It’s the thought that counts: management of infectious keratitis

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Corneal infectious disease

- Corneal infectious disease is caused by a wide variety of pathogens
- These pathogens can have vastly different case histories, clinical pictures and treatments
- To successfully manage these you have to know how to differentiate these from non-infectious pathologies, differentiate among infectious pathologies and then understand treatment differences between the groups

About Me

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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

- For corneal disease we are primarily concerned with exogenous organisms and endogenous viral group
- These two groups behave differently in their natural history which causes the mechanism they infect the cornea to differ
  - Exogenous infections work from the outside of the cornea inward
  - Endogenous infections infect from the inside of the body outward to the cornea

This is important for diagnosis

Scope of lecture

- We’ll be covering two broad groups of pathogens today
  - Microbial (Bacterial, fungal and protozoan)
  - Viral (herpes simplex, herpes zoster and CMV)
Infectious keratitis

- Both of these groups can be sight threatening
  - ~10% of MK patients go on to require corneal transplant, a number that is higher among certain pathogen groups
  - HSV is the widely reported to be the #1 infectious indication for corneal transplantation in the developed world
- Though from a timing standpoint, MK is generally more acutely sight threatening then viral
- These need to be effectively differentiated and treated on presentation to be best managed

Keratitis differential

- As microbial keratitis is the most acutely sight threatening of the group, it’s the first that we need to rule in or out
- How do we do that?

Differentiating Acute corneal pathology

- Your empiric diagnosis should be the logical result of the marriage of your clinical picture and case history

Identifying keratitis as infectious: The infiltrate

- The infiltrate is the hallmark of microbial keratitis
  - When microbial, almost always round or oval and well defined
  - Is made up of micro-organisms, necrotic tissue and white blood cells
  - Should not be confused with a simple epithelial defect.
  - Also, is not to be confused with corneal deposits/lipid
  - Or corneal edema

Infectious keratitis???

No infiltrate = no MK*

Acute Keratitis Flowchart

Microbial keratitis is not the only cause of corneal infiltrates
Infiltrate in Microbial Keratitis

- Typically solitary and;
- Typically larger than 2 mm
- Typically well-defined/densely infiltrated and;
- Typically round(ish) or oval(ish) and;
- Almost never peripheral and;
- Typically has an overlying epithelial defect, regardless of stage;
- Corneal neo almost never present
- Should have a clinical history consistent with MK

Summary of Types of infiltrates

**Microbial**
- Unilateral
- Generally solitary
- Generally round or oval and well defined
- Almost always ulcerated regardless of severity
- Rarely near limbus
- Avascular

**Herpes**
- Unilateral
- Often multifocal
- Often unusual shapes or diffuse
- Infiltrate less dense than MK
- If not dendritic, not ulcerated
- Varied location
- Often vascularized

**Sterile**
- May be paired with lid margin disease (bilateral)
- Maybe highly vascular
- Generally at limbus (if not, will likely be leashed to limbus by a vessel)
- Ulceration depends on severity
- Small, multifocal and diffuse or large, crescentic and peripheral

Step 2: Use the history to differentiate

Why is the route of infection taken by different pathogens important?

- Remember, the natural history of exogenous infections (MK) is different from that of endogenous infections (viral)
- Natural history shapes the possible clinical histories that accompany infection

How does natural history shape clinical history?

- Cornea has two functions:
  - Optical
  - Barrier

- Endogenous infections are already present systemically
  - Don’t need to breach corneal barrier
- Exogenous infect from the outside of the cornea inward
  - Must breach corneal barrier

Corneal barrier function: Microbial keratitis (MK)

- Weaker barrier function than skin but still pretty good
- Look at a normal, non-contact lens wearer:
  - Adherence, the initial step of bacterial infection is 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
The Cornea as a barrier

- Blocks adherence and colonization of microbes

Supportive history and MK

- Only 5 known bacterial pathogens of a group of ~100 possibly microbial pathogens can adhere to and penetrate an intact corneal epithelium
- However, when the corneal barrier is compromised, infection can occur much more readily

Supportive history of different infiltrates

- 90% of cases of MK will have a historic risk factor that predisposed the eye to developing an infection
- For microbial keratitis, you basically require a supportive history to feel good about your diagnosis
- For viral, no supportive history is needed!
- For sterile
  - Contact lens use, if involved
  - Or history of autoimmune, sometimes no known history

For MK, what history do we need to be looking for?

