

HERPETIC EYE DISEASE: FROM ACYCLOVIR TO ZOSTER
JESSICA STEEN OD, FAAO, DIPL.ABO




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On behalf of Vision Expo, we sincerely thank you for being with us this year.

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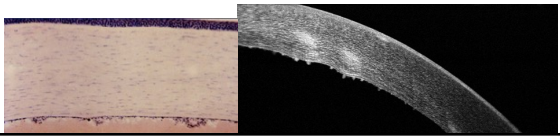
FINANCIAL DISCLOSURES

- Speaker-Carl Zeiss Meditec, Bausch and Lomb, Oyster Point Pharma, Thea Pharma, Alcon
- Advisory Board-Bausch and Lomb, Santen, Peripherex, OcuPhire, OcuTerra, Oyster Point Pharma, Allergan, Iveric Bio
- Shareholder-Clearside Biomedical (<0.01% ownership)
- All relevant relationships have been mitigated

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55 YEAR OLD BLACK MALE

- 2 week history of blurred vision OS
- No photophobia, ocular discomfort
- 20/25 OS; Stromal edema, Descemet's folds, KPs
- 2+ cells in the anterior chamber, I+ flare



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JUST ANOTHER ANTERIOR UVEITIS?

- Intraocular pressure: 12mmHg OS, **42mmHg OS**

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Now What?

- Why is the pressure 42mmHg?*
- Causes of hypertensive uveitis?*
- Lower the eye pressure in office?*
- How do we manage the inflammation?*
- How do we manage the most likely underlying cause?*

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HERPES SIMPLEX

- Primary HSV-1 infection following direct contact
 - At least 90% of the population carry latent HSV-1 by age 60
- Reactivation following a period of latency
 - Enters sensory neurons and moves into the sensory ganglia
 - Trigeminal ganglion
 - Ophthalmic division
 - Frontal nerve, nasociliary nerve, lacrimal nerve

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PRODUCT SELECTION

- Clinical presentation guides diagnosis
- Selective toxicity and resistance
- ADRs
- Route/mode of administration
 - Solutions/suspensions = conjunctiva, cornea
 - Ointments = may be better for external lid/lid margin
 - Oral = must be considered for internal infections
 - Oral antiviral agents for anterior segment disease

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FOR EFFECTIVE TREATMENT ...

- Accurate diagnosis
- Appropriate drug selection
 - Typically empirical
- Appropriate treatment strategy
 - Dosage, route of administration, patient characteristics, natural history of disease, ADRs, cost
- Informed follow-up

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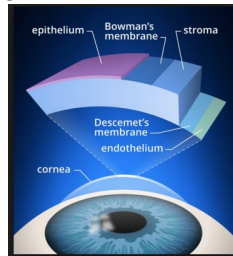
FAILURE OF THERAPY

- **May be due to:**
 - Inaccurate diagnosis
 - Organism resistance
 - Inadequate dosing regimen
 - Toxicity/allergy
 - Non-adherence

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Herpes Simplex Keratitis

Distinct mechanism of pathogenesis based on corneal layer



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HSV KERATITIS ORAL ANTIVIRAL DOSING

	HZV	Active HSV: Therapeutic dose (epithelial keratitis)	HSV prophylaxis (stromal keratitis without epithelial ulceration)
famciclovir	500mg TID 7-10 days	250mg BID-TID x 7-10 days	250mg BID
acyclovir	800mg 5x/day 7-10 days	400mg 3-5x/day x 7 days-10 days	400mg BID
valacyclovir	1g TID 7-10 days	500mg BID-TID x 7-10 days	500mg QD

▪ White, Chodosh 2014

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Which agent is best?

Acyclovir
Valacyclovir
Famciclovir

Most common adverse effects:

Headache
Nausea
GI upset

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SPECIAL POPULATIONS

- Pediatric patients
 - Acyclovir or valacyclovir
- Patients greater than the age of 65
 - Famciclovir may be preferred
- Pregnant patients
 - All agents are "FDA Pregnancy Category B"
 - May prefer acyclovir or valacyclovir
- **Caution and relative contraindication**
 - Kidney dysfunction

Remind patients to drink plenty of water while undergoing therapy!



