

Treatment and Management of Ocular Infection - Antivirals / Antifungals in Eye Care

Blair Lonsberry, MS, OD, MEd., FAAO
Pacific University College of Optometry
blonsberry@pacific.edu

Disclosures

Paid consultant for:

Maculogix: Honoraria-Advisory Board

Sun Pharmaceuticals: Honoraria: Advisory Board

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Agenda

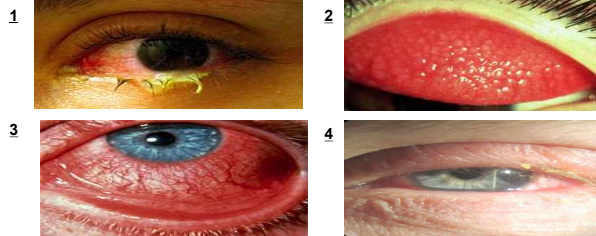
- Viral Infections and their management:
 - Adenovirus
 - Herpes simplex
 - Herpes Zoster
- Fungal Infection and their management

Case

- 27 year old pharmacy student presents to the clinic on emergent basis
 - complains about red/painful eyes for the past 2 days
 - started OD then transferred to OS
 - reports a watery discharge, no itching, and is not a contact lens wearer
 - reports that others in his class have had a similar red eye
 - no seasonal, food or drug allergies
 - has taken Visine 4-5 times/day since eyes became red but hasn't helped much

Question

Which of the following best represents your patient?



Conjunctivitis



Bacterial Conjunctivitis



Allergic Conjunctivitis

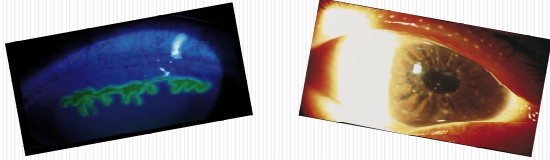


Viral Conjunctivitis



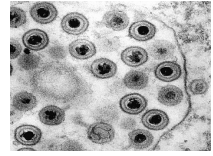
Blepharo-conjunctivitis

Antivirals



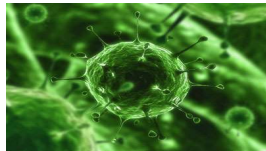
What is a Virus?

- Smallest of all infectious organisms.
 - Range from 20-300 nm
- Basic structure of a Virion:
 - Outer Protein Coat (Capsid)
 - Genome (DNA or RNA – single or double stranded)
- Some viruses are capable of incorporating their genome into the host cells and escaping the immune system = latency.



Viral Eye Disease

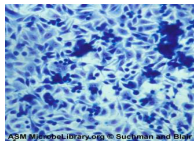
- Three Major Areas of Focus:
 - Adenoviral Infections
 - Herpes Simplex Disease
 - Varicella Zoster Disease



Adenovirus

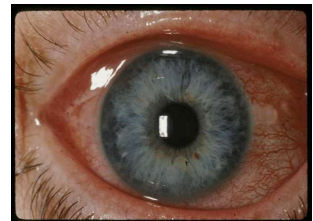
Adenoviral Infections

- Adenoviruses are much smaller than the herpes virus and do not have lipid envelopes.
 - They are capable of surviving on inanimate objects, making this a very contagious condition. (EKC virus may stay viable on surface up to 30 days)
- There are ~53 serotypes of this virus.
- No Antivirals available have been shown to be successful against adenoviral infections.
 - Some debate is ongoing over the efficacy of Ganciclovir Gel 0.15% (Zirgan). A current FDA trial is ongoing to test this.



Viral Conjunctivitis

- Most common infectious keratitis presenting on emergent basis
- 62% caused by adenovirus
- Two major types:
 - Pharyngoconjunctival fever (PCF)
 - Epidemic keratoconjunctivitis (EKC)



Viral Conjunctivitis



- PCF: history of recent/current upper respiratory infection
 - classic triad of fever, pharyngitis, and acute follicular conjunctivitis.
 - occurs more commonly in children, is caused by serotypes 3 and 7, and is spread by respiratory secretions.
 - tearing and foreign body sensation that is initially unilateral.

Viral Conjunctivitis



- PCF:
 - corneal involvement is not a key feature, there is occasionally a punctate keratitis;
 - SEIs are rare.
 - self-limiting condition that varies in severity and may last from 4 days to 2 weeks
 - Treatment if symptomatic though topical steroids are rarely needed.

Viral Conjunctivitis: EKC (Epidemic Keratoconjunctivitis)

- highly contagious with a history of coming in contact with someone having a red eye.
- rugged capsule of the adenovirus confers resistance to pH extremes and enables long-term viability on contaminated surfaces
 - results in high infectivity of adenovirus and frequent outbreaks of EKC among populations in close quarters, such as schools, camps, or nursing homes
 - particularly problematic in health care and eyecare clinics

<https://www.aao.org/eyenet/article/epidemic-keratoconjunctivitis-prevention-strategie>

Viral Conjunctivitis: EKC (Epidemic Keratoconjunctivitis)

