

# What's new with the Herpes Family ?

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CORNEA ASSOCIATES OF TEXAS  
DALLAS, TEXAS

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▶ I have no financial disclosures that pertain to this presentation

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- ▶ Clinical review of herpes simplex keratitis and herpes zoster ophthalmicus
- ▶ Look at national studies that may guide current or future treatment protocols

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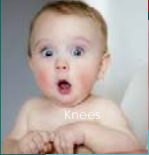
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### Herpes simplex review

- ▶ Major cause of visual morbidity worldwide
- ▶ 90% of adults are seropositive for HSV virus
- ▶ Only 25% of inoculated individuals develop clinical manifestations
  - ▶ Majority-herpes labialis
- ▶ 500,000 active HSV cases in USA per annum
- ▶ Ocular infection usually unilateral
- ▶ Bilateral cases occur rarely (1.3-12%)
  - ▶ Childhood
  - ▶ Atopic disease



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### Herpes simplex review

- ▶ Epithelial disease
  - ▶ Compromises 2/3 of ocular cases
  - ▶ Typically dendritic
    - ▶ May resolve spontaneously
    - ▶ Usually requires treatment
      - ▶ Zigan 5X daily for 10 days
    - ▶ May evolve into geographic ulcer
- ▶ Stromal keratitis
  - ▶ Non-necrotizing (interstitial keratitis)
  - ▶ Necrotizing
    - ▶ Stromal keratitis with progressive ulceration



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### Herpes simplex review

- ▶ Endothellitis
  - ▶ Disciform
  - ▶ Diffuse
  - ▶ Linear
- ▶ Iridocyclitis
  - ▶ May cause rise in IOP
  - ▶ Iris transillumination (ischemia)
- ▶ Corneal transplantation and HSV
  - ▶ Recurrence in donor
  - ▶ Acquired disease high (chronic steroid use)



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## Herpetic Eye Disease Study (HEDS 1)

Ophthalmol 1994;101:1871-1896

- ▶ Published in 1994
- ▶ Evaluated currently available protocols
  - ▶ Antivirals
    - ▶ Acyclovir
    - ▶ Trifluridine
  - ▶ Topical steroid
    - ▶ Prednisolone phosphate, prednisolone acetate



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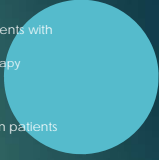
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## Herpetic Eye Disease Study (HEDS 1)

Ophthalmol 1994;101:1871-1896

- ▶ 1. Efficacy of topical steroid combined with trifluridine in patients with stromal keratitis
  - ▶ Faster resolution, fewer treatment failures with pred phosphate therapy
  - Topical steroid routine for stromal keratitis
- ▶ 2. Efficacy of oral ACV and concomitant steroid/trifluridine in patients with stromal keratitis
  - ▶ No statistical clinical benefit of oral acyclovir
    - ▶ Time to treatment failure occurred sooner in placebo group
    - ▶ Visual acuity improvement was greater in the ACV group
  - Adjunctive ACV for stromal keratitis controversial but frequently used



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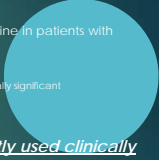
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## Herpetic Eye Disease Study (HEDS 1)

Ophthalmol 1994;101:1871-1896

- ▶ 3. Efficacy of oral ACV combined with topical steroid/trifluridine in patients with iridocyclitis
  - ▶ Treatment failures occurred at a higher rate in placebo group
  - ▶ Findings suggestive of efficacy but trial numbers too small to be statistically significant

Benefit of adding Acyclovir not clear but frequently used clinically



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## Herpetetic Eye Disease Study (HEDS 2)

NEJM 1998; 339:300-6

- ▶ 1. Efficacy of low dose ACV (400 mg BID) in preventing recurrent HSV in patients with previous eye disease
  - ▶ Reduced by 41% the probability that any form of HSV would recur
  - ▶ Reduced the recurrence of stromal keratitis by 50%
  - ▶ Reduced the recurrence of epithelial keratitis from 11% to 9%

