Infiltrative Keratitis: Etiology, Diagnosis & Management
Epidemiology

Ulcerative Keratitis
- Infiltrative
  - Infectious
  - Non-infectious
- Survey of Infectious and Non-infectious etiologies
- Brief Review of Laboratory Methods
- Practical Guide to Empiric Treatment of:
  - Bacterial ulcers
  - Fungal ulcers
- Culture-driven treatment brief
- Antiviral Treatment of Infiltrative Keratitis Update
  - HSV
  - Adenovirus

Epidemiology of Ulcerative Keratitis

- Annual incidence
  - >500,000 worldwide
  - >30,000 USA

- Complications of sight limiting corneal opacification (scarring 2nd most common cause of vision loss worldwide):
  - >1 Million worldwide
  - >100,000 N. America
The Social Acuity Chart

Epidemiology of Ulcerative Keratitis

- Contact lens–related infectious keratitis
  - ~50% result in reduced vision
  - Corneal opacification +/- perforation
    - 330 transplants per year USA
- Worldwide epidemic of corneal blindness from infectious keratitis

Epidemiology of Ulcerative Keratitis

Contact lens-associated Bacterial Keratitis

- 35-40 Million wearers in USA
- Majority fail at least in 1 aspect of contact lens hygiene
- Biofilm formation on contact lens and case
  - Potentiates infection by blocking antibiotics
  - Unchecked bacterial proliferation

Incidence of Ulcerative keratitis in CL wear

- 4-21 per 10,000 (DWCL+EWCL)
- DWCL’s 1/2500
- EWCL’s 1/500 (5X)
- Smokers 3X higher incidence

Epidemiology of Ulcerative Keratitis

Contact lens-associated Bacterial Keratitis

- 54% Gram-negative
  - Bind more efficiently to contact lenses
- 40% Gram-positive
- Fungal
  - Especially with soft lenses/multipurpose solutions
- Acanthameba
  - Increased frequency with soft lenses/multipurpose solution

Epidemiology of Ulcerative Keratitis

Predisposed patients:

- Subepithelial/basement membrane degenerations (EBMD), &
- Corneal surgery patients (PK, LASIK)
  - more susceptible to microbe invasion and corneal infection—life long
For all PK, DALK & LASIK Patients: (Physician responsible to educate)

RSVP rule:
Call within 24 hours for increasing:
- Redness
- Sensitivity to light
- Vision decrease
- Pain or discomfort

Epidemiology of Ulcerative Keratitis

Post PRK infections rare after 3-5 days

<table>
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<tr>
<th>Author</th>
<th>Prevalence</th>
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<td>Machat 1996 (20)</td>
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<td>Weblowski 2006 (18)</td>
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<td>do Oliveira 2006 (16)</td>
<td>9/4402</td>
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Post LASIK infections may occur anytime
Epidemiology of Infectious Keratitis

Post LASIK infections:

- **Early onset: 1-14 days**
  - Gram+ organisms (Staph, Strept)

- **Delayed onset: (weeks, months, years)**
  - Often opportunistic pathogens
    - Atypical mycobacteria
    - Fungus
    - Pseudomonas

Epidemiology of Infectious Keratitis

Penetration of Ocular Defense

- Tear Film
Epidemiology of Infectious Keratitis

Penetration of Ocular Defense

- Biologic adhesion (injured epithelium & glycocalyx)
- Bacterial glycocalyx & slime (e.g. pseudomonas): protection and adhesion

Corneal Defense Mechanisms

- Tear film
- Cell membrane glycocalyx (carbohydrate rich zone with glycoproteins and proteoglycans w/ affinity for lectins)
- Mucus; corneal epithelium
- Intact epithelial barrier

**Exceptions:**
- Neisseria gonorrhea,
- Listeria
- Corynebacterium diphtheria
- Haemophilus aegyptius
Epidemiology of Infectious Keratitis

Penetration of Ocular Defense

- Diffusion of toxins, bacterial products (e.g. contact lenses)

- Stromal invasion

Penetration of Ocular Defense: artillery
Epidemiology of Infectious Keratitis
Ulceration & Scarring

**Host** Enzymes from PMN’s, monos

Damage to:
- epithelial cells
- Keratocytes
- Collagen
- GAG’s (mps’s)

Chemokines, cytokines,
arachidonic acid cascade; leukotrienes,
prostaglandins...

