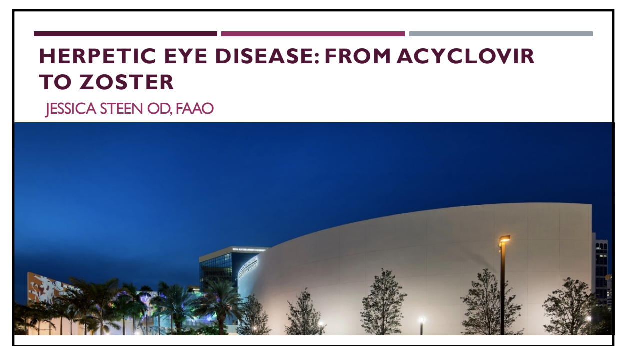
HERPETIC EYE DISEASE: FROM ACYCLOVIR TO ZOSTER

JESSICA STEEN OD, FAAO



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FINANCIAL DISCLOSURES

- None.

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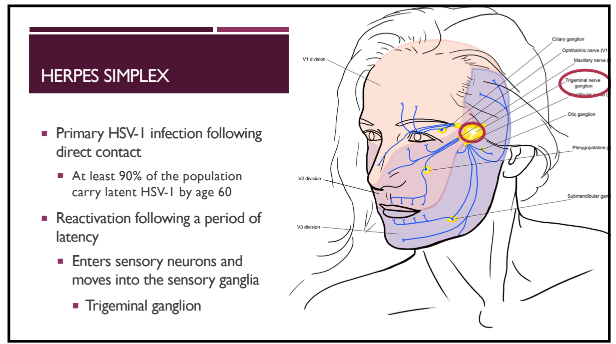
HERPES SIMPLEX



- 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

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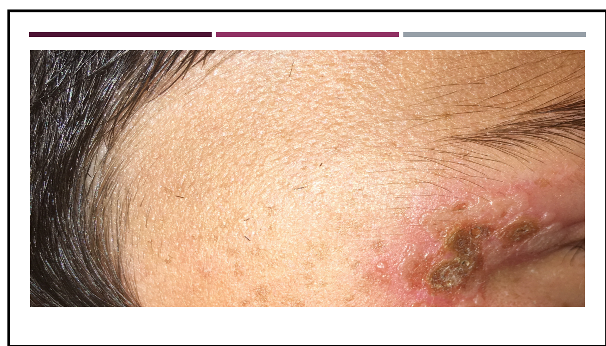

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Herpes Simplex Keratitis

Distinct mechanism of pathogenesis based on corneal layer

epithelium
Bowman's membrane
stroma
Descemet's membrane
endothelium
cornea

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PRODUCT SELECTION

- 1) Clinical presentation guides diagnosis
- 2) Selective toxicity and resistance
- 3) ADRs-allergy most common
- 4) Route/mode of administration
  - Solutions/suspensions = conjunctiva, cornea
  - Ointments = may be better for external lid/lid margin
  - Oral = must be considered for internal infections

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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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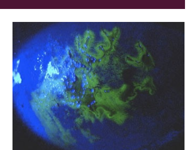
HSV EPITHELIAL KERATITIS



- 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*
- Corneal debridement

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TOPICAL OPTIONS (USA ONLY)

- 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 5%), vidarabine 3% (Vira-A)-compounded only
  - Applied to herpetic skin pustules

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HSV STROMAL KERATITIS

- Primarily due to **immune** response
- More common form of recurrent disease
  - Prophylactic dosage of antiviral + topical steroid
- Acyclovir: 400mg twice per day
- Valacyclovir: 500mg once per day
- Famciclovir: 125-250mg twice per day
- *Long term prophylaxis may reduce the likelihood of recurrence*

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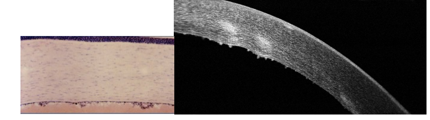
HERPES SIMPLEX STROMAL KERATITIS

- 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
- Valacyclovir 500mg BID** (+ Durezol QID, cyclopentolate TID)



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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

- Lactose intolerance
  - Valacyclovir preferred (generic)
- Pediatric patients
  - Acyclovir or valacyclovir
- Patients greater than the age of 65
  - Famciclovir 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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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 Ophthamol 1989

- UV exposure, laser treatment, trauma, surgery increase risk of recurrence
- Immunosuppressive medications
  - Including steroids

