GOING VIRAL: HZO, HSV, EKC

Nate Lighthizer, O.D., F.A.A.O.
Assistant Dean, Clinical Care Services
Director of Continuing Education
Chief of Specialty Care Clinics
Chief of Electrodiagnostics Clinic
Oklahoma College of Optometry
lighthiz@nsuok.edu

1

Disclosures

- Aerie Pharmaceuticals
- Biotissue
- Diopsys
- Ellex
- EyePromise
- Ivantis
- Lumenis
- Maculogix
- Nidek
- Nova Ocular
- Novartis
- Optovue
- Quantel
- Reichert
- RevolutionEHR
- Sight Sciences
- Shire
- Sun Pharma

2

Expected Learning Objectives

- To enable OD's to provide latest in care for viral eye diseases
- At the end of the session, attendees should be able to:
  - To become familiar with the risk factors for developing HSV.
  - To become familiar with the most common ocular symptoms/signs of HSV.
  - To become familiar with the most common ocular treatments for HSV.
  - To become familiar with the risk factors for developing HZO.
  - To become familiar with the most common ocular symptoms/signs of HZO.
  - To become familiar with the most common ocular treatments for HZO.
  - To become familiar with the risk factors for developing EKC.
  - To become familiar with the most common ocular symptoms/signs of EKC.
  - To become familiar with the most common ocular treatments for EKC.

3

Herpes Zoster

- Nearly 1 million Americans develop shingles each year
- Ocular involvement accounts for up to 25% of presenting cases
- Over 50% incur long term ocular damage

4

Herpes Zoster

Varicella-Zoster Virus

- Herpes DNA virus that causes 2 distinct syndromes
  1. Primary infection – Chicken pox (Varicella)
     - Usually in children
     - Highly contagious***
     - Very itchy maculopapular rash with vesicles that crust over after ≈ 5 days
     - 96% of people develop by 20 years of age
     - Vaccine now available

5

Herpes Zoster

- Herpes DNA virus that causes 2 distinct syndromes
  2. Reactivation – Shingles (Herpes Zoster)
     - More often in the elderly and immunosuppressed (AIDS)
       - Systemic work-up if Zoster in someone < 40
     - Can get shingles anywhere on the body
     - Herpes Zoster Ophthalmicus (HZO)
       - Shingles involving the dermatome supplied by the ophthalmic division of the CNV (trigeminal)
         - 15% of zoster cases

6

Herpes Zoster

- Symptoms:
  - Generalized malaise, tiredness, fever
  - Headache, tenderness, paresthesias (tingling), and pain on one side of the scalp***
    - Will often precede rash
  - Rash on one side of the forehead
  - Red eye
  - Eye pain & light sensitivity

7

Herpes Zoster

- Signs:
  - Maculopapular rash -> vesicles -> pustules -> crusting on the forehead
  - Respects the midline***
  - Hutchinson sign
    - rash on the tip or side of the nose***
  - Classically does not involve the lower lid
  - Numerous other ocular signs

8

Herpes Zoster

- Other Eye Disease (Acute):
  - Acute epithelial keratitis (pseudodendrites)
  - Conjunctivitis
  - Stromal (interstitial) interstitial keratitis
  - Endotheliitis (disciform keratitis)
  - Neurotrophic keratitis

9

Herpes Zoster

- Other Eye Disease (Acute):
  - Episcleritis
  - Scleritis
  - Anterior uveitis
  - IOP elevation
  - Retinitis
  - Choroiditis
  - Neurological complications (nerve palsies)
  - Vascular occlusion

  - Treat the complications just like as if they were primary conditions

10

Herpes Zoster

- Treatment:
  - Treat the complications just like as if they were primary conditions
  - Oral antivirals – must be started within 72 hours of symptoms**
    - Acyclovir 800mg 5x/day x 7-10 days
    - Valtrex 1000mg 3x/day X 7-10 days
    - Famciclovir 500mg 3x/day X 7-10 days
  - Topical ointment to skin lesions to help prevent scarring
    - Bacitracin, erythromycin

11

Herpes Zoster

- Prevention:
  - Zostivax vaccine
    - Live attenuated herpes virus
    - Only given to people who know they had chicken pox as a child***
    - Only studied in patients > 60 yo
      - 51% reduction in incidence of HZ
      - 60% reduction in symptom severity in those who got HZ
      - 66.5% reduction in post-herpetic neuralgia

