Ocular Herpes Management: Beyond the Herpetic Eye Disease Study
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I have no disclosures

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This lecture is in no way a critique of the Herpetic Eye Disease Study

Lasting results of the Herpetic Eye Disease Study
Aspects that still define standard of care 20 years later

Recurrence rates at 1 year on suppressive dose of oral acyclovir 400 mg bid vs. placebo:

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<th>Placebo</th>
<th>Acyclovir</th>
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<tr>
<td>Any ocular HSV</td>
<td>32%</td>
<td>19%</td>
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<tr>
<td>Stromal keratitis</td>
<td>29%</td>
<td>14%</td>
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<tr>
<td>Non-ocular HSV</td>
<td>36%</td>
<td>19%</td>
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Because of HEDS, we all currently have numerous patients with histories of recurrent stromal disease in our practices who have been on oral acyclovir suppressive therapy for years

For clinicians, despite the impact of HEDS, questions remain:

No guidance given for the use of topical vs. oral antivirals in forms of herpetic eye disease where equal efficacy was shown in HEDS

Medications are on the market that were not included in the HEDS study. When do we prescribe them and not acyclovir and trifluridine?:
- Valacyclovir (Valtrex®)
- Ganciclovir (Zirgan®)
- Famciclovir (Famvir®)

HEDS published prior to the use of vaccines for varicella in children and zoster in adults. How have these changed the epidemiology of herpes and what are our recommendations for vaccines?

HEDS addressed specific, common manifestations of herpetic eye disease. What are some atypical presentations we should be aware of?
To answer these questions, we must review some important topics.

What is the basic pathophysiology of all forms of herpetic eye disease?

Pathologically, what is the difference between epithelial, stromal, and less common forms of herpetic eye disease? Why is epithelial so common?

Is the mechanism of action of the newer antivirals different from acyclovir and trifluridine? Are they more ideal in certain scenarios?

What is actually going on during latency? How is latency advantageous for herpes? Why can’t antivirals clear the infection in neural cells?

What is the evidence that the herpes vaccines work? Which patients should get them? How have they influenced incidence of ocular HSV/VZV?

All members of the herpes virus family share a common structure.

- Double stranded DNA viruses
- Icosahedral capsid (20 triangular sided)
- Protein rich tegument (functional elements such as protein kinases)
- Lipid bilayer envelope (Docking and cellular entry)

There are eight herpesviruses with different targets and sites of latency.

- Herpes simplex 1 (and to a lesser extend 2)
- Varicella zoster, and cytomegalovirus are common causes of ocular infection

There are eight herpesviruses with different targets and sites of latency.

Herpes simplex virus 1 infection is ubiquitous.

- Spread by personal contact during childhood
- Over 92% of humans shed HSV-1 DNA in their tears at least once monthly
- Over 93% of human autopsy specimens have HSV-1 DNA in their trigeminal ganglion

I hate to break this to you, but you have herpes!

Varicella zoster virus infection is also ubiquitous.

- Primarily spread through respiratory droplets to the conjunctiva, nose, and mouth

Varicella zoster virus causes two diseases:
- Primary Infection: Chickenpox (Childhood disease)
  - Flu-like viral syndrome
- Reactivation: Herpes zoster / shingles (Adults)

Survival of childhood illness results in lifetime immunity, and 95% of population has immunologic evidence of infection

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I hate to break this to you, but you have herpes!
Varicella zoster virus infection is ubiquitous

Prior to 1995, chickenpox developed in almost 100% of US children, with incidence essentially equivalent to birth rate.

Children in United States have been vaccinated with live attenuated varicella virus since 1995 (Currently ~ 20 year-olds or younger)

I hate to break this to you, but you probably have either wild-type or attenuated strains of this herpes too!

Varicella zoster primary infection, latency, and reactivation

Ganglion latency resulting in ocular manifestations: Trigeminal

Just a reminder of the relative location of the trigeminal ganglion.

Ganglion latency resulting in ocular manifestations: Trigeminal

Ocular involvement occurs if either HSV or VZV reactivates and travels down specific terminal branches of the trigeminal nerve.

