduced chance the recurrence for any type of herpetic eye disease by 41%.
- Oral Acyclovir (400 mg BID x1 year) decreased risk of HSV stromal keratitis recurrence by 50% over one year post infection.

Let's Discuss Recurrences

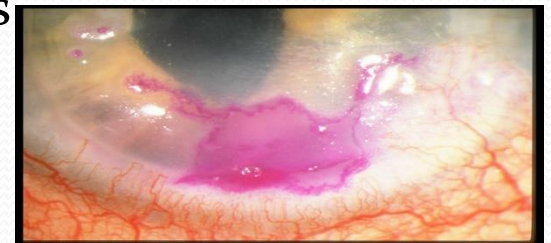
After one episode of epithelial keratitis, 25-68% of patients will have recurrent disease in 2 years.

Precipitating Factors*

- Stress
- Fever
- URI
- UV exposure
- Minor trauma
- Cold wind

Types of Recurrence

- Blepharitis
- Conjunctivitis
- Keratitis
 - Epithelial (37%)
 - Stromal (46%)
- Iridocyclitis
- Trabeculitis



*Not confirmed by HEDS study

HEDS II HERPETIC EYE DISEASE STUDY

ACYCLOVIR PREVENTION TRIAL

- **Objectives:**

- Evaluate whether early treatment oral acyclovir in simplex epithelial keratitis prevents progression to stromal keratitis or iridocyclitis.
- Evaluate efficacy of low -dose oral acyclovir in preventing herpetic recurrences in patients with previous episodes of herpetic eye disease.

- **Results:**

- Adding oral acyclovir to trifluridine does not prevent patients from developing stromal keratitis or uveitis.
- Risk of these patients developing stromal keratitis or uveitis is quite low with trifluridine treatment alone.
- **Oral acyclovir (400 mg BID x 1 year) reduced chance the recurrence for any type of herpetic eye disease by 41%.**
- **Oral Acyclovir (400 mg BID x1 year) decreased risk of HSV stromal keratitis recurrence by 50% over one year post infection.**

HSV: Let's Discuss Stromal involvement

- Symptoms: decreased VA, discomfort, watery
- May have had a prior history of epithelial disease
- May occur as primary presentation or at same time as epithelial disease



Stromal Keratitis

Significant inflammatory response

- **Without ulceration**

- Interstitial keratitis: endothelial dysfunction, uveitis, stromal vascularization, scarring
 - Immune stromal keratitis
 - Disciform: disc of edema with intact epithelium

- **With ulceration (less common)**

- Necrotizing keratitis:
tissue necrosis resulting in ulceration
& stromal bed destruction, risk of perforation

- Look for other signs of inflammation

- Cells in AC; keratic precipitates
- IOP low/high



Interstitial Keratitis: intact epithelium: vascularization/ghost vessels

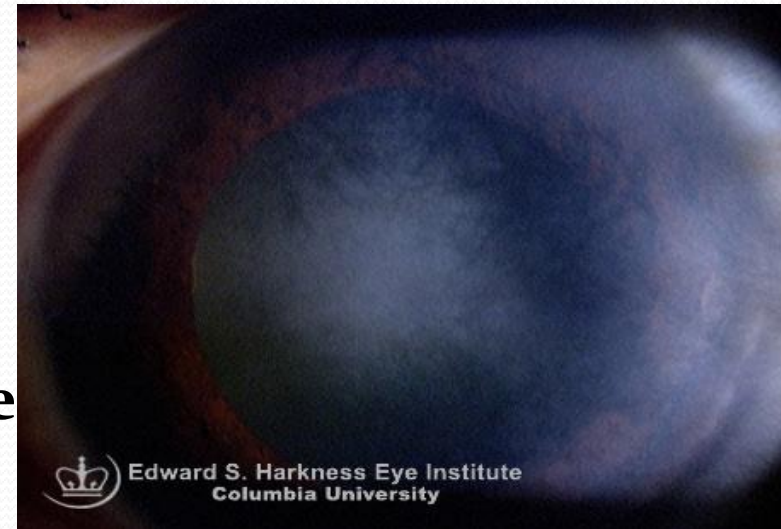


Interstitial Keratitis: Differentials

- Syphilis (congenital-bilateral)
- Herpes Simplex
- Mycobacterium tuberculosis
- Mycobacterium leprae
- Borrelia burgdorferi (Lyme)
- Rubella
- Epstein-Barr virus
- Chlamydia trachomatis
- Leishmania species
- Onchocerca volvulus