- 1) Contact lens use
- 2) Trauma
- 3) Ocular surface disease
- 4) Corneal surgery
- 5) Systemic disease (RA and Diabetes)

By the way, maybe this sort of thing should inform our treatment decisions beyond differentiating keratitis

Risk factors can also be used to differentiate further to “most likely pathogens”

- 1) Contact lens use – increases risk of both gram positive, gram negative, fungal pathogens and acanthamoeba
- 2) Trauma – depending on origin of trauma, increases risk of atypical bacteria, fungus and occasionally acanthamoeba
- 3) Ocular surface disease – increases risk for normal flora and occasionally fungal infection
- 4) Corneal surgery – increases risk for normal flora infection
- 5) Systemic disease (RA and Diabetes) – increases risk for normal flora infection

Wild card risk factor

- Immune Suppression (either locally or systemically) will enhance these risk factors – but also increases risk for viral keratitis and additionally can muddle the clinical appearance
Steps to diagnosing infectious keratitis

1) Use the clinical feature of the infiltrate to roughly differentiate
2) Use the patient's history/risk factors to roughly differentiate
Then, if you feel its MK... keep going
3) If, after taking account of the case, you feel the lesion is microbial, differentiate further to likely:
   - Gram positive typical
   - Gram negative typical
   - atypical bacteria
   - Fungal
   - Acanthamoeba

Why do we need to differentiate further?

- Will an antibiotic be effective against acanthamoeba?
- Should culturing strategy be informed by suspected etiology?
- Will routine monotherapy be effective against MRSA?
- Are steroid recommendations universal across etiologies of infiltrative keratitis?

General classifications of exogenous corneal pathogens

- Over 100 different pathogens can cause corneal infection
- Of this group, 6-10 pathogens cause 70-85% of infections — these are the “typical” pathogens
- Minimum initial empiric diagnosis of MK should include likelihood of:
  - Gram Positive Typical — staph spp, strep spp
  - Gram Negative Typical — Pseudomonas aeruginosa, serratia marcescens, maybe Moraxella
  - Atypical bacteria
  - Fungus
  - Acanthamoeba

Typicals: Gram Positive

- Staph and strep spp
- Dominant organisms of normal ocular and periocular flora
- Staph spp accounts for 25%-66% of all corneal ulcers
- Staph epi most common etiology
- Infiltrate
  - Generally slow to progress (though strep pneumoniae can be very aggressive)
  - Round or oval
  - White to grey to pale yellow in appearance
  - Dryer looking than gram negatives
- Cornea often edematous and hypopyon often present

Historic risk of typical gram positives

- As dominant organisms of the ocular and periocular flora these are associated with opportunistic infection developing in the setting of epithelial breakdown, rather than an inoculating event
- Ocular surface disease/neurotrophic superinfection
- Ophthalmic surgery
- Systemic disease: RA, diabetes
- And to a lesser degree, SCL use
- Older age patients

Challenge of gram positive pathogens

- This is the group where antimicrobial resistance is most problematic, specifically among staphylococcal species
  - Between 33-67% of all staph related eye disease is caused by MRSA or MRSE
  - This probably should shape treatment where you suspect gram positive etiologies
MRSA and MRSE

- Any cases where gram positive etiology is suspected based on risk factor, age of patient or clinical appearance of the infiltrate, the patient should at least be asked about history of other MRSA/MRSE infection/colonization/exposure risks
- We'll talk about how this should shape treatments later

Typicals: Gram negative

- Most common is Pseudomonas aeruginosa, but Serratia marcescens and Moraxella also contribute
- Not significant components of the normal flora and so needs a delivery vehicle in most cases
- Pseudomonas may be more common as a source of corneal infection than staph aureus in some settings
  - Southeast US
  - Contact lens populations