Relatively dense innervation to corneal epithelium. Significantly less in the stroma and the least in the endothelium.


Ocular involvement occurs if either HSV or VZV reactivates and travels down specific terminal branches of the trigeminal nerve.

Seems to be some biologic preference for trigeminal ganglion and ophthalmic division involvement (for HSV1).

**Corneal epithelium:**
- Squamous cells
- Winged cells
- Basal columnar cells

**Corneal endothelium:**
- Keratocytes (fibroblasts)

Relatively dense cellular concentration in the corneal epithelium.

Depending on which corneal cells are infected, a different type of keratitis develops.

Density of superficial nerve endings and density of cells in epithelium may predispose this location to disease, but stromal keratocytes and endothelium can be infected.

**Initial infection is usually in mucosal epithelial cells, but similar initial process seen in neural cells.**

- Envelope proteins bind with cell surface receptors to facilitate fusion of viral envelope to the cell plasma membrane
- De-enveloped capsids and tegument components enter the cytoplasm and travel down microtubules to the nuclear membrane
- Capsid docks with nuclear entry pores

**Viral DNA is injected into the nucleus:**
- Host cell RNA polymerase transcribes the viral genes and viral protein synthesis begins within 2-4 hours of initial infection
- Protein products include structural and tegument components
- DNA replication commences at nearly the same time. Nucleosides are phosphorylated by both virus and host cell thymidine kinases

**Once sufficient viral proteins are available in the nucleoplasm, capsids are assembled within the nucleus and newly replicated DNA is injected:**
- The initial viral envelope is formed when the capsid passes through the inner nuclear membrane. This initial immature envelope then fuses with outer nuclear membrane and the again naked capsid is ejected from the nucleus into cytoplasm
- Final viral envelope is believed to be made in the golgi apparatus before new viruses bud out of cell. The final result may be lysis of the inundated cell

**Herpes viruses have evolved to develop two life phases to maximize spreading potential:**
- **Lytic Phase:**
  - Usually occurs peripherally in mucosal epithelial or epidermal cells near ends of involved nerves
  - Highly transcriptionally active and destructive to infected cell
  - Results in cell death and dendritic advancement within involved tissues
- **Latent Phase:**
  - Usually occurs centrally in sensory or autonomic nerves
  - Highly transcriptionally inactive and non-destructive to infected cell
  - Results in host cell dormancy and peripheral latency within involved tissues

**Important step in antiviral drug mechanism**

**Budding of virus or resulting cell lysis allows for progressive infection of adjacent cells (Dendritic pattern)**

**Important step in antiviral drug mechanism**
Lytic phase results in characteristic clinical presentations

- Herpes simplex labialis
- Herpes simplex keratitis
- Herpes zoster vesicular rash
- Herpes simplex whitlow

Active infection of terminal respiratory mucosal and genital epidermal cells results in improved change of transmission through aerosolization or direct contact.

Active infection of terminal epidermal cells results in improved change of transmission through direct contact.

Latency isn’t just “not-detrimental,” it may be protective

Recent research showing LAT actually promotes cell survival:
- Inhibits nerve cell apoptotic pathways that are often active in virus-infected cells
- Codes for viral intra-cellular signaling molecules that are analogous to the host to avoid immune detection
- Down-regulates cell surface markers that signal the immune system that the cell is infected by viruses

End result: Nerve cells with latent virus infection are not killed, which allows life-long transmission during periodic active lytic phases occurring in peripheral tissues.

Herpes viruses have evolved to develop two life phases to maximize spreading potential

Latent Phase:
- Occurs primarily in neural cells
- Virus is retained in infected cell nuclei, but no new viruses are produced
- Minimal activity with only Latency Associated Transcript (LAT) being produced
- To this day, the full function of the LAT is yet to be determined

Determination of lytic vs. latent is not known, but distance from infection site to the cell nucleus may play a role

Advantageous as lytic phase in neural tissue could result in mortality to host.