*Commonly used for prophylaxis in patients with stromal keratitis, selectively in epithelial disease*
- ▶ 2. Efficacy of ACV in preventing stromal/iridocyclitis in patients with epithelial disease
  - ▶ No preventative benefit of adding oral ACV to topical trifluridine

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## Herpes Zoster Ophthalmicus (HZO)

- REVIEW CLINICAL FINDINGS AND TREATMENT
- NEW TRENDS IN OUR THINKING ABOUT HZO
- NEW NATIONAL STUDY

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## Herpes Zoster

- ▶ Varicella Zoster virus
  - ▶ Varicella (chicken pox)
  - ▶ Herpes zoster (shingles)
- ▶ Prior to vaccination
  - ▶ Reactivation of latent virus from childhood
    - ▶ Varicella vaccine approved 1995
- ▶ Risk factors
  - ▶ Increasing age
  - ▶ Immunosuppression (malignancy, HIV, organ transplants)




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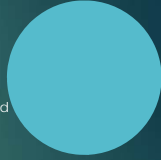
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## Herpes Zoster

- ▶ This is a common disease
  - ▶ 1,000,000 cases per year in USA
  - ▶ 1 in 3 in US will get zoster/shingles
    - ▶ 1 in 2 who live to 80 years old
    - ▶ 50X more common in immunocompromised
      - ▶ More severe
  - ▶ 1 in 4 immunocompetent will get zoster
  - ▶ 1-2 % of the population will have HZO




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## Age at Onset of Zoster

- ▶ Merck study: rate goes up with age, but number of cases increases in 40's, peaks in 50's-70's
  - ▶ Insigna J Gen Intern Med 2005
- ▶ US study of 1000 HZ cases
  - ▶ Mean age of onset 51.7 years
    - ▶ Hernandez J Clin Virol 2011
- ▶ Geriatric HZ 57.8% of patients < 60 years
  - ▶ Rogers J Am Geriatric Soc 1971



*HZ- not just a disease of elderly*

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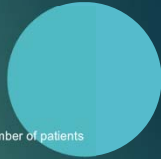
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## Age at diagnosis (HZO) at Wills Ghaznawi Ophthalmology 2011;118:2242-50




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## Herpes Zoster

- ▶ Systemic manifestations
  - ▶ Dermatitis
  - ▶ Pneumonia
  - ▶ Septicemia
  - ▶ CNS vasculitis
  - ▶ Cranial nerve palsies
  - ▶ Myelitis
  - ▶ Meningitis



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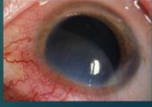



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## Herpes Zoster Ophthalmicus

- ▶ Ophthalmic findings
  - ▶ Vesicular skin rash V1-3
  - ▶ Episcleritis, scleritis
  - ▶ Cornea
    - ▶ Punctate keratitis
    - ▶ Pseudodendrites
    - ▶ Sclerokeratitis
    - ▶ Disciform keratitis
    - ▶ Neurotrophic keratitis



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## Herpes Zoster Ophthalmicus

- ▶ Treatment of acute HZO
  - ▶ ASAP (usually within 72 hours of onset)
    - ▶ Oral acyclovir 800 mg 5x/day 7 days
    - ▶ Oral valacyclovir 1000 mg 3x/day 7 days
    - ▶ Oral famvir 250 mg 3x/day 7 days



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# Herpes Zoster Ophthalmicus

- ▶ Treatment of HZO
  - ▶ Additional treatment according to type of involvement
    - ▶ Usually topical steroid and lubricants
    - ▶ Traditionally, most manifestations felt to be immunologic



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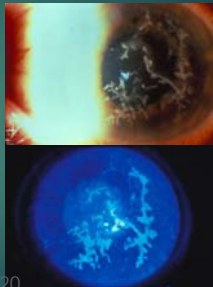
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# HZO Recent studies

