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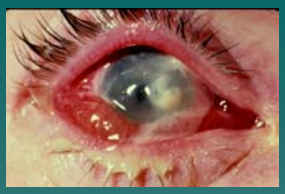
Infiltrative Keratitis: Etiology, Diagnosis & Management

Outline

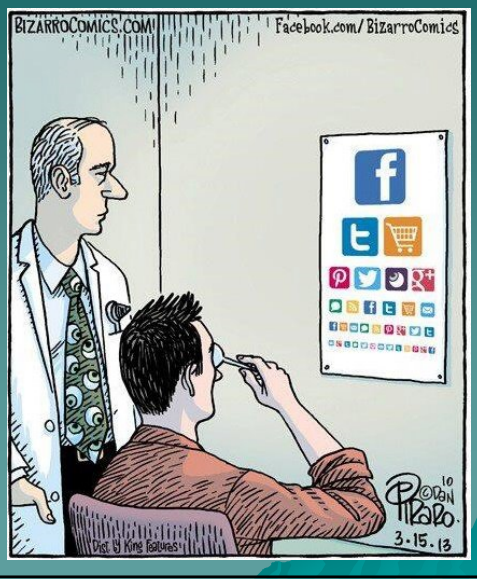


- Epidemiology
- Ulcerative Keratitis
  - -Infiltrative
    - Infectious
    - Non-infectious
- Survey of Infectious and Non-infectious etiologies
- Brief Review of Laboratory Methods
- Practical Guide to Empiric Treatment of:
  - Bacterial ulcers
  - Fungal ulcers
- Culture-driven treatment brief
-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

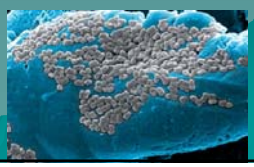
- Contact lens–related infectious keratitis
  - ~50% result in reduced vision
  - Corneal opacification +/- perforation
    - 330 transplants per year USA
- Worldwide epidemic of corneal blindness from infectious keratitis

Whitcher, Srinivasan, Upadhyay: Corneal blindess: a global perspective. *Bull World Health Organ.* 2001;79:214-221

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



Epidemiology of Ulcerative Keratitis

Contact lens-associated Bacterial Keratitis

- 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

Al-Mujaini et al. SQUnivMedJ 2009 Aug;9(2):184-195

Epidemiology of Ulcerative Keratitis

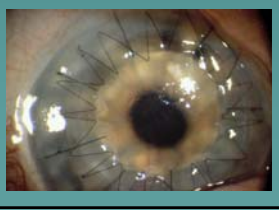
Contact lens-associated Bacterial Keratitis

- 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*



Epidemiology of Ulcerative Keratitis

For all PK, DALK & LASIK Patients:
(Physician responsible to educate)

RSVP rule:

Call within 24 hours for increasing:

- **R**edness
- **S**ensitivity to light
- **V**ision decrease
- **P**ain or discomfort

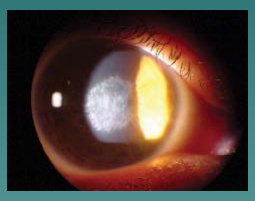
Epidemiology of Ulcerative Keratitis

- Post PRK infections rare after 3-5 days

Table 2. Prevalence of infections after surface ablation

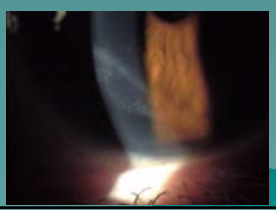
Author	Prevalence	
Machat 1996 (20)	1/1000	0.1%
Leccisotti 2005 (19)	2/10452	0.019%
Wroblewski 2006 (18)	5/25337	0.019%
de Oliveira 2006 (16)	9/4492	0.2%
De Rojas 2010 (¥)	39/18651	0.2%

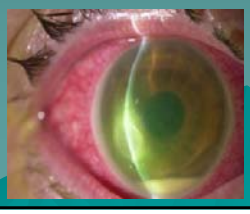
¥ (de Rojas V, Llovet F, Martínez M, Beltrán J, Baviera J. Infectious keratitis in 18,651 laser surface ablation procedures. XXVIII Congress of the ESCRS. Paris, 4-8/IX/2010). § Prevalence of infections demonstrated with positive culture.



- Post LASIK infections may occur anytime

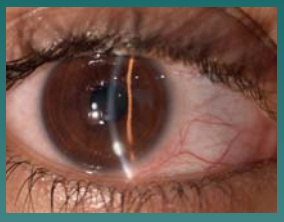
DLK





Epidemiology of Infectious Keratitis

Post LASIK infections:

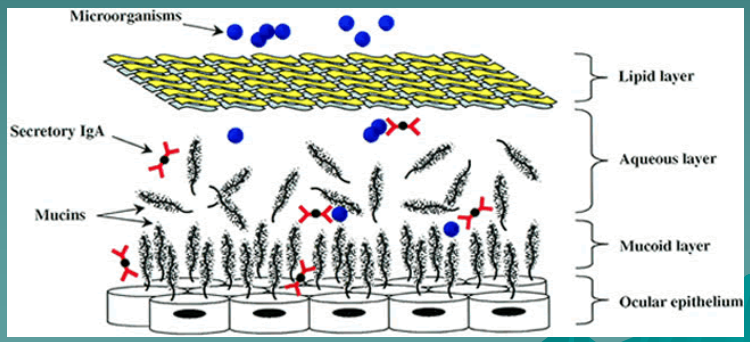


- Early onset: 1-14 days
  - Gram+ organisms (Staph, Strept)
- Delayed onset: (weeks, months, years)
  - Often opportunistic pathogens
    - Atypical mycobacteria
    - Fungus
    - Pseudomonas