Stromal Keratitis: Differential Diagnosis

- Bacterial Keratitis
- Fungal Keratitis
- Acanthamoeba keratitis
- Varicella zoster keratitis
- Autoimmune ulcerative disease
- EBV
- Mumps keratitis



Necrotizing Ulcer with Hypopyon



Sclerokeratitis



Stromal Keratitis: How do we treat?

- Topical steroid- how often?
- ? Topical antivirals for cover (TID-QID with taper as steroids tapered)
- Oral antiviral ? What does HEDS I say?
- Cycloplegia may be helpful
- Thinning/perforation – anti-collagenases (Doxycycline 100 mg BID)/ bandages/glue/lamellar/penetrating keratoplasty

Evidence based medicine:HEDS I

Objectives:

- Efficacy of topical corticosteroids with topical trifluridine in treating simplex stromal keratitis.
- Efficacy of oral acyclovir with topical trifluridine and topical steroid in simplex stromal keratitis
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- **Uveitis**
- Stopped prematurely due to recruitment difficulties.
- Data suggests there is a benefit of adding oral acyclovir to prophylactic treatment regimen of topical steroids and trifluridine

Treatment Recommendations: HSV Stromal Keratitis: AAO Guidelines

- A steroid treatment period greater than ten weeks recommended:
 - HEDS clinical trials found excessively high treatment failure rates six weeks after a ten-week prednisolone taper
 - Indicating the length of treatment may have been inadequate.
- The treatment course should be adjusted depending on the clinical response.
- Oral antiviral agents are recommended over topical antiviral agents for their safety profile and superior corneal penetration.

HSV Stromal Keratitis Treatment

General Guidelines

Without ulceration:

- Topical steroids q 1-2 h- QID, with slow taper, > 10 weeks
- Antiviral cover: topical (ex: Viroptic or Zirgan) OR oral:
 - Prophylactic dose:
 - Acyclovir 400 mg BID
 - Valacyclovir 500 mg QD
- Cycloplegics may be used
- Treat IOP

With ulceration:

Topical (ex: Viroptic or Zirgan) OR oral

- Oral antiviral treatment
 - Therapeutic Zoster dose 7-10-14 days (or more)*
 - Acyclovir 800 mg 3-5x/day*
 - Valacyclovir 1000 mg BID-TID*
- Topical steroids BID
- Oral antiviral is reduced to prophylactic dose and maintained as long as topical steroids are in use
- Cycloplegics may be used
- Treat IOP

Treatment Recommendations: HSV Stromal Keratitis: AAO Guidelines

- **Without ulceration:** should include a topical corticosteroid for at least ten weeks in conjunction with a **prophylactic** oral antiviral.
- **With ulceration:** the best treatment for HSV stromal keratitis with epithelial ulceration has not been studied adequately in randomized clinical trials, but available evidence suggests a **role for Zoster therapeutic doses** of oral antiviral combined with judicious use of topical corticosteroids.

Similar Treatment for Geographic Keratitis: AAO



b. Geographic

(Therapeutic dose of topical or oral antiviral agent)

Acyclovir (Zovirax®): 800 mg 5 times daily for 14–21 days **or**

Valacyclovir (Valtrex®): 1 g 3 times daily for 14–21 days **or**

Famciclovir (Famvir®): 500 mg twice daily for 14–21 days **or**

Trifluridine ophthalmic solution 1% (Viroptic®): instillation of 1 drop into affected eye(s) 9 times daily for 7 days; may decrease dose to 5 times daily after 7 days if ulcer is healed. Treatment should not extend beyond 21 days because of potential ocular toxicity.

or

Ganciclovir ophthalmic gel 0.15% (Zirgan®): instillation of 1 drop into affected eye(s) 5 times daily while awake until healing of corneal ulcer, followed by 1 drop 3 times daily for 7 days.