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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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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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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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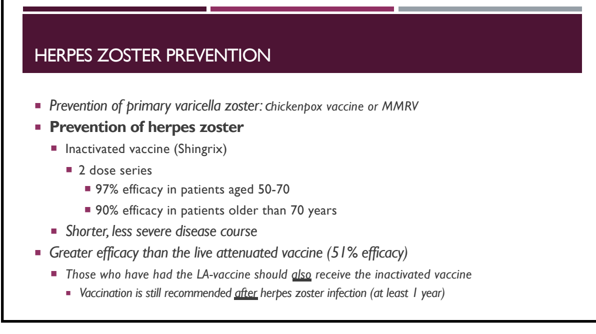

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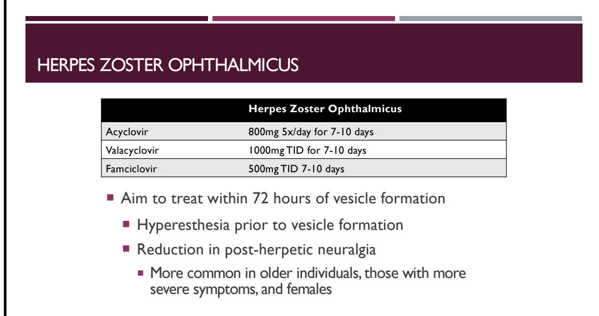

	Herpes Zoster Ophthalmicus
Acyclovir	800mg 5x/day for 7-10 days
Valacyclovir	1000mg TID for 7-10 days
Famciclovir	500mg TID 7-10 days

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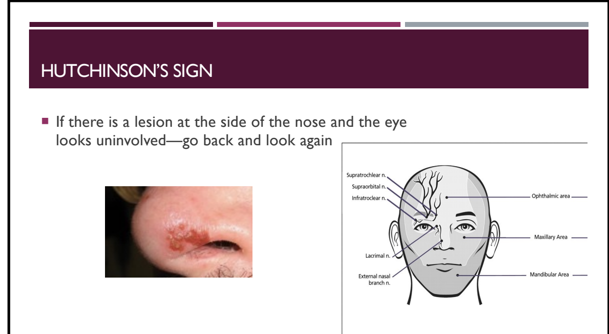

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Beyond Keratouveitis

Cranial nerve palsy
"Tolosa Hunt Syndrome"
Optic neuritis

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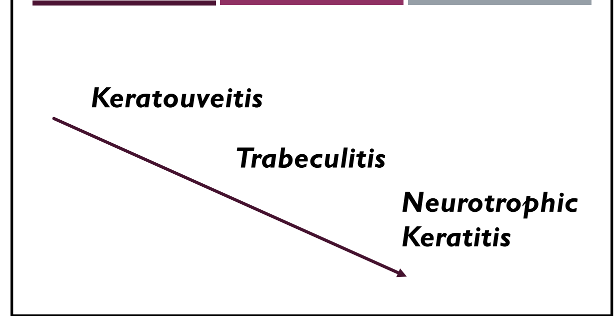

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HOW DO STEROIDS INCREASE INTRAOCULAR PRESSURE?

- Alter trabecular meshwork endothelial cells, cause accumulation of extracellular matrix, decrease phagocytosis, MMP/TIMPS balance
  - Intraocular pressure may remain elevated following discontinuation of the steroid

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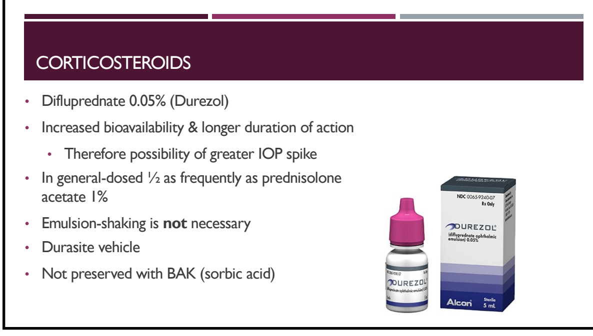
CORTICOSTEROIDS

- Difluprednate 0.05% (Durezol)
- Increased bioavailability & longer duration of action
  - Therefore possibility of greater IOP spike
- In general-dosed ½ 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 FORTE VS. GENERIC PRED ACETATE

Percent declared concentration (%)

Day of dosing

Lotemax® gel

Pred Forte®

Generic prednisolone acetate

[] after shaking (5sec by hand)

73%-132% of labeled concentration!

