Corneal Infections from A-Z (Acanthamoeba to Zoster)

Michael DePaolis, OD, FAAO Rochester, NY
Joseph P. Shovlin, OD, FAAO Scranton, PA

I. Risk Factors In Ulcerative Keratitis
II. Differential Diagnosis of Infiltrative Keratitis
III. Treatment and Management of Ulcerative Keratitis
IV. Fungal and Protozoan Infection of the Cornea
V. The Herpes Family

Disclosures

- Allergan Pharmaceutical Advisory Panel
- AMO Global Medical Advisory Panel
- Acanthamoeba Outbreak Panel (ad hoc)
- Bausch & Lomb Scientific Advisory Panel
- Global Steering Committee
- Panel On Fusarium Keratitis (ad hoc)
- Ciba Vision Post-Market Surveillance Study Group
- Johns Hopkins Adjudication Committee (ad hoc)
- Johnson & Johnson Global Professional Advisory Panel

Speaker’s Bureau: Vistakon, Ciba Vision, CooperVision, Bausch & Lomb, AMO, Alcon, Genzyme
Clinical Investigator (FDA): AMO, Ciba Vision, Vistakon, Allergan, CooperVision

Infectious Keratitis

Herpes Keratitis
Fungal Keratitis
Bacterial Keratitis
Amoebic Keratitis

Risk Factors for Ulcerative Keratitis

- Exogenous
- Ocular Adnexal Dysfunction
- Corneal Abnormalities
- Systemic Disease
- Immunosuppressive Therapy

Modifiable Risk Factors for MK
- Occasional CW Use: 1.87-3.96X
- Regular CW Use: 5.28X
- Smoking: 2.96X
- Poor Hygiene: 3.7X
- Purchase Lens from Internet/Mail Order: 4.76X
- Not Always Washing Hands: 1.49X
- >2 Days Wear/Wk.: 3.46X

Non-Modifiable Risk Factors

- < 6 Months CL Use: 4.42X
- High Socioeconomic Class: 2.66X
- Hyperopia 1.77X
- Age >50: .45X (protective)
- Male: 1.48X

Common Organisms Encountered

- Corneal injury including foreign body: Serratia, Proteus, Azotobacter, Neisseria, Bacillus species
- Concern for organisms that can penetrate an intact epithelium: *N. gonorrhoeae*, *Corynebacterium diphtheriae*, Listeria, *Hemophilus aegyptius*
## Clinical Features of Ulcerative Keratitis

**Symptomatology:** pain, photophobia, decreased acuity, foreign body sensation

**Signs:** significant lid edema and reactive ptosis, conjunctival and ciliary injection, discharge, papillary response, stromal infiltration, surrounding edema, epithelial defect, anterior chamber reaction, cellular debris of tear meniscus and hypopyon

## Differential Diagnosis of Ulcerative Lesions

- Herpes simplex keratitis
- Neurotrophic keratitis
- Peripheral marginal infiltrates
- Chemical keratopathy
- Keratoconjunctivitis sicca

## Culture Media

- **Blood:** aerobic organisms, saprophytic fungi
- **Chocolate:** Neisseria, Moraxella, Hemophilus
- **Sabouraud’s:** fungi
- **Thioglycolate broth:** aerobic and anaerobic bacteria
- **Lowenstein-Jensen or Middlebrook 7H-9:** Nocardia, Mycobacteria species

## When To Culture Corneal Ulcers

- History of *organic trauma*
- *Atypical ulcer* or if a rare infection is suspected
- *Infiltrate/ suppuration* involves the visual axis, infiltrate at 25% depth, 50% corneal thinning or scleral extension
- *Immune compromised or hospitalized* patient
- *Unresponsive* to seemingly appropriate treatment
Infectious Crystalline Keratopathy

**Corneal Scrapings**
- Useful to use two solid media (blood and chocolate). Helps to R/O contaminants and aids in ID if there’s sparse growth if only one is used chocolate is preferred.
- Add Lowenstein Jensen, amoeba culture or HSV swab if necessary.
- Hold fungal cultures longer.
- If you use non-solid media such as thioglycolate broth use a cotton-tip applicator that’s plastic, not wood broken into the tube.