Pseudomonas Aeruginosa

- Classic appearance is a wet, suppurative ulcer with rapid progression and deepening
- Classic “soupy” appearance
- Infiltrates look like they can just be wiped away
- May have non-uniform density and whirled appearance to the infiltrate

Pseudomonas Auerginosa

- Pseudomonal infections may get worse despite appropriate treatment for ~24 hours.
- Therefore, with most undifferentiated corneal infections give 48 hours before calling treatment failure

Historic risk of typical Gram negatives

- Not strong contributors to normal flora so role in ocular surface disease associated super-infection is limited but both pseudomonas and serratia are exceptionally able to develop biofilms on wet, abiotic materials both in natural environment and in man-made micro ecosystems
- Because of this, history is very tightly tied to CL use and occasionally trauma from watery environment
  - Accounts for ~15% of corneal ulcers overall, but ~40-65% in SCL users

Atypical ulcers

- Atypical bacterial ulcers
  - Remember, there are 78 known bacterial sources of corneal infection and we've talked about a handful which account for at least 70% of all corneal infections
- Fungal ulcers
- Acanthamoebal ulcers
Fungal Keratitis

- May constitute a minor part of the normal flora (primarily yeasts: Candida)
- Causative in 5-20% of corneal ulcers depending on geographic location
- Has a more negative prognosis than bacterial keratitis
  - Per Bascom Palmer review, accounts for disproportionately high # of corneal transplants
- Classification:
  - Yeasts (Candida), Nonpigmented Filamentary (Fusarium, aspergillus) and Pigmented filamentary (Curvularia, Mucor)

Fungal Keratitis: Evolving risk factors

- 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
  - Further, ocular surface disease is the risk for ~30% of fungal ulcers!

Fungal Keratitis

Risk factors vague, but at least there are a lot of clinical clues for fungal ulcers...

Fungal Keratitis

- Classic Clinical Picture
  - Feathery Margins
  - Satellite infiltrates
  - Dry/leathery infiltrate
  - Endothelial rings and plaques
- Occasional
  - Ring Infiltrate
  - Pigmented infiltrate
- Reality:……

Is that keratitis fungal or not?

- You cannot rule out fungal keratitis with any MK ulcer until you have:
  - 1) Positive response to treatment, or
  - 2) Positive culture results

Acanthamoeba

- Genus of protozoan
- Two metabolic states
  - Active trophozoite
  - Inactive cyst
- Ubiquitous distribution
- Opportunistic pathogen
- Neutrophils are pretty effective at killing this organisms
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 rgp's

- 15% of AK patients have no history of contact lenses

Clinical Picture
- Unlike other microbial keratitides, AK looks quite different depending on stage of infection
- Most important to RECOGNIZE EARLY FINDINGS
  - Early findings: localized superficial epitheliopathy, Perineuritis
  - Late finding: corneal ring ulcer
  - Extremely easy to misdiagnosis with HSV at this stage
- Degree of pain relative to clinical picture is also relative to where on the continuum the disease is at

Early AK
- Epithelial Disease/perineuritis
  - Course, localized cystic epitheliopathy. Quite prominent
  - No infiltrate
  - Often has dendriform appearance
  - Epithelial defect tends to absent during this stage
  - Stromal perineuritis

There is an exception to every rule
- Remember when I said "No infiltrate, no MK"?
- That doesn’t apply to early AK

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

These eyes almost invariably go onto to require corneal transplant to restore optical clarity of cornea

AK take home message
- This is not AK – AK does not look like bacterial keratitis
AK: the early diagnosis gets the worm

Outcome with early epithelial stage diagnosis and treatment: 20/20. No Scar

Next step

- At this point we’ve made our best empiric diagnosis
  - Gram positive bacteria
  - Gram negative bacteria
  - Fungal keratitis
  - Acanthamoeba keratitis

- It’s time to design a treatment based on that diagnosis
  - Options in initial treatment of MK
    - Culture based vs empiric
    - What medications (and how many) to use
    - Use of adjunctive agents and where new treatments fit in

