• Pathogens of Corneal infection
• Aaron Bronner OD, FAAO, Dipl AAO
• Pathogens of Corneal Infection
• Discussion on some (not all) of the infectious concepts on anterior segment section
• Will cover
  • Bacterial keratitis
  • Fungal keratitis
  • Acanthamoeba keratitis
  • HSV keratitis
• Will not cover
  • Zoster keratitis, adenoviral keratoconjunctivitis, CMV keratitis, syphilitic or Lyme keratitis
  • Two types of Corneal Infection
• 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
• We are most concerned with the Exogenous group (microbial keratitis) and the Endogenous Viral group
• Exogenous infection: Microbial Keratitis
• Bacterial, fungal and protozoan ulcers can threaten corneal function
• Despite its limitations as a barrier, the ocular surface is actually really good at preventing this
• How is microbial keratitis prevented?
• Look at a normal, non-contact lens wearer:
  • Adherence and colonization the initial steps of bacterial infection are inhibited by:
    • Mechanical forces of the blink reflex
    • Mechanical force of tear flow,
    • Mechanical and physiologic barrier activity of the epithelium and mucin layer
    • Biochemical immunologic properties of the tear film
• Importance of History in determining risk of microbial keratitis
  • Only 5 species of bacterial can adhere to and penetrate an intact epithelium:
    • *N. Meningitides, N. gonorrhoeae, H. aegyptius, C. diphtheria and L. monocytogenes*
  • Any historic element that disrupts the epithelium can predispose the cornea to infection:
  • Over 90% of infectious corneal ulcers will have a known supportive historic element
    • General classifications of exogenous corneal pathogens
• 78 different species of bacteria have been documented to cause infectious keratitis
• Of this group, 6-10 pathogens cause 80-90% of infections – these are the “typical” pathogens
• Typicals – Account for the bulk of MK cases
  • Gram Positives – *staph spp, step spp*
  • Gram Negatives – *Psuedomonas aeruginosa, serratia marcascens, moraxella*
• General classifications of exogenous corneal pathogens
• Atypical – less common sources of MK, but important to keep in mind
• Includes the vast majority of known bacterial pathogens as well as fungal and protists
• Often require specific culture media
• Often have somewhat unusual appearances
• Often have unique histories
• Members of this group have worse prognoses
• Each ulcer needs to be attempted to be roughly differentiated based on clinical picture and patient setting
  • Patient Setting of MK
• Risk factor and patient age determine most likely etiology
  • Risk factors
    • Contact lens use: gram negative most likely, gram positive fungus and AK all on differential
    • Ocular surface disease/ocular surgery/Systemic disease (primarily RA): gram positive
    • No risk factor – think viral
  • Trauma: all atypicals
  • Age
    • Young patients – gram negative
    • Elderly patient – gram positive

• Clinical Picture of MK
• The clinical appearance of MK is not preserved across cases due to individual differences in patient immune response and isolate differences, however general trends can be used to guide clinical suspicion
• Typicals: Gram Positive
• Staph and strep spp
• Infiltrate
  • Generally slow to progress
• Round or oval
• Grey to yellow in appearance
• Dry appearance in contrast to gram negative
• Often paired with corneal edema and possibly a hypopyon
• Staph ulcer
• Massive Sterile AC reaction
• Exception to slow progressing gram positives
• Strep pneumonia is a gram positive variant that can be rapidly progressive to perforation
• Staph and Strep Variant
• Infectious Crystalline Keratopathy
• Typical: Gram negative
• Most common is Pseudomonas aeruginosa, but serratia maracens and Moraxella also contribute
• Pseudomonas is the most common gram negative source of infection. May be more common than staph aureus in some settings
  • Accounts for ~15% of corneal ulcers among non SCL users, but ~40-65% in SCL users
• Pseudomonas Aeruginosa
• Classic appearance is a wet, suppurative ulcer with rapid progression and deepening
• Classic “soupy” appearance
• May have a fruity smelling odor, even noticeable on culture
• May have non-uniform density and whirled appearance to the infiltrate
• Pseudomonas Aureginosas
• Alternate appearances
  • May generate a ring infiltrate (acute onset)
  • May also manifest as a mild superficial vesicular epithelium, as the organism occasionally proliferates in the basal epithelium. This disease type is mild and may be self limiting\textsuperscript{5,6}
  • May generate perineuritis