- EKC initially manifests as a flu-like syndrome consisting of fever, malaise, and myalgias followed by the appearance of ocular signs and symptoms, including a red eye, eyelid edema, excessive tearing, irritation, foreign body sensation, and photophobia.
- EKC frequently begins as a unilateral condition but, in 70% of cases, will become bilateral within the first week of symptoms as a result of hand-to-eye transmission
 - Adenovirus 8 common variant leading to “rule of 8’s”
 - First 8 days red eye with fine SPK
 - Next 8 days deeper focal epithelial lesions
 - Following 8 potential development of infiltrates
 - Resolution

<https://www.aao.org/eyenet/article/epidemic-keratoconjunctivitis-prevention-strategie>

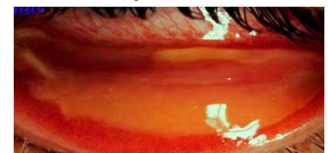
AdenoPlus^R

- AdenoPlus^R available to use for adenoviral confirmation
 - Reported **88% sensitivity and 91% specificity for adenoviral infection** (Sambursky RP et al. *Ophthalmology*. 2006;113(10):1758-1764)

Viral Conjunctivitis: Signs and Symptoms

- Gritty sensation
- Watery discharge
- Sticky in mornings
- **Follicular response**
- Chemosis
- Injection
- SPK
- Infiltrates possible
- Positive lymph nodes

- **Pseudomembranes in severe cases**
- Subconjunctival hemes



Management

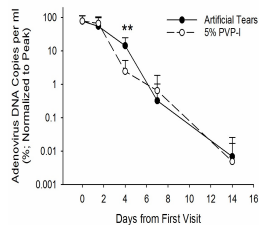
- Considering the use of anti-inflammatory treatment to relieve patient symptoms and improve comfort?
 - E.g. Lotemax[®] QID OU
- EKC patients are typically very uncomfortable and would benefit from anti-inflammatory treatment
 - especially if infiltrates or pseudomembrane present
- studies have shown that steroids are effective in reducing inflammation during the acute phase of EKC and decreasing the likelihood of development of corneal subepithelial infiltrates.
- However, the studies also showed that their use increased viral replication and titers and prolonged the mean duration of viral shedding
- routine corticosteroid use is generally not indicated for EKC
 - when managing a severe EKC inflammation, you should carefully weigh the risks and benefits of steroids

<https://www.aao.org/eyenet/article/epidemic-keratoconjunctivitis-prevention-strategie>

Management

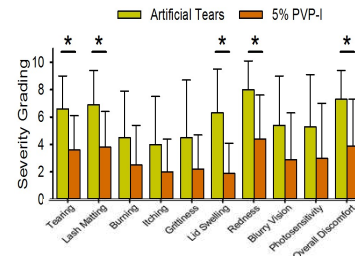
- Betadine (Melton-Thomas Protocol):
 - Proparacaine
 - 4-5 drops of Betadine 5%
 - Get patient to close eye and gently roll them around
 - After one minute, lavage the eye
 - Lotemax 4 times a day for 4 days
- Alternative: Betadine swabsticks.
 - 5% Betadine solution only comes in 30 ml bottles cost \$14.00.
 - Case of 200 Betadine swabsticks approx. 45 dollars.

Reducing Adenoviral Patient-Infected Days (RAPID) Study
Effect of 5% PVP-I on qPCR-Derived Viral Titers



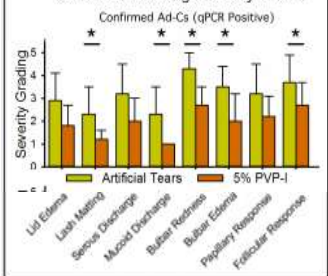
Andrew Hartwick, Tammy Than, Bojana Rodic-Polic, Spencer Johnson, Mary Migneco, Ellen Shorter, Jennifer S Harthan, Christina Moretton, Meredith Whiteside, Christian K. Olson, Matthew Margolis, Julia Huecker, Gregory Storch, Mae O Gordon; Reducing Adenoviral Patient-Infected Days (RAPID) Study: A Randomized Trial Assessing Efficacy of One-Time, In-Office Application of 5% Povidone-Iodine in Treatment of Adenoviral Conjunctivitis. Invest. Ophthalmol. Vis. Sci. 2019;60(9):6257-60. <https://doi.org/10.1167/60.9.6257>

Day 4: qPCR + Participant-Reported Symptoms



Andrew Hartwick, Tammy Than, Bojana Rodic-Polic, Spencer Johnson, Mary Migneco, Ellen Shorter, Jennifer S Harthan, Christina Moretton, Meredith Whiteside, Christian K. Olson, Matthew Margolis, Julia Huecker, Gregory Storch, Mae O Gordon; Reducing Adenoviral Patient-Infected Days (RAPID) Study: A Randomized Trial Assessing Efficacy of One-Time, In-Office Application of 5% Povidone-Iodine in Treatment of Adenoviral Conjunctivitis. Invest. Ophthalmol. Vis. Sci. 2019;60(9):6257-60. <https://doi.org/10.1167/60.9.6257>

Clinician-Graded Signs at Day 4 Visit



Andrew Hartwick, Tammy Than, Bojana Rodic-Polic, Spencer Johnson, Mary Migneco, Ellen Shorter, Jennifer S Harthan, Christina Moretton, Meredith Whiteside, Christian K. Olson, Matthew Margolis, Julia Huecker, Gregory Storch, Mae O Gordon; Reducing Adenoviral Patient-Infected Days (RAPID) Study: A Randomized Trial Assessing Efficacy of One-Time, In-Office Application of 5% Povidone-Iodine in Treatment of Adenoviral Conjunctivitis. Invest. Ophthalmol. Vis. Sci. 2019;60(9):6257-60. <https://doi.org/10.1167/60.9.6257>

