Keratitis?...sounds like herpes

- HSV is a significant public health problem
  - HSV is one of the most common infections to humans
  - Across the globe, 60%-100% of the adult population has evidence of HSV-1
  - Approximately 500,000 people in US have ocular herpes
  - Up to 40,000 cases per year progressing to significant vision loss

- Herpes Simplex keratitis is one of the most frequently encountered keratitis treated at my clinic
- The disease is well known by optometry
- However, most herpetic cases I am referred are diagnosed as “unspecified keratitis”
  - This implies a disconnect in our clinical knowledge
Keratitis?...sounds like herpes

• Goals
  • Help improve our ability to clinically recognize HSV keratitis
  • Understand appropriate interventions with these manifestations.

Herpes Simplex I Structure

• As a virus is an obligate intracellular pathogen
• Member of alpha herpes viruses (as is VSV)
• Has ~80 genes
• HSV infection is characterized by a few things:
  • Primary infection
  • Latency within the CNS:
  • Recurrence (both clinical and subclinical) of infection

HSV Natural history: primary infection

• Primary infection/transmission occurs with direct contact
  • No role in aerosolization or fomites
• Both the infector and the infectee may be asymptomatic
  • asymptomatic shedding is speculated to play a large role in transmission
Primary Infection
• Asymptomatic 90% of the time
• In cases where HSV primary ocular infection manifests clinically:
  • Most typically a unilateral follicular conjunctivitis
  • May be cultured for confirmation
  • Classically may have vesicles along lid, but this finding is often absent

HSV Natural History: Establishment of latency
• At some point during infection, virions encounter peripheral sensory nerves, where via retrograde flow the particles infect one side of the sensory ganglion
• Once in sensory ganglion, the virus will undergo low grade collateral replication and then halt production of viral material
• This establishes latency

Herpes Simplex latency
• During immunity
  • HSV reactivates
  • TG

https://www.ophthalmologyreview.org/test-prep/review-follicular-conjunctivitis/
Herpes Simplex Reactivation

- Defined as when latently infected ganglion neurons begin producing virions (which travel to the peripheral site via axonal transport)
- Subclinical reactivation probably occurs on regular intervals
- Triggers are associated with suppression of T cell function
  - Those T cells interacting with infected cells at the ganglion can actually block reactivation – most proposed triggers remain unproven

Herpes Simplex Reactivation

- A unilateral pathology
- Virions spread anterior to target site, with little to no collateral spread among sensory neuron at the ganglion
  - Many latently infected neurons will remain latent during reactivations – this leads to isolated lesions per episode, with multiple end infection sites being possible over time
- With HSV, reactivation becomes less common as we age due to depletion of viral DNA

Two types of Corneal Infection and how their natural history impacts clinical history

**Exogenous – works from the outside in**
- Bacterial Ulcers
- Fungal Ulcers
- Acanthamoeba
- EKC superficial keratopathy

**Endogenous – works from the inside out**
- HSV/Zoster/CMV
- Whipple’s Disease
- Leprosy
- Syphilis
- Lyme Disease
Two types of Corneal Infection and how their natural history impacts clinical history

**Exogenous – Microbial Keratitis**
- Basically requires a causative risk factor in their history:
  - Trauma
  - Contact lens use
  - Corneal surgery
  - Severe ocular surface disease

**Endogenous: HSV keratitis**
- No causative risk factor is needed...and we know just about everyone carries HSV

Clinical history follows natural history

Therefore, any acute unilateral keratitis without a historic risk factor for microbial keratitis should be considered high risk for HSV

**HSV Keratitis**
- There are four general groups of herpetic keratitis:
  1. Infectious Epithelial Keratitis (IEK)
  2. Herpes Stromal Keratitis (HSK)
  3. Neurotrophic Keratitis
  4. Endothelitis
- Each of these will have a number of manifestations they can present with
- Each has their own pathophysiology
- Their pathophysiology shapes their appearance and treatments
Once clinical reactivation occurs

- Infectious Epithelial Keratitis (IEK) ie dendritic keratitis –
  - true viral infections of the corneal epithelium
    - Vesicular/dendritic keratitis
    - Geographic keratitis
    - Marginal keratitis
  - Accounts for 50-80% of HSV keratitis yet only accounts for about 25-40% of referrals for HSV that I receive at a cornea clinic.
  - What's this mean?

