Herpes in Review: From Simplex to Zoster
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Objectives
- Review the etiology of herpes simplex and herpes zoster
- Present treatment options for herpetic eye disease
- Review the complications of herpetic eye disease
- Update on visual rehabilitation options

HSV and VZV
- Herpein = "to spread" or "to creep"
- Similar characteristics
  - Linear double stranded DNA surrounded by a icosahedral–shaped capsid
  - The production of virus particles within the host cell results in destruction of the host
  - All herpes viruses can establish latency in the sensory ganglia
  - Capable of producing unilateral (rarely bilateral) ocular disease

HSV

Herpes Simplex Virus
- Incidence of HSV
  - 20% from 6-12 months of age
  - 60% between 15 and 25
  - Reports up to 90%...
Herpes Simplex Virus

- HSV-1 infection occurs by direct contact of skin or mucous membrane with virus-laden lesions or secretions
  - Infection: Occurs most commonly in the mucocutaneous distribution of the trigeminal nerve
  - Latency: After the primary infection, the virus travels in retrograde fashion from the infected epithelial cells to nearby sensory nerve endings and is transported along the nerve axon to the cell body located in the trigeminal ganglion, entering into a latent state.
  - Infection: Intraneuronal spread of HSV within the ganglion allows patients to develop subsequent ocular disease without ever having had primary ocular HSV infection.

Herpes Simplex Keratitis

- United States: 20,000 new cases annually
  - 28,000 reactivations annually
- United States: Roughly 500,000 people with the disease
- Recurrence Rates of ocular HSV (Liesegang et al. 1989)
  - 122 patients over 33 years
    - Mean age of initial onset = 37.4 years
    - 9.6% at 1 year
    - 22.9% after 2 years
    - 63.2% after 20 years
    - After a second episode, 70-80% had another recurrence within 10 years

Ocular Manifestations of HSV

- Blepharitis
- Conjunctivitis
- Scleritis
- Keratitis
- Iridocyclitis
- Retinitis

Classification of HSV Keratitis

I. Infectious Epithelial Keratitis
II. Stromal Keratitis
III. Endotheliitis

- Different viral strands may produce different pattern of ocular disease with variability of recurrence (Wander et al, 1980)

Infectious Epithelial Keratitis

IEK
1. Cornea vesicles
2. Dendritic ulcer
3. Geographic ulcer
4. Marginal ulcer

Cornea Vesicles
- Cystic lesion of the epithelium
- Contains live virus
  - No epithelial defect
    - Negative staining early
    - Late staining
  - Precedes dendritic ulcer
  - Very rarely seen due to early presentation
Infectious Epithelial Keratitis

Dendritic Ulcer
- Branching linear ulceration
  - Dendron – Greek for “tree”
  - Contain live virus
  - Swollen epithelial borders
  - Staining centrally

Geographic Ulcer
- Enlarged dendritic ulcer
- Scalloped borders
- Contains live virus

Marginal Ulcer
- Also referred to as “Limbitis” (IEK near limbus)
- Active virus with moderate inflammatory reaction
  - Due to proximity to limbus
- Easily confused with Staph Marginal Ulcer
- Course:
  - Begins as a peripheral ulcer
  - Stromal infiltrate rapidly develops
  - Peripheral corneal neovascularization
  - Dilated limbal vessels
  - Antibiotic therapy fails

Classification of HSV Keratitis

I. Infectious Epithelial Keratitis
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Stromal Keratitis

1. Interstitial (Immune Stromal) Keratitis
2. Necrotizing Stromal Keratitis

Interstitial Keratitis
- Etiology
  - Immune reaction to retained viral antigen
- Clinical Findings:
  - Stromal haze / infiltration, often multifocal
  - Intact epithelium
  - Immune ring
  - Keratic precipitates
  - Previous stromal scars
Stromal Keratitis

Interstitial Keratitis

- Clinical Course
  - Often chronic and recurrent
  - May occur weeks or months after IEK
  - May occur w/o prior hx of IEK (~2%)
  - Persistent inflammation may lead to:
    - Scarring
    - Thinning
    - Neovascularization
    - Lipid deposition
    - Loss / distortion of vision

Stromal Keratitis

Necrotizing Stromal Keratitis

- Etiology
  - Rare manifestation of HSV
  - Viral invasion of stromal with severe inflammatory reaction
  - Dense stromal infiltrate with overlying epithelial defect
  - Thinning and perforation