• Pseudomonas Auerginosa
  • An unusual feature of Pseudomonas ulcerations is that they may initially get worse in the presence of effective antibiotic treatment. Why?
    • The destruction of the organism may create an initial liberation of proteases and exotoxins which perpetuates tissue destruction

• Atypical ulcers
  • Account for a much smaller percentage of ulcers than typicals, but important to be aware of as possibilities given worse prognosis

• Nocardia
  • Acid Fast, variably gram positive staining Rod
  • Saprophytic organisms Causative etiology in approximately 1-2\% of corneal infections in the US\textsuperscript{7}
  • Not part of the normal flora - near exclusive link to external trauma

• Nocardia Keratitis
  • Characterized by slowly progressive keratitis
  • Most prominent clinical feature is patchy anterior stromal infiltrates
  • May have wreath- like distribution which is felt to be pathogneugmonic
  • Many features may appear mycotic (funga

• Non-tuberculous Mycobacterium
  • Broad group of mycobacterium
  • Accounts for all species of the genus beyond \textit{mycobacterium leprae} and \textit{mycobacterium tuberculosis}
  • Accounts for 1-2\% of corneal ulcers in the US
• Not part of the normal flora
• Widespread environmental distribution – link to trauma, immune suppression and ophthalmic surgery
• Non-Tuberculous Mycobacterium
• Waxy focal infiltrates
• Minimal inflammation
• Cracked windshield appearance possible
  • Ring Infiltrate possible
  • Satellite lesions
  • Mycotic appearance
  • Other “atypical” bacteria
  • There's a bunch!
• Fungal Keratitis
• Family of saprophytic organisms
• May constitute a minor part of the normal flora – Candida is most common fungal element of normal flora
• Of the species that are known to cause disease, a number exist as pathogens only in ophthalmic literature
• Responsible for 5-20% of corneal ulcers depending on geographic location
• Has a more negative prognosis than bacterial keratitis
• Classification:
  • Yeasts (Candida), Nonpigmented Filamentary (Fusarium, aspergillus) and Pigmented filamentary (Curvularia, Mucor)
• Fungal Keratitis
• Historically primary risk factor was trauma with organic material
• Currently SCL use appears to be responsible for at least as high a percentage of fungal keratitis as trauma
• Candida has historically been associated with temperate climates and Fusarium with tropical
  • Fusarium may be predominating across the board now
• Fungal Keratitis
• Fungal Keratitis
• Classic Clinical Picture
  • Feathery Margins
  • Satellite infiltrates
  • Dry/leathery infiltrate
• Occasional
  • Ring Infiltrate
  • Pigmented infiltrate
• Reality:......
  • Candida albicans

Reality: Significant variability. Over 80% of fungal corneal ulcers originally misdiagnosed
• Acanthamoeba
• Genus of protozoa
• Ubiquitous distribution
• Opportunistic pathogen
• Two metabolic states
  • Active trophozoite
  • Inactive cyst
    • Cyst resists metabolic demands, heat, **UV exposure** and changes in pH
• Excystment occurs when cyst is exposed to hospitable environments
• AK
• Most AK cases will combine risk factors: Contact lens use, Trauma and ocular exposure to non-sterile water supply
  • Primary risk factor is contact lens use
    • 1st generation SiHi lenses have the highest risk
    • Daily Disposables have the lowest risk
    • SCL have a ~10 times greater risk than rgps\textsuperscript{16}
  • 15-25\% of AK patients have no history of contact lenses
• AK
  • Clinical Picture/ Symptoms
    • Classic – greater pain than clinical picture indicates
    • Reality - Its totally dependent on the stage of the disease
• AK
  • Clinical Picture
    • Seems to progress on a continuum
    • Most important to catch EARLY – RECOGNIZE EARLY FINDINGS
• Early AK
  • Epithelial Disease
    • Course, localized cystic epitheliopathy. Quite prominent
    • No infiltrate
    • Often has dendriform appearance
    • Epithelial defect tends to absent during this stage
    • Very good outcomes are possible if caught at this stage
• Early AK
  • Stromal Perineuritis
    • Not an early finding in all cases, but becomes less common the further from onset one moves
    • Nearly pathognomonic
• Leprosy and pseudomonas are other sources, though AK is 300 times more likely to cause\textsuperscript{16}