**Additional Clinical Features of Bacterial Keratitis**

**Gram Positive Organisms**
- Localized
- Round or oval gray-white infiltrates
- Distinct borders
- Minimal surrounding edema

**Gram Negative Organisms**
- Increased suppuration
- Adherent exudate to base
- Large, less defined infiltrate
- More rapid progression and stromal necrosis/excavation
Principles of Treatment

- Utilize broad spectrum of coverage: single agent v. multiple agents (with or without culture)
- Use rapid, intensive topical therapy. Best to avoid "heavy" pain medication.
- Daily evaluation until significant improvement is shown.
- Tailor antibiotic choice by culture results and clinical impression.

Treatment and Management

- In-patient v. out-patient therapy depends on patient profile
- Initial treatment should be broad spectrum despite gram stain results with severe infections
- Reasons for systemic medications: N. gonorrhoeae
- Fortified antibiotics v. fluoroquinolone use
  - Strep. is a deficiency, low toxicity, good corneal penetration, greater duration of use, off-the-shelf availability, cost, prolonged tear film concentration

Design for Drug Penetration

- **Topical**: every 15 min.-1 hr. for initial 24-48 hrs. or an altered loading dose
- **Subconjunctival injection**: once or twice daily for 1-2 days
- **Intravenous/oral antibiotics**: only for impending perforation or scleral suppuration

Termination of Therapy

- Measures of improvement: blunting of the perimeter of stromal suppuration, reduction in density of suppuration, reduction in cellular infiltrate and surrounding edema, reduction in anterior chamber reaction, progressive re-epithelialization
- Reducing anti-microbials and adjuvants: avoid abrupt cessation, prolonged therapy needed for Pseudomonas, Mycobacterium, Nocardia, anaerobes

Resistant Bacteria

- Methicillin resistant *Staphylococcus aureus*
- *Enterococcus Fecalis* (group D *Streptococcus*)
- Aminoglycoside resistant Pseudomonas aeruginosa
- Beta lactamase producing *Neisseria*
- Atypical *Mycobacteria*  
  - **Gram positive**: Vancomycin 20-30 mg/ml, 28% Lysostaphin, IV Linezolid (Zyvox)  
  - **Gram negative**: Amikacin 20 mg/ml
Newer Generation Fluoroquinolone Resistance Trends

- Ocular Trust data found 3rd and 4th generation fluoroquinolone effective against 30% of MRSA isolates, while Polytrim effective against 95% of the same isolates.
- McDonald & Blondeau Cat & Ref Surg 36(9): 2010
  - Up to 85% MRSA strains resistant to moxifloxacin & gatifloxacin
- Besifloxacin showed greater efficacy against multi-drug resistant S. aureus

Ocular TRUST 2: Overview

- Methicillin resistance in staphylococci marker for multi-drug resistance
- Fluoroquinolones most consistently active agents across ocular pathogens
- Fluoroquinolone susceptibility profile
  - Gatifloxacin = Levofloxacin = Moxifloxacin
  - Modest diminution in E. pneumo susceptibility to ciprofloxacin
- Polymixin B and penicillin most limited activity

Up to 85% MRSA strains resistant to moxifloxacin & gatifloxacin

New Antimicrobials

- 3rd and 4th Generation Fluoroquinolones and ITQs:
  - Trovofloxacin (Pfizer), Moxifloxacin (Bayer, Alcon), Gatifloxacin (Bristol-Myers/ Squibb, Allergan), Temafloxacin (Allergan), Gemifloxacin (Pharmacia)
- Peptide Antimicrobials and Inhibitors:
  - Defensins, quorum sensing, and efflux pump inhibitors
- Exazolidinones
- Pleuromutulins
- Oxazolidine linezolid
- Bacteriophages: new classes of viruses
- Aganocides