A reminder that the trigeminal ganglion lies in a complex location

Lytic phase in central nervous tissues = morbidity/mortality

- Herpetic encephalopathy

Extremely rare (1 case/million per year) despite 90% being infected

Necrotizing encephalitis usually localized in the frontal and temporal lobes

Results in severe neurologic symptoms:
- Fever
- Headache
- Lethargy
- Irritability
- Confusion
- Aphasias
- Seizures

Mortality rate around 70% with 97% of survivors not returning baseline

Reactivation from latent to lytic phase

Reactivation defined as a return to lytic phase after a period of latency

Nucleocapsids and viral proteins move down different set of neural axon microtubules to axon termini

The full virus re-assembles at axon termini and spreads to adjacent mucosal epithelium, epidermal cells, tears, or saliva

There is interplay between the virus and the immune system in the maintenance of latency:
- Explains the effectiveness of vaccinations in decreasing recurrences
- CD8+ T-cells are found docked to infected nerve cells. They secrete cytokines that modify the immune response and possibly maintain viral latency
**Reactivation from latent to lytic phase**

Known exogenous triggers of reactivation:
- Localized trauma (surgery)
- Mental stress and fatigue
- UV light exposure
- Hormonal changes (menstruation)
- Temperature changes
- Endogenous prostaglandins (Latanoprost)

We are still attempting to explain how these factors result in reactivation.

**Antivirals act as nucleotide analogs**

Nucleotides are subunits of nucleic acids (DNA and RNA).

Nucleotides are made up of three distinct parts:
- Nitrogenous base
- Five carbon sugar (Nucleoside)
- One or more phosphate group (Nucleotide)

Two types of nitrogenous bases:
- Purines (Adenine, Guanine)
- Pyrimidines (Thymine, Cytosine, Uracil)

Ribonucleotides are nucleotides where the added sugar is ribose (RNA) - AGUC

Deoxyribonucleotides are nucleotides in which the sugar is deoxyribose (DNA) - AGTC

**Nucleic acids (DNA / RNA) are macromolecules made from nucleotide monomers**

Addition of phosphate unit to nucleoside is final step in preparation of incorporation and is catalyzed by thymidine kinases.

**Acyclovir (Zovirax®): Mechanism of action**

Guanosine analog that inhibits viral DNA polymerase.

Competes with native guanosine for use by viral DNA polymerase and incorporation results in DNA chain termination of both viral and host cells.

Active form requires three phosphorylation steps, the first of which is done by a virus specific thymidine kinase. Therefore acyclovir only incorporates into viral DNA and the DNA of virus infected cells.

Makes acyclovir very safe as it requires the presence of virus kinases for activation.

**Topical trifluridine (Viroptic®) : Mechanism of Action**

Fluorinated pyrimidine nucleoside

Preserved with thimerosal

Phosphorylated by host thymidine kinase within epithelial cells to active form

Incorporated into both virus and host cell DNA in infected and non-infected cells.

Why drug is unsafe for systemic administration.
Why it is so tough on the entire corneal epithelium.
Because DNA and RNA transcription are almost non-existent during the latent phase, current antivirals have limited effect on herpes when in latent phase in the sensory ganglia. Topicals also don’t penetrate to the deep location of the sensory ganglia.

Changes that result in resistance:
- Gene mutations resulting in altered structure of virus thymidine kinase
- Gene mutations resulting in altered structure of viral DNA polymerase
- Significant reduction in the production of viral thymidine kinase

Rates of resistance differ depending on immune status:
- Immunocompetent: Rare (< 0.5%)
- Immunocompromised: 3.5 – 7.0%
- Proposed explanation is increased prophylactic exposure to antivirals over a lifetime

Topical delivery of trifluridine and mechanism of action for acyclovir explains why drugs are not effective during latency.

Microbewiki.com

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Microbewiki.com

Clin Microbio Rev 2003;16:114-128

Valacyclovir 500 / 1000 mg
Famciclovir mg 125 / 250 / 500 mg
Acyclovir 200 / 400 / 800 mg
Ganciclovir 0.15%

All these pyrimidine analogs are structurally very similar

But how are they different?