“Resting” PMN
Neutrophil Senses Chemoattractant

PMN Neutrophil, macrophages

Chemotaxis

Selectins, Integrins play important role
Phagocytosis

Degranulation into Lysosomes
PMN/ ECM Interactions

collagen

PMN Degranulation

Kreger, Gray: Infect. & Immun. 19(2): 630-638
PMN/ ECM Damage

Enzyme & Inflammatory Mediator Release
AA Cascade: Cyclooxygenase Pathway

Figure 2. The Cyclo-oxygenase Pathway of Arachidonic Acid Metabolism.
The numbers, 1, 2 and 3, represent the cyclo-oxygenase, thromboxanes synthetase and prostacyclin synthetase enzymes. Note that the endoperoxide intermediates are pivotal for the production of prostacyclin and thromboxane A2.

Respiratory Burst Free Radical System

Releases H2O2 & Superoxide anion radical
Myeloperoxidase System

- MPO produces hypochlorous acid from H2O2, and oxidizes tyrosine to tyrosyl radical
- Cytotoxic to bacteria, other pathogens

Ulcerative Keratitis

Classification
- Infiltrative Keratitis (suppurative)
  - Central
  - Marginal
Infiltrative (suppurative) Keratitis

- Usually caused by infection
  - Bacterial
  - Fungal
  - Viral
  - Parasitic

Infiltrative Keratitis: **Infectious**

- Central location common
- Marginal
- Ring ulcerations (PMN effects)
Infiltrative Keratitis: Non-Infectious

- More common peripherally (catarrhal)
  - Immunological infiltrates associated with lid disease, e.g. “staph” marginal infiltrates

Infiltrative Keratitis: Non-Infectious

- More common peripherally
  - Immunological infiltrates associated with lid disease
  - “Sterile” contact lens-related infiltrates
Infiltrative Keratitis: Non-Infectious

- More common peripherally
  - Immunological infiltrates associated with lid disease, e.g. “staph” marginal infiltrates
  - Sterile contact lens-related
  - Atopic “shield” ulcer

Infiltrative Keratitis: Non-Infectious

- More common peripherally
  - Systemic inflammatory disease
    Collagen vascular diseases (e.g. Wegener’s, rheumatoid arthritis), & Mooren’s
Infiltrative Keratitis: Infectious

Bacterial Ulcers

- Conjunctival injection
- Chemosis
- Lid edema
- Decreased vision
- Pain, tearing, photophobia
- Purulent discharge
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Signs (cont)
- Ulcerated corneal epithelium
- Gray-white to yellow stromal infiltrates
- Small ulcers may show punctate surrounding infiltrates (wbc’s)
- ± stromal necrosis/ loss

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Signs (cont)
- Surrounding stromal edema
- anterior chamber cells
- endothelial plaques
- hypopyon
Infiltrative Keratitis: Infectious

Bacterial Ulcers: **Gram positive**

*Often cause epithelial ulceration followed by worsening stromal keratitis*

- Staph epidermidis
- Staph aureus
- Strept sp.
- Strept pneumonia (rapid)
- Nocardia (Actinomycetes)
- Acid fast bacilli (Atypical mycobacteria)

Infiltrative Keratitis: Infectious

Bacterial Ulcers: **Gram negative**

*Often rapid onset inflammation w/ severe corneal abscess, hypopyon and perforation*

- Pseudomonas
- Serratia
- E coli
- Moraxella
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

*Staph epidermidis*

Suture abscess

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Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

*Staph aureus*
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

*Strept pneumoniae (pneumococcus)*

- Virulence due to polysaccharide capsule
- Resists phagocytosis

AC fibrin & hypopyon  Rapid perforation
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

α- hemolytic Strept “viridans” group
- S. mutans, salivarus, sanguis, mitis, milleri et al
- Specific body tissue receptors/ strept surface interactions
- Enzyme differences (e.g. strept mutans—dextran plaque
- Similar to pneumococcus

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Strept spp. (Infective crystalline k.)
Infiltrative Keratitis: Infectious

Crystalline keratitis
L.A.: 62 y.o. hf s/p liver transplant, immunosuppressives, graft vs host disease & filamentary keratitis

Infiltrative Keratitis: Infectious

Crystalline keratitis
L.A.: hypopyon crystalline keratitis
Infiltrative Keratitis: Infectious

Crystalline keratitis
L.A.: culture + for *Strept. pneumo* and *Staph coag neg.*

Infiltrative Keratitis: Infectious

Crystalline keratitis
- Invade immunocompromised host, e.g.
  - Corneal grafts
  - Diabetics
  - Cancer patients on chemotherapy
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms
*Nocardia (Actinomycetes)*

Many spp.
- Treat with sulfa, amikacin, newer FQ’s

*From Nocardia asteroides ulcer*

G+ obligatory anaerobe

R.B. Nocardia 1000x Gram stain

Sulfur granules

**Infiltrative Keratitis: Infectious**

Bacterial Ulcers: Gram+ Organisms
*Nocardia (Actinomycetes)*

- Many spp.
- Treat with sulfa, amikacin, newer FQ’s
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