Guidelines: The Use of Topical Steroids in Bacterial Keratitis

- **Risks vs. Benefit**: the rationale for and the case against using topical steroids
- **For**: Steroids do not interfere with the ability of a bactericidal antibiotic (in sufficient concentration) to kill susceptible organisms.
- **Against**: Difficult to quantify scarring, therefore it’s never been proven that steroids minimize scarring. If you kill the organisms, patients are “cured.” “The anti-inflammatory effects of an effective antibiotic are frequently sufficient in treating bacterial ulcers.” (Baum)

Steroids for Corneal Ulcers Trial (SCUT)

- **Steroids for Corneal Ulcers**: topical steroids offer no significant benefit (or risk) in treating bacterial keratitis.*
- Adjunctive steroid therapy may improve visual outcomes in severe bacterial ulcers (and may be most beneficial when used early).**
- Steroids should not be used in Nocardia infections.
- MIC correlates with clinical results; antibiotics with lower MIC are associated with better outcomes.

**Steroids for Corneal Ulcers Trial (SCUT) Update**

- 12 month SCUT data published on BSCVA and corneal scar size in 399 cases from the original sample.
- Myofibroblasts and fibroblasts, which are active during wound healing, may help restore corneal transparency.
- Topical corticosteroid benefit may be delayed.
- Immune-mediated tissue damage may be reduced, corneal remodeling may occur and scar density may be reduced long after steroid use has been discontinued.
- There may be a benefit with adjunctive topical corticosteroids if application occurs earlier in the course of bacterial corneal ulcers.


**Guidelines: Steroids in Ulcerative Keratitis**

- Principles for successful use of corticosteroids: (1) scrapings for stain and culture, (2) use of adequately dosed bactericidal antibiotics, (3) delay initiation of steroids until a clearly beneficial effect to antibiotic has been determined, (4) continue concurrent use of antibiotic with steroids, and (5) delay use of steroids if causative organism is not identified.
- **USE 2-5 days after appropriate antibiotic therapy.**
- **Avoid** if fungal infection or atypical mycobacterium is suspected, if there is severe thinning, enlarging epithelial defect, poor wound healing (diabetes), or immunosuppression.
- In Acanthamoeba keratitis, steroids may increase potential for pathogenicity and steroids likely cause an increase in the rate of excystment and suppress macrophages.

**Fungal Infections In Contact Lens Wear**

**CLASSIFICATION/MOST COMMON ORGANISMS**

- *Filamentous Fungi; Molds*
  - Septated: pigmented, non-pigmented
  - Non-Septated
- *Yeasts*

**Clinical Features of Fungal Infections**

- **MOLDS** - epithelium can be intact or ulcerated, usually non-suppurative with feathery infiltrates (focal or multifocal/satellite)
- **YEASTS** - epithelium is usually ulcerated, generally suppurative (focal or diffuse)

Specific: infiltrates with gray/brown pigmentation, elevated edges with rough texture.
Diagnosis of Keratomycoses

- Clinical Suspicion
- Corneal Scrapings and Suture Passes
  - Smears: gram, giemsa, acridine orange, calcofluor white
  - Cultures: blood agar, Sabouraud’s media
  - Polymerase chain reaction
- Superficial Keratectomy/ Biopsy
- Paracentesis
- Confocal Microscopy

Confocal Microscopy: Fungal Keratitis

Antifungal Drugs

- Sterol Binding
- Inhibition of Sterol Synthesis
- Interference of RNA Synthesis
- Inhibition of Mitosis
- Cationic Antiseptic
Initial Anti-fungal Treatment

**Hyphae:** Natamycin 5% suspension*, topical and oral Voriconazole, oral Ketoconazole, Fluconazole or Itraconazole

**Yeast or Pseudo-hyphae:** Amphotericin B, Miconazole, Clotrimazole, Posaconazole or Fluconazole

Sub-conjunctival injections of Fluconazole or intrastromal injection of Amphotericin B are helpful in recalcitrants.