Management

- Antivirals used in HSV keratitis have traditionally thought to be ineffective in treatment of viral conjunctivitis
 - Ganciclovir: In a double-masked, controlled, and randomized study it was found to shorten the mean time of recovery from 18.5 days to 7.7 days in patients who were treated vs. those who just received artificial tears.
 - Tabbara K, Jarade E. Ganciclovir effects in adenoviral keratoconjunctivitis. 2001; ARVO abstract 3111 (suppl); S579
 - In clinical trial Avenova[®]: proposed end date November 2020
 - The investigators propose a study to evaluate the role of Avenova[®] (0.01% hypochlorous acid) in the treatment of common ocular viral infections.
- Important to stress limited contact with others, frequent hand washing, not sharing of towels, etc.

Efficacy of Hospital Germicides against Adenovirus 8, a Common Cause of Epidemic Keratoconjunctivitis in Health Care Facilities. *ANTIMICROBIAL AGENTS AND CHEMOTHERAPY*, Apr. 2006, p. 1419–1424

An important finding from our study was that of the four disinfectants recommended by the CDC and Association for Professionals in Infection Control and Epidemiology for elimination of adenovirus type 8 from ophthalmic instruments, two **(70% isopropyl alcohol and 3% hydrogen peroxide) were found to be ineffective**. Based on these data, 3% hydrogen peroxide and 70% isopropyl alcohol are not effective against adenovirus that is capable of causing epidemic keratoconjunctivitis and similar viruses and should no longer be used for disinfecting applanation tonometers.

EKC Disinfection

- Commercial grade disinfectants that include compounds such as:
 - peracetic acid,
 - aldehydes [glutaraldehyde and ortho-phthalaldehyde],
 - chlorine-based products [1,900 to 6,000 ppm available free chlorine],
 - ethanol mixed with quaternary ammonium compounds)
- E.g. Cidex, DisCide

Case

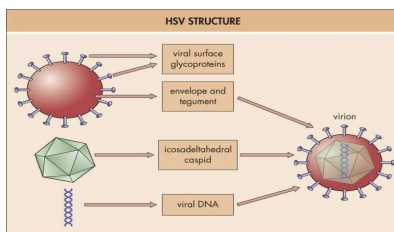
- 20 year old male presents with a red painful eye
 - Started that morning when he woke up
 - reports a watery discharge, no itching, and is not a contact lens wearer
- SLE:
 - See attached image with NaFl stain



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Herpes Simplex Virus

Herpes Virus



Classification of Human Herpes virus

Alpha herpes viruses	Beta herpes viruses	Gamma human viruses
Herpes simplex virus type 1 (HSV-1)	Cytomegalovirus (CMV) #5	Epstein-Barr virus (EBV) #4
Herpes simplex virus type 2 (HSV-2)	Human herpes virus type 6 (HHV-6)	Kaposi's sarcoma-related virus #8
Varicella-zoster virus (VZV) #3	Human herpes virus type 7 (HHV-7)	

Herpesviruses range in size from 120 - 300nm. Subgroups are based on duration of reproductive cycle, host ranges, and latency locations.

Herpes and Eye Infections

<https://www.ortho-bullets.com/hand/6100/herpetic-whitlow>



Virus	Disease Caused
HSV-1	Oral and Ocular Herpes, Genital Herpes, and Whitlow
HSV-2	Genital Herpes, Oral and Ocular Herpes, and Whitlow
VZV	Chickenpox, Shingles
CMV	Retinitis
EBV	Mononucleosis (conjunctivitis rxn mainly)

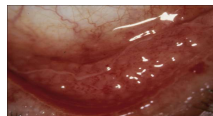
Herpes Simplex Virus



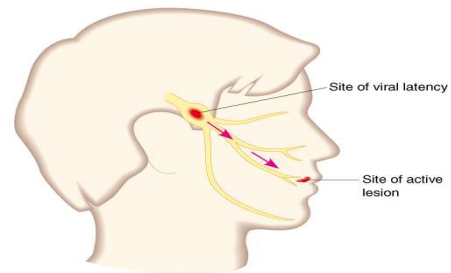
- More than 80% of the population has been infected with HSV (some studies say nearly 100%).
 - Herpes Labialis is the most common form of infection.
 - Less than 1% will have ocular manifestations
 - under a microscope **HSV 1** and **HSV 2** are virtually identical, sharing approximately 50% of their DNA

Herpes Virus

- Primary Infection usually occurs in children under 5.
 - Frequently is subclinical or very mild
 - Most common ocular finding is blepharoconjunctivitis.
 - Other findings Include:
 - Lid Vesicles
 - Flu-like symptoms
 - Corneal Signs



Ophthalmology by Yanoff and Duker 3rd Edition



Recurrent Infections: Herpes Simplex Keratitis (HSK)

- Herpes Simplex Keratitis (HSK) is the second most common cause of corneal blindness in the US.
 - Only trauma has a greater frequency.
 - 50,000 new or recurrent cases of HSK occur each year.
- Patients will complain of pain, photophobia, and decreased vision.