Epidemiology of Infectious Keratitis

Penetration of Ocular Defense

- Tear Film



MUC1
MUC4
MUC5AC

Epidemiology of Infectious Keratitis

Penetration of Ocular Defense

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

Slime: adsorbed polysaccharides

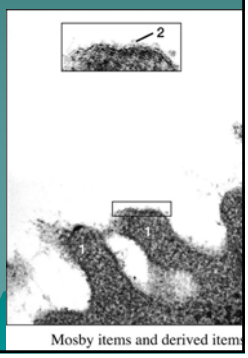
Healthy conjunctival epithelium

Epidemiology of Infectious Keratitis

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

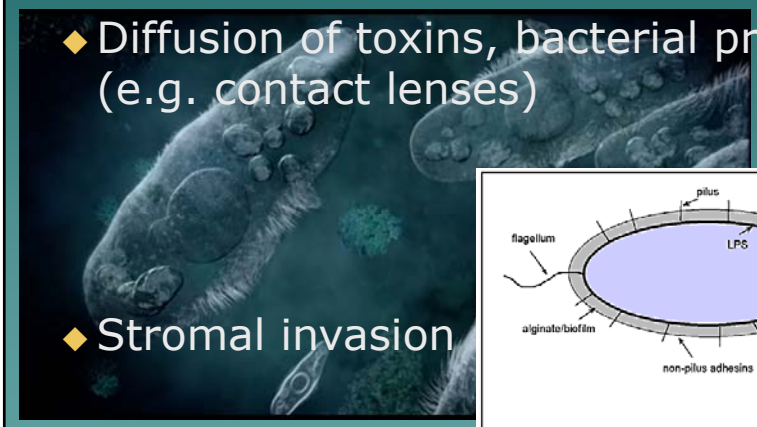


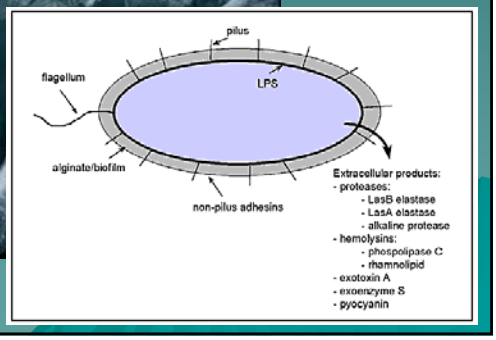
Mosby items and derived items

Epidemiology of Infectious Keratitis

Penetration of Ocular Defense

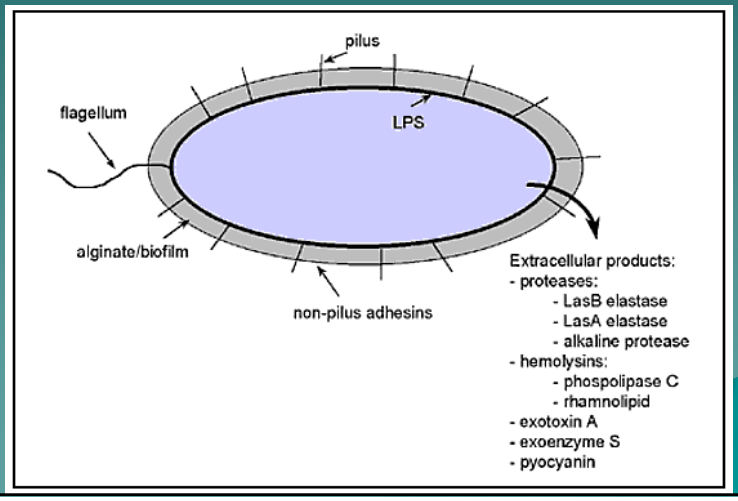
- Diffusion of toxins, bacterial products (e.g. contact lenses)
- Stromal invasion





Epidemiology of Infectious Keratitis

Penetration of Ocular Defense: artillary



Epidemiology of Infectious Keratitis Ulceration & Scarring

Host Enzymes from PMN's, monos

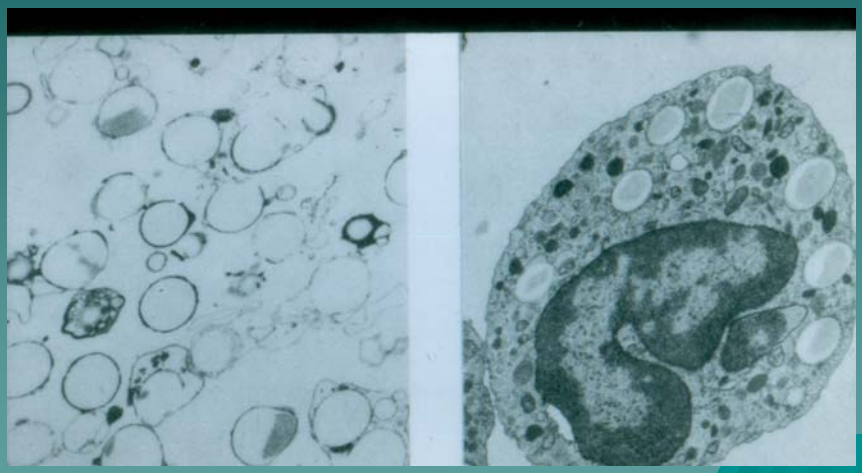
Damage to:

- epithelial cells
- Keratocytes
- Collagen
- GAG's (mps's)