*generally most effective especially in Fusarium treatment

MIC values (sensitivity) may be predictive of outcome for Natamycin.

CDC Case Control Study Results

- Adjusted odds ratio:
  - ReNu with MoistureLoc™-19 (2.4-94.9) p<.001
  - ReNu MultiPlus™-3.6 (0.3-189) p=0.5

**Conclusion:** “ReNu MultiPlus™ was not significantly associated with the recent outbreak of Fusarium keratitis. Cause of strong association with ReNu with MoistureLoc™ is unclear.”

On-going studies looking at environmental and formulation under stress risks are continuing.

Medical Management of Fusarium Keratitis

- **Topical:** Natamycin 5% Voriconazole 10mg/ml, Chlorhexidine 0.2%
- **Oral and IV:** Voriconazole (Vfend/Pfizer) 200mg BID
- **Surgical:** debridement, full thickness grafting

*if unresponsive, systemic posaconazole or liposomal or lyophilized Amphotericin B

**Natamycin may respond better than Voriconazole in monotherapy especially in filamentous infections. (Mycotic Treatment Trial, JAMA Ophthalmol. 131/4:422-29)**

Protozoan Infections in CL Wear

- **Acanthamoeba polyphaga**

  - Genotype (15): 97% of isolates are of the T4 genotype
  - Forms: 2 different life cycles
Acanthamoeba Keratitis can be an Outbreak disease: History in the USA

<table>
<thead>
<tr>
<th>Time period</th>
<th>Total cases</th>
<th>Cases average Per year</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974-1983</td>
<td>31</td>
<td>3</td>
<td>(new infection hard to diagnose)</td>
</tr>
<tr>
<td>1984-1991 Oulbreak</td>
<td>1150 estimate</td>
<td>115 (5 x normal rate) (1984-1990 cases)</td>
<td>85% soft contact lens wearers, nearly all used non-Sterile solutions to soak lenses due to FDA approved salt tablets</td>
</tr>
<tr>
<td>1994-2003 (June ‘03)</td>
<td>120 estimate</td>
<td>19</td>
<td>Excludes 137 cases in the Iowa flood outbreak June ‘93-’96; this is the normal disease rate</td>
</tr>
<tr>
<td>June 2004- June 2007 Outbreak</td>
<td>485 Data from CDC</td>
<td>121 (2008 continues at 60 cases/yr or 4.5 x the normal rate)</td>
<td>Outbreak cause? EPA decrease of water disinfection level and a constant small number of patients using water in their lens care regimen?</td>
</tr>
</tbody>
</table>

Annualized Incidence Rate of Acanthamoeba Keratitis

- One case/ 30,000-million contact lens wearers/ year
- Mathers data following Iowa floods (1/10,000)
- Chicago data-19/mil. (Joslin); 1/8-10,000 CMP users (Schein)
- Higher prevalence in Scotland and S. Korea

Acanthamoeba Keratitis Case Control Studies:

- CDC: Complete® MoisturePlus™ - 16.9, “top off” solution 2.8, <5 years wear 2.8
- Joslin: Complete® MoisturePlus™ - 18.51, Re-use of solution (>5/mo)- 3.17, “hub” (<10/mo)- 9.05, showering with lenses (>5/mo)- 9.07, case replacement (>3 mos)- 2.79

Epidemic Intelligence Conference CDC, April, 2012

- Multiple CL hygiene practices were associated with increased risk of AK. The observed persistence of AK might be due to enhanced disease awareness and clinical suspicion following the 2007 investigation.
- To prevent infection, CL wearers should observe recommended CL care practices.