As a profession, we've got IEK covered

IEK

- May progress over a continuum
  - If caught very early may be vesicular without ruptured epithelium, but in general is a true ulcer
  - Dendritic pattern may have to do with the distribution of nerves the virus tracks along
  - If caught late, the appearance will be a geographic ulcer

But not everything that looks like a dendrite is. What’s not:

- Thygeson's
- Healing line
- Post dendrite epitheliopathy
- Pseudo dendrite
- Mucous Plaque Keratitis following Zoster
- Acanthamoeba epithelial keratitis
- Sub-dendritic stromal HSK

- **NONE OF THESE HAVE AN EPITHELIAL DEFECT**
And sometimes things don’t look like dendrites but are
• Limbal dendritic infections can be more challenging to identify due proximity to the immune system

HSV Diagnostic Ledger

Infectious Epithelial Keratitis: Treatment
• These manifestations are active viral infection so treat them with:
  • Antivirals – oral or topical
IEK treatment options, is one option better?

- Cochrane Library for evidence based medicine found:
  - None of the conventional antivirals are superior to the other when dosed topically (no Zirgan)
  - Oral may be equivalent to topical – though limited good research in this regard
  - Combining oral and topical may speed recovery, but does not enhance outcomes (7 vs 14 days)
  - Wilhelmus K. Therapeutic interventions for herpes simplex virus epithelial keratitis (Review). Cochrane Library. 2009 Issue 1

Course and sequela of IEK

- In most cases the immune response of the untreated individual will contain the active infection within 2-3 weeks

  Sequela
  - Increased risk of reactivation
    - 20% at 1 year
    - 50% at 5 years
  - Scarring
  - Initiation of neurotrophy or HSK/endothelial disease – sets the stage for all other manifestations

HSV Sequella: IEK and Neurotrophy
HSV and neurotrophy

- The cornea is the most densely innervated tissue in the body
  - 40 times greater nerve density than dental pulp and
  - 400 times greater density than skin
- It is speculated that in addition to typical neural function, the corneal nerve plexus is critical in maintaining normal epithelial anatomy, blink rate and normal tear production

HSV and neurotrophy

- Clinical and subclinical viral shedding takes place via the basal nerve plexus
  - With each clinical and subclinical episode of IEK, regression of density of basal nerve complex occurs
- The nerve density gradually increases over time, but full function is not fully re-established
- This leads to progressive relative neurotrophy,
  - Severity of which is based on the number and intensity of the infectious episodes

HSV: IEK and Neurotrophy

Given the nerve plexus’s regulatory role in maintenance of the normal ocular surface, this reduction in the density of the basal nerve plexus has the potential to create chronic issues with epithelial health, depending on severity of the neurotrophy
HSV related neurotrophy

- Not as severe as Zoster neurotrophy (which occurs at the ganglion itself) rather than the basal plexus (with HSV)

HSV Neurotrophy/Meta herpetic disease

- Milder compared to some other forms but can require treatment
- Most typically results as chronic, somewhat mild epithelial disease
- When neurotrophic ulcers develop they may cause
  - Thinning
  - Stromal scarring
  - Perforation
  - Possibility for super infection

Treatment of Neurotrophy

- For chronic epitheliopathy:
  - Enhance tear volume
    - PF Tears and ointment, Restasis (*), punctal occlusion or cautery
- For ulcers
  - all of the above and: BSCL, Amniotic membrane, doxycycline, autologous serum for recurrent ulcers, temporary tarsorrhaphy
  - Those that are recalcitrant to supportive therapy may require a permanent lateral tarsorrhaphy or a conjunctival flap
HSV Neurotrophy

- Most cases of HSV will not develop severe neurotrophy/neurotrophic ulcers:
  - When treatment is indicated: PFATS, punctal occlusion is usually sufficient
- **Extremely diagnostically useful**
  - Key is its diagnostic utility in identifying stromal forms of HSV
    - Presence of asymmetric reduction in corneal sensation in an eye with unusual keratitis is very suggestive of possible HSV

HSV Diagnostic Ledger

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<td>Dendritic disease/IEK...obviously</td>
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HSV Sequela: Deep keratitis

- IEK
- Neurotrophsy
- HSK/endotheliitis
- IEK
- Neurotrophsy
- HSK/endotheliitis
- IEK
- Neurotrophsy
- HSK/endotheliitis
Herpes Stromal Keratitis (HSK) or Immune Stromal Keratitis (ISK)

- 20-48% of patients with IEK will develop deeper stromal form of HSV keratitis, broadly termed Herpes Stromal Keratitis (HSK)
- This simple sounding term has the potential to refer to several different clinical entities that are all bound by stromal inflammation
- More likely to cause significant vision loss than IEK

Theorized all forms of HSK are caused by a non-infectious immune response:
- Against non-vital viral proteins or
- A form of acquired autoimmunity in response to the initiating IEK episode
- Either way, generally accepted that this is a non-infectious manifestation of the disease

Regardless of precise mechanism, HSK is more likely to result in corneal blindness than IEK.
- Clinical appearance may vary dramatically
  - Sub-dendritic keratitis
  - Diffuse stromal inflammation, edema and haze
  - Corneal rings
  - Corneal neovascularization
  - Progressive scarring
HSK: Immune ring: Ag-Ab precipitate

HSV Corneal Neovascularization
• HSV is the number 1 cause of stromal vascularization in the US
• This has two phases:
  • During the early phase its probably a result of virally infected cells upregulating VEGF-A
  • These vessels will often regress after the infection
  • Late phase is probably due to the T cell mediated increase in a wide variety of cytokines
  • These vessels may persist chronically
• May threaten vision and becomes much more difficult to treat with transplant than a simple scar.