12

Shingrix Vaccine

- Shingrix is a non-live vaccine given intramuscularly in two doses.
- 38,000 patients in a phase III clinical tria
  - >90% efficacy sustained over 4 years

13

Shingrix vs. Zostivax

- Shingrix:
  - <u>Efficacy in preventing shingles:</u>
  - 96.6% effective in 50-59 year olds
  - 97.4% effective in 60-69 year olds
  - > 70 year olds
    - 97.6% in year 1
    - 84.7% in years 2-4
  - <u>Efficacy in preventing PHN</u>
    - 91.2% in > 50 year olds
    - 88.8% in > 70 year olds
  - More cost effective
  - Lasts longer
- Zostivax:
  - <u>Efficacy in preventing shingles:</u>
  - 70% effective in 50-59 year olds
  - 64% effective in 60-69 year olds
  - > 70 year olds
    - 38%
  - <u>Efficacy in preventing PHN</u>
    - 65.7% in 60-69 year olds
    - 66.8% in > 70 year olds

14

RZV use in immunocompetent adults aged ≥50 years. With high efficacy among adults aged ≥50 years, and modest waning of protection over 4 years following vaccination, RZV has the potential to prevent substantial herpes zoster disease burden. Vaccinating adults starting at age 50 will prevent disease incidence in midlife, and the vaccine will likely continue to provide substantial protection beyond 4 years as recipients age.

RZV use in immunocompetent adults who previously received ZVL. In separate clinical trials, RZV estimates of efficacy against herpes zoster were higher than ZVL estimates in all age categories. The difference in efficacy between the two vaccines was most pronounced among recipients aged ≥70 years. Studies have shown that ZVL effectiveness wanes substantially over time, leaving recipients with reduced protection against herpes zoster. RZV elicited similar safety, reactogenicity, and immunogenicity profiles regardless of prior ZVL receipt; therefore, ZVL recipients will likely benefit from vaccination with RZV.

Current herpes zoster infection. RZV is not a treatment for herpes zoster or postherpetic neuralgia and should not be administered during an acute episode of herpes zoster.

Pregnancy and breastfeeding. There are no available data to establish whether RZV is safe in pregnant or lactating women and there is currently no ACIP recommendation for RZV use in this population. Consider delaying vaccination with RZV in such circumstances.

General use. RZV may be used in adults aged ≥50 years, irrespective of prior receipt of varicella vaccine or ZVL, and does not require screening for a history of chickenpox (varicella). ZVL remains a recommended vaccine for prevention of herpes zoster in immunocompetent adults aged ≥60 years (*6*). Care should be taken not to confuse ZVL, which is stored in the freezer and administered subcutaneously, with RZV, which is stored in the refrigerator and administered intramuscularly.

Dosing schedule. Following the first dose of RZV, the second dose should be given 2–6 months later (*1*). The vaccine series need not be restarted if more than 6 months have elapsed since the first dose; however, the efficacy of alternative dosing regimens has not been evaluated, data regarding the safety of alternative regimens are limited (*30*), and individuals might remain at risk for herpes zoster during a longer than recommended interval between doses 1 and 2. If the second dose of RZV is given less than 4 weeks after the first, the second dose should be repeated. Two doses of the vaccine are necessary regardless of prior history of herpes zoster or prior receipt of ZVL.

15

Timing of RZV for persons previously vaccinated with ZVL. Age and time since receipt of ZVL may be considered to determine when to vaccinate with RZV. Studies examined the safety and immunogenicity of RZV vaccination administered ≥5 years after ZVL (*21*); shorter intervals have not been studied. However, there are no data or theoretical concerns to indicate that RZV would be less safe or less effective when administered at an interval of <5 years. Clinical trials indicated lower efficacy of ZVL in adults aged ≥70 years; therefore, a shorter interval may be considered based on the recipient's age when ZVL was administered. Based on expert opinion, RZV should not be given <2 months after receipt of ZVL.

Persons with a history of herpes zoster. Herpes zoster can recur. Adults with a history of herpes zoster should receive RZV. If a patient is experiencing an episode of herpes zoster, vaccination should be delayed until the acute stage of the illness is over and symptoms abate. Studies of safety and immunogenicity of RZV in this population are ongoing.