Risk Factors: Topping off solutions 4.54X, recently starting CL use 3.22X, disaster CL in water 5.37X, and handling CLs with wet hands 2.17X.
Symptomatology in *Acanthamoeba* Keratitis

- Symptoms: Usually unilateral,* pain disparate to findings, history to trauma and/or contact lens wear, symptoms wax and wane with chronicity
  * Large series shows 7-11% bilaterality at time of initial presentation or a few months later (Tu et al.)

Clinical Features of *Acanthamoeba* Keratitis

- **EPITHELIAL:** patchy epithelial involvement (stellate, irregular or pleomorphic epitheliopathy) "bull's eye" lesion, white spots, persistent epithelial defect, elevated corneal lines
- **STROMAL:** lack of vascularization, granulomatous or non-suppurative inflammation, radial nerve infiltrates ("lightning flash"), ring infiltrate
- **OTHERS:** pseudoguttata, hyphema, hypopyon, pseudomembrane, scleritis, episcleritis, adenopathy, decreased corneal sensation (initial)

* poor response to therapy may suggest co-infection
Clinical Suspicion
Comesal Scrapings
Superficial Keratectomy / Biopsy
Paracentesis
Confocal Microscopy and SD-OCT
Soft Lens Inspection
Higher resolution OCT can visualize pathogens

Confocal Microscopy: Acanthamoeba Keratitis

Therapy for Acanthamoeba Keratitis

- **ANTIBIOTICS** / Aminoglycosides**
- **ANTI FUNGALS** (anti-trophozoite agents)
- **ANTIPARASITICS** / Aromatic Diamidines
- **BIOCIDES / CATIONIC ANTISEPTICS**

Note: No one case acts in the same manner.

** Aminoglycosides have now shown increased neomycin resistant strains with an increased predisposition for trophozoite transformation; concentration of BAK in antibiotic can be therapeutic.

Clinical Outcome In Treating Acanthamoeba Keratitis

- Propamidine and neomycin: 9/19 (47%) Meisler
- Propamidine and PHMB: 8/10 (80%) McCulley
- 105/111 (96%) Wilhelmus
- Propamidine and chlorhexidine: 40/42 (96%) Seals

** Role of corticosteroid treatment is controversial!

Intensive monotherapy with either PHMB or chlorhexidine may be equally effective. Oral Voriconazole may be beneficial with deep corneal disease. (Tu et al.)

Acanthamoeba Keratitis Outcomes

- Keratoplasty was 5X more likely in pts. >40 years old.
- Ring infiltrate pts. were 40X more likely to proceed to keratoplasty and also predicted worse acuity with 3x risk of blindness.
- Any sign of stromal invasion was 10X more likely to proceed to keratoplasty.
- More advanced disease (late diagnosis) equates to poorer outcomes.

**Additional Protozoan**

- Naegleria
- Hartmanella
- Vahlkampfiid
- Microsporidia
- Rhinosporidia

**Microsporidia Keratitis**

- Presents as a superficial punctate, multifocal keratitis and a stromal keratitis possible following trauma
- Nasopharyngeal or urinary colonization in HIV infected patients
- Improvement with voriconazole, albendazole and topical fumagillin bicyclohexyl ammonium salts
- Repeated debridement (perhaps even swabbing) seems to be therapeutic especially in immunocompetent patients.
  *may be best classified as a fungus

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**The Herpesviridae Family**

- 8 distinct DNA viruses
- HSV and VZV are the most common; Epstein Barr is also found to cause corneal insult.
- HSV-1 is the most common ocular pathogen; HSV-2 is more responsible for genital infections.
- Neonates often infected with HSV-2.
- Healthcare costs for the herpes group are over $1 billion each year