• Stromal perineuritis

• AK late

• Mid and Late disease:
  • Ring infiltrate – more common the further progressed from presentation
  • Epithelial defect
  • Corneal opacification
  • Retro corneal spread is rare

• Treatment Considerations with MK

• Empiric vs Culture driven

• Fortifieds vs commercially available meds

• Empiric vs Culture Driven Treatment

• Empiric treatment

• Good:
  • Ease of initiation
  • All treatments really begin empirically
  • About 90% of infectious ulcers respond to this treatment\textsuperscript{25}

• Bad:
  • May confound later attempts at culture
  • May delay appropriate treatment and lead to worse outcomes

• Culture Driven Treatment

• Good
  • Offers the most diagnostic and treatment information possible
  • De-bulks infectious material
  • Antibiotic susceptibility information is derived from this

• Bad
• Overcoming inertia: learning to culture, buying equipment, keeping media stocked, etc
• Only 40-65% yield growth\textsuperscript{18, 21}

• Empirc Vs Culture Driven Treatment

• Value potentially derived from cultures
  • Gram Stain Smears – near immediate results which have significant impact on prescribed treatment
  • Cultures – may take several days but can provide:
    • Accurate identification of etiology
    • Antibiotic sensitivity
    • Debulks infectious load

• Empirc vs Culture Driven Treatment
• But....
  • Cultures are negative 40-60% of the time (and gram stain may be negative even more often)
  • Empirc treatment appears to be the most common practice among ODs and OMDs\textsuperscript{20}
  • Good outcomes are possible with this treatment strategy
  • Vast majority of infections will respond to empiric therapy\textsuperscript{25}
  • So…empirc treatment is fine…..right?
  • Two ways of looking at things:
    • One way:
      • What percentage of cases is broad spectrum empiric treatment effective?
        • most of the time
    • The other way:
      • When empiric therapy is ineffective, what is the impact of beginning with empiric treatment?

• Empirc or Culture Driven Treatment
  • Of patients who are placed on incorrect empiric treatment:
• 50% higher rate of PK
• Doubled overall cost of therapy\textsuperscript{18-20}

• Materials:
  Gram Staining

• Benefit: Near Immediate Diagnostic information available regarding gram positive, gram negative and fungal elements

• Drawback: Very spotty yields reported. As low as 0% in one study group\textsuperscript{26}
  • Theorizes that community and hospital based labs are not good dealing with minute samples that come in from corneal smears. Ocular microbiology labs are superior in this regard

• Materials:
  Culture Media

• Need:
  • General growth media – Blood Agar/Thyoglicolate
  • Fastidious organisms media – Chocolate agar/Heart brain infusion

• Specialty agar or broth
  • Fungal Culture – Saubarauds agar
  • Mycobacterium/Nocardia -Lowstein Jensen slant or Middlebrook agar