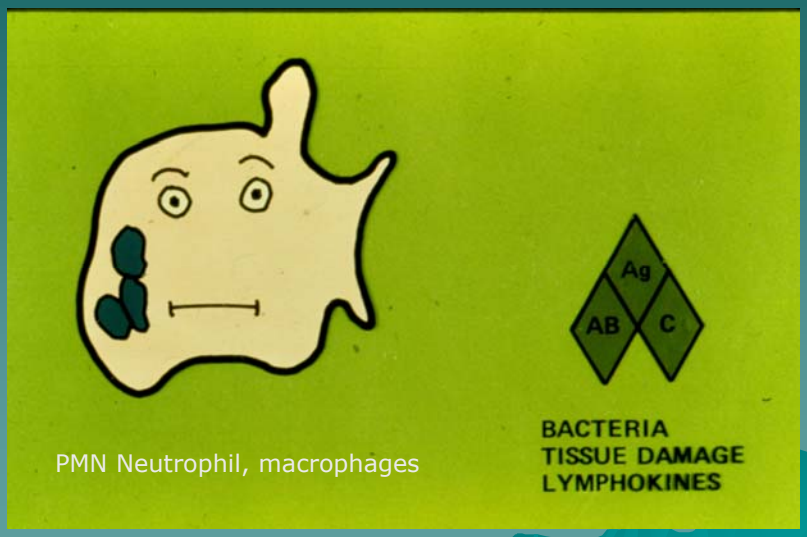
Chemokines, cytokines,

arachidonic acid cascade; leukotrienes, prostaglandins…

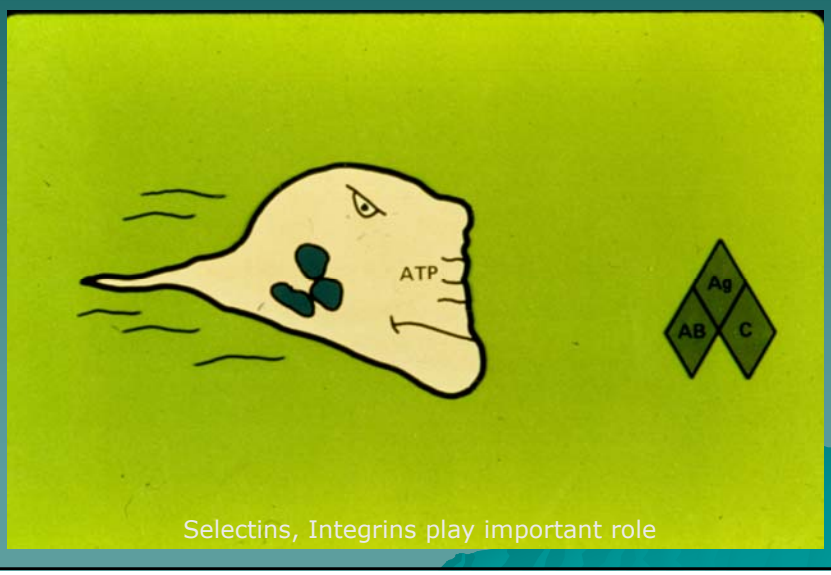
"Resting" PMN



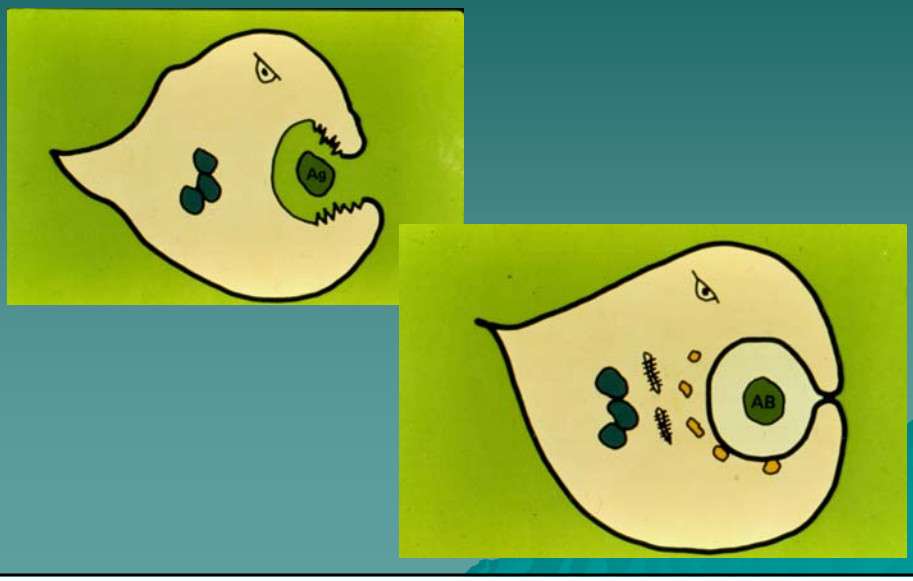
Neutrophil Senses Chemoattractant



Chemotaxis

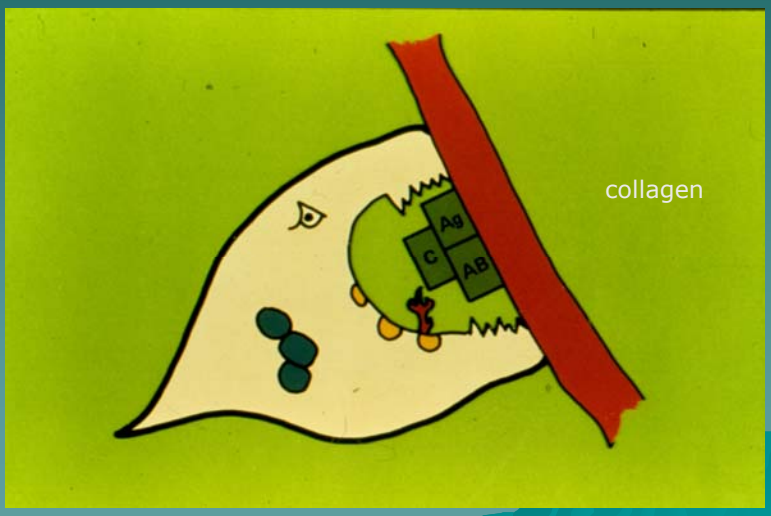


Phagocytosis

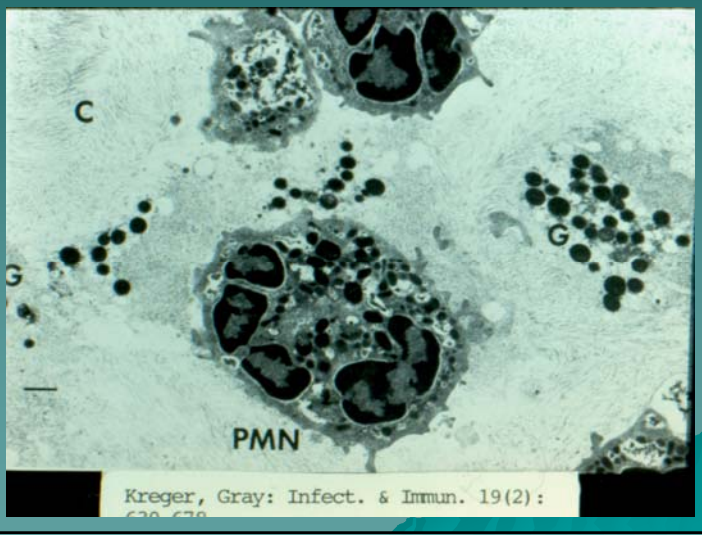


Degranulation into Lysosomes

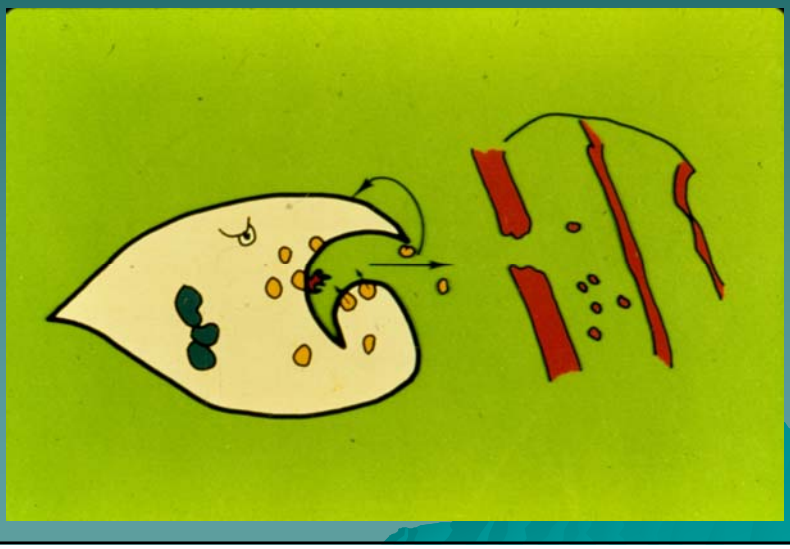
PMN/ ECM Interactions



PMN Degranulation



PMN/ ECM Damage



Enzyme & Inflammatory Mediator Release

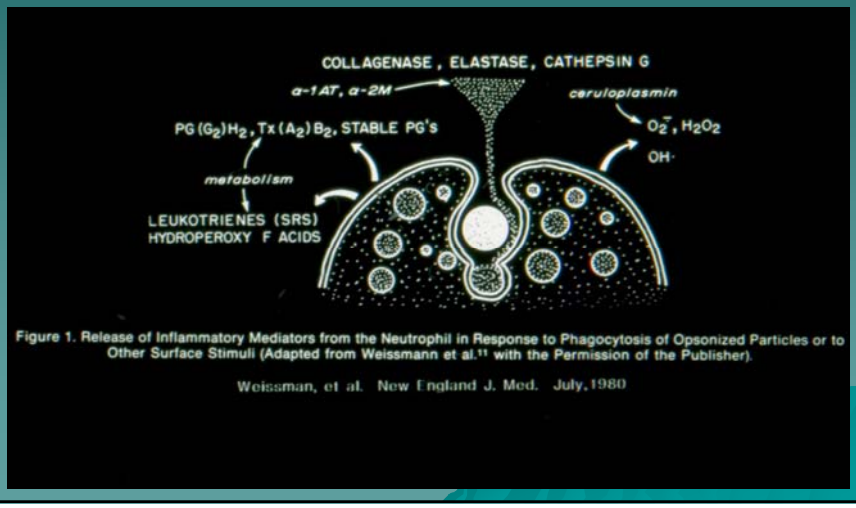


Figure 1. Release of Inflammatory Mediators from the Neutrophil in Response to Phagocytosis of Opsonized Particles or to Other Surface Stimuli (Adapted from Weissmann et al.[11] with the Permission of the Publisher).