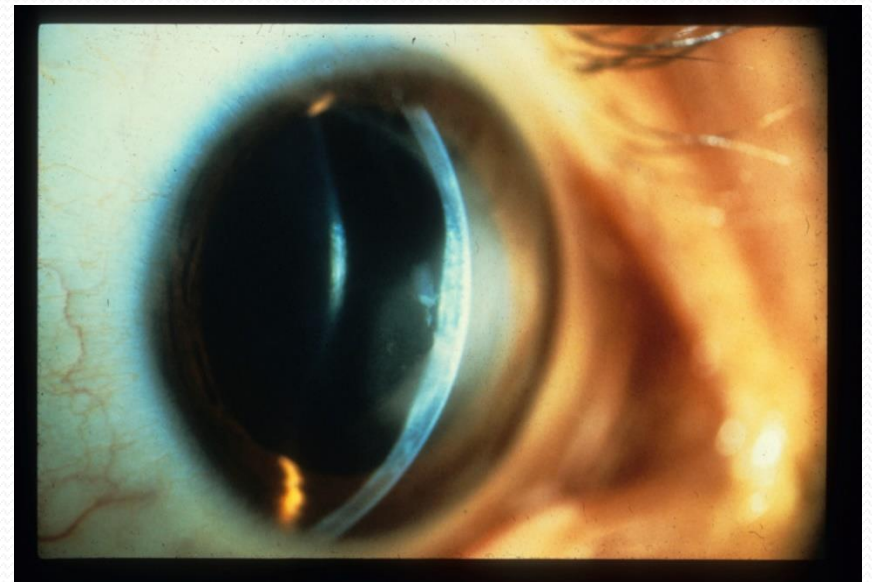
What About Endotheliitis?

- Not as common as stromal
- Corneal edema/folds
- Edema can be diffuse or disciform
- Keratic precipitates
- Uveitis
- Same symptoms as other HSV keratitis
 - Photophobia, blurred vision, redness
 - High IOP, trabeculitis



Disciform Keratitis

- Disc-shaped stromal edema due to localized endothelial dysfunction
- Often associated with focal keratic precipitates
- Typically, very sensitive to steroids



Treatment recommendations for HSV endothelial keratitis

- Only a few studies exist to guide treatment recommendations for HSV endothelial keratitis.
- Compared to patients with HSV stromal keratitis, those with HSV endothelial keratitis appear to respond more rapidly to steroid treatment and may not require prolonged therapy.
- Unlike topical acyclovir, the two topical antiviral agents, trifluridine and ganciclovir, do not achieve adequate corneal penetration and are not recommended for the treatment of HSV endothelial keratitis. An oral antiviral agent is recommended to ensure adequate corneal penetration in the treatment of HSV endothelial keratitis.

Summary:

HSV endotheliitis



- Topical antivirals: Zirgan and Viroptic may be ineffective.
- Preferred treatment:

A topical corticosteroid agent (6-8 x day) + oral antiviral agent (closer to therapeutic dose):