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DRUGS DISEASES INTERACTION CHECK PILL ID CALCULATORS TABLES GUIDELINES

Drug Lookup: [input] Browse: Drugs All Meds Help FDA Reporting Form

Formulary: No Formulary Selected

valacyclovir

generic

Pregnancy/Lactation

Pregnancy
Clinical Summary
May use during pregnancy; no known risk of teratogenicity based on limited human data and on animal data up to 15x recommended human dose

Lactation
Clinical Summary
May use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production

Drug Monograph

- Entire Monograph
- Black Box Warnings
- Adult Dosing
- Pediatric Dosing
- Contraindications/Cautions
- Drug Interactions
- Adverse Reactions
- Safety/Monitoring

Pharmacology

- Formulary
- Manufacturer/Printing
- Patient Education
- Pill Pictures

PHV: Add to Interaction Check

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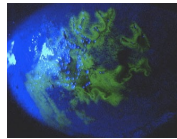
HYPERTENSIVE UVEITIS

- Herpes simplex virus should always be considered as an underlying cause
- Valacyclovir 500mg BID[®]
- Durezol QID (pink cap) OS
- Homatropine in office
 - Atropine 1% QD OS
- Dorzolamide-timolol BID OS
- Follow up?

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HSV EPITHELIAL KERATITIS

- Direct infection of epithelial cells
 - Active herpes virus
 - Requires **therapeutic** dosage of agent
- Acyclovir: 400mg 3-5 times per day for 7-10 days
- Valacyclovir: 500mg 2-3 times per day for 7-10 days
- Famciclovir: 250mg 2-3 times per day for 7-10 days



- Topical ocular antiviral medications may be considered in place of an oral agent[®]
- Corneal debridement

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EMERGING RESISTANCE

- Consider resistance of HSV-1 to acyclovir in immunocompromised individuals
 - Especially associated with prophylaxis and long-term treatment
- Most acyclovir-resistant HSV isolates are cross-resistant to penciclovir

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TOPICAL OPTIONS

- Zirgan (ganciclovir 0.15% ophth. gel); 5g
 - Inhibits viral DNA-polymerase
 - 5x per day in HSV epithelial keratitis until dendrite heals, then TID for approximately 5 more days
 - Preserved with BAK**
 - Preferred in pediatrics due to topical dosing
- Viroptic (trifluoridine 1%); 7.5mL
 - Toxic:** thimerosol & mechanism of action
 - Phosphorylation of thymidine kinase in viral and epithelial host cells
 - Prevents DNA synthesis
 - 9x/day until epithelium heals, then QID for one week
- Acyclovir ointment (acyclovir 3%)
 - Applied to herpetic skin pustules



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Risk of Recurrence of HSV Keratitis

- 9.6% at one year
- 22.9% at two years
- 40% at 5 years
- 67% at 10 years
- Liesegang TJ. Arch Ophthalmol 1989
- UV exposure, laser treatment, trauma, surgery increase risk of recurrence
- Immunosuppressive medications
 - Including steroids

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Herpes Simplex Blepharitis

Any concerns based on the patient's age?

Anything other than oral treatment?

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HERPES ZOSTER OPHTHALMICUS

- Occurs due to reactivation of the varicella zoster virus
- Prodromal sensation preceding vesicle development
 - Burning or shooting sensation

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HERPES ZOSTER PREVENTION

- Prevention of primary varicella zoster: chickenpox vaccine or MMRV
- **Prevention of herpes zoster**
 - Inactivated vaccine (Shingrix)
 - 2 dose series
 - 97% efficacy in patients aged 50-69; 91% effective in preventing PHN
 - 90% efficacy in patients older than 70 years; 89% effective in preventing PHN
 - Shorter, less severe disease course
 - Greater efficacy than the live attenuated vaccine (51% efficacy)
 - Those who have had the LA-vaccine should also receive the inactivated vaccine
 - Vaccination is still recommended after herpes zoster infection (at least 1 year)

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HERPES ZOSTER OPHTHALMICUS

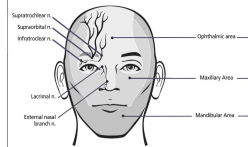
Herpes Zoster Ophthalmicus	
Acyclovir	800mg 5x/day for 7-10 days
Valacyclovir	1000mg TID for 7-10 days
Famciclovir	500mg TID 7-10 days