• Materials: General Growth

• Thyoglycloate
  • Grows most ocular pathogens liquid media may increase yield

• Blood Agar
  • Grows most ocular pathogens

• Materials: Fastidious growth

• Chocolate Agar
  • Contains factors that lyse
blood for organisms which are unable to: Neisseria,
Haemophilus
  • Heart Brain Infusion Broth
    • Good for fastidious species,
m moderate for fungus
  • Materials: Specialty Media
  • Sabouraud
    • Fungal media
  • Lowstein Jensen Slant
    • Grows Mycobacterium,
Nocardia
  • Middlebrook agar
    • Grows Mycobacterium
  • Confocal Microscopy
  • Non invasive way to identify AK in vivo
    • Very good sensitivity
    • Moderate Specificity
      • False positives may be as high as 20%\textsuperscript{39}
    • These may vary from operator to operator
  • What treatment is appropriate?
Fortified vs Commercially available antibiotics
  • Traditional Treatment of Corneal Ulcers
  • Dual broad spectrum fortified antibiotics – Historic Treatment of Choice
• Typical treatment has been broad spectrum dual therapy: Often fortified aminoglycoside (for gram negative species) and fortified cephalosporin (for gram positive)

• Fortified vs commercially available: community practice

• **82% of non-Cornea trained OMDs reported they would treat less severe infectious keratitis with a single new generation fluoroquinolone**

• 62% reported they would treat more severe ulcers in this manner

• This practice will be successful the majority of the time

• Is one approach better?

• Strengths and Weakness of Fortified Regimen

• **Strengths:**
  • Dual broad spectrum fortified antibiotics are the most likely empiric therapy to be effective in cases of bacterial keratitis

• **Weaknesses:**
  • Acquiring meds/Rxing meds can be difficult
  • Short shelf life
  • Epithelial toxicity

• **Common Fortifieds**

• **Gram Positive**
  • Cefazolin – 50mg/ml
  • Vancomycin -15-50mg/ml

• **Gram Negative**
  • Tobramycin/gentamicin 9-14mg/ml
  • Ceftazidime/ceftriaxone 50mg/ml

• **NTM/Nocardia**
  • Amikacin 20-40mg/ml

• **Cook book for fortifieds**

• **In Appendix 9 of Wills Eye Manual (4th Ed)**
• In Bacterial Keratitis chapter of Holland’s *Cornea*
• What about commercially available drops?
• Commercially available meds: Fluoroquinolones
• Fluoroquinolones have very good coverage against gram negative species
• Early generation fluoroquinolones have spotty gram positive coverage
• 4th Generation fluoroquinolones have enhanced coverage of gram positives
  • up to 4Xs that of ciprofloxacin for *Staph aureus*
  • even greater for Strep species
  • Somewhat reduced gram negative coverage
• Fortified vs Commercially Available
• MRSA/MRSE becoming an increasingly common pathogen
  • 28%-38% of Staph Aureus induced corneal infections are MRSA
  • 50% of SE induced corneal infection are MRSE 
• Per the Ocular TRUST 2, MRSA and MRSE strains exhibit only 15% sensitivity to fluoroquinolones
  • If you are exclusively using commercially available meds, keep this in mind:
• Fortified vs Commercially Available meds
• What about besifloxacin?
  • Besifloxacin (Besivance, B and L) is an ophthalmic only preparation
    • Theoretically reduced resistance due to its limited dosing
    • Lower MIC against Pseudomonas
    • Lower MIC against non-resistant *Staph aureus* isolates
    • Lower MIC against ciprofloxacin resistant MRSA isolates
  • Besifloxacin compared to gatifloxacin and moxifloxacin
    • In practice, besifloxacin’s molecular structure very similar, but not identical to, 4th generations. Relative resistance to moxifloxacin or gatifloxacin is likely to result in relative resistance to besifloxacin
• Fortifieds vs Commercially available: **putting it all together**
• For Pseudomonas and Strep spp, resistance is a minimal issue
• For staph spp, resistance is a **BIG** issue
• When treating empirically, lean on the data we have RE most effective treatments
  • Besifloxacin +
  • either tobramycin/gentamicin or polytrim
• Treatment of Fungal Keratitis
  • Natamycin 5% - the only commercially available topical antifungal
    • Good efficacy against filamentary fungus – may be reasonably employed as monotherapy in cases of filamentary fungal keratitis
  • Voriconazole compounded at 1% levels
    • Better efficacy against yeasts (Candida)
    • Equal efficacy against filamentary keratitis
  • Amphotericin B 1.5 mg/ml
    • Good efficacy against yeasts
• Oral Ketoconazole 200-400mg/day
  • Due to poor penetration of most topical antifungals may be used adjunctively in cases of deep fungal keratitis
• Treatment of Fungal Keratitis
  • No anti-fungal agent effectively penetrates intact epithelium and remember *fungal keratitis can deepen beneath an intact epithelium*
  • Epithelial debridement is an important component of therapy
• Treatment of AK
  • Needs to exhibit both anti-trophozoiite and anti-cyst activity
• Biguanides: May be effective monotherapy
  • Polyhexylmethylene biguanide PHMB (0.02%)
  • Chlorhexadine 0.02%
• Dosed at 100 times greater concentration than a minimally cysticidal concentration MCC
• Treatment of AK
• Diamidines: Secondary medications
  • Propimidine isethionate 0.1% (Brolene)
  • Heximidine 0.1%
• Not as strong as biguanides, useful adjunctive therapy added to biguanides