Herpes Simplex Keratitis

- Findings Include:
 - Lid Lesions – Clear Vesicles on erythematous base.
 - Conjunctivitis
 - Epithelial Keratitis
 - Stromal/Endothelial Keratitis

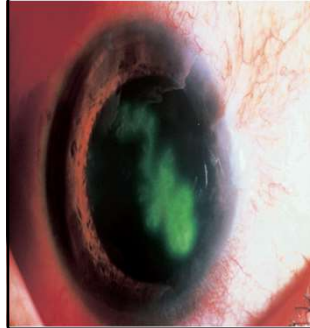


Herpes Simplex Keratitis: Epithelial

- Results from actively replicating virus on the corneal surface.
- Initial findings include photophobia, tears, and foreign body sensation.
 - Pain diminishes with each recurrence.
- Signs:
 - Swollen opaque epithelial cells arranged in a coarse punctate or stellate pattern
 - Central desquamation results in a dendrite***
 - Central ulceration
 - Terminal end bulbs
- ***Corneal sensation is reduced***
- Findings Include:
 - Dendritic Ulcers
 - Geographic Ulcers
 - Marginal Keratitis
 - Metaherpetic (Neurotrophic)

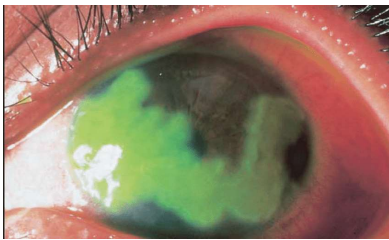


Dendritic Ulcers



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HSV Geographic Ulcer



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https://www.researchgate.net/figure/Geographic-corneal-ulcer-caused-by-herpes-simplex-virus-keratitis_fig1_26730111

Pediatric HSV Keratitis

- pediatric herpes simplex keratitis has an 80% risk of recurrence, a 75% risk of stromal disease, and a 30% rate of misdiagnosis
- 80% of children with herpes simplex keratitis develop scarring, mostly in the central cornea
 - results in the development of astigmatism
 - 25% of children have more than 2 D of astigmatism, most of which is irregular
- consider pediatric HSV when a patient has unilateral recurrent disease in the anterior segment

Herpes Simplex Keratitis Management

- Topical:
 - Viroptic (trifluridine) q 2h until epi healed then taper down for 10-14 days.
 - Viroptic is toxic to the cornea.
 - Zirgan (ganciclovir) available, use 5 times a day until epi healed then 3 times for a week (US only)
 - ?? Consider having this compounded??

Anti-Viral Medication

Drug	Mechanism of Action	Bioavailability	Dosing	Side Effects
Acyclovir	Acyclovir interferes with DNA synthesis inhibiting viral replication	10-30% gets absorbed Short ½ 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 1/2 life	Simplex: 500 mg tid Zoster: 1 g tid	Same as acyclovir
Famciclovir (Famvir)	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

HSV Stromal Disease



- HSV Stromal disease is an immune-mediated disease
- Increased risk of scarring and high risk of poor visual prognosis
- Requires corticosteroids (HEDS: corticosteroid reduced risk of progression by 68%)
 - Without epithelial defect: corticosteroids and prophylactic anti-viral dosage
 - With epithelial defect: active infection anti-viral dosage with judicious corticosteroids

How much to dose steroid?

- HEDS used QID of *prednisolone phosphate*
- Current Recommendations:
 - Mod – severe (especially with neo): 1% Prednisolone or Lotemax QID to 6x/day
 - Want the lowest dose needed to control the inflammation
 - AAO EBM Treatment Guideline 2014
 - Topical steroid for 10 weeks (this is based on HEDS results) with oral antiviral

Herpes Simplex Epithelial Keratitis

- Treatment Regimen:
 - Viroptic every 2 hours until epi lesion healed then 4 times/day for rest of the week
 - Oral Valtrex 500 mg 3x/day for 7-10 days
 - Artificial tears
 - L-Lysine 2 grams daily?
 - Proven to “slow down” and retard the growth of the herpes virus and inhibit viral replication
 - Debride the ulcer?
 - Prior to topical antiviral therapy debridement was treatment of choice
 - Generally try to avoid use of sharp instruments and use of cotton swab and anesthetic
- RTC 1 day, 4 days, 7 days

Herpes Simplex Keratitis

- Prophylactic Treatment:
 - Reduces the rate of recurrence of epithelial and stromal keratitis by ≈ 50%
 - Acyclovir 400 mg BID
 - Valtrex 500 mg QD
 - Famvir 250 mg QD
 - L-lysine 1 gram/day:
 - Proven to “slow down” and retard the growth of the herpes virus and inhibit viral replication
 - Frequent debilitating recurrences, bilateral involvement, or HSV infection in a monocular patient

HSV Prophylaxis

400 mg acyclovir BID x 12 months
Strong Recommendation for prophylaxis and decrease in visual morbidity for anyone with stromal disease

- (HEDS) 50% reduction in risk of recurrence over 12 months
- Works best in:
 - Those with history of HSV stromal disease
 - Those with multiple recurrences of any type of ocular HSV disease
 - Anyone going through a circumstance that could aggravate corneal disease

HEDS: Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Herpetic Eye Disease Study Group. N Engl J Med 1998; 339:300–306.

