Pathogens of Corneal Infection
Diplomate of Academy in Anterior Segment Prep Course

Aaron Bronner OD, FAAO, DipAAO
About Me

• Practice at Pacific Cataract and Laser Institute in Kennewick, WA
  • Cornea clinica

• Adjunct faculty at Pacific University College of Optometry with Jonathan Wainwright Memorial VA Residency Program

• Editorial Board of Review of Optometry and Review of Cornea and Contact Lenses

• Columnist RCCL – Cornea Consult

• Columnist PCON – Co-management Blog

• President’s Council of AAO

• Anterior Segment Section Diplomate Chair-Elect and Chair of Slide Practical Test

• No disclosures
Corneal infectious disease

• Corneal infectious disease is caused by a wide variety of pathogens
• These pathogens can have starkly different case histories, clinical pictures and treatments
• Important to know how to differentiate among them
Pathogens of Corneal Infection

• Discussion of some (but not all) of the infectious concepts on anterior segment section tests

• Will cover
  • Bacterial keratitis
  • Fungal keratitis
  • Acanthamoeba keratitis
  • HSV keratitis

• Will not cover
  • Zoster keratitis, adenoviral keratoconjunctivitis, CMV keratitis, syphilitic or Lyme keratitis
  • Any conjunctivitis
  • Any periorbital/adnexal infections
  • No time! Sorry!
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

• These two groups behave differently in their natural history which causes the mechanism they infect the cornea in to differ

• We are most concerned with the Exogenous group (microbial keratitis = bacterial, fungal and protists) and the Endogenous Viral group
Initial Clinical Goal – solve this corneal ulcer equation

Case History/Risk factor + Clinical Appearance of ulceration = Your best empiric diagnosis
Microbial Keratitis and Corneal function

• Optical function:
  • transmission and refraction of light

• Barrier function:
  • Separation of internal from external environment
  • As a mucous membrane, is not as effective in barrier function skin
  • Infection with microbes threatens both optical and barrier function
    • Optical function is often compromised to preserve barrier function
Exogenous infection: Microbial Keratitis

• Despite its limitations as a barrier, the ocular surface is actually really good at preventing this

• In almost all cases, uncompromised ocular surface is able to repel infection by short circuiting adhesion and colonization of microbes
Importance of history in determining risk for exogenous infectious 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*
• All others require some sort of compromise to the corneal epithelium to create infection.
  • Therefore any historic element that disrupts the epithelium can predispose the cornea to infection:
  • Over 90% of microbial corneal ulcers will have a known supportive historic element
Patient Setting of MK

• Risk factor for developing MK, location and patient age determine most likely etiologies
  • 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
    • Trauma: atypicals
    • No risk factor – think viral
  • Location – in southeastern US gram negative may predominate while fungus is also much more common, otherwise gram positive is more likely
  • Age
    • Young patients – gram negative
    • Elderly patient – gram positive
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*, *strep* *spp*
  • Gram Negatives – *Psuedomonas aeruginosa*, *serratia marcascens*, maybe *moraxella*
General classifications of exogenous corneal pathogens

• Atypicals – 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 risk factors
Typicals: Gram Positive

• Staph and strep spp
• Infiltrate
  • Generally slow to progress
  • Round or oval
  • Grey to pale yellow in appearance
  • Dry appearance in contrast to gram negative
  • Often paired with corneal edema and/or a hypopyon
Exception to slow progressing typical gram positives

- Strep pneumonia is a gram positive variant that can be rapidly progressive to perforation

Image from Duane’s Clinical Ophthal.
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
  - Ocular surface disease/neurotrophic superinfection
  - Ophthalmic surgery
  - Systemic disease: RA, diabetes
  - And to a lesser degree, SCL use
Challenge of gram positive pathogens

• This is the group where antimicrobial resistance is most problematic

• Any cases where gram positive 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 maracens and Moraxella also contribute.
- Not significant components of the normal flora.
- Pseudomonas may be more common than staph aureus in some settings.
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 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 among non SCL users, 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 as being common

• Fungal Ulcers

• Acanthamoebal ulcers
Nocardia Keratitis

• Acid Fast, variably gram positive staining rod
• Characterized by slowly progressive keratitis
• Wreath infiltrate felt to be pathognomonic
• Not part of the normal flora - near exclusive link to external trauma

From: Garg P. Fungal, Mycobacertial and Nocardia infections and the eye
Non-Tuberculous Mycobacterium

• Broad group of mycobacterium
• Clinical appearance
  • Waxy focal infiltrates
  • Indolent infection
  • Ring infiltrate possible
  • Satellite lesions
  • Mycotic appearance
• Not part of normal flora
  • Risks:
    • External trauma (widely found in soils)
    • AND Ophthalmic surgery
Fungal Keratitis

• May constitute a minor part of the normal flora (primarily 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

• 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
  • Large multicenter study with over 700 fungal ulcers showed
    • 37% association with SCL
    • 25% associated with trauma
Fungal Keratitis