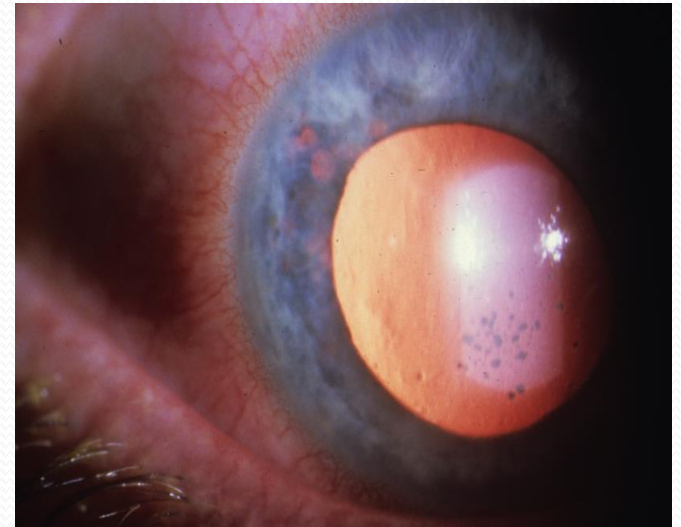
Acyclovir 400 mg 3-5 x day

Valacyclovir 500 mg BID

Famciclovir 250 mg BID

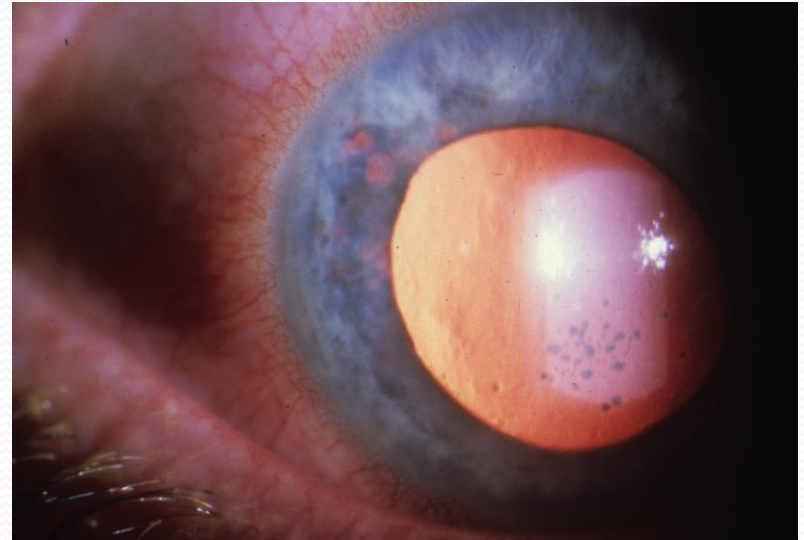
What about HSV Uveitis?

- KPs, cells & flare
- Ant and post synechiae
- More common during reactivation vs. in primary disease
- **Don't forget to dilate to look for vitritis****
- May have trabeculitis- high IOP !



HSV Uveitis: How to treat?

- Topical corticosteroids
- Cycloplegics
- What does HEDS say about the antivirals?



HEDS I

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HEDS Key Clinical Questions and Studies

QUESTION

FINDINGS

Are topical steroids beneficial in treating HSV stromal keratitis?

Yes. Topical steroid significantly reduced stromal inflammation and duration of keratitis.

Is oral acyclovir helpful in treating iridocyclitis?

Too few patients to attain statistical significance, although the trend favored treatment with oral acyclovir.

Does oral acyclovir prevent development of stromal keratitis in patients with epithelial keratitis?

No difference was apparent between the acyclovir and placebo groups.

Does prophylaxis with oral acyclovir reduce recurrence of HSV?

Yes. Recurrence was reduced by 45% in the acyclovir group compared with placebo.

What triggers HSV recurrence?

None of the factors studied were confirmed as triggers as recorded by patients in weekly logs.

Adapted from: BCSC Section 8, *External Disease and Cornea*, 2020-20.

Steroid Treatment Overview

- Avoid (or minimize) steroids in active replicating virus phase
- In patients using steroids, antiviral coverage is often used to prevent epithelial recurrence
- Patients with stromal disease may need prolonged steroid treatment > 10 weeks
- Once steroids are started, it is difficult to wean patients off of them
 - Sudden discontinuation of corticosteroids may cause rebound inflammation
 - They should be tapered gradually to minimize the risk of rebound inflammation, but also keep the keratitis in check.

Effects of Inappropriate Steroid Use



HSV is “The Great Imitator”

- HSV keratitis
 - May not give classic appearance
- Keratitis with focal underlying KP
 - HSV until proven otherwise
- Recurrent unilateral iridocyclitis may be HSV
 - Even without keratitis



Think Herpes If:

- If a patient is in far less pain than what the findings show
- If a patient is photophobic or has uveitis and high intraocular pressure
- Always suspect herpes in patients with a history of herpes

Summary of HSV Treatment: Orals

- **Acute epithelial keratitis:**
 - Zovirax 400 mg 5 x day x 7 days
 - Valtrex 500 mg TID x 7 days
- **Prophylactic Treatment** for approximately 1 year
 - Zovirax 400 mg BID
 - Valtrex 500 mg QD
- **Patients who have had more than one episode of HSVK and those with HSV stromal keratitis are good candidates for a maintenance course of antiviral medication.**