**Herpes Simplex Features**

- Initial ocular presentation occurs on lid and conjunctiva 50% of the time; anterior cornea 60% and stroma 6%.
- Unilateral follicular conjunctivitis is always suspicious for HSV infection. Steroids will trigger infectious keratitis.
- Conjunctival dendrites may be present without corneal findings. An IOP with high KPa is suspicious for HSV.
- In children, primary infection manifests with fever and cutaneous outbreak around the lids. Outbreak is prolonged and less responsive to therapy.
- Bilateral involvement or prolonged HSV suggests congenital disease (i.e., atopy, immunodeficiency, or immunosuppression). See or more atopic conditions increase risk 8.9 fold for HSV (2.9 fold for HZO)  
  
*Borkar DS et al: Association between atopy and herpetic eye disease results from the Pacific Ocular Inflammation Study Group Ophthalmology 2013; 130(3):326-341*
Four clinical presentations: epithelial, stromal, endothelial, and neurotrophic keratopathy

Epithelial (Infectious): corneal vesicles, dendritic ulcer, geographic ulcer, marginal ulcer

Stromal (Immune): infiltration, vascularization and scarring

Endothelial: an infectious and inflammatory reaction (HSV or CMV); use anti-viral orals and topical steroids

Neurotrophic: results from altered corneal innervation and decreased tear production
Case 14 - painless Herpes Simplex (not a classic dendrite)

**Viral Detection**

- Cell Cultures
- ELVIS (enzyme-linked virus inducible system)**
- PCR (polymerase chain reaction/DNA detection)- Intelligent MDx

HSV can be recovered by swabbing an untreated dendrite with a soft tipped applicator inoculating it into viral transport media or a viral culturette.

** high degree of sensitivity and specificity within 24 hrs.

**Eczema Herpeticum**

- Manifests as a rash, fever with typical viral lab results; buccal mucosal swabs will likely show active virus.
- Bilateral eye involvement (simultaneous) includes disciform corneal findings and atopic dermatitis or other pre-existing skin disorders.
- Diagnosis: culture for HSV, secondary bacterial infections are common.
- Treatment: compresses, antiviral therapy (topical and systemic); anti-pruritics; patients are in great need of desensitization therapy.
Pediatric Herpes Simplex

- Frequently misdiagnosed as simply blepharitis or conjunctivitis.
- Recurrence rates are higher than adults (50%).
- Generally show severe inflammation and stromal disease; adults most commonly have dendritic keratitis.
- Managed best with adjusted oral doses of acyclovir.


Herpes Simplex Masquerades

- Various conditions present with branching lesions (dendritic): Acanthamoeba, healing abrasions, stromal dystrophy, Fabry, tyrosinemia, HZV, and Danler.
- Drug Corneal Toxicity
- HSV is the only ulcerative lesion; the rest are excavated!
Treatment and Management of HSV

- Topical and orals can be used for any infectious process.
- Steroids are the mainstay for stromal/immune disease.
- Avoid prolonged use of topical agents beyond 14-21 days. Limbal deficiency and conjunctival scarring are possible due to toxicity. At >10-14 days, a neurotrophic state is playing a role.
- Debridement is only indicated if there are new epithelial lesions with a history of stromal disease in the past.
- Oral prophylaxis is indicated with 2 or more episodes of infectious keratitis. Must monitor renal function.

Treating Principles

- Treat the epithelial disease first (virtually ignoring the immune/stromal response) and then treat stromal disease.
- When using steroids, use a prophylactic dose of orals to hopefully prevent epithelial recurrence.
- Taper steroids using a “full” dose of orals and/or topicals until the dendrite has cleared waiting for medicamentosa effects. Steroids can be increased with a prophylactic oral dosing (Valtrex 500mg daily, ACV 400mg BID, Famvir 500mg daily).
- When stromal disease is controlled taper steroids gradually. You might never be able to DC completely to control stromal disease. Prophylactic orals may be required indefinitely.