Classification of HSV Keratitis

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Endotheliitis

Clinical Findings:
- Keratic precipitates
- Overlying stromal & epithelial edema
- Iritis
- Trabeculitis with increased IOP
  - This is often the primary presentation

Types
1. Disciform
2. Linear
3. Diffuse

Endotheliitis

Disciform
- Most common primary presentation of endotheliitis
- Central or paracentral area of KP’s with overlying secondary stromal/epithelial edema
- NOT a stromal disease

Endotheliitis

Linear
- Progressive line of keratic precipitates
- Stromal edema follows leading edge of KP’s
- Difficult to manage
**Endotheliitis**

- Diffuse keratic precipitates
- Diffuse stromal and epithelial edema
- Retrocorneal plaque

**Varicella Zoster Virus**

- VZV is a human pathogen that infects approximately 95% of the adult population in the United States (Straus, 1994)
  - Typically during childhood as varicella (chickenpox)
- Transmission is through respiratory secretions or from direct contact with cutaneous lesions
  - Varicella much more contagious than zoster

**Herpes Zoster (Shingles)**

- Annual incidence: 3.2-4.2 / 1,000
  - Not a reportable condition
- More than 1,000,000 new cases annually in US
- Age is significant risk factor
  - Those >60 years and older: 10 / 1,000
  - Immunocompromised

**Image from the CDC website, updated May 15, 2008**

- During the viremic phase, VZV gains access to epidermal cells, causing the typical varicella rash.
- VZV is then transported from the vesicular lesions along the sensory nerves to the sensory dorsal root ganglia adjacent to the spinal cord.
- Establishes permanent latency in neuronal cell bodies

- 1 of 3 persons will develop zoster
- Caused by the reactivation of the latent VZV in the sensory ganglion.
  - Typically begins with 1-4 days of prodromal symptoms of headache, photophobia, and malaise, with fever being less common.
  - Abnormal skin sensations and pain of varying severity radiate through the affected dermatome
Herpes Zoster (Shingles)

- Fever
- Ultraviolet Light Exposure
- Cold Wind
- Systemic Illness
- Surgery
- Menstruation
- Emotional Stress
- Local Trauma
- Immunosuppression

Herpes Zoster (Shingles)

- Zoster: "girdle" or "zone"
- HZ is typically unilateral and does not cross the mid-line, erupting in 1-3 adjacent dermatomes
- Most common dermatomes are cervical, thoracic, and ophthalmic

Herpes Zoster Ophthalmicus

- First described by Hutchinson in 1865
- Involves the reactivation of VZV in the trigeminal ganglia with ophthalmic involvement
  - Accounts for 10%-25% of zoster episodes
  - Nasociliary branch of the ophthalmic nerve innervates the skin of the eyelids, conjunctiva, sclera, cornea, iris, choroid, and the tip of the nose
  - 20-70% develop ocular manifestations
  - Chronic disease can be present in 20-30% of HZO cases (Liesegang, 2008)

Herpes Zoster Ophthalmicus

- Hutchinson’s sign
  - Presence of vesicles at the side of the tip of the nose
  - Indicator of nasociliary involvement
    - Associated with a 50-76% chance of ocular complications
    - The risk lowers to 34% without nasociliary involvement (Cobo, 1988; Womack et al, 1983; Harding et al, 1993.)

Herpes Zoster Ophthalmicus

Signs

- External
  - Lid edema and vesicles
  - Conjunctival hyperemia
  - Episcleritis and scleritis
- Cornea
  - Epithelial keratitis
  - Stromal Keratitis
  - Endothelitis

VZV Epithelial Keratitis

- Punctate Epithelial Keratitis
  - Initial corneal presentation
  - Usually peripheral and has associated conjunctivitis
  - Stains with rose Bengal, not NaFL
**VZV Epithelial Keratitis**
- Pseudodendrites
  - Multiple dendritic or stellate lesions of edematous, raised epithelium
  - Probably are a result of a coalescence of PEK
  - More superficial and lack central ulceration when compared with HSK
  - Can progress to ulceration

**VZV Stromal Keratitis**
- Anterior Stromal Infiltrates
  - Isolated or multiple patches of infiltrate, usually occurring past 10 days
    - "Can be recurrent in nature"
  - Interstitial Keratitis / Lipid Keratopathy
    - Occurs following extensive inflammation, resulting in scarring, vascularization, and lipid deposition