- Classic Clinical Picture
  - Feathery Margins
  - Satellite infiltrates
  - Dry/leathery infiltrate
- Occasional
  - Ring Infiltrate
  - Pigmented infiltrate
- However

Reality: Significant variability. Over 60% of fungal ulcer will have no characteristic of fungal ulceration and 80% of fungal corneal ulcers are originally misdiagnosed
Acanthamoeba

- Genus of protozoa
- Ubiquitous distribution
- Opportunistic pathogen
- Two metabolic states
  - Active trophozoite
  - Inactive cyst
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
• 15% of AK patients have no history of contact lenses
AK

• 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
  • 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
  • Very good outcomes are possible if caught at this stage
AK late

• 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
Treatment Considerations with MK

- Empiric vs Culture driven
- Fortifieds vs commercially available meds
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.
  • 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
When initiating empiric therapy

- Have a solid idea you know what pathogen you are dealing with based on historic risk and clinical picture
- Consider dual therapy if a gram positive source/resistant source is likely based on history, appearance, age, or if the patient has a known history of MRSA infection
- Assess closely for treatment failure and immediately change treatment if this occurs
An aside about Antimicrobial resistance

• Becoming much more frequently encountered
  • Approximately 50% of staph ulcers are MRSA or MRSE
  • These respond poorly to even new generation fluorquinolones
  • If you suspect a staph etiology based on appearance of the ulcer or the risk factor for developing the ulcer consider MRSA as a possibility and consider adjusting your treatment somewhat
  • 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
- No way to confirm this in clinical practice as community micro labs as besifloxacin MIC discs are not available
- You need to be aware of this
For culture based practice

- Swabs are “culture-lite”
  - May be ineffective at gathering material from small ulcers (though no tool is great with small ulcers)
  - Unable to use to apply material to gram slide
  - Some organisms require specific media to culture and swabs can’t be used

- Full culturing involves a slide from 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 -Lowstein Jensen slant or Middlebrook agar
Culture based practice

• Unfortunately, unless you are doing in house gram stains, 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

• 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 OD clinics or even most OMD clinics
  • Single new generation fluoroquinolone is the standard of community practice
Whenever initiating empiric therapy

• Again: Have a solid idea you know what pathogen you are dealing with

• Consider dual therapy if a gram positive source/resistant source is likely
  • Besivance, plus:
    Aminoglycoside or polytrim

• Assess closely for treatment failure and immediately change treatment if this occurs
What about when the clinical picture and patient history don’t add up

• If the patient has no historic risk factor for microbial keratitis, or
• If the clinical picture is not consistent with microbial keratitis
• But the case has an ulceration/infiltrate
What about when the clinical picture and patient history don’t add up

• Its always HSV!
  • Well, not always, but most of the time
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- Leprosy
- Syphilis
- Lyme Disease
Herpes Simplex keratitis

- No specific risk factors are needed
- Remember this?
- Because everyone (basically) has HSV-1, everyone is at risk

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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
HSV 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 Stromal Keratitis – HSK – or Immune Stromal Keratitis – ISK – (subdendritic keratitis, diffuse stromal keratitis, marginal HSK, HSK linked corneal neo)
  • Necrotizing stromal keratitis
  • Herpetic endotheliitis (Disciform, diffuse, linear)
IEK – a clinical reactivation of viral shedding

• Infectious Epithelial Keratitis (IEK) ie dendritic keratitis

• true viral infections of the corneal epithelium
  • Vesicular/dendritic keratitis
  • Geographic keratitis
  • Marginal keratitis
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
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 Neurotrophin
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 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
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

• 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

IEK

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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 linked 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.
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
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
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
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
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
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
HSV diagnostic ledger:

- Dendritic ulcer...obviously
- Unilateral, pattern shaped 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 transplant)
HSV treatment

• Please understand the HEDS study and know the dosing recommended by it

• IEK is a viral infection and is treated with antiviral

• HSK is inflammatory and is treated with anti-inflammatories, but must be paired with prophylactic antiviral

• Endotheliitis is not clearly defined – some cases will respond to steroid alone, others require oral antiviral as well
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 wide spread clinical concern

• Acyclovir is poorly bioavailable and filtered heavily through the kidneys. Patients with renal failure need their doses adjusted via consult with nephrologist
Pathogens of Corneal Infection

Conclusion

• When faced with an acute keratitis, you need to establish what the patient’s risk factor is for developing MK.

• When faced with an acute keratitis, you need to establish whether the ulcer looks like one that might be associated with MK.

• If either or both of these points are lacking, consider the possibility of a viral (or immune) etiology.

• Treatment is based on both specific suspected etiology (which is arrived at by considering risk and appearance).

• Consider how likely antimicrobial resistance is to impact your treatment when initiating therapy.

• Obviously:
  • follow-up closely on all cases of suspected infectious keratitis to ensure a treatment response.
Thanks!