**AVAILABLE ONLINE OTC!!!**
• Viral Corneal Infection

• Adenoviral infection, an exogenous corneal infection, can produce superficial punctate keratitis that preceded the inflammatory SEI
• For the most part, however, we are concerned with endogenous systemic infections that winds up in the cornea, ie herpes viral infection and primarily herpes simplex virus
• Herpes Simplex Keratitis
• 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
• 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, virons 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 Reactivation
  • Defined as when latently infected ganglion neurons begin producing virons (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
• Remember this grouping?
• 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) Endotheliitis

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

Sets the stage for all other problems which follow

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

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

• 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

• HSV Neurotrophy/Meta herpetic disease

• Milder compared to some other forms but can require treatment

• Generally, when clinically significant only causes mild chronic epithelial dryness issues

• When neurotrophic ulcers develop they may cause
  • Thinning
  • Stromal scarring
  • Perforation
  • Possibility for super infection

• HSV neurotrophic ulcer

• 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 it’s 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 Sequela: Deep keratitis
• 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
• HSK
• 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
  • Herpes Stromal Keratitis
• 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: Subdendritic
• HSK: Sub-dendritic
• HSV: marginal HSK
• HSK: Sub-dendritic Chronic expanding scar
• HSK: Diffuse stroma haze:
  Ag-AB precipitate
• 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
• HSK:CN
• Sequela of Herpetic CN: Lipid keratopathy
• 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

- Two arms of HSK treatment
- Primary: Anti-inflammatory
- Secondary: prevention of viral reactivation
  - Two forms – during acute stages and long term maintenance therapy

- 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

• 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 epi defect

    • Dense infiltrate – consistent with density of microbial keratitis

• Necrotizing Stromal 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
• **HSV 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**

  • HSV endotheliitis

  • Chief concern is almost always reduced VA due to corneal edema
    
    • Patients usually present with only mild pain
    
    • Disciform endotheliitis, before and after treatment

  • Mild diffuse endotheliitis before and after treatment

  • HSV Linear Endotheliitis

  • 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

  • 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 widespread enough, the patient can develop a permanently decompen-sated corneal endothelium and require endothelial transplant

• Summary

• To effectively diagnose and treat corneal infection, it's important to pay attention to

• Risk factors:
  • If present, think MK if absent think viral

• Clinical appearance
  • Round or oval ulcerated infiltrate think typicals, irregular ulcerated infiltrate think viral or atypical, non-ulcerated infiltrate think hypersensitivity reaction or viral, sudden corneal edema think viral
  • CN suggestive of viral
  • Neurotropgy suggestive of viral