Marlowe & Davio. Clinical Ophthalmology 2014

Not shaken

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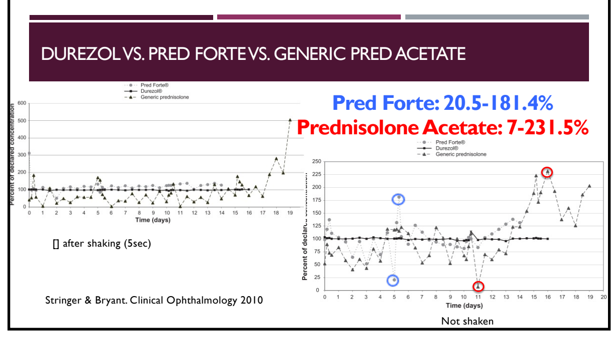
DUREZOL VS. PRED FORTE VS. GENERIC PRED ACETATE



[] after shaking (5sec)

Pred Forte: 20.5-181.4%

Prednisolone Acetate: 7-231.5%

Stringer & Bryant. Clinical Ophthalmology 2010

Not shaken

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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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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, actively recruiting!

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56 YEAR OLD FEMALE

- History of intraocular "pressure spikes" in the right eye for about ten years (40-60mmHg range); has never had an episode in the left eye
  - Currently taking brimonidine 0.1% BID OU, dorzolamide-timolol BID OU, and latanoprostene bunod 0.024% QHS OU
- Episodes occur every 4-5 weeks and respond well to topical steroids

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56 YEAR OLD FEMALE

- History of plaque psoriasis diagnosed in 2018; complete resolution of lesions with etanercept
  - TNF alpha inhibitor
- Gastric bypass May 2021
  - Discontinued etanercept perioperatively with no significant increase the number of ocular 'flare-ups'; but new psoriatic lesions on shins and lower arms

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THOUGHTS REGARDING HYPERTENSIVE EPISODES?

- What does the anterior chamber look like?
  - Anterior uveitis with elevated IOP should always be suspicious for underlying *Herpesviridae* infection
- What does the angle look like?
- Trabeculitis
- Scleritis
  - Can increase episcleral venous pressure
- **Posner-Schlossman syndrome or glaucomatocyclitis crisis**

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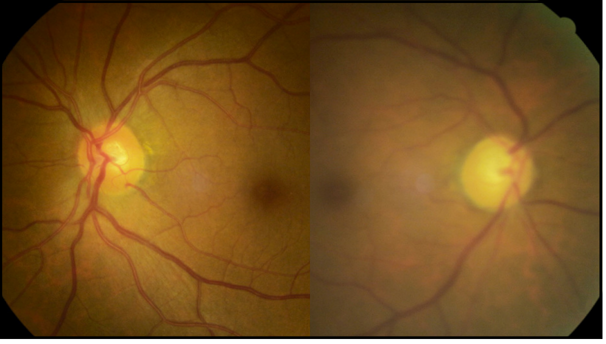

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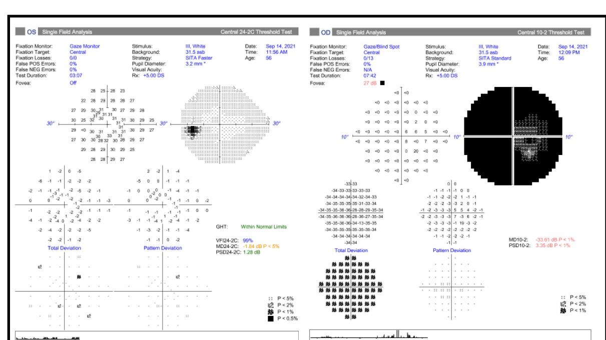

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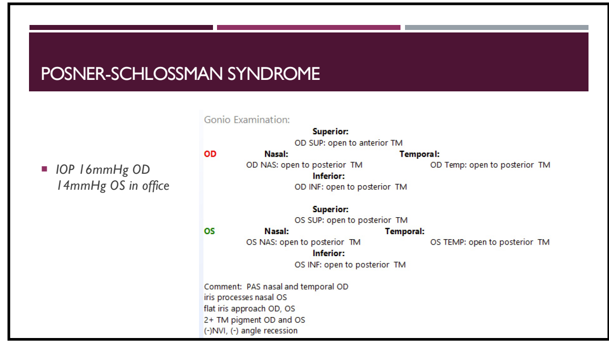
POSNER-SCHLOSSMAN SYNDROME

- *IOP 16mmHg OD 14mmHg OS in office*



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HAIL MARY?

- Well, some patients have underlying cytomegalovirus or *H. pylori* infection
  - Anterior chamber tap during an episode and PCR

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HAIL MARY?

- Is there a role for a prophylactic oral antiviral medication?
- Is there a role for oral (and/or topical) antiviral medication during an episode?
- Should patients be on long-term IOP lowering medication when IOP between episodes is low?
- Do these patients need incisional glaucoma surgery?

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Currently

s/p glaucoma drainage device

s/p cataract surgery, canaloplasty, goniotomy

Currently taking dorzolamide-timolol BID OD

…IOP 30mmHg

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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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