*Bacillus sp.*

- Rod-shaped facultative or obl anaerobe
- Found in soil
- Tough endospore allows tolerance of extreme environmental conditions

M.Don.: Bacillus from ulcer

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

*Bacillus sp.*

- ring ulcer from organic trauma and topical anesthetic abuse
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Atypical mycobacteria: epidemics w/ LASIK

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Atypical mycobacteria: Acid Fast Bacilli
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

*Pseudomonas*

- 2 major processes of ulceration
  - Pseudomonal enzymes & toxins
  - Host derived enzymes

- Pseudomonal enzymes & toxins
- Clear halos persist around killed organisms 2 days
  - Proteases: degrade proteoglycan GAG’s
  - Collagenases: intact collagen fibrils disperse
  - Endotoxin
  - Slime
  - Exotoxin A
  - Hemolysin
  - Et al.

Gray, Kreger. Infect. Immun. 12:419, ’75
Kessler, Mondino, Brown IOVS 16:116, ’77
Kessler, Pennah, Brown IOVS 16:488, ’77
Mondino, Kessler, Gipson Arch. Ophth. 94, 2140, ’79
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

*Pseudomonas*

Host response to heat killed organisms:
(endotoxin [cell wall lipopolysaccharides];
slime [adsorbed polysaccharides])

PMN infiltration
- Collagenase
- Proteases (e.g. MMP’s)
- Ulceration within 1 week

J.F., USN CPO; note adherent pus obscuring ulcer
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

*Pseudomonas*

J.F., USN CPO; peripheral ulceration moving centrally

4 mos later

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Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

*Pseudomonas aeruginosa*

E.A., bilateral soft contact lens ulcers, Required subpalpebral lavage treatment
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms
*Pseudomonas aeruginosa*

1/3 residual stroma left

E.A., bilateral soft contact lens ulcers, 6 weeks later

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms
*Pseudomonas aeruginosa*

Special situation of *sclerokeratitis*

M.R. Hispanic female contact lens wearer
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms
*Pseudomonas aeruginosa*

Special situation of *sclerokeratitis*

W.W., female sclerokeratitis 2 months after intensive tx & lavage

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms
*Pseudomonas aeruginosa*

Special situation of *sclerokeratitis*

G.T., endophthalmitis, not salvageable
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

*Serratia (motile)*
- ~2% of hospital acquired infections
- Respiratory tract, urinary tract, catheters, surgical wound infections, contact lenses, (cases/biofilms), NLD & possibly punctal plugs

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

*Serratia*

H.W. 81 yo wm infected bullous keratopathy
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms
*Serratia*
H.W. 81 yo wm perforated ulcer

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms
*Serratia*
H.W. 81 yo wm urgent graft; wound infection 3 wks later
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

*Serratia*

H.W. 81 yo endophthalmitis

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

*Serratia*

H.W. 82 yo wm endophthalmitis

5 days after onset

Wks later
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram (-) Organisms

*Moraxella*
- Seen in immunocompromised host e.g. alcoholics, diabetics, contact lenses, trauma
  - Especially respiratory tract infections
  - May have ring infiltrates, hypopyon

Diabetic patient with Indolent superficial non-healing ulceration

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Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram (-) Organisms

*Moraxella*
- Treat with aminoglycosides, newer FQ’s
- May take combination therapy
- SLOW response to treatment

Diabetic patient with Indolent superficial non-healing ulceration
Infiltrative Keratitis: Infectious

Bacterial Ulcers: **Anaerobes**
- Usually predisposing condition, e.g. CL wear
- Over 1/3 occur in mixed cultures with other organisms
- Probable lone cause of ulcers <5%
- Routinely susceptible to most tested antibiotics

Perry, Brinser, Kolodner Ophthalmol 1982 June 89(6):636-42

Fungal Ulcers
Fungal Ulcers

Infiltrative Keratitis: Infectious

**Fungal Ulcers: Signs**
- Epithelium may be intact
- Surface of infiltrate may be elevated above plane of uninvolved cornea
- Satellite lesions
- Ring infiltrates surrounding main (advanced cases)
- Any infiltrate pigment (e.g. brown)
- ± Endothelial plaque & hypopyon
- Slower progression than bacterial
Infiltrative Keratitis: Infectious

Fungal Ulcers: Organisms
• Candida
• Fusarium
• Aspergillus
• Penicillium
• Cephalosporium

Infiltrative Keratitis: Infectious

Fungal Ulcers: Signs
• May be indistinguishable from bacterial
• History of trauma with plant matter may be suggestive
Infiltrative Keratitis: Infectious