- Aim to treat within 72 hours of vesicle formation
- Hyperesthesia prior to vesicle formation
- Reduction in post-herpetic neuralgia
- More common in older individuals, those with more severe symptoms, and females

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HUTCHINSON'S SIGN

- If there is a lesion at the side of the nose and the eye looks uninvolved—go back and look again



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LONG-TERM OUTCOMES

- Prevention of recurrence
- Management of low grade, chronic inflammation
- ZEDS
 - Zoster Eye Disease Study
 - 12 month study: Valacyclovir 1000mg daily^{***} vs. masked placebo
 - Impact on the rate of new or worsening epithelial keratitis, stromal keratitis, endothelial keratitis or iritis vs. placebo
 - Does oral suppressive treatment reduce the severity and duration of post-herpetic neuralgia?
 - 780 patients; quadruple-masked; estimated completion date January, 2024

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Beyond Keratouveitis

*Cranial nerve palsy
"Tolosa Hunt Syndrome"
Optic neuritis*

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Keratouveitis

Trabeculitis

**Neurotrophic
Keratitis**

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CORTICOSTEROIDS

- Difluprednate 0.05% (Durezol)
- Increased bioavailability & longer duration of action
 - Therefore possibility of greater IOP spike
- In general-dosed 1/2 as frequently as prednisolone acetate 1%
- Emulsion-shaking is **not** necessary
- Durasite vehicle
- Not preserved with BAK (sorbic acid)



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DUREZOL

- What happens if you're treating an adult patient with acute anterior uveitis and after 6 days; IOP is 34mmHg?
 - Stop the steroid?
 - Taper the steroid?
 - Manage the pressure!
 - Prostaglandin analog vs. something else

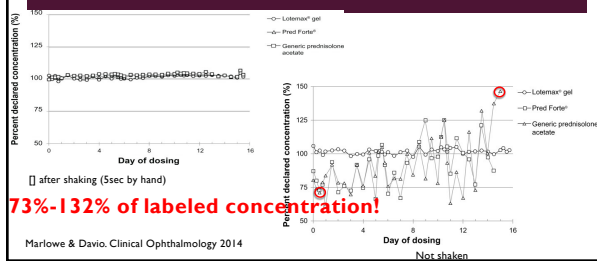
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CORTICOSTEROIDS

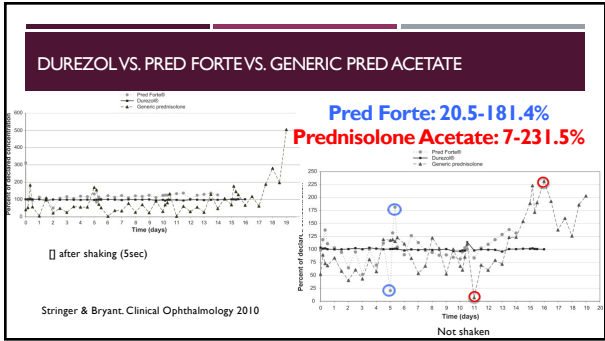
- Prednisolone acetate 1%
 - Suspension; preserved with BAK
 - Dosage based on severity of inflammation
 - Never less than QID to begin
 - Under-treatment is a significant concern
 - *What's the difference between branded and generic prednisolone acetate?*

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LOTEMAX VS. PRED FORTEVS. GENERIC PRED ACETATE



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- IMPACT OF LABELED CONCENTRATION VARIABILITY**
- Besides the obvious...
 - At first: drug levels not reaching clinical efficacy
 - Poor response to treatment—clinically appears as treatment failure
 - Change medication? Refer to uveitis specialist? Order serological evaluation?
 - Later: higher dose of steroid
 - Increased risk of adverse effect

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- BOTTOM LINE**
- Effective treatment begins with an accurate diagnosis
 - ...Which involves taking a very careful history
 - Carefully assess the risks and benefits of medication use prior to prescribing and monitor patients for effectiveness and side effects while undergoing treatment
 - Consider risk of recurrence and long-term complications in individuals with herpetic disease

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Thank you!

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