Prophylaxis??

- **Pitfalls to Prophylaxis:**
 - Reduction of recurrence does not persist once drug stopped
 - Resistance????
 - van Velzen, et. al., (2013) demonstrated that long-term ACV prophylaxis predisposes to ACV-refractory disease due to the emergence of corneal ACVR HSV-1.

Viroptic (Trifluridine)

Trifluridine (Viroptic)

- Antiviral approved for the treatment of keratitis caused by HERPES SIMPLEX VIRUS.
 - Effective against HSV-1 and HSV-2
 - This has been the longstanding standard of care in the treatment of HSV epithelial keratitis.
- MOA: Analog of thymidine that interferes with DNA synthesis of both viral and mammal cells.

Trifluridine (Viroptic)

- Ocular SE's Include:
 - Stinging and burning
 - Conjunctival Hyperemia and Chemosis
 - Increased IOP
 - Punctate keratitis and corneal edema
 - Corneal Signs can mimic the infection and may make judging improvement difficult.
- This is corneal toxic – must always consider this in developing your treatment protocol.

Viroptic Recommended Dosages

- Initial Dosage: 1 drop every 2 hrs, up to 9x/day
 - Improvement should start within 2 days of treatment and resolution within 14 days.
 - Dosage should be tapered as soon as improvement occurs.
- Continuous administration for periods exceeding 21 days should be avoided because of potential ocular toxicity.
 - 97% of cases resolve within 2 weeks.
- After the condition is resolved (no staining visible) perform slow taper - usually one drop four times/day for 4-5 more days to allow time for the dormant virus to be shed as well.

Ganciclovir Gel (Zirgan)

Ganciclovir Gel (Zirgan) (US Only)

- FDA approved September 2009
 - Available in Europe for 10+ years before that.
 - Sold by Bausch and Lomb.
- 0.15% topical gel approved for the treatment of acute herpetic keratitis
- Dosage: 5X daily until the ulcer heals, followed by TID for an additional seven days

Ganciclovir Gel (Zirgan)

- Guanosine derivative that is transformed by the viral thymidine kinases to ganciclovir triphosphate, where it acts only on virus-infected cells.
 - Dual Acting MOA: Inhibits DNA replication by competitively inhibiting DNA polymerase and directly incorporating into the viral DNA polymer to cause termination of the DNA chain.
- Determined in European studies to be as effective as acyclovir ointment in herpetic keratitis.
 - Might result in more rapid healing in comparison.

Ganciclovir Gel

- Side Effects are Limited
 - Mild irritation and visual disturbances.
 - Medication is formulated with pH of 7.45 increasing the tolerability of this over Viroptic.
 - The drop given at 5X/day provides a dose of 0.375 mg total (which is less than 0.1%) of the oral/IV dose given so systemic SE's are virtually impossible.
- Not studied for use in children <2.
- Pregnancy C.

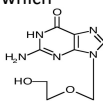
Anti-virals

- Zidovudine: It can treat HIV infection, which causes AIDS. It can also be used during childbirth to keep the mother from passing HIV to her baby.
- **Valacyclovir** is converted to acyclovir and L-valine by first-pass intestinal and/or hepatic **metabolism**
- Famciclovir: is an oral prodrug of penciclovir which has a broad spectrum antiviral activity against HSV-1, HSV-2, VZV, and EBV.
- **Ribavirin**, also known as tribavirin, is an antiviral medication used to treat RSV infection, hepatitis C and some viral hemorrhagic fevers.

Acyclovir (Zovirax^R)

Acyclovir (Zovirax^R)

- Purine analogue to guanine.
- Selective for viral DNA, thus minimally toxic to host cell.
 - Phosphorylated by virally-encoded thymidine kinase and cellular enzymes, yielding acyclovir triphosphate, which competitively inhibits viral DNA polymerase.
 - Specific for HSV-1, HSV-2, and VZV.



Acyclovir (Zovirax)

- Available in:
 - IV Formulation
 - 200-mg capsules,
 - 400 and 800 mg tablets
 - 200 mg/teaspoon oral suspension for children
- Poor oral bioavailability, thus must be dosed frequently.
 - 10-30% gets absorbed
 - Short ½ life of 2 – 3 hours



Acyclovir Side Effects

- Side Effects Include:
 - Nausea and Vomiting
 - Abdominal Pains
 - Skin Rash and Photosensitivity
 - Headaches, dizziness, and confusion
- Most common reason patients discontinued therapy in HEDS study was upset stomach. This could be the result of having lactose as an inactive ingredient.
- Rarely causes seizures, coma, anemia, renal failure, and hepatitis – More with IV Medication.

Acyclovir (Zovirax)

- Eliminated via the kidneys – need to alter dose patients with renal issues.
 - Important the patient remains hydrated to prevent kidney problems from developing.
- Caution must be used in elderly, immunocompromised, pregnant/nursing, and patients with renal or liver disease.
 - Pregnancy Category B

Kidney Function Tests

- Kidney function:
 - BUN (blood urea nitrogen) and serum creatinine
 - Elevated in renal failure
 - Glomerular filtration rate
 - Reduced in chronic kidney disease/renal failure

Acyclovir Topical (Zovirax)

NOT ophthalmic!!!