Fungal Ulcers: Signs
- Feathery margins, irregular extensions, “corraliform”

Infiltrative Keratitis: Infectious

• Fungal Ulcers: *Aspergillus fumigatus*
  • L.M.: 55 yo wm truck driver L eye; Vfend tx
Infiltrative Keratitis: Infectious

- Fungal Ulcers: Candida
  - R.B. 64 y.o. wm w/ atopy, indolent ulceration eventually colonized

100X wet mount Candida albicans

Budding yeast, pseudohyphae, C. albicans
Infiltrative Keratitis: Infectious

- Fungal Ulcers: *Candida*
  - BB: OS: fungal ulcer urgent patch graft, subsequent endophthalmitis

Infiltrative Keratitis: Infectious

- Fungal Ulcers: pigmented fungi
Viral Ulcers

Infiltrative Keratitis: Infectious

Viral Ulcers: *Herpes simplex*
Usually easy to distinguish from bacterial
  • Epithelial dendrite
Infiltrative Keratitis: Infectious

Viral Ulcers: *Herpes simplex*
Usually easy to distinguish from bacterial
- Epithelial dendrite

Infiltrative Keratitis: Infectious

Viral Ulcers: *Herpes simplex*
- Epithelial dendrite
- Geographic/ metaherpetic
- Subepithelial & stromal infiltrates
Infiltrative Keratitis: Infectious

Viral Ulcers: *Herpes simplex*

- Subepithelial & stromal scarring
- Disciform edema

Wessely ring

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Infiltrative Keratitis: Infectious

Viral Ulcers: *Herpes simplex*

- Endotheliitis
Infiltrative Keratitis: Infectious

Note on Endotheliitis

Cytomegalovirus
- Newer recognized cause
- May exhibit coin shaped lesions
- OCT shows bleblike structures
- Treat with ganciclovir (Zirgan) +/- systemic ganciclovir

CMV (a herpes virus)

Infiltrative Keratitis: Infectious

- *Herpes simplex*
  - R.M.: 47 yo wf—HSV iritis, geographic ulceration and permanent scarring
Infiltrative Keratitis: Infectious

- *Herpes simplex*
  - R.M.: 47 yo wf—stromal loss

Viral Ulcers: *Herpes simplex*

Necrotizing keratitis less common

- May be indistinguishable from bacterial
- Bacterial secondary infection possible
- Often relatively little infiltrate for the degree of ulceration
- Corneal anesthesia may be suggestive of previous herpetic infection
Infiltrative Keratitis: Infectious

Viral Ulcers: *Herpes simplex*
Necrotizing keratitis: dense infiltrative vs minimally infiltrative forms

Infiltrative Keratitis: Infectious

Less common Viral Ulcers:
- Herpes Zoster (VZV varicella/ chickenpox)
- Measles (Kwashiorkor, vit A deficiency)
- Mumps
- CMV (newborns with disseminated disease/ immunosuppressed host)
**Infiltrative Keratitis: Infectious**

- *Herpes zoster* (varicella/ chickenpox)
  - Early stage: mucus dendrites
  - Routinely anesthetic cornea
  - Steroids required for control + ganciclovir

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**Infiltrative Keratitis: Infectious**

- *Herpes zoster* (varicella/ chickenpox)
  - S.M.: Limbitis in a 45 yo w male (immunocompromised)
Infiltrative Keratitis: Infectious

- **Herpes zoster** (varicella/ chickenpox)
  - K.K: 55 yo wf—interstitial keratitis, vascularization & permanent scarring

Infiltrative Keratitis: Infectious

- **Herpes zoster** (varicella/ chickenpox)
  - K.K: 55 yo wf—stromal loss/ visual impairment
Infiltrative Keratitis: Infectious

- *Herpes zoster* (varicella/ chickenpox)
  - F.G.: 70 yo wm  *H* zoster ulceration OD
  - 3 years later  *HSV keratitis* &  *S. pneumo*

- *Herpes zoster* (varicella/ chickenpox)
  - B.H.: 50 yo wm with zoster and  *acanthameba*
Parasites

Infiltrative Keratitis: Infectious

Parasites
- Acanthamoeba spp
- Microsporidia
Infiltrative Keratitis: Infectious

Protozoal Infections:

*Acanthamoeba* keratitis

- Pain often greater than expected from appearance, esp. aggravated w/ CL’s
- Initially see epithelial/subepithelial infiltrates mimicking EKC, chalky, granular deposits or pseudodendrites

Infiltrative Keratitis: Infectious

Protozoal Infections:

*Acanthamoeba* keratitis

- Pseudodendrites (trophozoites)
- Radial keratoneuritis infiltrates
Infiltrative Keratitis: Infectious