Culture vs Empiric therapy

- Culturing provides some valuable information regarding the causative pathogen and its treatment.
- Given spill-over in clinical appearance and historic risks, the only way you can really be certain you know what you are treating is to culture

Culture vs Empiric Therapy

- That said, since the advent of broad spectrum commercially available antibiotics, most cases treated with broad spectrum topical agents empirically will be successful
- Most…but not all cases treated empirically work out.
  - Some studies suggest failure with initial treatment reduces subsequent culture yields
  - Initiating treatment with incorrect/ineffective empiric therapy has important consequences –50% higher rate of surgical outcome and doubled cost of therapy...
  - Further, antimicrobial resistance may be altering efficacy of empiric monotherapy

For culture based practice

- At minimum, culture or refer for culturing when:
  - The ulcer is in or near the visual axis,
  - The ulcer has unusual histories (involving vegetative matter, highly compromised ocular surfaces, etc)
  - The ulcer is bigger than 3mm x 3mm
  - The ulcer has unusual features such as satellite lesions, feathery margins, etc

- Full culturing involves direct inoculation to a slide for gram staining, general growth media (solid or liquid, fastidious growth media (solid or liquid) and specialty media

Materials: Culture Media

- Need:
  - Gram slide
  - General growth media –
    - Thioglycolate broth/blood agar
  - Fastidious organisms media –
    - Chocolate agar/Heart brain infusion

- Specialty agar or broth
  - Fungal Culture – Saubarauds agar
  - Mycobacterium/Nocardia –Lowenstein Jensen slant or Middlebrook agar
The rub: Culture based practice usually begins as empiric

- Unfortunately, unless you are doing in house gram staining and interpretation, all treatment begins empirically.
- Depending on pathogen, definitively negative cultures can take about 3-4 weeks to achieve.
- So you need to initiate your therapy based on the best guess of infectious etiology and what medicines will be effective, and then assess for response as if you were not culturing at all.

Treatment options: Where to begin?

- Dual broad spectrum fortified agents are the cornea clinic standard of care, and debatably the most likely initial empiric therapy to be effective.
  - Usually a cephalosporin and aminoglycoside or vancomycin and aminoglycoside when MRSA is likely.
  - But this isn't what's happening in most OD and OMD clinics.
    - Single new generation fluoroquinolone is the standard of community practice.
      - Again, this works out most of the time, or at least it has...

An aside about MRSA and MRSE

- Becoming much more frequently encountered.
  - Approximately 25-67% of staph eye disease is caused by MRSA or MRSE.
  - Extrapolated with known incidence of SE and SA ulcers suggests that 10-30% of all ulcers you treat will be MRSA or MRSE.
  - These respond poorly to even new generation fluoroquinolones.

An aside about MRSA and MRSE

- How do we apply this information clinically?
  - If you suspect a staph etiology based on appearance of the ulcer, the risk factor for developing the ulcer or even patient age, consider MRSA as a possibility and consider adjusting your treatment somewhat.
  - Recommend dual therapy with two of the below agents:
    - Besivance, polytrim, tobramycin, gentamicin and vancomycin (fortified) have all been shown to be active against MRSA.

An aside about the aside:

- Besifloxacin's role in MRSA treatment
  - ARMOR study showed it performed well against MRSA.
  - But because it is ophthalmic only there is no way to confirm with sensitivity testing as besifloxacin MIC discs are not available.
  - You should be aware of this.
  - If you are using Besivance here, it would be wise to pair it with: polytrim, tobramycin, gentamicin.

Initial treatment options

- Probably not totally important as long as you don't treat this like a one size fits all.
  - Again: Have a solid idea you know what pathogen you are dealing with—treatment should reflect your suspicions.
    - Monotherapy with fluoroquinolone is ok for suspected gram negatives.
    - Consider dual therapy if a gram positive source/resistant source is likely.
  - Assess closely for treatment failure and immediately change treatment if this occurs.