Persons with chronic medical conditions. Adults with chronic medical conditions (e.g., chronic renal failure, diabetes mellitus, rheumatoid arthritis, and chronic pulmonary disease) should receive RZV.

Immunocompromised persons. As with ZVL, the ACIP recommends the use of RZV in persons taking low-dose immunosuppressive therapy (e.g., <20 mg/day of prednisone or equivalent or using inhaled or topical steroids) and persons anticipating immunosuppression or who have recovered from an immunocompromising illness (*6*). Whereas RZV is licensed for all persons aged ≥50 years, immunocompromised persons and those on moderate to high doses of immunosuppressive therapy were excluded from the efficacy studies (ZOE-50 and ZOE-70), and thus, ACIP has not made recommendations regarding the use of RZV in these patients; this topic is anticipated to be discussed at upcoming ACIP meetings as additional data become available.

Persons known to be VZV negative. Screening for a history of varicella (either verbally or via laboratory serology) before vaccination for herpes zoster is not recommended. However, in persons known to be VZV negative via serologic testing, ACIP guidelines for varicella vaccination should be followed. RZV has not been evaluated in persons who are VZV seronegative and the vaccine is not indicated for the prevention of chickenpox (varicella).

16

Herpes Zoster

- Post-herpetic Neuralgia
  - Constant or intermittent pain that persists for more than one month after the rash has healed
  - Older patients with early severe pain and larger area are at greater risk
  - Can be so severe that it leads to depression & suicide
  - Improves with time
    - Only 2% of pts affected 5 years out
  - Tx:
    - Cool compresses
    - Topical capsaicin ointment or lidocaine cream
    - Analgesics (Tylenol 3, Vicoden)
    - Amitriptyline 25mg PO TID
    - Neurotin (Gabapentin)

17

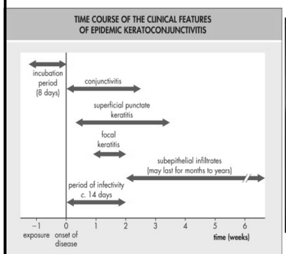
Viral conjunctivitis

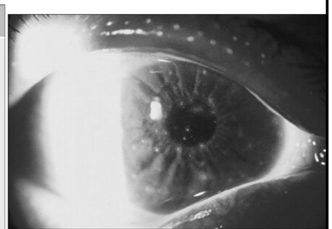
- Signs:
  - Red eye (conj hyperemia)
  - Watery discharge
  - Follicles in the inferior fornix & conj
  - (+) PA node***
  - Red/swollen eyelids
  - Petechial sub-conj hemes
  - SPK
  - SEI's (sub-epithelial infiltrates)
  - Pseudomembranes/membranes often seen in EKC

18

EKC

- Timecourse





19

Viral conjunctivitis

- Signs:
  - Red eye (conj hyperemia)
  - Watery discharge
  - Follicles in the inferior fornix & conj
  - (+) PA node***

  - Red/swollen eyelids
  - Petechial sub-conj hemes
  - SPK
  - SEI's (sub-epithelial infiltrates)
  - Pseudomembranes/membranes often seen in EKC

20

EKC conjunctivitis

- Diagnosis
  - Based on clinical symptoms
- Treatment:
  - Cool compresses
  - Artificial tears
  - "get the red out drops"
    - Vasoconstrictors such as Visine
  - Hygiene***
  - Quarantine/Isolation

  - Betadine 5% solution???
  - Zirgan???
  - Lotemax/Pred Forte QID??? – not until late

21

EKC conjunctivitis

- Diagnosis
  - Based on clinical symptoms
- Treatment:
  - Cool compresses
  - Artificial tears
  - "get the red out drops"
    - Vasoconstrictors such as Visine
  - Hygiene***
  - Quarantine/Isolation

  - Betadine 5% solution???
  - Zirgan???
  - Lotemax/Pred Forte QID??? – not until late

22

Off-Label Adenoviral Treatments

- Povidone Iodine (0.4%) – Dexamethasone (0.1%)
  - 9 eyes of 6 patients with confirmed Adenovirus enrolled
  - 8/9 enrolled showed clinical resolution by day 4
  - 6/6 patients with significant reduced DNA copies by day 5
  - 5/6 cultures positives with no infectivity by day 5

23

Herpes Simplex

- Most common virus found in humans
  - 60-99% are infected by 20 years old
- Double stranded DNA virus
  - HSV type 1 (HSV-1)
  - HSV type 2 (HSV-2)

