Objectives

- To understand the etiology of herpes simplex and herpes zoster
- Compare and contrast the treatment for herpetic ocular disease
- Review the complications of herpetic eye disease

HSV and VZV

- Similar characteristics
  - Linear double stranded DNA surrounded by an 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

Herpes Simplex Virus

- HSV-1 infection occurs by direct contact of skin or mucous membrane with virus-laden lesions or secretions
  - Occurs most commonly in the mucocutaneous distribution of the trigeminal nerve
  - 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.
  - Interneuronal spread of HSV within the ganglion allows patients to develop subsequent ocular disease without ever having had primary ocular HSV infection

Ocular Manifestations of HSV

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

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
    - 36% after 5 years
    - 63% after 20 years
    - After a second episode, 70-80% had another recurrence within 10 years
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

Infectious Epithelial Keratitis

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

Infectious Epithelial Keratitis

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

Infectious Epithelial Keratitis

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
Stromal Keratitis

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

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

Necrotizing Stromal Keratitis
- Etiology
  - Rare manifestation of HSV
  - Viral invasion of stromal with severe inflammatory reaction
- Clinical Findings:
  - Dense stromal infiltrate with overlying epithelial defect
  - Thinning and perforation

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

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 disc-shaped area of edema
- KP’s corresponding to edema
**Endotheliitis**

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

Linear
- Progressive line of keratic precipitates
- Stromal edema follows leading edge of KP’s
- Difficult to manage – requires aggressive treatment

**Varicella Zoster Virus**

- VZV is a human pathogen that infects approximately 98% of the adult population in the United States.
  - Typically during childhood as varicella (chickenpox)
  - Transmission is through respiratory secretions or from direct contact with cutaneous lesions
  - Varicella much more contagious than zoster

- During the viremic phase, VZV gains access to epidermal cells, causing the typical varicella rash.
  - The virus then enters sensory nerves in mucocutaneous sites and travels through retrograde axonal transport to the sensory dorsal root ganglia adjacent to the spinal cord
  - Establishes permanent latency in neuronal cell bodies

**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 even higher

- 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)

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

- Viral release from the sensory nerve endings forms a rash that is initially erythematous and maculopapular, but progresses to form coalescing clusters of clear vesicles containing high concentrations of VZV
- HZ is typically unilateral and does not cross the mid-line, erupting in 1-3 adjacent dermatomes.
- In general, thoracic, cervical, and ophthalmic involvement are most common

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

- 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

Herpes Zoster Ophthalmicus

Signs
- External
  - Lid edema and vesicles
  - Conjunctival hyperemia
  - Episcleritis and scleritis
- Cornea
  - Punctate epithelial keratitis
  - Pseudodendrites
  - Anterior stromal infiltrates
  - Keratouveitis
  - Uveitis

Herpetic Complications

- Iridocyclitis
- Dendritic Epitheliopathy
- Neurotrophic Keratopathy
- Corneal Scarring
- Iris Atrophy
  - Specific to HSV
Herpetic Complications

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

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

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

1. Topical Antiviral
2. Oral Antiviral
3. Corticosteroid

Active vs. Immune?
...or both?

Topical Antiviral

Treatment of IEK  **Dendrite present**
- Viropic (1% trifluridine):
  - 1 gtt Q2H W.A. x 10-14 days
- Vidarabine ointment 3%:
  - Applied 5x per day
  - Especially in children
  - Less potent and more toxic than trifluridine
- Acyclovir ointment
  - Not commercially available in USA
  - Better control against some resistant strands

Topical Antiviral

NEW Treatment
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
- Better tolerated and effective then trifluridine

Topical Antiviral

Treatment of IEK  **Dendrite present**
- Treat at maximum dose for 5-7 days, then taper to minimize epithelial toxicity
- Treat for 10-14 days
- Exceptions
  - Immunocompromised
  - Resistant strain (very rare)

Topical Antiviral

Treatment of HZO
- Topical acyclovir may be effective, but not commercially available in US
- Some vidarabine success in recurrent strands
- New success with off-label use of Zirgan (ganciclovir gel)

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
  - Oral antiviral is effective in treatment and prophylaxis of HSK
  - Interstitial Keratitis with concurrent topical steroid use
  - Endotheliitis (especially linear)
  - Iridocyclitis
  - Recurrent Disease

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 HZO

Ideally within 72 hours

- Acyclovir (Zovirax)
  - 800mg 5x/d for 7-10 days (HSV was Acyclovir 200mg 5x/d)
- Valacyclovir (Valtrex)
  - 1000mg TID for 7 days (HSV was 1000mg QD)
- Famciclovir (Famvir)
  - 500mg TID x 7 days (HSV was 250 mg TID)

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

Oral Antiviral

Prophylactic Indications

- Post-PK patients
- Monocular patients
- Recurrent Disease

Topical Steroids in HSV

Advantages

- Effective tx for corneal and intraocular inflammation
- Reduces corneal scarring and neovascularization
- Reduces intraocular complications of inflammation

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 Steroids in HSV**

- **Topical Steroids**
  - Flare dose
    - 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

**Topical Steroids in HZO**

- **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

**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

**Postherpetic Neuralgia**

- **Treatment**
  - Rapid administration of antiviral (within 72 hours)
  - Analgesics
  - Corticosteroids
  - Nerve blocks
  - Cimetidine
  - Tricyclic antidepressants
  - Famvir?
**HZO Treatment**

**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


**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 PHN 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