**VZV Endotheliitis**
- Represents direct viral invasion of the endothelium with an immune reaction
- Occurs weeks or months after acute HZO
- Subsequent stromal and epithelial edema
  - "Analogous to HSV Disciform Endotheliitis"

**Complications and Treatment of HSK and HZO**

**Viral Complications of Anterior Segment**
- Iridocyclitis
- Iris Atrophy
- Dendritic Epitheliopathy
- Neurotrophic Keratopathy
- Corneal Scarring

**Viral Complications of AS**

**Iridocyclitis**
- Clinical Situations
  - Concomitant with keratitis
  - Subsequent to keratitis
  - Without history of keratitis
    - Tougher to confirm herpes etiology
- Clinical Findings
  - Stellate keratic precipitates
  - Mild to moderate anterior chamber reaction
  - Chronic, recurrent course
  - Iris atrophy
### Viral Complications of AS

#### Iris Atrophy
- Results in iris transillumination defects, creating increased glare sensitivity
- Painted iris lenses
- Implantable prosthetic iris implants available, although not FDA approved at this time

#### Dendritic Epitheliopathy
- Healing epithelium following dendritic ulcer
- Negative staining gives dendritic appearance
- Pseudodendrite: No active virus
- May persist for weeks to months
- Made worse by toxic agents
  - Antivirals, antibiotics, etc.
- Treat by:
  - Discontinuing toxic agents!

#### Neurotrophic Keratopathy
- **Etiology**
  - Neither immune nor infectious
  - Impaired corneal innervation combined with decreased tear secretion
  - Inflammation
  - Toxicity from medication
- **Clinical appearance**
  - Punctate epithelial erosions
  - Neurotrophic ulcer
  - Dendritic epitheliopathy

- **Treatment**
  - Punctal occlusion / cauterization
  - Autologous blood serum ophthalmic drops
  - Tarsorrhaphy
  - Conjunctival flap
  - Scleral lens

#### Management of Scarring
- Observation
- Rigid Contact Lenses
- Penetrating keratoplasty
  - Success rate has improved with oral antivirals
- Complications
  - Recurrence
  - Increase rate of rejection
  - Poor wound healing

### Treatment
1. Antiviral
2. Corticosteroid
3. Antibiotic

Active vs. Immune?  
…or both?
### Topical Antiviral

**Treatment of IEK  **Dendrite present**

- **Viroptic (1% trifluridine):**
  - 1 gtt Q2H W.A. x 10-14 days

- **Acyclovir ointment**
  - Not commercially available in USA
  - Better control against some resistant strands

- **Vidarabine ointment 3%:**
  - Applied 5x per day
  - Less potent and more toxic than trifluridine
  - Better control against some resistant strands

- **Treat at maximum dose for 5-7 days, then taper to minimize epithelial toxicity**
- **Treat for 10-14 days**

**Exceptions**

- Immunocompromised
- Resistant / recurrent strains

### Topical Antiviral

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### Topical Antiviral

**Zirgan (ganciclovir gel) – Sirion Therapeutics**

- FDA approved September 2009
- Acquired by B&L June 2010
- 1 gtt 5x per day until dendrite heals, then TID for 7 days
- More tolerated and effective than trifluridine

### Topical Antiviral

**Treatment of IEK  **Dendrite present**

- **If topical antiviral is used for > 14d and a dendritic appearance is still present:**
  - **Rethink diagnosis**

  - Dendritic epitheliopathy
  - Neurotrophic keratopathy

### Oral Antiviral

**Herpetic Eye Disease Study (HEDS)**

- Multicenter, randomized, placebo-controlled trials sponsored by the NEI
- Oral antiviral prophylaxis reduces recurrences of epithelial and stromal keratitis, particularly stromal with a prior history of recurrence.
- Oral antiviral may help control herpetic iridocyclitis
Oral Antiviral

• Primary treatment in all new HZO
• Studies indicate that acyclovir use in HZO leads to reduced incidence of dendritic keratopathy, episcleritis, iritis, and stromal keratitis.
• However, there is conflicting reports of the benefit of systemic antivirals in preventing or treating the more severe complications of HZO.