Protozoal Infections:
*Acanthamoeba* keratitis
- Diffuse or sectoral stromal keratitis
- Ring infiltrates & ulceration
- Adjacent scleritis
Infiltrative Keratitis: Infectious

• **Acanthamoeba** keratitis
  - R.G. 74 y.o. wm: Acanthameba resistant to treatment (topical chx, Brolene, neomycin, systemic ketoconazole)
  - Scleritis & hemorrhage

Infiltrative Keratitis: Infectious

**Microsporidiosis** (Nosema, Brachiola algerae) parasites:
- Not uncommon in India (mosquitoes)
- Consider immunosuppressed host
Roger crams for his microbiology midterm.
Sterile Infiltrative Keratitis

Sterile Infiltrative Keratitis

“Stimulus, response! Stimulus, response! Don’t you ever think?”
Infiltrative Keratitis: Sterile

Often in contact lens wearers
- Tend to be smaller (<1mm)
- Multiple
- Arcuate, mid peripheral or peripheral
- Minimal pain, photophobia, discharge, epithelial defect, or anterior chamber reaction

Infiltrative Keratitis: Sterile

- Not possible to be certain any infiltrate is sterile
Infiltrative Keratitis: Sterile

Catarrhal ulcers

- Delayed Cell Mediated Immunologic reaction to lid margin organisms
  - Staphylococci

- Usually marginal
- Usually small, multiple, may coalesce
- “ring around the cornea” with repeated episodes (PUK)
- Note old scarring nearby

Infiltrative Keratitis: Sterile

Rosacea keratitis/ ulcer

- Responds to lid hygiene, steroids and tetracyclines, ± antibiotic
Infiltrative Keratitis: Sterile Phlyctenulosis

- May involve conjunctiva or cornea
- Cell mediated hypersensitivity to various infectious antigens
- Small ulcers central to areas of superficial vascularization

**Etiology:**
- Staph
  - Responds to lid hygiene, steroids and tetracyclines, ± antibiotic
- Mycobacteria
- TB
- Coccidioides
- Candida
Laboratory Evaluation
Laboratory Evaluation

Can one predict proper treatment without cultures?

Prospective study of 15 ophthalmologists

- Attempted prediction of microbial category of 104 ulcers
- Scraped ulcer for masked lab processing

Dahlgren, Lingappan, Wilhelmus AJO 2007 143(6):940-44
Laboratory Evaluation

Can one predict proper treatment without cultures?

Results:
- 76% predicted whether microbial recovery +
- Of culture+ infections:
  - 73% predicted if bacterial, fungal, amebic
  - 65% pseudomonas predicted correctly
  - 48% for 38 other bacterial infections
  - 45% fungal

Dahlgren, Lingappan, Wilhelmus AJO 2007 143(6):940-44

Laboratory Evaluation

Can one predict proper treatment without cultures?

Results (cont):
- 65% correctly identified pseudomonas, esp. if large
- 89% acanthameba, especially if ring

Dahlgren, Lingappan, Wilhelmus AJO 2007 143(6):940-44
Laboratory Evaluation

Practice patterns are changing

- If infiltrate and epithelial defect ≤1mm, not immune compromised, no marked anterior chamber reaction
  - Empiric broad-spectrum antibacterial therapy can be initiated without cultures

Laboratory Evaluation

Empiric vs culture retrospective study—general ophthalmology clinic Tx vs Cornea clinic Tx

157 ulcers (75 general ophth; 82 Cornea clinic)

Results:

- 75 ulcer group: were smaller, more peripheral, shorter duration of sx’s, fewer risk factors other than contact lens wear
  - All did well with empiric treatment

Rodman, Spisak, Sugar, Meer, Soong, Musch Ophthalmol 1997 Nov;104(11):1897-901
Laboratory Evaluation

Empiric vs culture retrospective study—
general ophthalmology clinic vs Cornea clinic
157 ulcers (75 general ophth; 82 Cornea clinic)
Results (cont) :
◆ 82 Cornea clinic—10% had treatment altered based on C&S results
Rodman, Spisak, Sugar, Meer, Soong, Musch Ophthalmol 1997
Nov;104(11):1897-901

Laboratory Evaluation

Practice patterns are changing
Empiric broad-spectrum antibacterial therapy can be initiated without cultures:
◆ If infiltrate and epithelial defect ≤1mm, not immune compromised, no marked anterior chamber reaction, more peripheral
◆ If ulcer is significant (central, >1mm) should culture
◆ If Cornea specialist can see within few hours, may be better not to initiate antibacterial therapy to improve C&S
◆ Caveat: empiric treatment recommendations may change as resistant organisms increase e.g. MRSA and MRSE
Laboratory Evaluation