Topically administered

Geniclovir 0.15%

T.I.D. dosing

Valacyclovir 500 / 1000 mg

5x/day dosing

Famciclovir 200 / 400 / 500 mg

T.I.D. dosing

Acyclovir mg 125 / 250 / 500 mg

Dosage: 800/400 mg 5x/day

Dosage: 1 gram t.i.d.

Different pill formulations: Look for lactose as inactive ingredient in pill formulation

Dosage: 500 t.i.d.

Valaciclovir (125 mg, 250 mg, or 500 mg of acyclovir, together with the following inactive ingredients: Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, ethyl alcohol, maltose, yellow and blue iron oxide, red iron oxide, and titanium dioxide)

Dosage: 500 t.i.d.

Acyclovir vs. Valacyclovir vs. Famciclovir: What is the difference?

Ganciclovir is a guanosine analog. Same mechanism of action as orals:
1) Competitive inhibition of viral DNA polymerase
2) Incorporation and termination of the growing viral DNA chain
3) Inactivation of viral DNA polymerase.

What about topical ganciclovir? What role does it play?

Zirgan (0.15% ganciclovir ophthalmic gel):
- FDA approved for herpetic “dendritic ulcers”
- Dosage 1 drop 5x/day until ulcer healed, then t.i.d. x 7 days

Similar to the oral antivirals, the active form requires three phosphorylation steps, the first of which is done by a virus specific thymidine kinase. Therefore, ganciclovir only incorporates into viral DNA and the DNA of virus infected cells.

Active against multiple members of the herpes family:
- Herpes simplex
- Varicella zoster
- Cytomegalovirus
- Epstein-Barr

Acyclovir: 5x/day until ulcer heals t.i.d. x 7 days after

Acyclovir, Valaciclovir, and Famciclovir: What is the difference?

Dosage: 1 gram t.i.d.

Another guanosine analog. Same mechanism of action as orals:
1) Competitive inhibition of viral DNA polymerase
2) Incorporation and termination of the growing viral DNA chain
3) Inactivation of the viral DNA polymerase.

Main reason for early discontinuation of oral acyclovir in HEDS:
Gastrointestinal side effects
Rash

Virtually all my patients on oral acyclovir have at least one GI side effect (usually diarrhea)

Besides different dosing frequencies, what else is different about the oral antivirals?

Valaciclovir 500 / 1000 mg
Famciclovir mg 125 / 250 / 500 mg
Acyclovir 200 / 400 / 800 mg
Ganciclovir 0.15%

But how are they different?

Topically administered

Geniclovir 0.15%

T.I.D. dosing

Valacyclovir 500 / 1000 mg

5x/day dosing

Famciclovir 200 / 400 / 500 mg

T.I.D. dosing
Oral acyclovir (Zovirax) in herpes simplex dendritic cornal ulceration

60 patients with HSV dendritic ulceration included a small number with stromal involvement keratitis randomized to oral vs. topical acyclovir

No statistically significant difference in time to resolution (mean = 5 days)

"Oral acyclovir alone appeared as effective as topical antiviral therapy in the treatment of simplex epithelial keratitis."

Oral delivery appears to get to corneal target even though it is an avascular tissue!

Antiviral induced crystalline nephrotoxicity

Those inflicted have a decreased in renal functioning that occurs 12-48 hours after initiation of systemic acyclovir.

This reduced function is associated with marked rise in serum creatinine

Drug crystals can eventually lead to obstruction

Symptoms:
- Nausea
- Vomiting
- Anorexia
- Abdominal pain
- Headache
- Malaise
- Inability
- Intestinal

Hospitlization
- Immediate discontinuation of antiviral intravenous fluids
- Hemodialysis

Creatinine crystals in the urine

Prescribing oral antivirals in patients with renal disease will require lab values and calculations!!!