HEDS Studies

- Oral Acyclovir 400mg BID for one year significantly reduced the risk for recurrence of ocular HS, stromal keratitis (only in those who had a history of stromal disease) and oro-facial HSV.
- No benefit of oral prophylaxis to prevent progression from surface (epithelial) involvement to stromal disease.
- Oral antivirals are considered for epithelial disease to reduce the viral load in the ciliary ganglion and associated nerves. Its value in acute disease is still being debated.

Herpetic Eye Disease Study (Barron et al, 1994)

Neurotrophic Keratopathy

- Loss of trigeminal innervation in recurrent HSV and HZV
- Full range of corneal signs: PEK/PEE to frank ulceration/melt
- Management: D/C meds that are toxic, taping at night to ensure adequate closure (tarsorrhaphy may be necessary)
- Topical Treatment: glue, autologous serum, amniotic membrane application (multi-layer), scleral lenses
- Experimental: Substance P and insulin-like growth factor with nerve growth factor

HSV Resistance

- If viral resistance is suspected, send a viral culture for PCR and sensitivities.
- “Super” strains (TK mutants) encode for key enzyme and prolonged prophylactic use of orals may play a role. Consider Vira A under these circumstances.
- Non-compliance can certainly mimic resistance.
- GI absorption of polar medications, even with a pro-drug may limit serum concentrations of antiviral medications (especially with lactose intolerance). In this case, IV ACV may be helpful.
- Viral resistance in an immunocompetent patient is rare, but if suspected HSV-DNA polymerase inhibitors can be injected intravenously (i.e. Foscarnet). Any resistance raises the concern for immune-suppression or compromised state.
Herpes Zoster: Shingles

- HZV is the etiologic agent of both varicella (chickenpox) and reactivation (shingles)
- Unlike HSV, HZV typically happens once in life (30% of adults). Half of adults who live to age 85 will get zoster. The rate rises sharply after 50.
- HZV established latency in the sensory root ganglia (maintained by a T-cell immune response that wanes with advancing age)

Exposure to cases of chickenpox may serve as a "booster vaccine".

Recurrent disease: concern for reduced cell mediated immunity... HIV, thymoma, occult CA (especially lymphoid malignant lkd, etc.)

Most common diseases associated with HZV infection are pulmonary, diabetes mellitus and cardiovascular.

Overall, no increased risk for CA among HZV patients. Risk for multiple myeloma is increased in older women; risk for bone and soft tissue cancers in men following HZV infection.

Does Herpes Zoster Increase Cancer Risk? CME Medscape Education
Herpes Zoster Ophthalmicus

- Involves the ophthalmic division of the fifth cranial nerve.
- Without oral antivirals, 50% of HZV patients will experience ocular involvement. 30% will be chronic.
- Long list of ocular complications including: persistent keratitis, uveitis, acute retinal necrosis, cranial nerve palsies and optic neuropathy.
- **ASSOCIATED COMPLICATIONS:** HZO increases the risk of stroke by 4.5X within one year of infection; varicella zoster vasculopathy causes stroke secondary to chronic viral infection of large and small cerebral arteries; VZV has been associated with temporal arteritis.

Pseudodendrites in Herpes Zoster

- Part of the list of corneal complications of acute/chronic infectious and immune keratitis (4-13%).
- Can be found in the acute stages or months to years later (Herpes zoster pseudodendrites, dendritic plaques, or late Varicella zoster dendritiform keratitis).
- The lesions harbor viral DNA and warrant antiviral treatment to prevent further corneal damage.
- **CASE SERIES:** Pavan-Langston et al.: topical 0.15% ganciclovir gel (and maybe a repeat of oral) is an effective treatment for persistent pseudodendrites.