Oral Antiviral

Prophylactic Indications
• Post-PK patients
• Recurrent herpes infection
• Monocular patients with herpes virus

Oral Antiviral in HSV

➢ Acyclovir (Zovirax)
  • Active: 200-400 mg 5x/day
  • Suppression: 400-800 mg BID

➢ Valacyclovir (Valtrex)
  • Prodrug of acyclovir
  • Active: 1000-3000 mg QD
  • Suppression: 500-1000 mg QD

➢ Famciclovir (Famvir)
  • Active: 250 mg TID
  • Suppression: 125-250 mg BID

Oral Antiviral in HZV

Oral Antiviral – within 72 hours

➢ Acyclovir (Zovirax)
  • 800mg 5x/d for 7-10 days

➢ Valacyclovir (Valtrex)
  • 1000mg TID for 7 days

➢ Famciclovir (Famvir)
  • 500mg TID x 7 days

Note: With HZO, often the duration of the oral antiviral is extended weeks to months

Topical Steroids in HSV

Herpetic Eye Disease Study (HEDS)
• Topical steroids are a benefit in stromal keratitis

Advantages
• Effective for corneal and intraocular inflammation
• Reduces corneal scarring and neovascularization
• Reduces intraocular complications of inflammation

Topical Steroids in HSV

Disadvantages
• Enhancement of viral replication
• Slows collagen synthesis with subsequent corneal thinning
• Secondary infections
• Cataract
• Glaucoma
• Induction of steroid dependant inflammation by allowing the build up of viral antigens
Topical Steroids in HSV

- **Indications**
  - Marginal keratitis, interstitial keratitis, endotheliitis, iritis
  - Severe or chronic inflammation, decrease in vision
  - Avoid use in
  - Active epithelial disease or ulceration
  - Mild inflammation
  - Avoid abrupt discontinuation
  - Dosage dependent on level of inflammation

- **Topical Corticosteroids**
- Avoid use in minimal to mild inflammation
- Corticosteroids are thought to create an anti-inflammatory dependency, resulting in prolonged treatment and recurrences
- If uveitis is worsening or severe, start with small dosages of topical drops and taper quickly as disease improves

Steroids in HZO

Systemic corticosteroids

- Studies indicate that receiving adjacent therapy along with oral antivirals significantly accelerates the cutaneous healing rate and acute pain
- No beneficial effect on PHN

Topical Steroids

- Flare dose of topical steroids
- Chronic inflammation requires chronic steroids
- Most patients have a critical level of steroids that prevents inflammation
- Goal is to stay above flare dose for several months before any attempt to taper
- Most Common Management Error:
  - Under treatment with topical steroids

Postherpetic Neuralgia

- Persistent dermatome pain after resolution of the rash
  - 10%-18% of HZO patients
- Caused by axonal and cell body degeneration, atrophy of the spinal cord dorsal horn, scarring of the dorsal root ganglion, and loss of epidermal innervation
- Neuronal damage might be caused by ongoing viral replication
- PHN can last for weeks or months and occasionally persists for many years

**FIGURE 3. Rate of zoster and postherpetic neuralgia (PHN), by age — United States**

- Per 1,000 person-years
- Defined as ≥14 days of pain
Postherpetic Neuralgia

Treatment
- Rapid administration of antiviral (within 72 hours)
- Analgesics
- Injected corticosteroids
- Nerve blocks
- Cimetidine
- Tricyclic antidepressants
- Famvir?

Zoster Vaccine

Drop in immunity to VZV may occur due to:
- Immunosuppressive conditions
- Immunosuppressive therapy
- Loss of Exogenous Boosts in Immunity
  - Healthy adults who have had chicken pox get new bursts of immunity when exposed to their children with chicken pox = exogenous immunity
  - With the advent of varicella vaccine, it is postulated that the incidence and perhaps severity of shingles will increase and occur at younger ages

Zoster Vaccine

Shingles Prevention Study
- In 1999, a double-blind randomized, placebo-controlled trial was started which included 38,546 patients over the age of ≥60 who had had varicella in the past.
  - Identical strain as used in the varicella vaccines (Varivax, Proquad) with 14-times the potency
  - Half given vaccine and other half given placebo
  - Study was completed in 2005
  - Vaccine reduced the chance of developing shingles by 51.3%
  - In those that developed shingles, also reduced PNH and the severity of the outbreak

Zoster Vaccine

ZOSTAVAX (Merck)
- Zoster vaccine is recommended for all persons aged ≥60 years who have no contraindications, including persons who report a previous episode of zoster or who have chronic medical conditions
  - Single 0.65 mL subcutaneous dose
  - Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing PHN, or to treat ongoing PHN
  - No booster recommendations at this time
  - 7,500 zoster-free patients followed for 10 years