Corneal smears

- Gram stain (bacteria, some fungi)
- Acid fast stain (atypical mycobacteria-NTM)
- Giemsa stain, PAS, Gomori methenamine-silver (fungus)
- Calcofluor white (fungus, acanthameba)

Laboratory Evaluation

Inoculated media

- Blood, chocolate agar, thioglycolate (bacteria)
- Lowenstein-Jensen optimal for AFB (NTM)
- Sabouraud’s dextrose agar (fungus)
- M-4 medium (Herpes simplex, zoster for culture or DNA (PCR))
- Sterile saline (acanthameba—transferred to E coli or similar plated medium in lab)

Contact lens cases:
- Consider culturing
Laboratory Evaluation

- Herpes simplex & Varicella zoster
- PCR (DNA) rapid detection
  - Replaces need for viral cultures
  - Swab and transport to lab

M-4 viral transport media
Laboratory Evaluation

Confocal Specular Microscopy

- Histological analysis of all corneal layers
- Image:
  - Bacteria
  - Fungus
  - Amebas
  - Microsporidia
  - Viral (Langerhans’ cells)
Laboratory Evaluation

Confocal Specular Microscopy

- Acanthameba

Laboratory Evaluation

OCT/ Corneal module

- Acanthameba
TREATMENT OF INFILTRATIVE KERATITIS

The Corneal Ulcer Patient circa -1980's
Goals of Treatment

- Rapidly stop replication of organisms
- Prevent host tissue/ collagen destruction
- Get epithelium to heal (stops corneal melting)
- Reduce scarring
- Avoid neovascularization
- Preserve vision
Infiltrative Keratitis: Infectious

Central Corneal Ulceration
• Emergency/ threat to vision & eye
• Generally requires laboratory testing

Empiric Treatment?

Ulcer:
♦ Determined to be likely infectious
♦ Decision to treat (vs refer)
♦ Not central (usually should culture if possible, or consider referral)
♦ Refer all post surgical/LASIK infiltrates—potential for disaster
Empiric Treatment

- Most practices treat with 3rd or 4th generation fluoroquinolone
  - Moxifloxacin 0.5% (Vigamox, Moxeza)
  - Gatifloxacin 0.3% (Zymar); 0.5% (Zymaxid)
  - Levofloxacin 1.5% (15 mg/ml) (Iquix)
  - Besifloxacin 0.6% (Besivance)

Besifloxacin 0.6% Special Note

- Only fluoroquinolone reserved for eye treatment
- Indicated for treatment of bacterial conjunctivitis—tid
- Contains BAK 0.005%
- Switch to preservative-free later if necessary
Besivance™ Microbiologic Activity

- Inhibition of both bacterial DNA gyrase and topoisomerase IV
  - DNA gyrase: essential enzyme for replication, transcription, and repair
  - Topoisomerase IV: essential enzyme for partitioning of chromosomal DNA (division)

- Bactericidal with MBCs generally within 1 dilution of MICs

MBC = Minimum bactericidal concentration; MIC = Minimum inhibitory concentration

Source: Besivance™ full prescribing information. April, 2009.

Besivance™ Microbiologic Activity

- Balanced inhibition of bacterial reproduction

Besifloxacin Mechanism of Action

Besifloxacin binds to and inhibits two enzymes that are essential for maintaining bacterial DNA in the proper conformation.

Source: Besivance™ full prescribing information.
Besivance™: Indication

Indication: for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:

- CDC coryneform group G
- Corynebacterium pseudodiphtheriticum*
- Corynebacterium striatum*
- Haemophilus influenzae
- Moraxella lacunata*
- Staphylococcus hominis*
- Staphylococcus lugdunensis*
- Staphylococcus aureus
- Staphylococcus epidermidis
- Streptococcus pneumoniae
- Streptococcus oralis
- Streptococcus mitis group
- Streptococcus salivarius*

Source: Besivance full prescribing information. April, 2009.

Empiric Treatment of Bacterial Keratitis

- Most practices treat with 3rd or 4th generation fluoroquinolone
- Advanced generation fluoroquinolones: Still a good choice for initial Tx
  - Broad spectrum potency (G+, G-)
  - High bioavailability and penetration
  - However, ~50% of S. aureus are now methicillin resistant (MRSA), & susceptibility to fluoroquinolones is declining
Antibiotic Resistance

ARMOR STUDY (Antibiotic Resistance Monitoring in Ocular Microorganisms surveillance study)

- US Nationally ongoing study examples:
  - *S. pneumonia* non-susceptibility doubled for PCN, Azith and Chloro 2013-2014
  - *S. aureus* more susceptible to Oxacillin, Cipro and Azith 2013-2014
  - Coag Neg *Staph* more non-susceptible to Tobramycin
  - 25% *S. aureus*, 50% CoagNS were methicillin resistant, many multidrug resistant
  - Some *Pseudomonas a.* non-susceptible to polyB, imipinem, cipro

