MANAGING HERPES SIMPLEX KERATITIS

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Learning Objectives

- Describe clinical presentations of herpes simplex keratitis
- Explain available therapies
Structure of Herpes Simplex Virus

- Herpes simplex virus types I and 2 (HSV-1, HSV-2)
  - Double-stranded DNA
  - Viral-derived capsid
  - Host-cell derived envelope
  - Glycoprotein projections
Epidemiology of Ocular HSV

- Initial exposure: childhood “viral” illness
- Ocular manifestation: reactivation of latent virus
  - Blepharitis, follicular conjunctivitis, keratitis, keratouveitis, acute retinal necrosis
- 50,000 new and recurring cases annually
  - Recurrence rate: 27% at one year
Primary HSV Ocular Infection

- Less common presentation
- Pediatric age
- Fever, malaise
- Skin rash
- Unilateral follicular conjunctivitis – suspect HSV
Life Cycle of Herpes Simplex Virus
Recurrent HSV Infection

- Orofacial: Cold sores on lip, cheek or tongue

- Ocular: Most frequently involves cornea
  - Epithelial keratitis – active virus
  - Stromal keratitis – immunologic
# HSV Keratitis Classification

<table>
<thead>
<tr>
<th>HSV CATEGORY</th>
<th>COMMON NOMENCLATURE</th>
<th>TREATMENT</th>
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</thead>
<tbody>
<tr>
<td>Epithelial Keratitis</td>
<td>▪ Dendritic Keratitis ▪ Geographic Keratitis</td>
<td>Antiviral (topical or oral) or debridement</td>
</tr>
<tr>
<td>Stromal Keratitis without ulceration</td>
<td>▪ Interstitial Keratitis ▪ Immune Stromal Keratitis</td>
<td>Topical steroid + oral antiviral prophylaxis</td>
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<tr>
<td>Stromal Keratitis with ulceration</td>
<td>▪ Necrotizing Keratitis</td>
<td>Oral antiviral in therapeutic doses + topical steroid</td>
</tr>
<tr>
<td>Endothelial Keratitis</td>
<td>▪ Disciform Keratitis</td>
<td>Oral antiviral in therapeutic doses + topical steroid</td>
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</table>
Epithelial Keratitis

- Dendritic ulcer
- Geographic ulcer
- Others:
  - Marginal ulcer
  - Metaherpetic (trophic) ulcer
Epithelial Keratitis: Dendritic Ulcer

- Classic corneal lesion
- Branching with terminal bulbs
- Raised borders
- Consist of HSV-infected cells
- Dendritic scar (ghost dendrite) may remain
Epithelial Keratitis: Geographic Ulcer

- Caused by replicating virus
- Larger epithelial defect
- Branching and terminal bulbs at periphery
- Immunocompromised, on topical steroids, untreated dendrite
Epithelial Keratitis: Marginal Ulcer

- Lesion near limbus
- Resembles Staph ulcer
- More stromal inflammation
- More resistant to treatment
Epithelial Keratitis: Metaherpetic (Trophic) Ulcer

- Epithelial ulceration
- No live virus
- “Trophic”: de novo
- “Metaherpetic”: follows dendritic or geographic ulcer
- Inability of epithelium to heal
- Smooth borders
- “Reverse staining”
Treatment: Metaherpetic Ulcer

- Form of epithelial ulceration that does not have live virus
- Goal: rapidly heal epithelial defect
  - Stop use of toxic meds
  - Punctal occlusion
  - Tear film supplements
  - Bandage contact lens
  - Tarsorrhaphy
  - Cautious use of topical steroids
Stromal Keratitis

- Immune-mediated response to nonreplicating viral particles in stroma
- Immune stromal keratitis
  - Interstitial keratitis
- Necrotizing keratitis
- Disciform keratitis (Endothelial keratitis)
- Keratouveitis
Stromal: Immune Stromal Keratitis

- Inflammatory response to viral antigen in stroma
- Focal, multifocal, diffuse stromal opacities
- Interstitial keratitis – vascularization
  - Ghost-like
  - HSV most common cause
Stromal: Necrotizing Keratitis

- Reaction to live viral particles in stroma
- History multiple recurrences
- Corneal melting, perforation
- Significant associated uveitis
Stromal: Disciform Keratitis (Endothelial Keratitis)

- Endothelial dysfunction from inflammatory response to viral antigen
- Disc-shaped area corneal edema
- Minimal inflammation in stroma
- Unilateral
- Confused with Fuchs
  - bilateral
Stromal: Keratouveitis

- Uveitis predominates
- Mutton-fat KP
- Immune-mediated
- Unilateral uveitis with high IOP – suspect HSV
Diagnosis: HSV Keratitis

- Clinical findings
- Lab tests seldom needed
  - Of no use in stromal keratitis
- Herpes Culture
  - HSV-1 or HSV-2 typing
- Serum Antibody Testing
  - Positive titers in adults indicates past infection
  - Nearly universal
Diagnosis: Clinical Findings

- Patient is in far less pain than findings would suggest
- Photophobic or uveitis and high IOP
- Patient has history of ocular HSV
Diagnosis: Reduced Corneal Sensation

- Hallmark of HSK
- Viral replication kills host neuron
  - Leads to hyposensitivity, poor tear production, persistent epithelial defects
- Test prior to topical anesthetic
  - Use dental floss or cotton wisp
Long-Term Complications

