Epidemic Keratoconjunctivitis

- EKC
  - Serotypes 8, 19 most typical
  - Seasonal
  - Primarily bilateral
  - Atypical serotypes: Enterovirus 70

Clinical Presentation

- Chemosis
- Injection
- Infiltrates
- Ac/reaction?
- FBS

EKC

- Treatments
  - Palliative
    - Cold compress
    - Tears
  - Interventional
    - Anti-inflammatory agents
    - Decongestants
    - Combination agents
    - Cidofovir
    - Betadine
    - Zirgan

EKC

- Treatments
  - Betadine wash
  - Surgical Debridement
EKC Betadine Protocol

- Topical anesthetic x 2
- Non Alcohol betadine applied to inferior/superior cul de sac
- One minute wait
- Rinse with artificial tears
- Apply Topical steroids x 3-4 in post treatment period

Clinical “Pearls”

- Most effective if treated within 3 days of onset
- Less effective in advanced cases
- SPK incidence is close to 100%
- Patients will complain of FBS 1-2 hours later

Adenovirus

- Conjunctivitis and keratoconjunctivitis caused by adenoviruses are common and highly contagious
- Usually affect both eyes and may cause epidemics
- Patients may have painful conjunctival membranes and palpable preauricular adenotherapy
- Zirgan is active in vitro against adenovirus as 1
- Tabbara did a controlled randomized double-masked clinical study of patients with adenovirus keratoconjunctivitis and found that ganciclovir significantly reduced both the duration of disease and the incidence of subepithelial infiltrates 2

Tabbara K, Jarade E. Ganciclovir effects in adenoviral keratoconjunctivitis. [ARVO abstract 3111] (suppl), S579 (2001)


Adenovirus clinical trial (Tabbara, 2001)

- Controlled randomized masked series of 18 patients with adenoviral keratoconjunctivitis
- Compared treatment with GCV ophthalmic gel 0.15% versus preservative-free artificial tears
- Mean time to recovery
  - Significantly shorter for ganciclovir treated patients: 7.7 days, in contrast to 18.5 days for those receiving artificial tears (P < 0.05)
- Subepithelial opacities
  - Developed in 7 (77%) patients treated with artificial tears, compared to 2 (22%) patients in the GCV-treated group.

Tabbara K, Jarade E. Ganciclovir effects in adenoviral keratoconjunctivitis. [ARVO abstract 3111] (suppl), S579 (2001)

ZIRGAN® (ganciclovir ophthalmic gel) 0.15%

- FDA approval 9/16/2009
- Available in Europe under the trade name Virgan (Laboratoires Théa) since 1996
- Purchased from Sirion by Bausch & Lomb 2010

Herpes Simplex Keratitis

**Incidence and Prevalence**
- Leading cause of corneal blindness
- Affects approximately 10 million people worldwide
- 60% of the U.S. population shows evidence of infection by age 5
- 95% of the population by age 15
- Approximately 1% of infected patients develop ocular outbreaks
- 20,000 new primary cases are diagnosed in the U.S. each year
- 28,000 recurrences a year in the U.S.

**After primary infection, typically becomes latent in the trigeminal ganglion or cornea**
- Stress, UV radiation, and hormonal changes can reactivate the virus
- Lesions are common in the immunosuppressed (i.e. recent organ transplant or HIV patients)
- Recurrences tend to occur in the cornea and uvea and may cause dendritic or geographic corneal ulcers

**ANTI-VIRALS**

**CLINICAL APPLICATIONS**
- **ACUTE VS CHRONIC INFECTION**
- **PRIMARY LESIONS**
- **EPITHELIAL HERPES SIMPLEX**
- **STROMAL HERPES SIMPLEX**
- **HERPES ZOSTAR**
- **HERPETIC IRIDOCYCLITIS**

**Indications**
- Infectious disease/Prophylaxis
  - Acyclovir (Zovirax)
    - Treatment: 400mg 5x/d 1 week
    - Maintenance: 400mg 2x/d
  - Valaciclovir (Valtrex)
    - Treatment: 500mg tid 1 week
    - Maintenance: 500mg qd
  - Famciclovir (Famvir)
    - Treatment: 250mg tid 1 week
    - Maintenance: 250mg qd