Weissman, et al. New England J. Med. July, 1980

AA Cascade: Cyclooxygenase Pathway

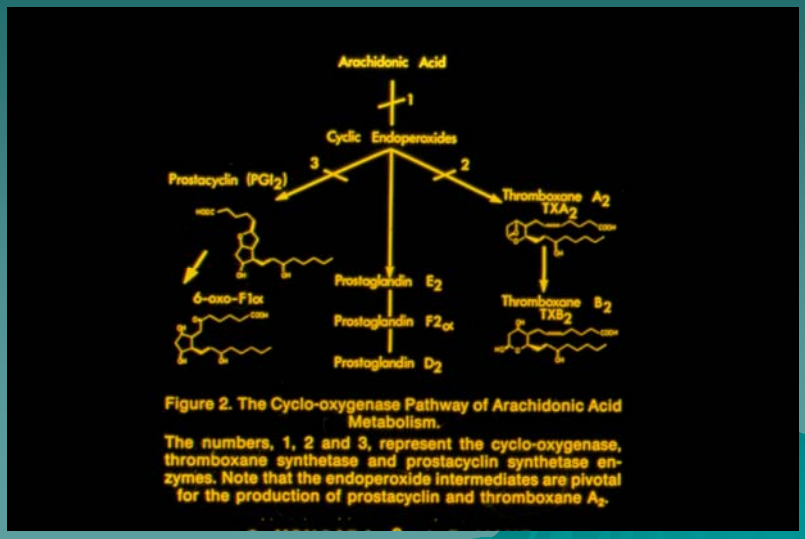
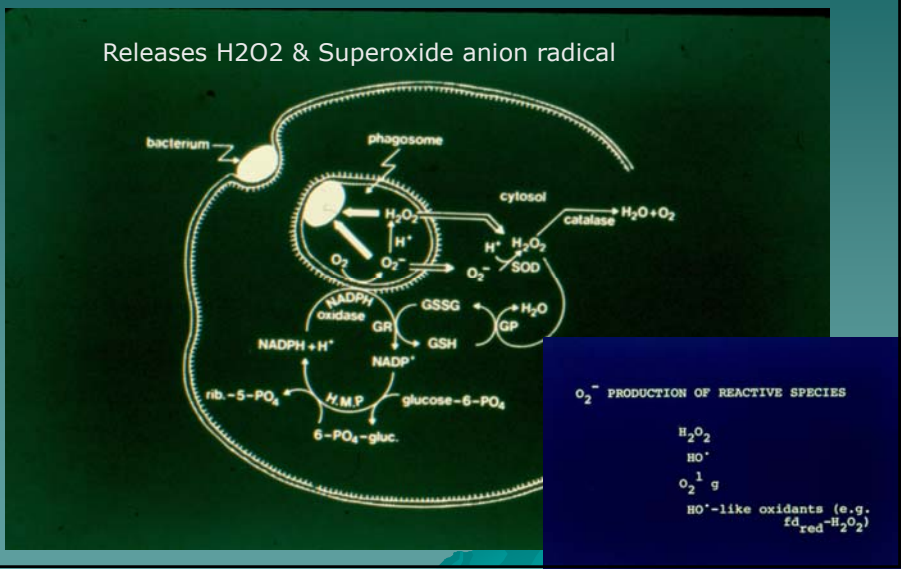


Figure 2. The Cyclo-oxygenase Pathway of Arachidonic Acid Metabolism.
The numbers, 1, 2 and 3, represent the cyclo-oxygenase, thromboxane synthetase and prostacyclin synthetase enzymes. Note that the endoperoxide intermediates are pivotal for the production of prostacyclin and thromboxane A_2.

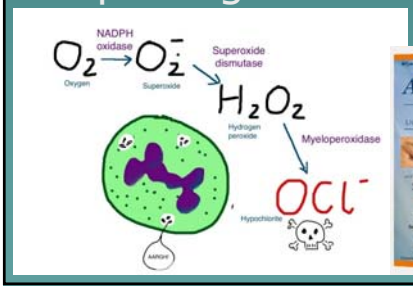
Respiratory Burst Free Radical System

Releases H2O2 & Superoxide anion radical

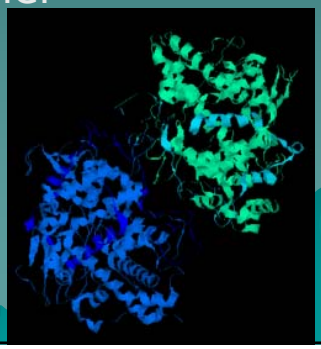


Myeloperoxidase System

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



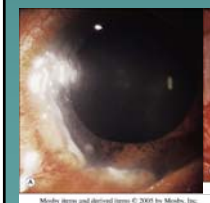
MPO

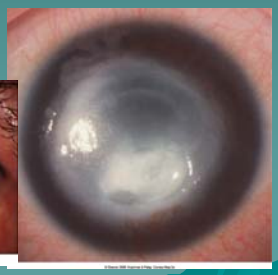


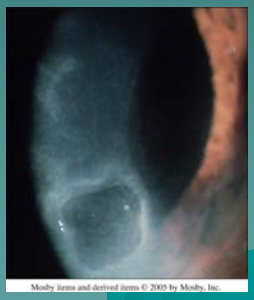
Ulcerative Keratitis

Classification

- Infiltrative Keratitis (suppurative)
  - Central
  - marginal





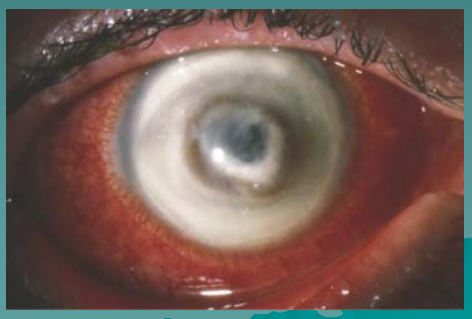


Infiltrative (suppurative) Keratitis

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

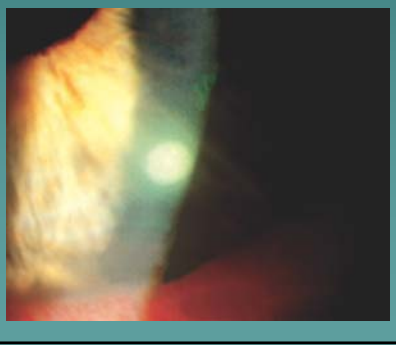
Infiltrative Keratitis: **Infectious**

- Central location common
- Marginal
- Ring ulcerations (PMN effects)



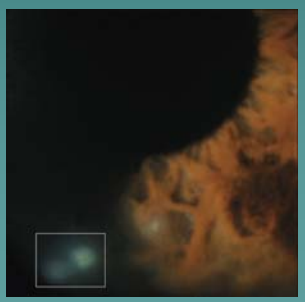
Infiltrative Keratitis: **Non-Infectious**

- 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**



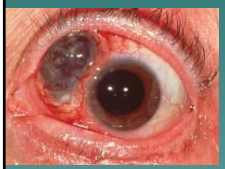
Infiltrative Keratitis: **Non-Infectious**

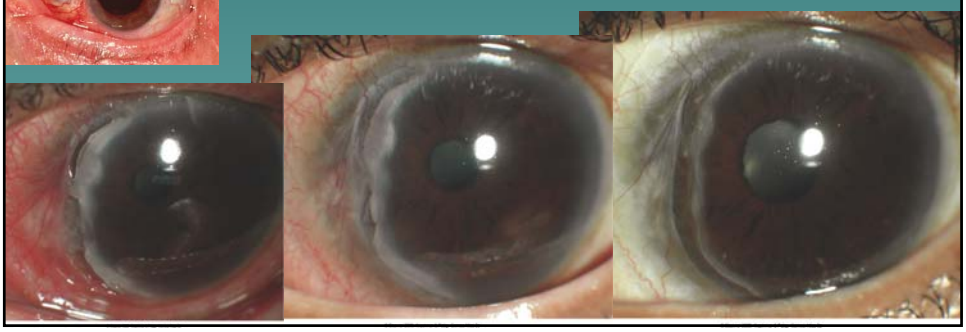
- More common peripherally
  - Immunological infiltrates associated with lid disease, e.g. "staph" marginal infiltrates
  - Sterile contact lens-related
  - **Atopic "shield" ulcer**

Infiltrative Keratitis: **Non-Infectious**

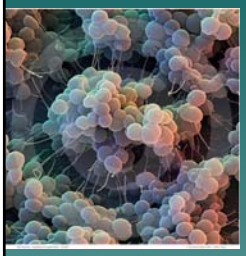
- More common peripherally
  - **Systemic inflammatory disease**

    Collagen vascular diseases (e.g. Wegener's, rheumatoid arthritis), & Mooren's





Infiltrative Keratitis: infectious

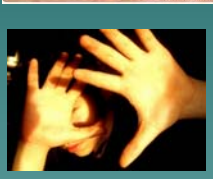


Bacterial Ulcers

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Signs

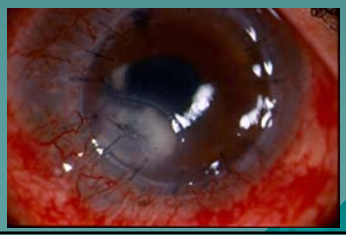
- Conjunctival injection
- Chemosis
- Lid edema
- Decreased vision
- Pain, tearing, photophobia
- Purulent discharge