- Treatment failures are expected periodically, but absolutely must have value.
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
- Possible synergistic effect when combined with Natamycin
- Amphotericin B 1.5 mg/ml
  - Gold standard 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 AK

- **Biguanides**: May be effective monotherapy
  - Polyhexamethylene biguanide PHMB (0.02%)
  - Chlorhexidine 0.02%
  - Dosed at 100 times greater concentration than a minimally effective concentration MCC
- **Diamidines**: not strong enough to be monotherapy
  - Propimidine isethionate 0.1% (Brolene) – available OTC online
  - Heximidine 0.1%

New and adjunct therapies in MK

- **Biguanides**: May be effective monotherapy
- **Diamidines**: not strong enough to be monotherapy
  - Propimidine isethionate 0.1%
  - Heximidine 0.1%

Steroids for Corneal Ulcers

- Topical Steroids inhibit local cytokine production and chemotaxis which mutes local immune response...this can be bad when you want the immune response, i.e., during an infectious process
- However:

Steroid Guidelines for Corneal Ulcers

- **SCUT Study**
  - In general, no harm or good with initiation of topical corticosteroids in cases of bacterial keratitis
  - Greatest benefit seen in the worst ulcers
  - Outcome was poorer with steroid in cases of Nocardia
Practical limitations of SCUT

- SCUT patients had attempts at sterilization prior to initiation of steroid
- Only applies to bacterial keratitis
  - Because you can't easily differentiate fungal from bacterial ulcers, you can't even think about adding steroid until you have a positive response to therapy or a culture result in hand

Steroids for fungal and acanthamoeba infection?

- Fungal:
  - **DO NOT USE**
  - Impacts efficacy of antifungal medications
- Acanthamoeba:
  - Not as clear cut as fungal keratitis
  - Should only be considered after effective anti-amoebic therapy has been utilized for a couple of weeks and then on case by case basis
  - Probably a decision for a cornea clinic

Steroids for keratitis practical guidelines

For unknown infiltrative keratitis, if:

- There is a risk factor for MK and:
  - Its paracentral and
  - Its bigger than a pinhead and
  - Its ulcerated
- **DON'T ADD STEROID RIGHT AWAY**
- For presumed MK: Understand SCUT does not give carte blanche to add steroid at will
  - if you are going to invoke SCUT to justify therapy, you have to follow SCUT protocol

When to consider steroid for ulcers?

May consider adding steroid, but only when you see some sign that sterilization of the cornea is occurring

Amniotic Membrane in the treatment of MK

- AM has well established anti-inflammatory properties and is purported to be at least somewhat antimicrobial.
- Further, through it's positive effects on wound healing, AM may be expected to have some role in the treatment of microbial keratitis
- Where does it fit in?

AM in management of microbial keratitis

- AM may be somewhat antimicrobial compared to a BSCL, but it is not antimicrobial
- So it should not be thought of as a supplement to the antimicrobial component of treatment
AM in management of microbial keratitis

- There are two arms to the treatment of microbial keratitis, although one is largely ignored
  - Primary: sterilization of the cornea
  - Secondary: closure of epithelial defect

- Poor healing epithelial defects are frequently encountered in the management of MK, particularly among the elderly
  - These behave the same way as any poor healing epithelial defect
    - MMPs are upregulated and corneal melt and even perforation may occur
    - Any melt will increase the resultant scar

- Where AM really shines is in the healing of these chronic epithelial defects
  - Hastening the healing of these defects reduces scarring
  - AM can accelerate the healing of these
  - This should be interpreted conservatively:
    - All stromal ulcers will scar. AM will not impact this
    - If epithelization is slow to take place after sterilization, AM can reduce this resultant scar

Treatment options

- New technology
- New treatment options seek to avoid the need to differentiate ulcers by broadening spectrum of coverage
  - PACK-CXL
  - Topical Disinfectants

PACK-CXL

- Photo-Activated Chromophore for infectious Keratitis
- Fancy name for basically the same procedure as conventional CXL
- Works theoretically by
  - Irreversibly suppressing bacterial replication
  - Oxidative destruction of pathogen with ROS
  - Inhibition of binding of collagenases and subsequent proteolysis of stroma
PACK-CXL