HSV: Treatment Summary

HSV CATEGORY	COMMON NOMENCLATURE	BASIC TREATMENT APPROACH
Epithelial keratitis	• Dendritic keratitis • Geographic keratitis	Antiviral (topical or oral) or debridement
Stromal keratitis without ulceration	• Interstitial keratitis • Immune stromal keratitis	Topical steroid + oral antiviral prophylaxis
Stromal keratitis with ulceration	• Necrotizing keratitis	Oral antiviral in therapeutic doses + topical steroid
Endothelial keratitis	• Disciform keratitis	Oral antiviral in therapeutic doses + topical steroid

Let's move on: Neurotrophic Keratopathy



NK

- Characterized by decreased corneal sensitivity and poor corneal healing.
- Which leaves the cornea susceptible to injury and decreases reflex tearing.
- Epithelial breakdown can lead to ulceration, infection, melting & perforation secondary to poor healing.

Potential Causes

- **Herpetic eye disease- MOST COMMON**
- Post refractive surgery or other corneal surgery
- Tumor- acoustic neuroma where 5th and 7th cranial nerves effected (or effects from brainstem stroke, trauma, MS)
- Chronic contact lens wear
- Diabetic neuropathy
- Dental surgery, radiation eye area, chemical injury

Neurotrophic Keratitis

- PF Lubrication
- Antibiotic prophylaxis
- Reduce any preservative exposure
- Bandage contact lens
- Amniotic Membrane
- Autologous serum
- Regener-Eyes
- Patching



Oxervate: for neurotrophic keratitis

- Cenegermin .002%, Dompe Pharm, FDA approved
- Eye drop delivery of human nerve growth factor
- Promotes corneal healing and stimulates epithelial cell growth
- 6 times daily (at an interval of every 2 hours) for eight weeks



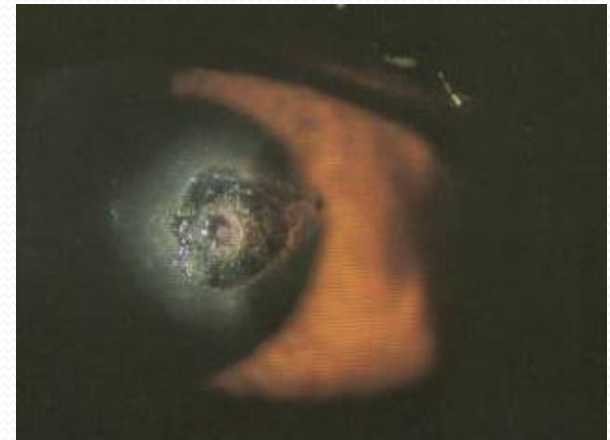
COURTESY: DOMPE U.S.

Surgical Treatment for Epithelial Defects

- Tarsorrhaphy
- Conjunctival flap (partial/full)
- Conjunctival transplant (if underlying stem cell deficiency, ex: alkaline burns/Stevens-Johnson Syndrome)
- Keratoplasty (lamellar/penetrating)

Impending or Frank Corneal Perforation

- Glue + Bandage CL
- Cyanoacrylate - medical grade
- De-epithelialize area to be treated
- Apply with patient in supine position
- Bandage contact lens necessary
- Appropriate adjunctive medical therapy, i.e. topical antibiotics, lubricants, steroids, etc.



Treatment of Bell's Palsy related to HSV

- If started within 72 hours
 - Acyclovir 400 mg 5 x day x 7 days
 - Prednisone: 60 x 4 days, 40 x 4 days, 20 x 4 days
 - Other: 30-40 mg BID tapered and stopped at 10 days
- Prednisone 60-80 mg x 1 week with no taper