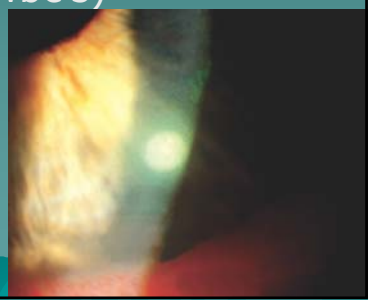


Infiltrative Keratitis: Infectious

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





mycobacteria

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Signs (cont)

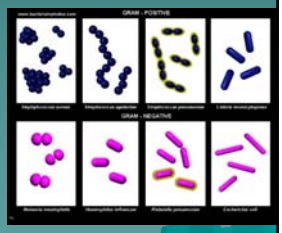
- Surrounding stromal edema
- anterior chamber cells
- endothelial plaques
- hypopyon

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)

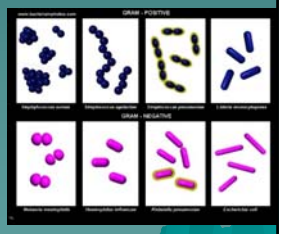


Infiltrative Keratitis: Infectious

Bacterial Ulcers: **Gram negative**

Often <u>rapid</u> onset inflammation w/ severe corneal <u>abscess, hypopyon and perforation</u>

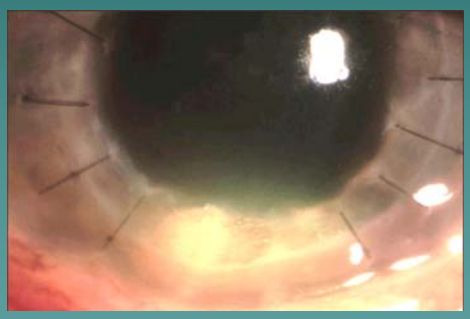
- Pseudomonas
- Serratia
- E coli
- Moraxella



Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Staph epidermidis

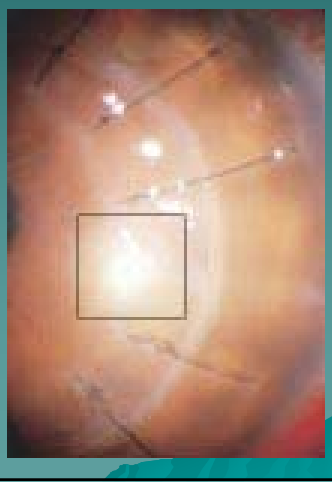


Suture abscess

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Staph aureus

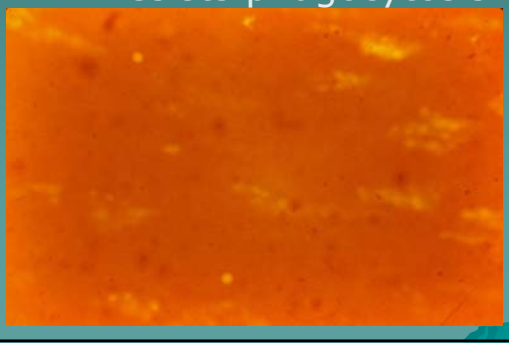


Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Strept pneumonia (pneumococcus)

- Virulence due to polysaccharide capsule
- Resists phagocytosis

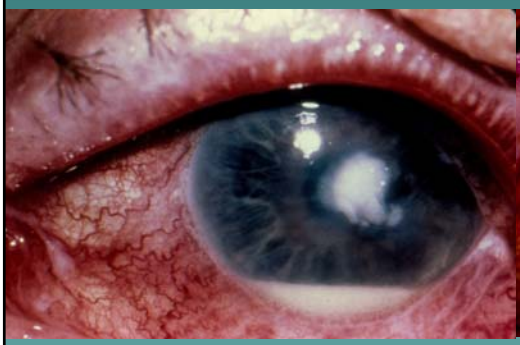


India Ink negative staining

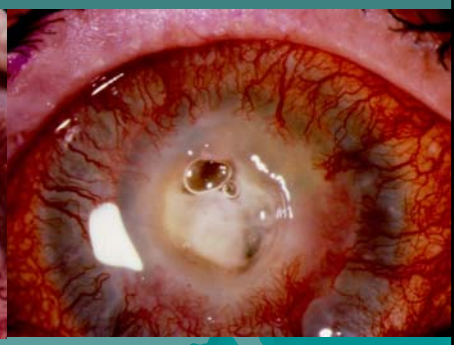
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Strept pneumoniae



AC fibrin & hypopyon



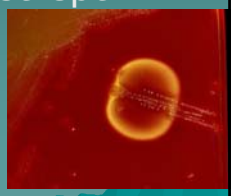
Rapid perforation

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



Alpha hemolytic strept, bile insoluble (not S pneumo)

Infiltrative Keratitis: Infectious

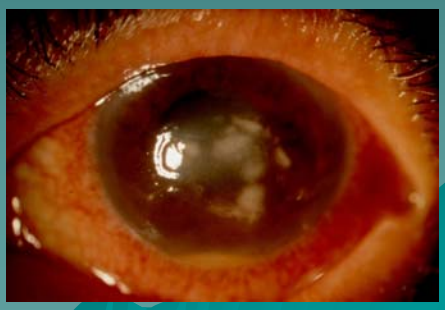
Bacterial Ulcers: Gram+ Organisms

Strept spp. (Infective crystalline k.)

Infiltrative Keratitis: Infectious

Crystalline keratitis

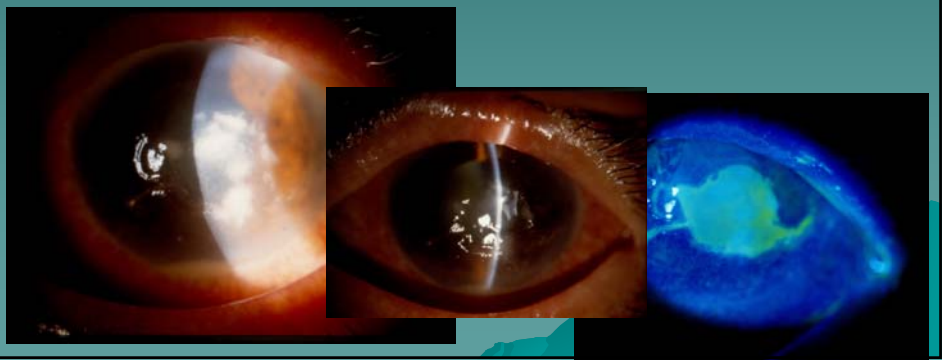
L.A.: 62 y.o. hf s/p liver transplant, immunosuppressives, graft vs host disease & filamentary keratitis