HSK: CN and thinning
Sequela of Herpetic CN: Lipid keratopathy

What corneal neo is not HSK?

- Bilateral Neo
  - Circumferential limbal neo seen with contact lens over use
  - Irregular patchy neo seen with Rosacea/blepharokeratitis
  - Cogan’s Syndrome
- Unilateral Neo
  - phlyctenule


Treatment of HSK

- CD-4+ T-cell is the primary immune mediator of HSK
  - T cell deficient mice don’t develop HSK or HSK related neovascularization
- CD4+ T cell’s main role is production of cytokines and chemokines to upregulate other immune cells.
- How do we treat this?
  - Focus on reducing T-cell activity and cytokine production
Treatment of HSK: anti-inflammatory

- Topical corticosteroids primary effect is to reduce production of cytokines and chemotaxis which reduces immune cells to the tissue
- Other options?
  - Cyclosporin – inhibits T cell production and activation via blockage of interleukin-2
  - Lifitegrast?
  - Ocular surface anti-VEGF for CN?
  - Doxycycline when CN begins
  - Surgery when warranted

HSK Antiviral prophylaxis (acute)

- Corticosteroid use – as inhibitors of T-cell function – is a risk factor for viral reactivation and new episodes of IEK
- Therefore, their use in the treatment of HSK should be paired with antiviral, either topical or oral

HSK Antiviral prophylaxis (chronic)

- In HEDS, stromal disease had incidence reduced by ½ when suppression dosing was used – so this population has the best rationale for maintenance therapy
- 400 mg acyclovir bid is standard but not universal
  - This dose was just sort of picked out of the blue
  - Some patients need higher maintenance dosing
Surgical management of HSK
• Always best to have the patient inactive for 6 months prior to any surgery
  • There is a risk of reactivation with surgical process and that risk is compounded by more recent episodes
• PTK
• DALK
• PK
• All surgical approaches are complicated by CN

Impact of CN on surgical options
• Corneal neovascularization essentially eliminates PTK as an option and complicates grafting procedures
• We are making efforts to get rid of significant vascularization as both a treatment itself and to prime the eye for more substantial surgeries

Pre and post bevacizumab for HSV
How to diagnose HSK?

- The sub dendritic form of HSK is easy to diagnose.
- The other forms? not so much
  - No pathognomonic findings
  - Diagnosing HSV without a dendrite requires a certain leap of faith
  - Look for clues where you can get them – multiple indicators of HSK should taken as suggestive of the diagnosis

How to diagnose HSK?

- Any unusual unilateral stromal keratitis without an epithelial ulcer requires HSK be on the differential
- No supportive historic risk factor is needed – if a keratitis occurs out of the blue, think about HSK
- CN strengthens your diagnosis
- Asymmetrically reduced corneal sensation strengthens your diagnosis

HSV Diagnostic Ledger

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Necrotizing Stromal Keratitis

• Exception to rule of non-infectious HSV stromal disease
• Rarely IEK may progress to an active infection of the stroma/keratocytes which leads to profound inflammation of the stroma

Necrotizing Stromal Keratitis

• Characterized by:
  • Overlying epithelial defect
    • Other forms of HSK will not have an epithelial defect
    • Dense infiltrate – consistent with density of microbial keratitis
Necrotizing Stromal Keratitis

- Looks more bacterial or fungal compared to typical viral disease—**to differentiate, most cases need cultured**
- Other clues to help differentiate HSK will often be available to aid in diagnosis of necrotizing stromal keratitis
  - vascularization and
  - reduced corneal sensation
- These eyes are at risk for perforation

Necrotizing stromal keratitis

- Treatment = Kitchen sink
  - High dose oral antiviral +
  - High dose topical antiviral +
  - Corticosteroid
  - If stromal melt develops should add doxy as well
  - Prophylactic antibiotic

Moving deeper: endotheliitis

- The final general classification of HSV keratitis is endotheliitis
- Unclear mechanism
  - Responds to steroids and roughly mirrors endothelial rejection with corneal transplants= immunologic
  - Some studies have identified viral DNA in endothelial cells with endotheliitis = viral infection
HSV Endotheliitis

- Nomenclature is varied, but the system proposed by Holland and Schwartz in 1999 has predominated in Cornea literature
- This proposed classification (which is not accepted around the globe) recognizes three forms of HSV endotheliitis
  - Diffuse Endotheliitis
  - Linear Endotheliitis
  - Disciform Endotheliitis