**Oral Anti-virals**
- Effective against HSV and HZV
- Targets virally infected cells only
- Inhibits DNA synthesis – activated by a virus-specific thymidine kinase then phosphorylated by host enzymes into its active form
- Few side effects
  - Nausea most common
  - Don’t use with diminished kidney function

**Oral Antivirals**
- Indications in Infectious HSV
  - Endotheliitis
  - Iridocyclitis
  - Primary Herpetic Disease
  - Immunocompromised patients
  - Post keratoplasty
  - All cases of Infectious Epithelial Keratitis
ANTI-VIRALS

- SIDE EFFECTS
  - RENAL FAILURE/IMPAIRMENT
  - HYPERSENSITIVITY REACTIONS
  - FACIAL EDEMA
  - VISUAL HALLUCINATIONS

Topical Treatments for Herpes Simplex Keratitis

- 6 topical ophthalmic antivirals have been or are currently used in the U.S. and Europe
- 1st & 2nd Generation Antivirals
  - Idoxuridine (IDU)
  - Iododesoxycytidine (IDC)
  - Vidarabine (Ara-A)
  - Trifluridine (TFT): Approved in U.S. 1980
- IDU, IDC, and Ara-A have been abandoned by clinicians due to high toxicity
- 3rd Generation Antivirals: more selective, less toxic
  - Acyclovir (ACV): Europe only
  - Ganciclovir (GCV): Europe and available in US in early 2010

The Antiviral for the 21st Century

- Ziran 0.15% Gel
- Sirion Pharmaceuticals
- HSK 2 years and older
- Ganciclovir: Selectively targets replication of HSV DNA within corneal cells.
- Dose: 5 x / day till lesion resolves then tid for one week
- Toxicity:
  - 60% blur
  - 20% irritation
  - 5% Hyperemia

Ganciclovir Structure and Activity

- Synthetic nucleoside analog of 2’-deoxyguanosine
  9-(1,3-dihydroxy-2-propoxymethyl) guanine

In vitro activity:
- Mean effective dose for HSV1 and HSV2 in clinical isolates is 0.23 μg/ml
- Inhibitor of viral replication for HSV1, HSV2, HZV, EBV, CMV, adenovirus and HHV6 viruses

Ganciclovir Mechanism of Action

- Penetrates cell infected with the virus
- Phosphorylated within the cell to ganciclovir monophosphate by a viral thymidine-kinase
  - Affinity for viral thymidine-kinase allows for specificity in its action
- Activation continues due to several cell kinases leading to formulation of ganciclovir triphosphate, which:
  - Inhibits viral DNA polymerase
  - Incorporates into viral DNA preventing replication

Notes:

Ganciclovir 0.15% (Zirgan™)
Clinical Efficacy Results

Results from 3 randomized, single-masked, controlled multicenter clinical trials evaluating ganciclovir ophthalmic gel 0.15% compared to acyclovir ophthalmic ointment 3% patients with dendritic ulcers

<table>
<thead>
<tr>
<th></th>
<th>GCV 0.15%</th>
<th>ACV 3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>57</td>
<td>49</td>
</tr>
<tr>
<td>Clinical Resolution By Day 7</td>
<td>41 (72%)</td>
<td>34 (69%)</td>
</tr>
</tbody>
</table>


Zirgan® (ganciclovir ophthalmic gel) 0.15% vs Acyclovir 3%

Safety - Most Common Adverse Effects - 4 studies

<table>
<thead>
<tr>
<th></th>
<th>Ganciclovir 0.15%</th>
<th>Acyclovir 3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision Blurred</td>
<td>93/161 (57.8%)</td>
<td>112/157 (71.3%)</td>
</tr>
<tr>
<td>Eye Irritation</td>
<td>32/125 (25.6%)</td>
<td>55/119 (46.2%)</td>
</tr>
<tr>
<td>Punctate Keratitis</td>
<td>11/125 (8.8%)</td>
<td>19/119 (16.0%)</td>
</tr>
<tr>
<td>Conjunctival Hyperemia</td>
<td>7/125 (5.8%)</td>
<td>6/119 (5.0%)</td>
</tr>
</tbody>
</table>