Asbell et al ARVO 2015
Antibiotic Resistance

- US Govt initiative to stem resistance
  - Target end of 2016
  - No “lacing” of feed for cows, hogs, poultry et al with medically important antibiotics to promote animal growth
  - Federally operated cafeterias to serve meat produced with responsible antibiotic use

Treatment of Sight-Threatening Bacterial Corneal Ulcers & Related Infiltrates
Severe Corneal Ulcer Treatment

Shotgun Therapy
Empiric Treatment

3rd & 4th generation fluoroquinolones

- Still a good choice for initial Tx: e.g.
  - S. aureus
  - S. epidermidis
  - Strept. pneumoniae
  - Strept. viridans
  - Pseudomonas
  - Serratia marcescens

Empiric Treatment

Moxifloxacin (Vigamox)
Gatifloxacin (Zymaxid)
Levofloxacin (Iquix)
Besifloxacin (Besivance)

Day 1

If >1mm ulcer, pericentrally or centrally
- 1 drop q 5 min. x 15-30 minutes
- 1 drop q 30 minutes while awake
- 1 drop q 1-2 hours after bedtime

If <1mm or peripheral
- May use less frequently
Empiric Treatment

Moxifloxacin (Vigamox)
Gatifloxacin (Zymaxid)
Levofloxacin (Iquix)
Besifloxacin (Besivance)

Day 2
Examine the patient:
- If ulcer hasn’t worsened it is probably responding to treatment
- 1 drop q 2 hours while awake
- 1 drop q 2-3 hours after bedtime
If ulcer is worse, refer to cornea specialist

Empiric Treatment

Moxifloxacin (Vigamox)
Gatifloxacin (Zymaxid)
Levofloxacin (Iquix)
Besifloxacin (Besivance)

Day 3 or 4
Examine the patient:
- If epithelializing, & infiltrate decreasing, it is probably responding to treatment
- 1 drop q 2 hours while awake, 1 drop at 2AM
- Consider corticosteroid
Corticosteroids

Empiric Treatment

Use of topical steroids: benefits

- Help modulate inflammation
- Assists epithelialization
- Reduces scar formation
- Rarely used Day 1 or 2
- Must prove antibiotic efficacy
  - "Never, if not cultured"
- Usually started day 2 - 4 if infiltrate is not worsening but not improving
- If used, must see patient next day
Steroid Treatment

SCUT—Steroids for Corneal Ulcers Trial
- 48 hours moxifloxacin treatment
- 500 Culture positive ulcers
- Randomized placebo vs Pred phosphate 1%
- Results:
  - Overall, no BSCVA improvement @3 months
  - HOWEVER: worst presenting BSCVA (<=CF) or completely central ulcers did obtain better VA
    p=0.03, p=0.02, respectively

Srinivasan and SCUT study group: Arch Ophthalmol 2012:Feb 130(2):143-50

Steroid Treatment

Use of topical steroids: Caution w/ Pseudomonas

- Corticosteroids allow pseudomonas organisms to “smolder”
- Organisms can live inside PMN’s for up to 4-6 weeks
- Require concomitant antibiotic treatment 4-6 weeks
Empiric Treatment

Moxifloxacin (Vigamox)
Gatifloxacin (Zymaxid)
Levofloxacin (Iquix)
Besifloxacin (Besivance)

**Day 7-14**
Examine the patient:
- If epithelialized, with less infiltrate
- 1 drop 4-6x/day depending on severity and location

Empiric Treatment

Special situations:
- Marginal infiltrates
  - Can be infectious or immunologic (sterile)
  - Catarrhal most commonly related to staph
  - 0.5-2mm long
  - Usually lucent interval from limbal vessels
  - Usually have epithelial defect
  - Often multiple
  - Evidence of previous nearby scarring
Empiric Treatment

Special situations
Marginal infiltrates:
Catarrhal related to staph:
- Responds well to topical antibiotic/ steroid combination, e.g. Tobradex, or Zylet
- If in doubt, try 48 hours of antibiotic and if not worsening or slowly improving, then add loteprednol or fluorometholone
- Start lid hygiene ~1 week later, after infiltrate/ ulceration resolved
- Follow for recurrences

Phlyctenulosis:
Staph blepharitis

- Responds to steroids and tetracyclines, ± antibiotic; tobramycin + steroid (e.g. Zylet, Tobradex)
- Lid hygiene once inflammation resolving
Culture Driven Treatment