Advancement in Treatment
- Scleral lenses
- Amniotic membranes

Scleral Lenses
- 1800’s:
  - The first contact lenses described in medical literature originally made from blown glass
  - Use of a blown glass “contact shell” to improve vision in a patient with keratoconus was reported in 1888
- Early 1900’s:
  - Polymethylmethacrylate (PMMA) was introduced, made it somewhat easier to manufacture lenses.
  - Moldable, but still difficult to reproduce
Scleral Lenses

- Why the return?
  Permeability of gas (P) = Dk
  - D is coefficient of diffusion
  - k is coefficient of solubility

  Transmissibility (t) = Dk / L
  - L is the thickness of the lens

- Old school: Dk 12
- New: Dk 163

Evaluating the Fit

Scleral Lens Basics

- Determine appropriate base curve by observing the relationship of the cornea to the lens.

- Once the base curve is chosen, then adjust the peripheral curves to enhance the fit.

Case CP

- 39-year old male
- H/O Chicken pox at age 10, Presumed herpetic keratitis to follow 1 year later

  Uncorrected VA
  OD 20/400
  OS 20/20

  Refraction
  OD NI
  OS -0.75 -1.00 x 049
**Case CP**

- Keratometry
  - 49.1D @ 138 / 39.5D @ 048
  - 42.1D @ 094 / 41.0D @ 004
- Apex OD 50.4D
- OS 42.1D

**Case CP**

- Fit with reverse geometry scleral lens
  - 7.71 (43.75D) REV GEO / -0.25 / 18.20
  - 20/40

**Scleral Lens Summary:**
- Correction of vision
- Tool for ocular surface disease

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**Amniotic Membranes**

- The amniotic membrane is the thin, but tough innermost lining of the placenta (amnion) that holds a developing embryo (and later fetus) until shortly before birth.
- The primary function of the amniotic membrane is to protect the fetus from injury.
  - Anti-inflammatory
  - Anti-scarring
  - Anti-angiogenic

**What is the Amniotic Membrane?**

- Amniotic membrane shares the same cell origin as the fetus
  - Stem cell-like behavior
  - Structural similarity to all human tissue
- Amnion is made of Collagen I, III, IV, V and VII, laminin and fibronectin of which Collagen IV, VII, laminin and fibronectin are also found in conjunctiva and cornea

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**History of Amniotic Membranes**

- 1910 - In dermatology, Davis was the first to report the use of fetal membranes for skin transplantation.
- 1913 - Stern and Sabella separately began using amniotic membrane for management of skin burns and superficial wounds.

**History of Amniotic Membranes**

- 1940 - de Rotth
  - First reported use of fetal membranes on the ocular surface using amnion and chorion as a biological dressing for the management of conjunctival defects.
- Sorsby in 1946 and Simmons in 1947
  - Used chemically processed and dried amniotic membrane for ocular chemical burns.

Poor outcomes due to insufficient tissue processing
History

- Dr. Juan Batlle reported on the ophthalmic use of amniotic membranes in 1992
- Now, multiple companies specialize in harvesting and processing amniotic membranes.

Amniotic Membranes

Actions
- Promotes Stem Cell Expansion
- Suppresses pain
- Promotes cellular migration
- Expedites recovery

Treatment Goals
- Accelerate the time to heal
- Strengthen the tissue post-healing
- Temporarily reverse the effects of ocular surface disease

Case BW

- 55 YO Caucasian female
- 15+ year H/O repeated recurrent infections OD secondary to herpes simplex, complicated by concurrent fungal infections
- Meds: Vigamox OD TID and 1G Valtrex PO QD with past h/o bacitracin-polymyxin B ung and Ambisone
- VA OD 20/150   OS 20/20

Case BW

- 02/20/2015 – Initial treatment
  - Dehydrated AM for 2 week duration due to uncontrolled neurotrophic keratoconjunctivitis (370.35)
  - Increased Vigamox OD to QID plus added 1% prednisolone acetate OD QID
  - Coverage with oversized bandage contact lens

Case BW

- 03/12/2015 - Second Treatment
  - Cryopreserved AM for 1 week duration due to uncontrolled neurotrophic keratoconjunctivitis (370.35)
  - Continued Vigamox OD TID, no additional drops or BCL required
AM Treatment Goals

- Accelerate the time to heal
- Strengthen the tissue post-healing
- Temporarily reverse the effects of ocular surface disease

References