- Primary infection
  - Occurs in childhood via droplet exposure
  - Subclinical infection in most
- Secondary infection (recurrence)

24

Herpes Simplex

- Recurrent infection:
  - After primary infection the virus is carried to the sensory ganglion for that dermatome (trigeminal ganglion) where a latent infection is established.
  - Latent virus is incorporated in host DNA and cannot be eradicated
  - Stressors (trauma, UV light, fever, hormonal changes, finals week, etc) cause reactivation of the virus and it is transported in the sensory axons to the periphery -> clinical signs/symptoms
  - Ocular recurrence -> 10% at one year, 50% at ten years

25

Herpes Simplex Keratitis

- **Epithelial Keratitis:**
  - Symptoms:
    - Ocular irritation, redness, photophobia, watering, blurred vision
  - Signs:
    - Swollen opaque epithelial cells arranged in a course punctate or stellate pattern
    - Central desquamation results in a dendrite***
      1. Central ulceration
      2. Terminal end bulbs
    - ***Corneal sensation is reduced***

26

Herpes Simplex Keratitis

- **Epithelial Keratitis:**
  - Symptoms:
    - Ocular irritation, redness, photophobia, watering, blurred vision
  - Signs:
    - Swollen opaque epithelial cells arranged in a course punctate or stellate pattern
    - Central desquamation results in a dendrite***
      1. Central ulceration
      2. Terminal end bulbs
    - ***Corneal sensation is reduced***

27

Herpes Simplex Keratitis

- **Epithelial Keratitis:**
  - Treatment:
    - Zirgan (ganciclovir gel 0.15%)
      - 5x/day until the dendrite disappears
      - 3x/day for another week
    - Viroptic (trifluridine solution 1%)
      - 9x/day until the dendrite disappears
      - 5x/day for another week
    - Oral antivirals (if topical not well tolerated):
      - Acyclovir 400 mg 5x/day X 7-10 days
      - Valtrex 500 mg 3x/day X 7-10 days
      - Famvir 250 mg 3x/day X 7-10 days

28

Herpes Simplex Keratitis

- **Epithelial Keratitis:**
  - Treatment (con't):
    - Debridement of the dendritic ulcer???
    - Oral antivirals???
    - IOP control
      - Avoid prostaglandins???
    - Steroids???
  - Follow-up
    - Day 1, 4, 7

29

Herpes Simplex Keratitis

- **Marginal keratitis:**
  - Very rare
  - Looks like a marginal infiltrate....but
  - In HSV marginal keratitis:
    1. Much more pain
    2. Deep neovascularization
    3. No clear zone between infiltrate and limbus

30

Herpes Simplex Keratitis

- **Immune Stromal Keratitis (ISK):**
  - 2% of initial ocular HSV presentations
  - 20-61% of recurrent disease
  - 88% non-necrotizing
  - 7% necrotizing
  - ***Can be visually devastating***

31

Herpes Simplex Keratitis

- **Immune Stromal Keratitis:**
  - Symptoms:
    - Gradual blurred vision
    - Halos
    - Discomfort/Pain
    - Redness

32

Herpes Simplex Keratitis

- **Immune Stromal Keratitis:**
  - Signs (non-necrotizing):
    - Stromal haze (inflammation & edema)
    - Neovascularization (deep)
    - Immune ring
    - Scarring and/or thinning
    - Intact epithelium***
  - Signs (necrotizing):
    - All of the above
    - More dense infiltration
    - Often w/ overlying epithelial defect
    - Necrosis and/or ulceration
    - ***high perforation risk***

33

Herpes Simplex Keratitis

- **Immune Stromal Keratitis:**
  - Treatment:
    - Topical steroids
      - Pred Forte QID-q2H
      - Durezol BID-QID
      - Lotemax QID
    - Topical anti-viral cover
      - Viroptic (trifluridine 1%) QID
      - Zirgan (ganciclovir 0.15%) QID
    - Topical cyclosporin (Restasis), AT's, ung's to facilitate epithelial healing if ulceration is present

34

Herpes Simplex Keratitis

- **Endotheliitis:** AKA Disciform Keratitis
  - Not considered a primary form of stromal keratitis
    - Stromal edema is present secondary to endothelial inflammation
  - Symptoms:
    - Blurred vision
    - Halos
    - Discomfort/Pain
    - Redness