- Available as both a 5% Cream and 5% ointment
 - Cream approved for treatment of herpes labialis (Cold Sores) only.
 - Ointment approved for treatment of genital herpes only.
- No studies have shown improved resolution of eyelid infections with the use of antiviral topicals at this time.

Valacyclovir (Valtrex^R) and Famciclovir

Valacyclovir (Valtrex^R)



- Pro-drug of acyclovir
 - After absorption, valacyclovir is 95% converted to acyclovir.
 - Provides greater oral bioavailability (3-5X better than Acyclovir) thus less frequency of dosing is required.
- Available in 500 mg and 1 g tablets

Famciclovir



- Pro-drug of penciclovir
 - Penciclovir is only available as topical for cold sores.
- After absorption, famciclovir is rapidly converted by intestinal and liver tissues to penciclovir.
 - Penciclovir is structurally similar to acyclovir but with much longer half-life.
- Available in 125 mg, 250 mg, and 500 mg **film-coated tablets** (taken without meals).

Varicella Zoster Virus

Varicella Zoster Virus



- Primary infection (Chickenpox) with Varicella frequently occurs during childhood.
 - In US commonly before age 10, but hits children at older ages in tropical countries.
- Symptoms of Primary Infection:
 - Febrile illness characterized by crops of pruritic maculopapular and vesicular lesions.
 - Primary infection can have ocular sequelae such as SPK and anterior uveitis.
- Virus is limited by cell-mediated immunity and becomes latent.

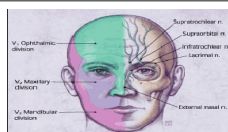
Herpes Zoster (Shingles)



- Found worldwide affecting both sexes equally.
- Herpes Zoster affects approximately 500,000 people in the US every year.
 - Highest incidence of all neurologic diseases.
 - Affects 50% of individuals living to age 85.

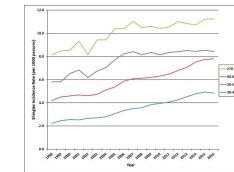
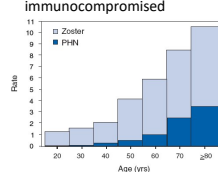
Zoster Reactivation

- Viruses pass along the sensory nerve where it has been latent in the ganglion.
 - Tissue innervated by that nerve (dermatome) becomes affected.
 - This reactivation occurs in 10 – 25% of the population.
- Thoracic ganglion is the most common site, followed by the trigeminal ganglion.
 - The ophthalmic division is 20X more affected than the maxillary or mandibular.



Herpes Zoster

- Associated factors include increasing age, immune deficiency and stress.
 - Traditionally thought to only affect patients over the age of 60 and those patients under 60 should be worked up for immune deficiency
 - Increasing trend to affect patients of younger age who are not immunocompromised



Herpes Zoster

- Only people who had natural infection with wild-type VZV or had varicella vaccination can develop herpes zoster.
- Children who get the varicella vaccine appear to have a lower risk of herpes zoster compared with people who were infected with wild-type VZV
 - cuts the risk of shingles by more than half in children over two years old (Weinmann S et al. Incidence of herpes zoster among children: 2003–2014. *Pediatrics* 2019 Jun 10.
- A person's risk for herpes zoster increases sharply after 50 years of age.
- Almost 1 out of 3 people in the United States will develop herpes zoster during their lifetime.
- A person's risk of developing post-herpetic neuralgia also increases sharply with age.

Herpes Zoster Ophthalmicus

- If the ophthalmic division is involved ocular involvement will occur in 70% of the patients.
- If the nasociliary nerve is involved and lesions are found on the tip of the nose (Hutchinson's sign) or inner corner of the eye the risk of ocular involvement is much more likely.

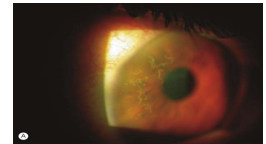
Signs and Symptoms of Shingles



- Flu-like illness (fever, malaise, headache, and chills) first.
 - Some patients may report pain, itching, burning, and stinging in the area of the nerve.
- 2-3 days later: Develop rash and vesicles
 - SEVERE Pain will be reported both while the lesions are present and after they heal.
 - Lesions will become pustular in 3-4 days and crust over in 7-10 days if untreated.
 - This will not cross the midline.
- Studies show the importance of initiating treatment in the first 48 hours.

Ocular Involvement in HZO

- Can develop days to years after the vesicles have formed.
- Signs:
 - Lid Edema
 - Follicular conjunctivitis
 - Corneal Changes
 - Uveitis
 - Optic Neuritis
 - EOM palsy
 - Chorioretinitis



Herpes Zoster

- Management includes:
 - oral antivirals:
 - 800mg acyclovir 5x/day
 - valacyclovir (Valtrex) 1g TID,
 - famciclovir (Famvir) 500 mg TID
 - effectiveness of therapy is best started within 72 hours
 - oral steroids, and
 - management of pain (tricyclic antidepressants, gabapentin).
 - If ocular complications, consider topical steroids (Pred Forte QID).

NEW!! Shingrix HZ Vaccine

- Approved in US/Canada as of October 2017
- non-live antigen, to trigger a targeted immune response, with a specifically designed adjuvant to enhance this response and help address the natural age-related decline of the immune system
- Shingrix is 97% effective against shingles for people between the ages of 50 and 69 and 91% effective for people 70 or older.
- It is 91% effective against postherpetic neuralgia for people 50 and older.
- These rates are based on evidence presented to the committee from clinical trials with over 38,000 total participants.