Serum Creatinine:
- Byproduct of muscle metabolism, and primarily synthesized in the liver
- Produced consistently throughout life and found in the blood
- It is continually removed from the blood and excreted by the kidney
- These properties make it an ideal marker for renal function
- Expressed in the units mg/dl, Reference range 0.6 – 1.3 mg/dl

Creatinine Clearance:
- Volume of blood plasma that is cleared of creatinine per unit time
- In clinical practice, the creatinine clearance is estimated from the serum creatinine based on weight and age (Crockraft Gualt Formula)
- Expressed in milliliters / minute

Expressed in milliliters / minute

\[ eC_\text{cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times 0.85 \text{ if Female}}{72 \times \text{Serum Creatinine (in mg/dl)}} \]

Oral antivirals in patients with kidney disease probably requires communication with nephrologist / pharmacist!

Creatinine clearance must be ~ 50 mL/min for standard dosing

Valacyclovir Dosing

I use oral antivirals for all for anterior segment herpetic eye disease:
- Epithelial keratitis
- Stromal keratitis
- Uveitis

I use 1 gram valacyclovir t.i.d. instead of 800/400 mg acyclovir 5x/day:
- Patients who can't take that many acyclovir pills (Fewer doses per day)
- Patients with a lot of GI upset or who are lactose intolerant

Must inquire about renal disease for oral antivirals: Creatinine clearance must be ~ 50 mL / min or greater for standard dosing
Common walk-in patient at the SFVA Eye Clinic from ER:
"Rule out ocular involvement"

Switching gears slightly to herpes zoster and its manifestations

"Rule out ocular involvement"

The social / medical burden of Herpes Zoster

Occurs in ~30% of adults over a lifetime
1 million new cases in US every year
Increased risk with increased age as cellular immunity declines and any immunocompromise

Over half of people over age 85 years are affected
Approximately 2-3% of zoster patients will have ophtalmic involvement:
- Pseudo-epithelial dendrites
- Stromal keratitis
- Uveitis
Approximately 10-15% of patients with herpes zoster will develop postherpetic neuralgia

Dilate all herpes patients regardless of anterior segment findings!
Warn them of delayed onset posterior segment involvement and need to RTC!

Consults for Herpes Zoster: Ruling out Ocular Involvement

Look for anterior involvement:
- Conjunctivitis
- Corneal pseudo-dendrites (Role for Ganciclovir gel?)
- Keratitis (If stromal, add topical steroid to oral antiviral)
- Iridocyclitis (Add topical steroid to oral antiviral)

Rule-out posterior involvement:
- Acute retinal necrosis (ARN)
- Vasculitis
- Non-ARN necrotizing retinitis
- Vitritis

How have vaccines changed the clinical burden of herpes zoster?

Chicken pox vaccine (kids) ~1995:
- First generation of vaccinated kids entering adulthood!
Shingles vaccine (adults > 60) ~2006:
- Average US citizen will live 20 years after vaccination
How have vaccines changed the clinical burden of herpes zoster?

The Singles Vaccine (Zostavax®):
- Attenuated Oka/Merck strain of live varicella virus
- Originally approved for vaccination of adults over the age 60
- Now FDA approved for adults over the age of 50
- Current recommendation of only a single boosting dose

Each ~0.5 ml dose delivers ~ 1350 plaque forming units

38,546 adults greater than 60 years
Randomized to HZV vaccine or placebo
Followed for median of 3.12 years
Vaccine reduced the incidence of herpes zoster by 49%
Vaccine reduced the burden of the acute disease
Vaccine reduced the incidence of post-herpetic neuralgia by 67%

Zostavax Efficacy and Safety Study: ZEST
22,439 patients between 50-59 years randomized to shingles vaccine or placebo
Primary outcome was incidence of herpes zoster through 1 year
Compared to placebo, the vaccine reduced the 1-year incidence of herpes zoster by 69%
Vaccine group 30 individuals: (0.27%) / Placebo group 99 individuals: (0.88%)
Severity of pain score was lower in vaccine group

With drop in natural varicella incidence, the rates of zoster increased
The disappearance of exogenous immune boosting by children shedding wild-type varicella hypothesized as cause of increased zoster rates in adults prior to booster with shingle vaccine!!