- It's been shown that PACK-CXL + antimicrobial is non-inferior to antimicrobial alone and has been assessed for all major pathogen groups
  - Bacterial
  - Fungal
  - Protazoan
- Poorly defined protocol and post op regimen
- Seems to work better for less severe ulcers

PACK-CXL:

- "50% of energy absorbed in 1st 100um"
  - Due to this depth effect, probably more appropriate as front line therapy
  - Due to the fact it's experimental, it's use as front line therapy is unappealing

Other treatment options: Antiseptics/disinfectants

- Agents that impede microbial growth typically applied to non-biologic surfaces to clear or skin to prep for surgery
- The distinction with antibiotics is that they are safe to use within the body – The deepest traditional application of antiseptics is the skin…which is a barrier tissue.
- Non-specific antiseptic medication already have a role in the management of MK
  - Chlorhexidine
  - PHMB
- There are also some other agents that are somewhat appealing to consider
  - Betadine
  - Hypochlorous acid…?

Iodine

- Iodine...a delightfully toxic element
  - Povidone iodine works on a number of cellular mechanisms, but most importantly short circuits electron transport which is used by all living organisms use to produce energy
  - Due to these multiple mechanisms, some of which target fundamental actions of the microbe, resistance is not likely to develop

Povidone iodine

- Consistently effective against pretty much everything!
  - Gram positive bacteria
  - Resistant or not to antimicrobial
  - Both planktonic and biofilm based
  - Gram negative bacteria
  - Resistant or not to antimicrobials
  - Both planktonic and biofilm based
  - Fungus
  - Protazoan
  - Cysts and trophs
- And...it has a pretty rapid kill time!!
  - MRSA colonies killed within 30 seconds of exposure based on one study
  - And relatively low cytotoxicity!!

Povidone Iodine for infectious keratitis

- Study out of India and Philippines in cases of bacterial keratitis
- All patients hospitalized
- Treatment arm received 1.25% PI hourly around the clock
- Control arm used either ciprofloxacin or neomycin + gromicidin hourly around the clock
Povidone Iodine for infectious keratitis

- Results
- Mean time to cure was 7-17 days with both PI and Abs
- No increase in adverse outcome
- Final VA was similar among groups
- These will probably free community clinics up to use in office PI to supplement (or even replace) traditional antimicrobial strategies
- This has enormous potential benefit to developing countries

Summary of MK

- History and exam should shape differential
  - Empiric diagnosis should seek to be more specific than bacterial keratitis
- Differential should shape primary treatment
  - Expanding antimicrobial resistance should alter initial therapy in select cases
  - Fungal keratitis cannot be reliably differentiated from other sources of MK on exam or history and has a worse prognosis
- Culture recommendations depend on characteristics of the infiltrate and clinical history, and to a lesser degree, availability of culturing material
- Steroids should be avoided unless there is culture result that eliminates fungal ulcers, or a positive response to treatment, in which case they can be introduced cautiously
- Amniotic membrane can be particularly helpful in elderly patients with ulcers where re-epithelization can be slow to occur

What about when the clinical picture and patient history don’t add up

- When the pieces don’t fit together

  - It’s always HSV!
    - Well, not always, but a lot of the time of the time

Why is everything Herpes Simplex keratitis?

- Because everyone (basically) has HSV-1, everyone is at risk
- No specific risk factors are needed
- Remember this?
  - Because endogenous infections are already in the person, no apparent ophthalmic risk is necessary to trigger Herpes Simplex keratitis
- A very significant ophthalmic/public health problem
  - 500,000 case of ophthalmic HSV in US
    - 40,000 go on to lose some degree of vision each year
    - #1 infectious cause of corneal blindness in the developed world
    - #1 infectious indication for keratoplasty in the US