NEW!! Shingrix HZ Vaccine

- recommended for healthy adults aged 50 years and older to prevent shingles and related complications
- recommended for adults who previously received the current shingles vaccine (*Zostavax*®) to prevent shingles and related complications
- the preferred vaccine for preventing shingles and related complications

Oral Dosages for HSK

- Acyclovir: 400 mg - 5X/day for 7 - 14 days
 - Preventative for HSK: 400 mg BID x 12 months
- Valacyclovir: 500 mg - 3x/day for 7 - 14 days
 - Preventative for HSK: 500 mg Daily X 1 year
- Famciclovir: 250 mg - 3x/day for 7 - 14 days

Treatment for HZO

- Acyclovir: 800 mg – 5X/day for 7 - 14 days for healthy adults
 - If immunocompromised may need to consider 10 mg/kg IV q8hrs
- Valacyclovir: 1000 mg - 3x/day for 7 days
- Famciclovir: 500 mg - 3X/day for 7 days
- ****Beneficial if treatment can begin within 72 hours of onset.

Antifungals

Fungal Infections



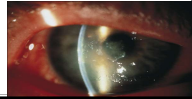
- Keratomycosis are relatively rare in developed countries.
 - ~ 1500 Cases/Year in the United States.
- Fungi are opportunistic invaders which rarely infect a healthy cornea. Predisposing factors include:
 - Compromised cornea resulting from history of disease
 - History of Contact Lens Wear
 - Trauma, especially associated with vegetable material
 - Immunosuppression
 - Improper use of corticosteroids (suppressed immune system)

Fungal Ocular Infections

- Fungi can infect virtually every eye structure from the cornea to the entire uveal tract.
 - Ex) *Histoplasma* results in choroidal neovascular membranes.
- Most common fungi that cause corneal infection in the United States are:
 - *Fusarium*
 - *Aspergillus*
 - *Candida*

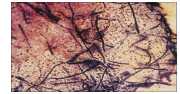
Fungal Keratitis: Signs and Symptoms

- Can appear very similar to bacterial ulcers:
 - Findings may depend on organism causing the mycosis.
 - *Fusarium*: Borders of the infiltrate often have feathery, poorly defined borders.
 - *Candida*: Yellow, White stromal appearance.
- Presume ulcers are bacterial until proven otherwise and treat with antibiotics until cultures show fungus.



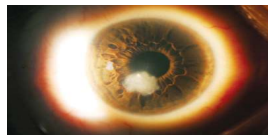
Treating Fungal Keratitis

- Corneal Damage results from:
 - Physical damage from fungal organism
 - Inflammatory Response
 - Secondary damage from fungal toxins/enzymes
- Superficial epithelium may heal while the organism continues to invade deeper corneal layers making the keratitis very difficult to treat completely.
- High Failure Rate Exists!



Antifungals

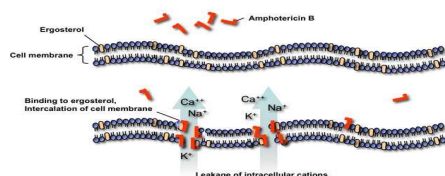
- All Antifungals have limits:
 - Poorly penetrate epithelium
 - Narrow spectrum of activity
 - Resistance
 - Significant side effects.
- 4 Classes Exist:
 - Used Commonly In Optometry:
 - Polyenes
 - Azoles
 - Not Used Commonly in Optometry:
 - Pyrimidines
 - Echinocandins



Polyenes

- Work by binding to ergosterol of cell membranes to increase permeability.
- Effective against filamentous and yeast fungi.
- Concentration dependent and rarely develop resistance.
 - Fungistatic at low levels and Fungicidal at high.
- Examples Include: Amphotericin B and Natamycin

Mechanism of Action



natamycin 5% (Natacyn)

- Only FDA approved and commercially prepared drop.
 - All other topicals must be compounded.
 - Brand name is manufactured by Alcon and sold in 15 mL bottle preserved with BAK.
- Broad spectrum of activity.
 - Drug of Choice for filamentous fungi.
- Well Tolerated SE's:
 - Hyperemia and Chemosis.
 - Length of treatment can lead to toxicity findings.
 - Pregnancy Category C.

Amphotericin B 0.15%

- Produced by a strain of bacteria: *Streptomyces nodosus*
- Drug of Choice for *Candida* infections.
 - Much less effective against filamentous fungi.
- ★ Compounded from IV medications to 0.15% - 0.3% topical.
 - Toxicity is much greater if use above 0.15%, but well tolerated.
 - Can also use intracamerally and intravitreally, but has very poor ocular bioavailability and causes retinal toxicity.
- Highly toxic IV with side effects such as anemia, renal disease, HA, fever, chills, nausea, vomiting, muscle and joint pain.
- Pregnancy Category B.