Infiltrative Keratitis: Infectious

Crystalline keratitis

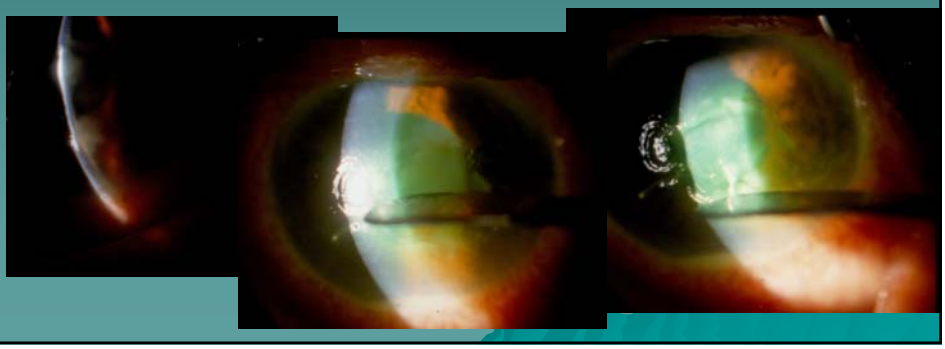
L.A.: hypopyon crystalline keratitis



Infiltrative Keratitis: Infectious

Crystalline keratitis

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



Infiltrative Keratitis: Infectious

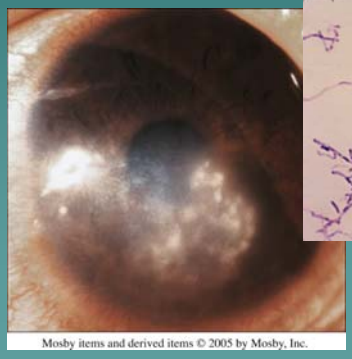
Crystalline keratitis

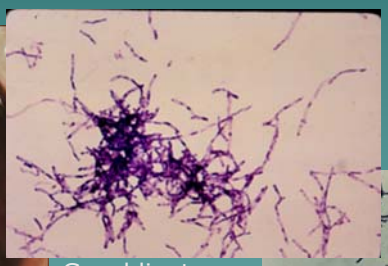
- Invade immunocompromised host, e.g.
  - Corneal grafts
  - Diabetics
  - Cancer patients on chemotherapy

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Nocardia (Actinomycetes)





G+ obligatory anaerobe

R.B. Nocardia 1000x Gram stain

From Nocardia asteroides ulcer

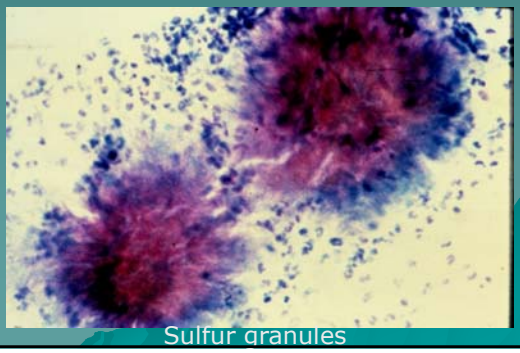
Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Nocardia (Actinomycetes)

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

culture



Sulfur granules

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

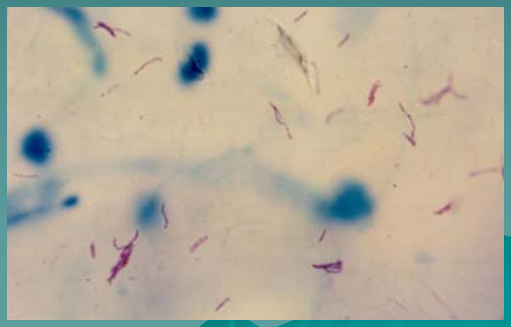
Atypical mycobacteria: epidemics w/ LASIK

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram+ Organisms

Atypical mycobacteria: Acid Fast Bacilli

Lowenstein-Jensen Media

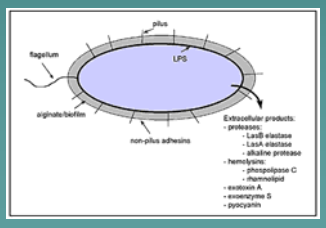


Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Pseudomonas

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



Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Pseudomonas

- 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, Kennah, Brown IOVS 16:488, '77
Mondino, Kessler, Gipson Arch. Ophth. 94: 2149, 197

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

Kessler, Mondino, Brown IOVS 16(2):116, '77

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

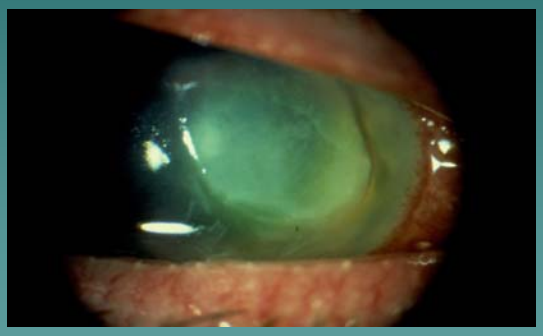
Pseudomonas

J.F., USN CPO; note adherent pus obscuring ulcer

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Pseudomonas



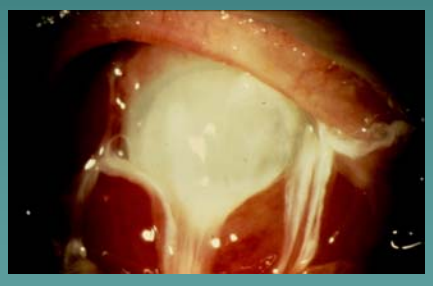
J.F., USN CPO; peripheral ulceration moving centrally

4 mos later

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Pseudomonas aeruginosa



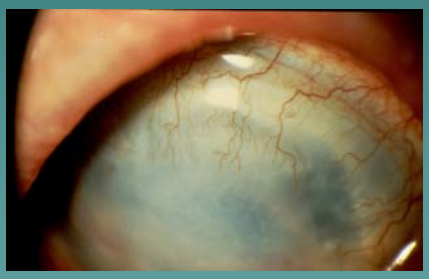
E.A., bilateral soft contact lens ulcers,
Required subpalpebral lavage treatment

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Pseudomonas aeruginosa

1/3 residual stroma left



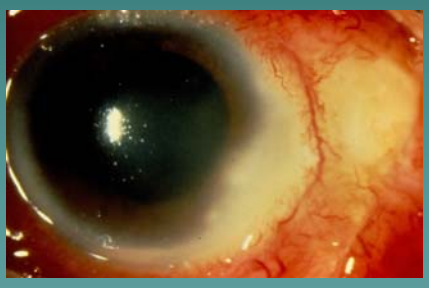
E.A., bilateral soft contact lens ulcers, 6 weeks later

Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Pseudomonas aeruginosa

Special situation of ***sclerokeratitis***



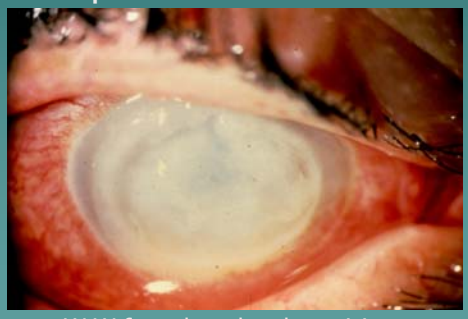
M.R. Hispanic female contact lens wearer