HSK
- DENDRITIC KERATITIS
- WITH OR WITHOUT DENDRITE
- DIFFERENTIAL Dx
  - VARICELLA-ZOSTAR
  - EPSTEIN-BARR
  - VACCINIA
  - THYGESON’S

HSK
- IMPAIRED EPITHELIAL HEALING
  - ANTIVIRALS
  - ANTIBIOTICS
  - PRESERVATIVES
  - POST INFECTIOUS
  - SCL’s

HSK
- CLINICAL FINDINGS
  - ACANTHAMOEBA
  - EPITHELIAL DEPOSITS
  - MUCOUS PLAQUES
  - GEOGRAPHIC KERATITIS
  - STROMAL KERATITIS
  - NECROTIZING KERATITIS

HSV Disease – Recurrence
- Risk of Recurrence
  - 25% recurrence risk over two years after a first episode of epithelial keratitis
  - Second episode has a 43% recurrence risk
- Natural Course
  - Little scarring first recurrences
  - Scarring increases with increased recurrence
  - Vascularization
  - Stromal keratitis
Oral acyclovir has not been demonstrated to be more effective than topical agents in the treatment of epithelial herpes keratitis. Long term oral acyclovir may reduce the recurrence of epithelial keratitis. Oral acyclovir, as part of the treatment of epithelial keratitis, does not reduce the risk of developing stromal keratitis.


Herpes Epithelial Keratitis

- Oral acyclovir has not been demonstrated to be more effective than topical agents in the treatment of epithelial herpes keratitis.
- Long term oral acyclovir may reduce the recurrence of epithelial keratitis.
- Oral acyclovir, as part of the treatment of epithelial keratitis, does not reduce the risk of developing stromal keratitis.

Herpetic Keratitis Prophylaxis Case Series (Tabbara, 2005)

- Prospective interventional case series studied the use of topical ganciclovir ophthalmic gel 0.15% for treatment and prophylaxis of herpetic epithelial keratitis.
- Evaluated the effects of treatment among 16 cases and prophylaxis among 6 of those cases.
- Instillation once every 6 hours for 2 weeks.
- Complete resolution of herpetic keratitis noted in all pts.
- During follow-up, none of the 6 patients on prophylactic ganciclovir developed a recurrence.
- 3 of 10 patients without prophylaxis developed recurrences.
- No ocular side effects were noted.


Herpes Simplex Keratitis (HSK)

- **DIAGNOSIS**
  - **CYTOLOGY**
    - SCRAPE - ACTIVE VESSELES
    - PAPANICOLAOU STAIN
    - MULTINUCLEATED GIANT CELLS
  - **ANTIGEN DETECTION TESTS**
    - IMMUNOFLOURESCENCE
    - IMMUNOPEROXIDASE
    - ENZYME IMMUNOASSAY
    - DNA PROBE
    - PCR

- **MANAGEMENT/EPITHELIAL DISEASE**
  - DEBRIDEMENT
  - ROSE BENGAL / LISSAMINE GREEN
  - DRUG THERAPY
    - TRIFLURIDINE
    - IDOXURIDINE
    - VIDARABINE
    - ORAL AGENTS
    - CIDOFIR
  - TREATMENT
HSK

- STROMAL KERATITIS
  - RULE OUT MICROBIAL DISEASE
  - VIROPTIC
  - ORAL AGENTS
  - CYCLOSPORINE A
  - SURGERY
    - PKP
    - CONJUNCTIVAL FLAPS
    - TISSUE ADHESIVES

Herpes Stromal Keratitis

- Oral acyclovir has demonstrated no benefit in the treatment of stromal keratitis\(^1\)
- Long term (one year) oral acyclovir reduces the risk of recurrent stromal keratitis\(^2\)

If It wasn’t for Bad Luck I would have none at all!

DR a really nice 58 y/o white male presented with a 4 year history of recurrent HSK with stromal involvement.

Medical Hx positive for Leukemia well controlled until last 6 months.

Patient complained of LOV x 6-7 days progressing.

Additionally patient demonstrated 50-60 lbs weight loss since last visit.