- Recurrent disease
  - Increased inflammation, scarring, decreased corneal sensation
- Risk of stromal disease increases with recurrences of HSV epithelial keratitis
- Recurrent episode occurs adjacent to site of previous episode
Treatment Fundamentals

- HSV epithelial keratitis (live virus)
  - Topical or oral antivirals
  - No steroids

- HSV stromal disease (little, if any, virus)
  - Topical steroids
  - Oral (never topical) antivirals as prophylaxis
Managing HSV Epithelial Keratitis

- **Debridement**
  - Removes infected cells
  - Faster resolution, less scarring

- **Topical antiviral**
  - Viroptic (Trifluridine)
  - Zirgan (Ganciclovir gel)

- **Oral antiviral**
  - Zovirax (Acyclovir)
  - Valtrex (Valacyclovir)
  - Famvir (Famciclovir)
## Topical Antivirals for HSV Epithelial Keratitis

<table>
<thead>
<tr>
<th></th>
<th>Viroptic</th>
<th>Zirgan</th>
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<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>1 drop every 2 hours (daily dose: 9) until ulcer heals, then 5 times daily for 7 days</td>
<td>1 drop every 3 hours (daily dose: 5) until ulcer heals, then 3 times daily for 7 days</td>
</tr>
<tr>
<td><strong>Refrigeration</strong></td>
<td>Refrigerate</td>
<td>Room temp</td>
</tr>
<tr>
<td><strong>Preservative</strong></td>
<td>Thimerosol 0.001%</td>
<td>BAK</td>
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Managing HSV Stromal Keratitis

- Topical steroids
- Simultaneous oral antiviral prophylaxis
  - Reduces risk of HSV reactivation at the trigeminal ganglion level
    - Zovirax
    - Valtrex
    - Famvir
#### Oral Antiviral Agents for HSV Keratitis

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<tr>
<th>Agent</th>
<th>Treatment Dose</th>
<th>Prophylactic Dose</th>
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<tr>
<td>Zovirax (Acyclovir)</td>
<td>400 mg five times daily</td>
<td>400 mg twice daily</td>
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<tr>
<td>Valtrex (Valacyclovir)</td>
<td>500 mg three times daily</td>
<td>500 mg once daily</td>
</tr>
<tr>
<td>Famvir (Famciclovir)</td>
<td>250 mg three times daily</td>
<td>250 mg once daily</td>
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Using Steroids Correctly

- **Not** used in acute epithelial keratitis
- **Essential** for stromal keratitis
- Prednisolone acetate 1% QID
- S-l-o-w-l-y taper
Using Antiviral Prophylaxis Correctly

- Oral antivirals
  - Primarily against reactivation at ganglion level
  - During topical steroid treatment for stromal disease
  - Patients with multiple recurrences (2 or more / year)
  - Keratitis close to visual axis
  - Immunocompromised patients
  - Long-term use for 1 year or more reduced risk of recurrent HSV
Quiz Time

No Cheating!
Case 1

- 42 year old female complains of red, irritated OD
- SLE: single dendrite
- Dx: first episode of HSV epithelial keratitis

Options:

A. Viroptic drops 9x/day for 1 week, then taper
B. Zovirax 400 mg 5x/day for 1 or 2 weeks
C. Both regimens combined
Case 1: Recommendation

- Each approach reasonable
- Consider full dose Viroptic drops
  - 9x/day until ulcer heals
  - then 5x/day for 1 week
  - then stop
Case 2

- 51 year old male complains of irritated OS and mild photophobia, vision good
- History of three previous episodes HSV epithelial keratitis
- SLE: minimal scarring with adjacent new dendrite
- Dx: recurrent HSV epithelial keratitis
- Options:
  A. Viroptic drops
  B. Zovirax oral
  C. Combination therapy
Case 2: Recommendation

- Combination therapy
  - Viroptic 9x/day until ulcer heals, then 5x/day for 1 week
  - Full therapeutic dose Zovirax 400 mg 5x/day
  - Discontinue topical Viroptic within 2 weeks
  - Taper Zovirax to 400 mg BID for long-term prophylaxis (1 year)
Case 3

- 46 year old female complains of blurry vision OS.
- History of treated herpetic dendrite 1½ years ago
- Vision: 20/40
- SLE: Mild stromal edema, no scarring
- Dx: First episode of HSV stromal keratitis

Options:

A. Viroptic drops
B. Steroid drops
C. Zovirax oral
D. Combination therapy
Case 3: Recommendation

- Combination therapy of topical steroids with oral antiviral coverage
  - Pred Forte QID and taper as necessary
  - Zovirax 400 mg BID until inflammation subsides
Case 4

- 62 year old male complains of blurry vision OD
- History of two previous episodes of stromal keratitis
- Vision 20/50
- SLE: Mild to moderate edema and patchy scarring
- Dx: Recurrent HSV stromal keratitis

Options:

A. Viroptic drops
B. Steroid drops
C. Zovirax oral
D. Combination therapy
Case 4: Recommendation

- Combination therapy
  - Pred Forte 1% QID
  - Zovirax 400mg BID
  - Taper steroids s-l-o-w-l-y to avoid recurrence
  - Continue Zovirax long-term (1 year)
Congratulations!
THANK YOU