35

Herpes Simplex Keratitis

- **Endotheliitis:** AKA Disciform Keratitis
  - Signs:
    - Central zone of stromal edema often with overlying epithelial edema
    - KP's underlying the edema
    - AC reaction
    - IOP may be elevated
    - Reduced corneal sensation
    - Healed lesions often have a faint ring of stromal or subepithelial opacification and thinning

36

Herpes Simplex Keratitis

- **Endotheliitis:** AKA Disciform Keratitis
  - Treatment:
    - Topical steroids
      - Pred Forte QID-q2H
      - Durezol BID-QID
      - Lotemax QID
    - Topical anti-viral cover
      - Viroptic (trifluridine 1%) QID
      - Zirgan (ganciclovir 0.15%) TID
    - Topical cyclosporin (Restasis), AT's, ung's to facilitate epithelial healing if ulceration is present

37

Herpes Simplex Keratitis

- **Neurotrophic Keratitis:**
  - Keratopathy occurs from loss of trigeminal innervation to the cornea resulting in complete or partial anaesthesia
  - The cornea is numb so the pt doesn't blink
  - Sx's:
    - Irritation/burning/FB sensation
    - Redness
    - Tearing
    - Decreased vision

38

Neurotrophic Keratopathy

- Signs:
  - Decreased corneal sensation***
  - Interpalpebral SPK
  - **Persistent epithelial defects** in which the epithelium at the edge of the lesion appears rolled and thickened, and is poorly attached
  - Advanced cases may have sterile ulceration, keratitis, and/or corneal melt
    - Pt may be surprisingly asymptomatic**

39

Neurotrophic Keratopathy

- Tx:
  - Find out the cause
  - D/C any meds that may be responsible
  - Lubricate, lubricate, lubricate***
    - Preservative free AT's, gels, and ung's q1h-QID
  - Topical Ab drops and/or ung (Polytrim QID, etc)
  - Taping the eyelids at night to ensure adequate closure
  - In severe cases:
    - Patching, tarsorrhaphy, Botox to induce ptosis

40

Neurotrophic Keratopathy

- Tx:
  - Healing an ulcer that won't heal
    1. Autologous serum
    2. Prokera
       - Amniotic membrane in a CL skirt
    1. Also could use a scleral lens

41

Autologous Serum

1. Draw 40cc of blood through venipuncture
2. Centrifuge for 5 minutes @ 1500 rpm
3. Centrifuging will divide the blood into its separate components
4. Place 1cc of serum in each bottle
5. Add 4cc of saline to make a concentration of 20% serum eye drops
6. 20% serum eye drop concentration

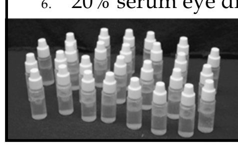


Table 1. Comparison of the biochemical properties of normal human tears and serum[2,5]

	Tears	Serum
pH	7.4	7.4
Osmolarity	298	296
EGF (ng/ml)	0.2-3.0	0.5
TGF-β (ng/ml)	2-10	6-33
Vitamin A (mg/ml)	0.02	46
Lysozyme (mg/ml)	1.4	6
IgA (μg/ml)	1190	2
Fibronectin (μg/ml)	21	205

EGF= epithelial growth factor; TGF= transforming growth factor

42

Herpes Simplex Epithelial Keratitis

- My Regimen:
  - Zirgan 5x/day until the ulcer heals, then 3x/day for one week
  - Oral Valtrex 500 mg 3x/day for 7-10 days
  - Artificial tears
  - L-Lysine 2 grams daily?
  - Debride the ulcer?
- RTC 1 day, 4 days, 7 days

43

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
    - Frequent debilitating recurrences, bilateral involvement, or HSV infection in an only eye

44

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

45

Herpes Simplex

- Visual Prognosis:
  - 90% 20/40 or better after 12 years
  - 3% 20/100 or worse after 12 years

46

HSV, HZO, & EKC: VIRAL EYE DISEASE ALPHABET SOUP

Nathan Lighthizer, O.D., F.A.A.O.
Assistant Dean, Clinical Care Services
Director of Continuing Education
Chief of Specialty Care Clinics
Chief of Electrodiagnostics Clinic
Oklahoma College of Optometry
lighthiz@nsuok.edu

47