Chicken Pox Vaccine (Varivax®):
- In use since 1995
- Attenuated Oka/Merck strain of live varicella zoster virus
- Approved for vaccination of children one year of age or older
- Aged 1-12 years, two doses with at least a 3 month interval
- Adolescents aged 13 and above, two doses with at least a 1 month interval

Each ~0.65 ml dose delivers ~ 19,400 plaque forming units
Almost 15x larger concentration than in shingles vaccine

How have vaccines changed the clinical burden of herpes zoster and who should get it?

Twenty years since the universal recommendation of varicella vaccination, there has been an increase in zoster incidence in all age groups

Peak incidence appears to be in the decade prior to recommended shingles vaccine booster. This decade may shift from 50 year olds to 40 year olds as vaccine given to younger adults.

I recommend getting the shingles vaccine to all my patients over the age of 50 years
Herpetic Corneal Endotheliitis

Spectrum of disorders in which the endothelium is primary site of infection and inflammation

There is no stromal inflammation

Known to be caused by three different members of herpesvirus family:
- Herpes simplex
- Varicella zoster
- Cytomagalovirus

There is no stromal inflammation

Herpetic Corneal Endotheliitis

Characterized by corneal edema, keratic precipitates, and mild anterior chamber reaction

Classified by KP distribution and extent of associated edema:
- Linear
- Sectoral
- Disciform
- Diffuse

KP limited to area of subtle corneal edema. Not necessarily inferiorly (Arlt's triangle)

Herpes Simplex 1

Herpetic Corneal Endotheliitis

Limited patient pain or photophobia. Main symptom is reduced vision

Relatively little anterior chamber reaction (< 1+)

Anterior chamber-associated immune deviation (ACAID) likely responsible

Variable reports of positive PCR for HSV, VZV and CMV

Responds to topical steroid in addition to oral antivirals

Repeated bouts of inflammation result in reduced endothelial density

Herpetic Linear Corneal Endotheliitis: Variants

Linear herpetic endotheliitis:
- Sectoral herpetic endotheliitis

Hori. Cornea 2008;27(1):103-106


Electron microscopy shows endothelial involvement in 43% of herpetic keratitis patients (90% of patients had stromal keratitis)

Variety of transient changes to endothelium seen:
- Cellular edema (pseudo-guttata)
- Loss of cell boundaries
- Enlarged intercellular gaps
- Spot like holes between cells
- Inflammatory cell infiltration

All eyes with recurrent keratitis showed eventual reduced density of endothelial cells

Herpetic Peripheral Keratitis

Peripheral crescent-shaped ulceration with underlying stromal inflammation

Uncontrolled cases can lead to peripheral corneal thinning

Variable amounts of anterior chamber reaction

Clinical appearance classically associated with autoimmune disease:
- Rheumatoid arthritis
- Polyarteritis nodosa
- Reiter's syndrome
- Lupus erythematosus
- Granulomatosis with polyangiitis
Cases were all initially treated for suspected autoimmune associated Herpetic Peripheral Keratitis Later confirmed to be caused by Herpes simplex by PCR or histology When left untreated they can eventually mimic a primarily inflammatory ulcerative keratitis, initially they can look like staff marginal disease Peripheral Ulcerative Keratitis Keep herpes in mind in non-responsive cases Delayed onset and atypical forms of ocular herpetic infection I dilate every patient with suspected ocular herpes regardless of absence or severity of anterior segment findings I warn patients to come back immediately with any change in vision or increased floaters due to possibility of delayed onset posterior disease I look for localized and linear KP in all uveitis patients, especially when not in Arlt’s Triangle, and subtle corneal edema in known herpes patients, even when they are relatively asymptomatic, as signs of herpes endotheliitis and need for topical steroid in addition to oral antivirals I think about herpes in peripheral keratitis that is non-responsive to typical therapy or in the absence of blepharitis or other common causes. The Herpetic Eye Disease Study was a landmark study that defined how we treat numerous aspects of a commonly presenting disease While HEDS concentrated on herpes simplex keratitis and uveitis, delayed and atypical forms of herpes must be recognized for proper treatment initiation