Herpes Simplex keratitis: more than a dendrite

- Considering the dendrite as the only important manifestation of HSV is naive
  - Infectious epithelial keratitis – IEK - (dendrite, vesicular lesions/pre-dendrite, marginal IEK)
  - Neurotrophic keratitis/meta herpetic disease
  - Herpes Stomal Keratitis – HSK – or Immune Stromal Keratitis – ISK – (sub-dendritic keratitis, diffuse stromal keratitis, marginal HSK, HSK linked corneal neo)
  - Necrotizing stromal keratitis
  - Herpetic endothelitis (Disciform, diffuse, linear)
Infectious Epithelial Keratitis

- Infectious Epithelial Keratitis (IEK) or dendritic keratitis is an umbrella term to describe an episode of clinical reactivation of viral shedding of the cornea.
- May manifest as:
  - Vesicular/dendritic keratitis
  - Geographic keratitis
  - Marginal keratitis
- Represents a true viral infection of the cornea.

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
- Accounts for 50-80% of HSV keratitis yet only accounts for about 25% of referrals for HSV that I receive at a cornea clinic.
  - What’s this mean?

Course and sequela of IEK

- In most cases the immune response of the untreated individual will contain the active infection within 2-3 weeks.
- Impact of IEK:
  - Increased risk of reactivation
  - Scarring
  - Initiation of all other manifestations

HSV Sequella: IEK 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 corneal 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 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 Neurotrophy

- Not difficult to differentiate from infiltrative keratitis
- Most cases of HSV will not develop severe neurotrophy/problematic neurotrophic ulcers
  - When treatment is indicated: PJanuary 27, punctal occlusion is usually sufficient
- **THE POINT: 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

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 linked Corneal Neovascularization

- HSV is the number 1 cause of stromal vascularization in the US
- Very important diagnostically as CN is rare with other sources of infectious keratitis
- May threaten vision and becomes much more difficult to treat with transplant than a simple scar.
Severe HSV link CN

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

Balancing the risk of inappropriately adding steroid due to a misdiagnosis of HSK

• When considering adding steroid to a case you suspect but can’t confirm HSK
  • Look for absence of historic risk factors for MK
  • Look for a history of previous HSV keratitis or even cold sore history
  • Infiltrate should be less dense than MK
  • Infiltrate less well defined and more irregular than MK
  • TEST FOR NEUROTROPY
  • Look for corneal neo
  • Almost always unilateral
  • UNDERSTAND THERE IS NO HARM IN WITHHOLDING STEROID FOR A FEW DAYS TO ASSESS CLINICAL COURSE

Two arms of HSK treatment

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 induced scars

- 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

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
- 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

HSV endotheliitis

- Nomenclature is varied across the globe, but the system proposed by Holland and Schwartz in 1999 has predominated in Cornea literature in North America
- This proposed classification 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
  - Mild anterior uveitis may be present, but will likely not be visible
  - NOTE: No ulceration, no stromal infiltrate is present
  - Treatment is steroid as the primary agent paired with oral antiviral

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
  - In cases of unilateral acute onset corneal edema without stromal infiltrate, extreme IOP or bilateral dystrophy you start steroid + antiviral and assess for response

HSV diagnostic ledger:

- Dendritic ulcer... obviously
- Unilateral, pattern shaped or diffuse infiltrate without ulceration
- Unusual unilateral keratitis in an eye that has asymmetric neurotrophy compared to fellow eye
- Unusual unilateral keratitis that has asymmetric corneal neovascularization
- Sudden onset unilateral corneal edema in an eye without risk factors (no angle closure, no endothelial dystrophy, no transplant)
- No historic risks required, but be on the look out for red herring MK risks
Variations on HSV themes

• Kids much more frequently develop bilateral disease (25% compared to 3% of adults)
• Patients with HSV as indication for corneal transplant have 25% risk of recurrence in the first year post transplant and shortened life expectancy of the graft
• Acyclovir resistant strains have been identified, but are not a widespread clinical concern
• Acyclovir is poorly bioavailable and filtered heavily through the kidneys. Patients with renal failure need their doses adjusted via consult with nephrologist

Summary

• When faced with an infiltrative keratitis:
  • Think about each case critically
  • Carefully weigh the historic risk with the clinical picture
  • Let that guide your therapy
  • If the pieces don’t fit well together consider HSV as an option

Thanks GOA!
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