- ▶ Evidence that Herpes Zoster is associated with chronic active infection with the varicella zoster virus (VZV)
- ▶ Chronic infection contributes to
  - ▶ Chronic ocular disease
    - ▶ Dendritic keratitis PCR:
      - ▶ Pavan Langston D. Arch Ophthalmol 1995; 113:1381-5
      - ▶ Hu AY. Am J Ophthalmol 2010; 149:214-220
  - ▶ Postherpetic neuralgia
  - ▶ Strokes, temporal arteritis
    - ▶ Gilken D. Future Neurol 2009; 4:103-117
    - ▶ Nagesh. Neurology. 2103; 80:2017-2021



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# Herpes Zoster Ophthalmicus

- ▶ Paradigm Shift #1
  - ▶ Increased frequency of antivirals
    - ▶ Oral
    - ▶ Topical ganciclovir (@Zirgan)



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### Antiviral Therapy in Herpes simplex

- ▶ Herpetic Eye Disease Study (HEDS) Acyclovir Prevention Trial (APT)
  - ▶ Herpetic Eye Disease Study Group N Eng J Med 1998; 339:300-306
  - ▶ Long-term suppressive treatment with oral acyclovir resulted in 45% reduction in recurrent Herpes Simplex Virus (HSV) disease over 1 year
  - ▶ Antiviral treatment was most beneficial in reducing stromal keratitis

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### Herpes Zoster Ophthalmicus

- ▶ Paradigm Shift #2
  - ▶ Should we treat all HZO patients with antiviral suppression for one year ?
  - ▶ Do we have any evidence in the current literature ?

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### Herpes Zoster Ophthalmicus

- ▶ Zoster Eye Disease Study (ZEDS)
  - ▶ To study the efficacy of long term oral antiviral treatment

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### Zoster Eye Disease Study (ZEDS)

NIH trial to study the efficacy of long term oral antiviral treatment

- ▶ Principal Investigator/Study Chair
  - ▶ Elisabeth Cohen, MD
    - ▶ New York
- ▶ Study Co-Chair
  - ▶ Bennie Jeng, MD
    - ▶ Baltimore
- ▶ Funded by The National Eye Institute

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### Rationale for Zoster Eye Disease Study (ZEDS)

- ▶ Multicenter, randomized, double masked, placebo controlled study
- ▶ Enroll 1050 immunocompetent patients
- ▶ Inclusion criteria of HZO (unilateral vesicular rash V1 distribution) with an episode of epithelial dendritic keratitis, stromal keratitis, endothelial keratitis, or iritis in the year prior to enrollment

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### Rationale for Zoster Eye Disease Study (ZEDS)

- ▶ ZEDS trial analogous to the HEDS APT study for ocular disease caused by varicella zoster virus (VZV)
- ▶ Valacyclovir, prodrug of acyclovir, chosen due to higher plasma concentrations achieved, which are more effective against VZV
- ▶ 1 gram daily for one year
- ▶ Exams every 3 months for 18 months

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### Rationale for Zoster Eye Disease Study (ZEDS)

- ▶ In addition to primary endpoint of reduced new or worsening ocular disease during treatment, secondary endpoints include reduction of incidence, duration and severity of postherpetic neuralgia, and treatment effect following completion of study medication
- ▶ *If suppressive valacyclovir effective with regard to PHN, may benefit persons with HZ elsewhere, in addition to HZO*
- ▶ *Projected start of ZEDS in 2nd quarter 2017*
  - ▶ *Enrollment is now open and study has started*
- ▶ *Cornea Associates of Texas IS a Texas Study Site*

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- ▶ Jennifer Raines
  - ▶ Clinical Research Director
- ▶ Greg Nettune, MD
  - ▶ Medical Monitor
  - ▶ All CAT physicians are participating

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