Acute Retinal Necrosis

- A rare presentation of herpetic disease; varicella zoster is most common cause, but possible in HIV infections.
- Characterized by large areas of retinal whitening and necrosis that spread centrifugally with a high rate of accompanying detachment and vascular occlusion.
- Can be seen in patients with some level of immune dysfunction.
- PCR analysis of the vitreous is confirmatory, but diagnosis is generally made by clinical assessment.
- Treatment includes IV acyclovir 10-15mg/kg TID for 5-10 days followed by oral regimen for 6-12 weeks. Intra-vitreal injection of foscarnet or ganciclovir can be considered.
Post Herpetic Neuralgia

- Most frequent and debilitating complication of HZV regardless of the dermatomal distribution.
- A neuropathic pain syndrome that persists or develops after shingles' rash has resolved.
- Main PHN risks: advancing age (>60), severity of acute zoster pain and rash, a painful prodrome and ocular involvement.
- Treatment: cool compresses, topical capsaicin, analgesics, lidocaine patch, amitriptyline, gabapentin, and acupuncture.

Antivirals

- Oral Agents
  - Acyclovir
  - Valacyclovir*
  - Famciclovir*
  - Penciclovir*

- Topical Agents
  - Trifluridine (Viroptic/non-selective)
  - Ganciclovir (Zirgan/selective)

*Better bioavailability and longer intracellular half-life than Acyclovir

Interferon has been used as an adjunct.

Prevention Through Vaccination

- Controversies:
  - Should healthcare providers be vaccinated?
  - When is vaccination appropriate after having the shingles?
  - Is vaccination appropriate for the high risk groups in certain cancer protocols/therapies.
  - When should one stop antivirals before/after vaccination?
  - Should patients with active kerato-uveitis or corneal dendriform be vaccinated?

Zostavax (Merck & Co.) Vaccine

- Vaccination does not confer lifelong immunity (most studies suggest 5-7 years, but exact duration is unknown).
- About a 50% reduction in HZV occurrence after vaccination. Only a 60% reduction of the risk of experiencing post-herpetic neuralgia.
- Should probably be avoided in individuals who are experiencing any significant post-HZV corneal/intraocular inflammation.
- FDA recommendation over 50 yrs. of age and CDC is 60. (age for neuralgia is >60 and concern for duration without a booster). However, average age of onset is 52 and half are under 60.

Key Points to Remember……..

- New "bugs" are emerging and showing variable resistance with significant geographic differences (Nocardia, Cladosporium, Paecilomyces, Micropolyspora, Rhinosporidia).
- There's a paucity of anti-fungals and most penetrate the cornea poorly. Consider frequent corneal debridement.
- Polymicrobial infection is not uncommon.
- It’s important to culture the edge and base of most infiltrates/ulcers using assorted media. Suture-pass technique may be required for best yield.
- Secondary glaucoma is not unusual due to the direct effect on the trabecular meshwork and carries a poor prognosis especially in fungal disease.
- 5 DAY RULE: a C.L related non-specific keratitis should show significant improvement with seemingly appropriate therapy after 5-7 days.

- Bilateral HSV and recurrent HZV may signal a more sinister condition due to reduced cell mediated immunity.
- Poor treatment responses may be due to resistant conditions (including prolonged prophylaxis), poor compliance, and a neurotrophic state.
- Vaccine concerns include inoculating corneal graft patients, those already taking oral antivirals, and patients with persistent ocular disease following an initial HZV infection. This doesn't impart life-time immunity. Varivax for kids reduces exposure for adults.
- Antiviral suppression therapy (prolonged) may have a role in chronic HZV as in HSV.
Key Points to Remember........

• A “spider bite” is often MRSA or shingles, and not a bug bite.
• Be concerned for systemic viral dissemination in those with debilitating diseases (i.e. diabetes, rheumatoid conditions, etc.), especially when oral steroids are used.
• Lifelong immunity benefits are not achieved with vaccination.
• Acute retinal necrosis may not be as obvious as expected in an immuno-compromised or suppressed individual.
• Avoid the use of Valtrex in HIV+ patients (concern for TTP/HUS).
• Iritis with high IOP is generally HSV until proven otherwise!