**Bad Luck**

- Clinical presentation showed:
  - VA – FC @ 3 ft
  - 2+3 Injection
  - Ptosis 2mm
  - Discharge 2+
- SLE: 7mm central lesion with staining. Peripheral white cell ring. AC 2+3 cell with posterior KP’s
Bad Luck

- Initial Therapy
  - Valtrex 1000 mg tid
  - Zymar qid
  - HA 5% TID
  - Neosporin Ung TID
  - Follow up 24 hrs

- 24 hour follow up:
  - Patient c/o increased pain
  - VA; HM @ 3ft
  - Lesion melting @ 1:00 with 60 % thinning
  - Increased white cell perimeter
  - 1/8 chamber hypopyon
  - TX:?

Bad Luck!

- Day two:
  - No change!
  - Tx?

- Day Three:
  - Decreased white cell skirt
  - Hypopyon 90 % cleared
  - Decreased pain

The Non-Healing Eye

- BC a 54 y/o white male was referred for evaluation of a non-healing corneal wound following abdominal surgery 6 and 2 weeks earlier.
- The patient was wheelchair bound and unable to ambulate, had suffered a 40 lb weight loss in two weeks and complained of severe LOV.
The Non-Healing Eye

- Clinical exam:
  - VA: LP OD, 20/25 OS ph no change
  - SLE: 9 mm area of confluent staining OD with 4+ edema. Anterior chamber 1+ cells.
  - Ta 19/13 mmHg
  - DFE: No view OD/OS wnl
  - External: 3/5/minimal reaction/-MG

One week after initial therapy
- VA 20/400
- AC= trace cell
- Corneal lesion 4 mm with stromal haze 2+

Following therapy at 4 weeks the epithelial defect closed with residual hyperplasia.
- VA: 20/50 ph 20/40+
- BCL removed
- Ta 26/20 mmHg
- See Photo!
The Non-Healing Eye

- Next visit patient on Alphagan-P bid OD, PF qid, A T's PRN.
- Complains of Photophobia, pain OD.
- VA 20/30 OD ph 20 25-
- Ta 38 /20 mmHg
- SLE: 1+2 cell, Cornea as shown
- DFE- Negative

Patient did very well for 3 weeks, then returned with complaint of severe photophobia and redness.
- Joint pain @ knee, shoulder and hip.
- Urethritis returned x4 days
- VA decreased, IOP 19mmHg, VF- Non specific loss
- Meds: Cosopt 2/2, Alpha-P 2/2, PF qd

Patient saw GMD was Diagnosed with Reiter’s (Non STD), secondary to “dirty” surgery.
- Current meds Cosopt 2/2, AP 2/2, PF 4/0
- VA 20 30+ ph 20/20-
- SLE : see photo
- Ta 15 mmHg

VARICELLA ZOSTAR-KERATITIS
- PRIMARY INFECTION
  - CHICKEN POX
  - VACCINATION RECOMMENDED BY AMERICAN ACAD of PEDIATRICS
- RECURRENT INFECTION
  - OPHTHALMIC INVOLVEMENT 10-255
  - OPHTHALMIC ZOSTAR > OVER AGE 60
  - UNDER 40 50% IMMUNOCOMPRIMISED
HZK

- V1, V2, V3
- CONJUNCTIVA
- CORNEA
- MUCOUS PLAQUE
- DECREASED CORNEAL SENSATION
- ENDOTHELEITIS

STROMAL KERATITIS

- BASIC FEATURES
  - IMMUNOGENIC RESPONSE
- CLINICAL FEATURES
  - DISCIFORM
  - SUPPlicative
  - MIXED
- TREATMENT

Dose Uniformity – Durezol versus Generic Prednisolone Acetate Suspension

<table>
<thead>
<tr>
<th>Time (Days)</th>
<th>Inverted, not shaken (generic pred)</th>
<th>Upright, shaken (generic pred)</th>
<th>Inverted, not shaken (Durezol)</th>
<th>Upright, shaken (Durezol)</th>
</tr>
</thead>
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<td>0</td>
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A New Potent Topical Steroid
Backg round Information and Clinical Experience
HZK

**TREATMENT**

**ORAL AGENTS**
- ACYCLOVIR 800 mg
- FAMVIR 500 mg
- VALTREX 1000 mg
- SORIVUDINE
- VRIVUDIN

**Vaccines**
- Adults – Zostavax
- Children – Varivax

**Relationship between them**