Infiltrative Keratitis: Infectious

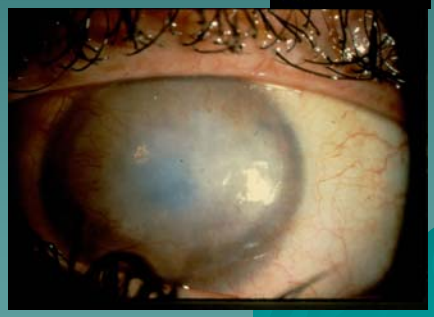
Bacterial Ulcers: Gram- Organisms

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***

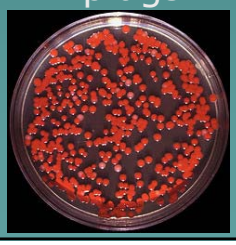
G.T., endophthalmitis, not salvageable

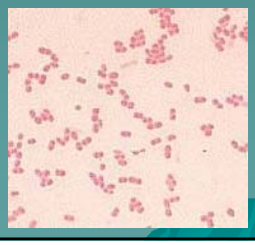
Infiltrative Keratitis: Infectious

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



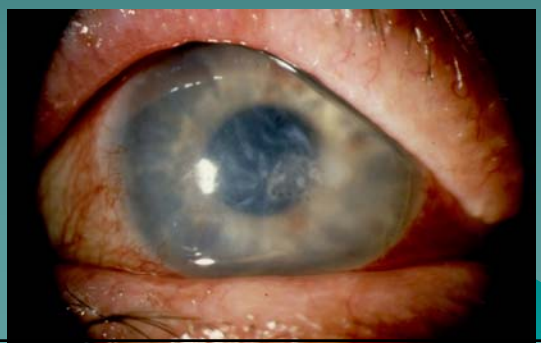


Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Serratia

H.W. 81 yo wm infected bullous keratopathy

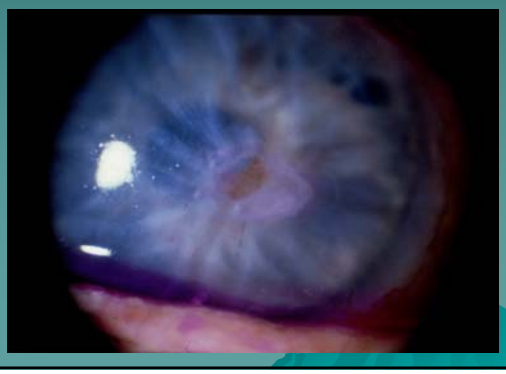


Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Serratia

H.W. 81 yo wm perforated ulcer

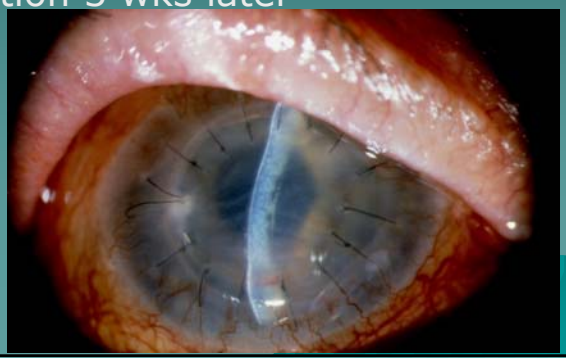


Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Serratia

H.W. 81 yo wm urgent graft; wound infection 3 wks later

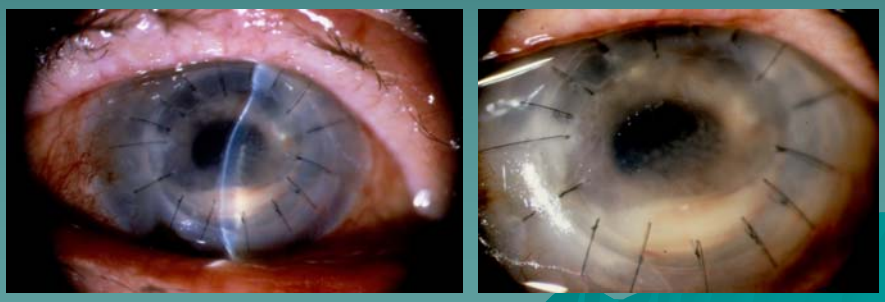


Infiltrative Keratitis: Infectious

Bacterial Ulcers: Gram- Organisms

Serratia

H.W. 81 yo endophthalmitis



Infiltrative Keratitis: Infectious

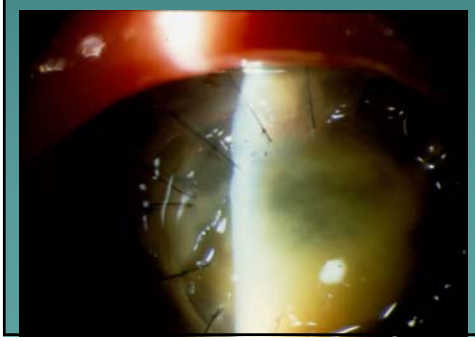
Bacterial Ulcers: Gram- Organisms

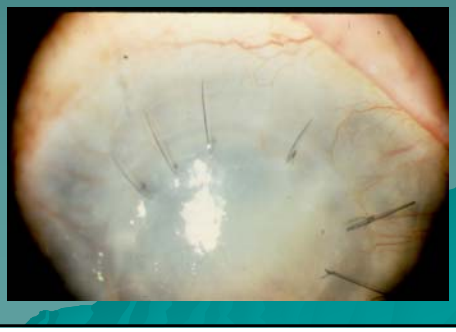
Serratia

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

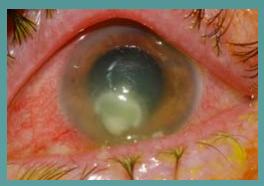
Diabetic patient with Indolent superficial non-healing ulceration

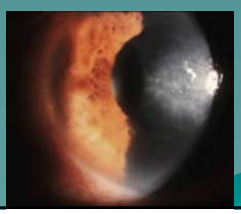
Infiltrative Keratitis: Infectious

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

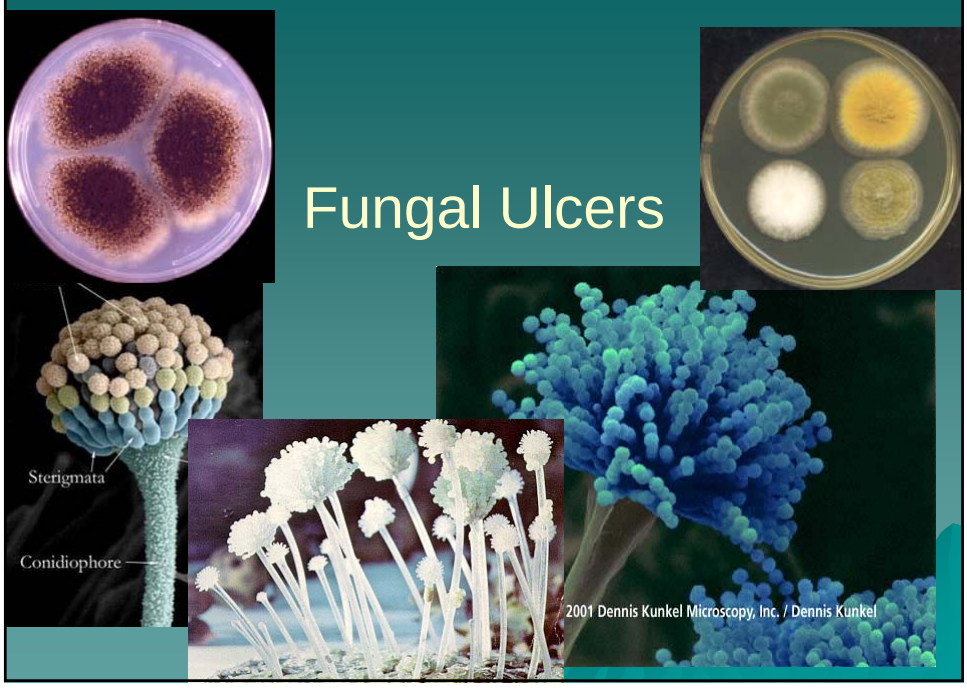
Infiltrative Keratitis: Infectious

Bacterial Ulcers: **Anaerobes**

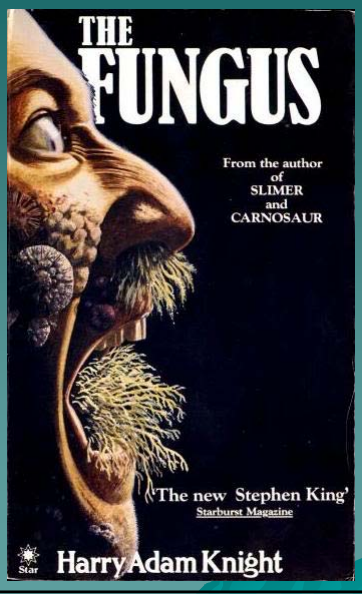
- Usually predisposing condition, e.g. CL wear
- Over 1/3 occur in mixed cultures with other organisms
- Probable lone cause of ulcers **<5%**
- Routinely susceptible to most tested antibiotics