- Generally performed by corneal specialist
- Gram, Giemsa, Calcofluor white stains may change therapy within a day
- Culture results 2-3 days
- Typical fortified antibiotics used:
  - Tobramycin 14 mg/ml
  - Vancomycin 25 mg/ml

Culture Driven Treatment: Compounding Pharmacy Peril

- Gov’t regulation of “big guns”
Fungal Ulcer Treatment

Filamentous Fungal *culture results* typically take 3-4 weeks (fusarium, aspergillus)

Filamentous fungal ulcer study (108 pts)
- Natamycin (pimaricin) 5% topical still the best overall choice for initial therapy of filamentous fungi
  (24-48h delay at pharmacy)
- Oral Ketoconazole 200 mg adjunct may be of no additional benefit


Other similar studies

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Fungal Ulcer Treatment

- Non-Filamentous fungi
  - Yeasts
  - Drug of choice: Amphotericin B
HSV TREATMENT UPDATE

HSV Treatment Update

- Evolution of Treatment
- 1960’s IDU (idoxuridine 0.1%) 9x/day
- 1970’s Vira-A (vidarabine 3% ointment)
  TFT (trifluridine 1%/ Viroptic)
  *Significant toxicities, frequent dosing of above*
- 1980’s ACV (acyclovir 3% ungt)
- 1990’s GCV (ganciclovir 0.15%/ Virgan)
- 2010’s GCV (USA ganciclovir 0.15%/ Zirgan)
HSV Treatment Update

- Ganciclovir 0.15% FDA approved for HSV keratitis 2009 (Zirgan)
- Tube/ gel form
- 1 application 5x/day until ulcer heals, then tid for 7 days
- Targets only replication of HSV DNA
- Little toxicity, similar to acyclovir ointment (unlike TFT)
- Zirgan B&L (Valeant)

HSV/Infiltrative Keratitis Update

- Ganciclovir 0.15% gel advantages
  - Activated by enzyme present only in viral-infected cells
  - TFT affects both normal and viral infected cells, thus more toxicity and slower healing
  - TFT (Viroptic brand) contains thimerosal
  - GCV: More convenient dosing (5 vs. 9 X/day)
  - Zirgan contains 0.00075% BAK
- Steroid use:
Stromal keratitis treatment

• Disciform edema & stromal keratitis:
  - poor response to antivirals alone
  - primarily immunologic mediated

• Herpetic Eye Disease Study (HEDS)
  - TFT + steroids do not increase early or late recurrences of HSV or cause other complications

Long-term treatment

- ~3 months drop for drop steroid + TFT or GCV or steroid + oral ACV
- long-term advantage with oral ACV and topical steroids (no topical antiviral)
- At least 2 years oral ACV in my practice (400mg bid)
Adenovirus Treatment Update

- Prompt diagnosis and treatment reduce likelihood of subepithelial infiltrates (SEI's)
- Adenovirus DNA in-office dx aid (AdenoPlus)
  - Immunochromatography assay
  - Detects adenoviral Hexon protein in tear fluid
Adenovirus Treatment Update

Saudi Arabian randomized trial: adenovirus 8 (PCR)
- 18 subjects
- GCV gel vs PF AT’s
- 9 patients on GCV recovered in 7.7 days
  - 2 developed SEI’s subepithelial opacities
- 9 patients on PF AT’s recovered in 18.5 days (p<0.05)
  - 7 developed SEI’s

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Adenovirus Treatment Update

Brazilian study: “Clinical AKC”
- GCV Treatment (19 pts)
- PF AT Treatment (14 pts)
- Results
  - Trend of better response with GCV
  - Lower transmission to other eye and to housemates
  - Statistically less pain, itch, photophobia
  - No p difference in ocular complications

Arq Bras Oftalmol 2011 Nov-Dec;74(6):417-21
Adenovirus Treatment Update

Treatment

- Ganciclovir (Zirgan) 5x/day for 5-7 days
- PF tears (refrigerated) for symptomatic relief
- Isolation 7 vs 14 days?
- Cyclosporine ~4 weeks for SEI’s
- Topical steroids if visually debilitating for employment after isolation

Outline

- Epidemiology
- Ulcerative Keratitis
  - Infiltrative
    - Infectious
    - Non-infectious
- Survey of Infectious and Non-infectious etiologies
- Brief review of Laboratory Methods
- Practical Guide to Empiric Treatment of:
  - Bacterial ulcers
  - Fungal ulcers
- Culture-driven treatment brief
- Antiviral Treatment Update
  - HSV
  - Adenovirus
THANK YOU ALL!
&
PACIFIC UNIVERSITY
ON THE
25TH ANNIVERSARY
VICTORIA CONFERENCE!

Questions

"Mr. Osborne, may I be excused?
My brain is full."
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