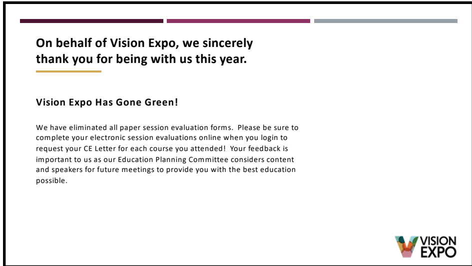

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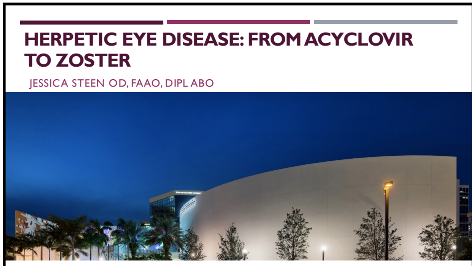

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FINANCIAL DISCLOSURES

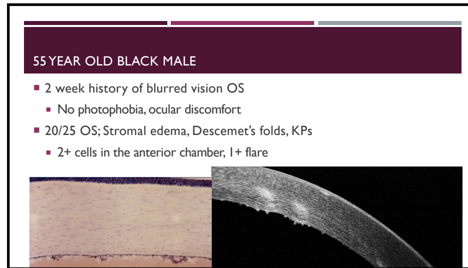
- Speaker-Carl Zeiss Meditec, Bausch and Lomb, Oyster Point Pharma, Thea Pharma, Alcon, Allergan
- Advisory Board-Bausch and Lomb, Carl Zeiss Meditec, Santen, Peripherex, Ocuphire, Ocuterra, Oyster Point Pharma, Allergan, Iveric Bio
- Shareholder-Clearside Biomedical (<0.01% ownership)

- *All relevant relationships have been mitigated*

3

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, 1+ 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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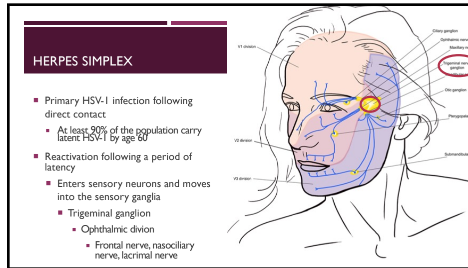

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PRODUCT SELECTION

- 1) Clinical presentation guides diagnosis
- 2) Selective toxicity and resistance
- 3) ADRs
- 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
    - 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

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

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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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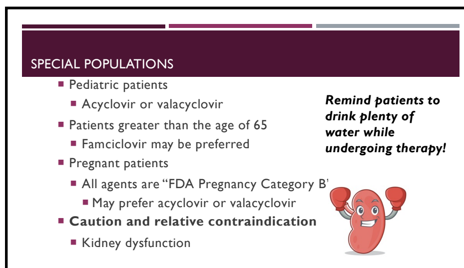

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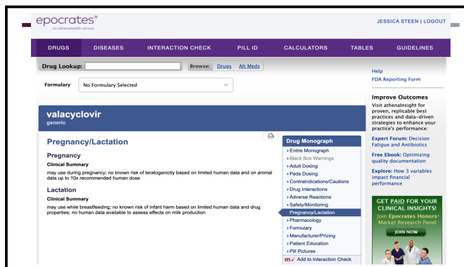

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HYPERTENSIVE UVEITIS

- 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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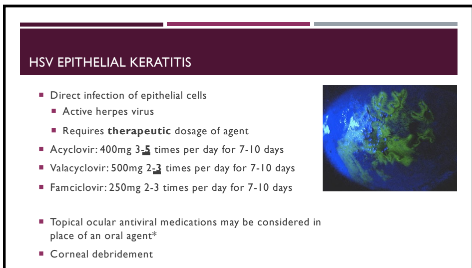
HSV EPITHELIAL KERATITIS

- 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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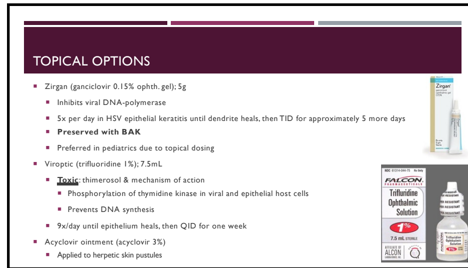

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Risk of Recurrence of HSV Keratitis

- 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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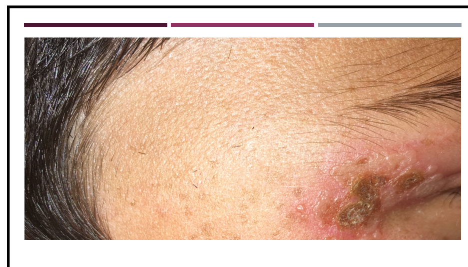

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Herpes Simplex Blepharitis

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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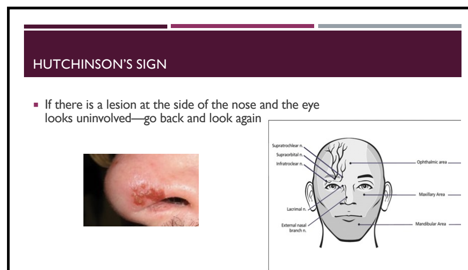

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LONG-TERM OUTCOMES

- 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?
    - 652 patients; quadruple-masked; estimated completion date 7-31-2024

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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 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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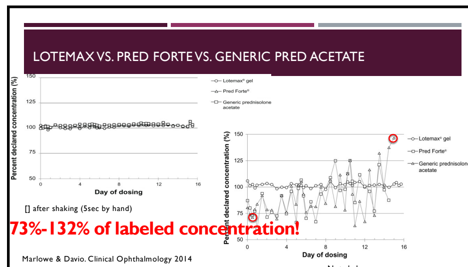
LOTEMAX VS. PRED FORTE VS. GENERIC PRED ACETATE



[] after shaking (5sec by hand)

73%-132% of labeled concentration!

Not shaken

Marlowe & Davio. Clinical Ophthalmology 2014

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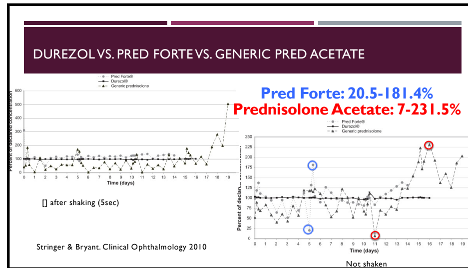

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IMPACT OF LABELED CONCENTRATION VARIABILITY

- 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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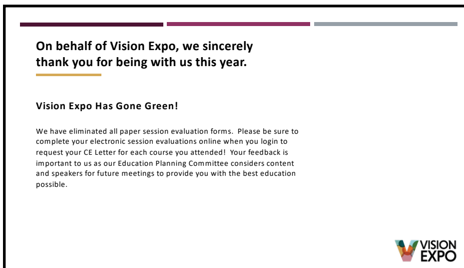

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