We will likely be consulted for eyes for these patients****

Lubricating ointment at night

Case

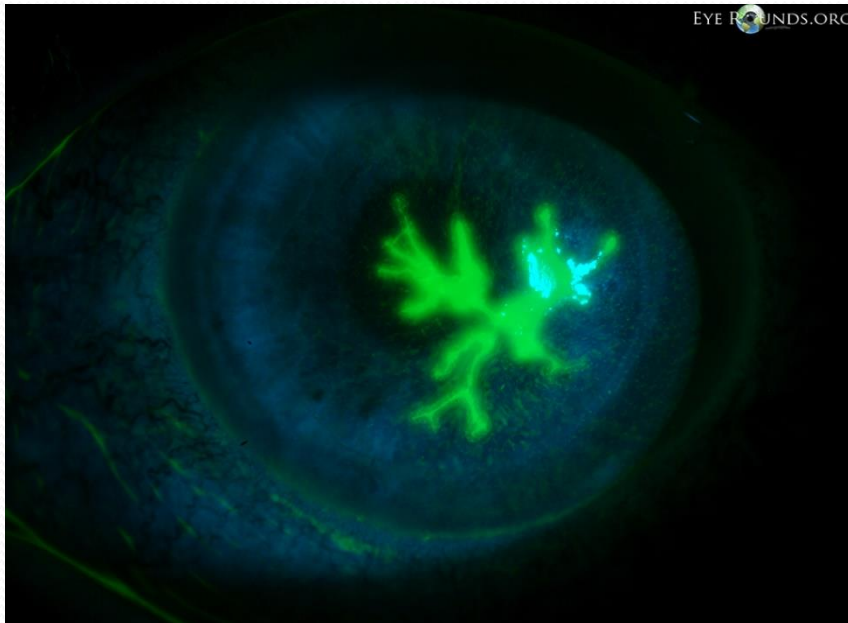
- 75 yo male reports with foreign body sensation OS x 3 days. Denies trauma or discharge. Denies contact lens wear.
- POHx: Cataract surgery OD 2018 OS 2019
- MHX: HTN, Hyperlipidemia, Parkinson's disease
- Meds: Lisinopril 10 mg, HCTZ 10 mg, Sinemet- (Carbidopa-levodopa) 10/100 BID PO

Exam

- Vision with correction OD 20/25 OS 20/40
- Slit lamp exam see next slide

Anterior segment examination

- A/C Deep and Quiet
- Conjunctiva: grad 1 + injection.
- Decreased corneal sensation



Best next step?

- A. Start patient on Viroptic / preservative free tears
- B. Start patient on Gancyclovir gel 5 x per day
- C. Debride cornea. Start Valacyclovir 500 mg po TID
- D. Start Vigamox TID OS

Poor ability to instill drops

- Reasonable reason to RX oral in this case.
- Oral may be a better treatment given manual dexterity with topicals.
- Stay... tuned..... Might need topical if stroma becomes involved.
- Other option might include having a family member help with drop instillation if you go with topicals.

Clinical Pearls

- HZV – Be aware of possible complaints prior to obvious vesicular eruptions (check scalp). Consider mimickers.
- Dilate every patient with HZV. Viral and choroidal retinitis is an ocular emergency (send to retina immediately).
- For the treatment of HZO, a good rule of thumb is to double the doses of the medications used for HSV keratitis
- If starting on antivirals, make sure you co-manage with primary: immunocompromised status? Systemic complications (disseminated disease), post herpetic neuralgia.

Clinical Pearls

- “ It is widely believed that uveitis associated with involvement of any corneal layer is a manifestation of herpetic disease until proven otherwise.”
- Recurrent herpetic infection per the HEDS study shows benefit of prophylactic antivirals.
- We are not able to prescribe beyond 7 days, therefore co-management is critical.

Summary of HSV oral treatment

Dendritic Epithelial Keratitis (Seven to 10 days)	
<i>Antiviral</i>	<i>Dosage</i>
Acyclovir	400mg five times daily
Valacyclovir	500mg three times daily
Famciclovir	250mg two or three times daily
Geographic Epithelial Keratitis (14 to 21 days)	
Acyclovir	800mg five times daily
Valacyclovir	1g three times daily
Famciclovir	500mg three times daily

Stromal Keratitis Without Ulceration* (At least 10 weeks)	
Acyclovir	400mg two times daily
Valacyclovir	500mg once daily
Famciclovir	250mg two times daily
Stromal Keratitis <u>With</u> Ulceration** (Seven to 10 days)	
Acyclovir	800mg three to five times daily
Valacyclovir	1g three times daily
Famciclovir	500mg two times daily

Endothelial Keratitis*** (Variable)	
Acyclovir	400mg three to five times daily
Valacyclovir	500mg two times daily
Famciclovir	250mg two times daily
Prophylaxis of Recurrent HSVK (At least one year)	
Acyclovir	400mg two times daily
Valacyclovir	500mg once daily
Famciclovir	250mg two times daily