Though these may be three distinct entities, they all share some features:
- Corneal edema without inflammatory infiltration of stroma (unlike HSK linked edema)
- Keratic precipitates underlying the zones of edema -
  - the distribution of KP is essentially how the classification system works
  - Very frequently the KP will not be initially visible due to prominent edema
- Iritis
- **NOTE: No ulceration, no stromal infiltrate is present**

Chief concern is almost always reduced VA due to corneal edema
- Patients usually present with only mild pain
Disciform endotheliitis

- The most common form of endotheliitis
- Characterized by marked, circular area of corneal edema
- KP will underlie this zone of edema only. Non-edematous cornea will not have underlying KP
  - KP are often obscured by edema prior to treatment.

Diffuse endotheliitis

- More diffusely distributed KP and corneal edema.
- Edema here tends to be less severe
- When there are diffuse KP but no edema, think Fuchs Heterochromic

Linear Endotheliitis

- The most severe form of endotheliitis.
- Most intense inflammation and most difficult to treat
- CMV is also a frequent cause of linear endotheliitis
  - As opposed to CMV retinitis which affects immunocompromised, CMV endotheliitis may occur in immune competent individuals
Diagnosis of Herpetic endotheliitis

• The diagnostic feature, KP, are often obscured when patient presents, making diagnosis more difficult
• For this reason, HSV must be considered in any case of unilateral sudden onset corneal edema without infiltration (assuming there is no transplant).
• Important to assess fellow eye to make sure there are no signs of an endothelial dystrophy which may be causing edema

What acute unilateral edema is not HSV?

• Contact lens related edema
• Angle closure glaucoma
• Rejection or failure of an endothelium containing transplant
HSV diagnostic ledger

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Treatment of herpetic endotheliitis

- They all respond to topical corticosteroid
- Oral antiviral is generally indicated as well

HSV endotheliitis

- Disciform, diffuse and linear endotheliitis all cause permanent loss of endothelial cells
- If damage is wide spread enough, the patient can develop a permanently decompensated corneal endothelium and require endothelial transplant
Special Populations of HSV

- Certain populations may manifest the disease or respond to treatment in unexpected ways.
- These exceptional populations are important to be aware of.

Immune compromised patients

- Those with primary or secondary immune compromise have a few exceptions
  - Disease may present bilaterally (with atopy as well)
  - Will often require higher antiviral prophylaxis
  - Occasionally will develop acyclovir resistance

Immune compromise and antiviral resistance

- Due to the immune suppressed body’s inability to aid clearance of the virus, antiviral resistance has been reported among strains affecting this population – may occur at levels near 5%
- Despite in vitro resistance, these patients can still respond positively to acyclovir
Grafted Eyes

- HSV is the number 1 source of infectious vision loss in the US
- As such, it’s one of the primary infectious indications for corneal transplant
- Grafts that carry HSV as a primary indication have a 25% risk of reactivation within the first year post transplant
  - These patient should be on prophylactic antiviral often at higher than standard dosing
  - Eyes with an HSV indication for transplant have a reduced graft survival compared to most other common indications

HSV post-transplant

Patients with Renal Failure

- Acyclovir is excreted through the kidneys
  - Patients with renal failure do not effectively clear acyclovir
- So these patients get a “mega-dose” with standard dosages – by the time they take their next pill, they may have cleared less then half of what they should causing the medication to build up to toxic levels
Renal Failure Dosing

- This doesn’t mean they can’t use acyclovir or valacyclovir, simply that they need to use at a reduced dosage
- Topical remain an unadjusted option, though punctal occlusion would be advisable

Renal Dosing of Acyclovir

- Adjustments are made based on the patient’s creatinine clearance or whether they have dialysis with the help of their nephrologist

<table>
<thead>
<tr>
<th>Normal Dosage Regimen</th>
<th>Creatinine Clearance (mL/min/1.73 m²)</th>
<th>Adjusted Dosage Regimen</th>
<th>Dose (mg)</th>
<th>Dosing Interval</th>
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<td>200 mg every 4 hours</td>
<td>&gt;10</td>
<td>200</td>
<td>every 4 hours, 5x daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>200</td>
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<td>800</td>
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Kids

- The disease tends to be more recurrent (51% of cases)
- The disease is much more frequently bilateral (up to 25% of cases compared to the ~3-5% of adult cases)
- Children need weight adjusted dosing of acyclovir
  - 12-80mg/kg/day – review with pharmacist
  - Adjustments are also made to suppression dosage depending on age/weight
HSV diagnostic summary

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Final word

• Please hear the following in JFK voice:
• My fellow optometrists, ask not why a unilateral keratitis is herpetic, instead, ask why it is not

Thanks MOA!