Treatment Regimen Suggested for Fungal Keratitis:

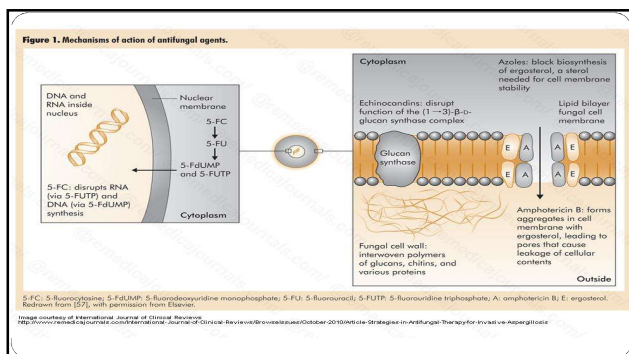
- Natamycin 5% drops or Amphotericin B 0.15% drops every hour to start.
 - Loading dose every 15 minutes for first hour.
 - Depending on clinical response can slowly taper medications.
 - Many doctors believe in rotating Natamycin/Amphotericin each hour.
- Alternative treatment: every 30 minutes for the first 24 hours, every hour for the second 24 hours, and then is slowly tapered according to the clinical response.
- Treatment will generally last at least 4 – 6 weeks.
- Need to perform debridement of superficial tissues so medications can penetrate to deeper layers.

Treatment Regimen Suggested for Fungal Keratitis:

- Consider adding oral anti-fungals for increasing severity.
 - Deeper ulceration
 - Multiple ocular structures
 - Poor immune system
- Most frequently used orals include:
 - Fluconazole, Voriconazole
- Treatment response will be slow and these patients should be examined daily (at least at first).

Azole Antifungals

- MOA: Impair the conversion of lanosterol into ergosterol by inhibiting the fungal cytochrome p-450 system, therefore the cell membrane cannot be formed efficiently and there is increased permeability leading to cell lysis and death.
- ★ Inhibits many cytochrome p-450 enzymes in humans also.
 - If patient is taking medications that undergo metabolism via the p-450 pathway they can reach toxic levels if administered with imidazoles or triazoles.
 - Meds include: Cyclosporine, warfarin, metformin, phenytoin, calcium channel blockers such as Verapamil, statins, etc.



Azole Antifungal Drugs

- Two Classes of Azoles Exist: Imidazoles and Triazoles.
 - Imidazoles Include: Ketoconazole, Miconazole
 - Triazoles Include: Fluconazole, Voriconazole, Itraconazole, and Posaconazole
- Imidazoles are used much less frequently today due to decreased efficacy and higher side effect profiles.

Ketoconazole (Nizoral)

- Imidazole that was the first successful broad spectrum antifungal that could be administered orally.
 - Effective against filamentous and yeast fungi.
 - Available as 200 mg tablet.
- Dosage:
 - 200 – 400 mg daily.
 - Absorption is improved with acidic gastric pH.
 - Can also be administered subconjunctivally to achieve effective corneal levels.

Ketoconazole (Nizoral)

- Side Effects: Hepatotoxicity, Papilledema, adrenal insufficiency, Headaches, dizziness, pruritus, and GI upset.
 - Potent inhibitor of CYP4A – must avoid drug interactions.
 - Excreted mainly via the liver – thus easy on the kidneys.
 - Pregnancy Category C
- Hepatotoxicity has earned this medication a BLACK BOX WARNING!

Fluconazole (Diflucan)

- Effective against most yeast species, but due to increasing resistance becoming less effective against *Aspergillus*.
- Available in 50, 100, 150, 200 mg tablets and IV formulation
- One of the best tolerated oral anti-fungals.
 - Main symptoms include GI upset and Rash.
 - 80% excreted unchanged in the urine – must consider renal function.

Fluconazole (Diflucan)

- Excellent oral bioavailability (~90%) due to hydrophilic nature.
 - Dosage: Loading dose of 200-400 mg, followed by 100-200 mg daily.
 - Absorption is not affected by gastric pH.
 - Medication has 24+ hour half-life.

Itraconazole (Sporanox)

- Very little clinical experience in treating fungal keratitis.
- Broader spectrum against fungi than fluconazole.
- Generic Available in 100 mg capsules.
 - Brand Name also has oral suspension.
- Highly variable bioavailability. Capsule needs acidic gastric pH (full stomach), but oral suspension should be taken on empty stomach.

Itraconazole (Sporanox)

- Extensively metabolized in the liver – must monitor for hepatotoxicity.
- Side Effects: Hypokalemia, drug interactions, GI problems, rash, cardiac dysrhythmias, HTN, edema, HA, etc.
 - This inhibits the cytochrome p450 pathway more than fluconazole.
- Contraindicated if CHF, renal impairment, hepatic impairment, sensitivity to other azoles, etc.
 - BLACK BOX WARNING for Heart damage.
- Pregnancy Category C (unlike other Triazoles which are D).

Voriconazole

- 2nd generation broad-spectrum triazole.
 - Derivative of fluconazole, with less resistance.
 - Drug of choice for *Aspergillus* infections, but also effective against *Fusarium*.
- ★ Dosage: 200 mg BID
 - Available as 50 and 200 mg tablets, oral suspension, and IV
 - Oral suspension is made from a powder, that can also be compounded into topical.
 - Excellent oral bioavailability when taken on an empty stomach.

Voriconazole (Vfend)

- Multiple contraindications exist for mixing with other medications, such as anti-retrovirals.
- Major Side Effects:
 - Visual changes such as seeing wavy lines and flashing are very common.
 - Rash are commonly reported.