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

Fungal Ulcers



Fungal Ulcers



Infiltrative Keratitis: Infectious

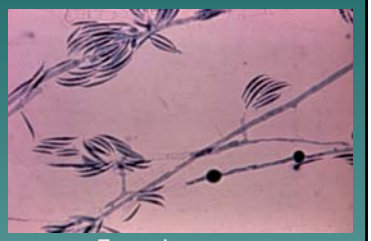
Fungal Ulcers: Signs

- 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

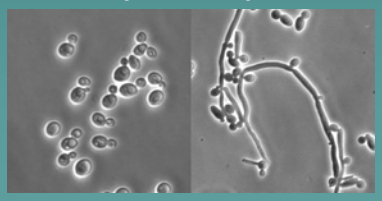
Infiltrative Keratitis: Infectious

Fungal Ulcers: Organisms

- Candida
- Fusarium
- Aspergillus
- Penicillium
- Cephalosporium



Fusarium



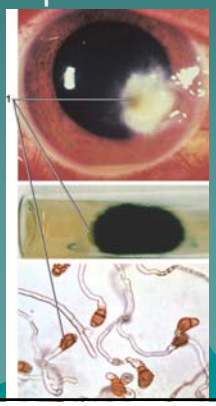
candida

Aspergillus

Infiltrative Keratitis: Infectious

Fungal Ulcers: Signs

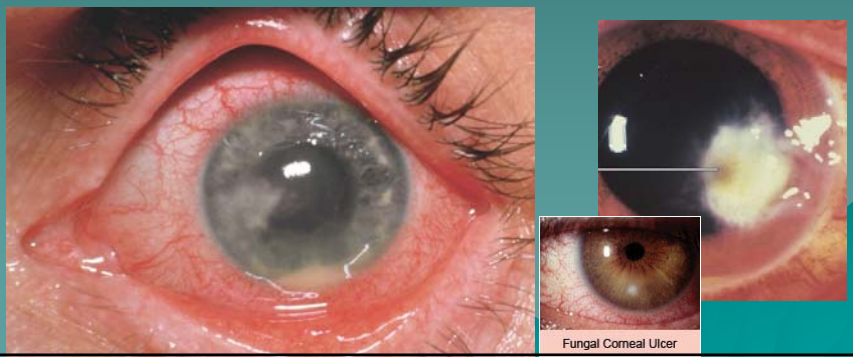
- May be indistinguishable from bacterial
- History of trauma with plant matter may be suggestive



Infiltrative Keratitis: Infectious

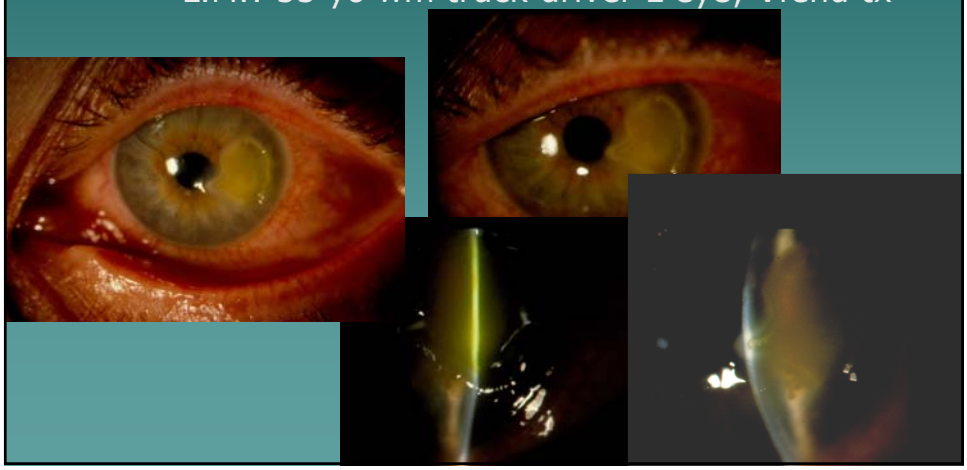
Fungal Ulcers: Signs

- Feathery margins, irregular extensions, "corraliform"



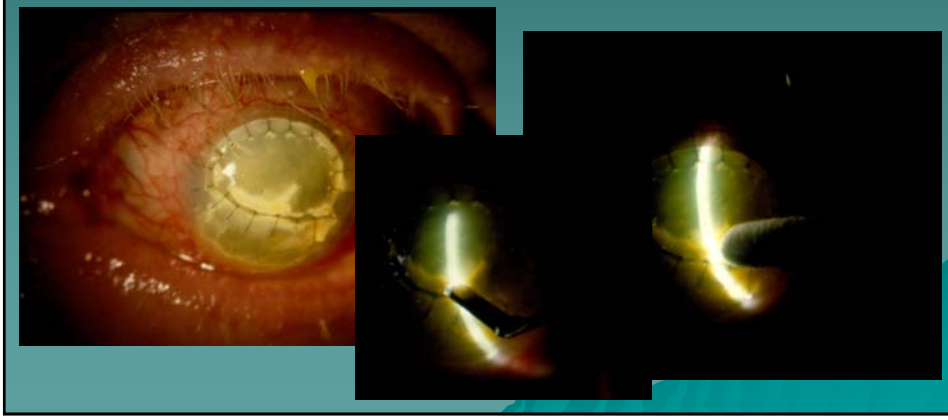
Infiltrative Keratitis: Infectious

- Fungal Ulcers: ***Aspergillus fumigatus***
  - L.M.: 55 yo wm truck driver L eye; Vfend tx



Infiltrative Keratitis: Infectious

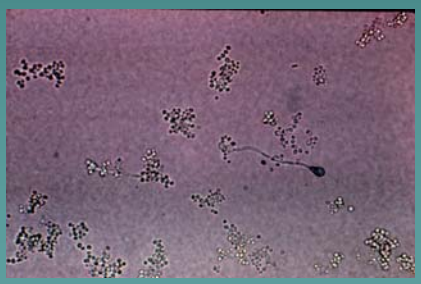
- Fungal Ulcers: ***Candida***
  - R.B. 64 y.o. wm w/ atopy, indolent ulceration eventually colonized



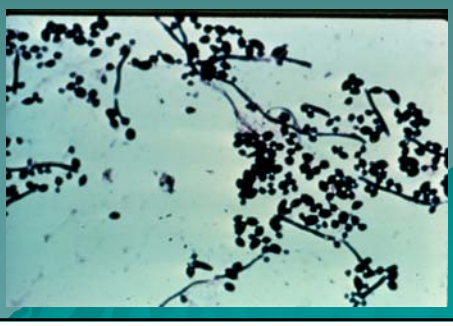
Infiltrative Keratitis: Infectious

- Fungal Ulcers: ***Candida***

100X wet mount Candida albicans

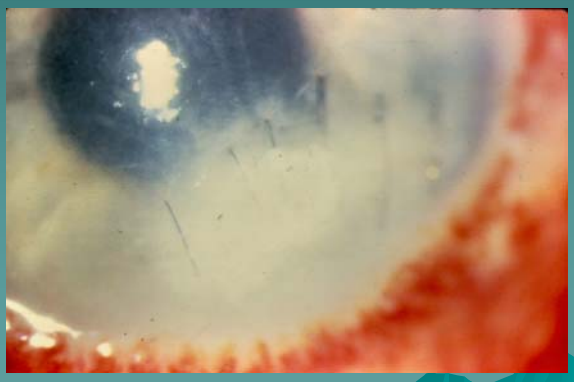


Budding yeast, pseudohyphae, C. albicans



Infiltrative Keratitis: Infectious

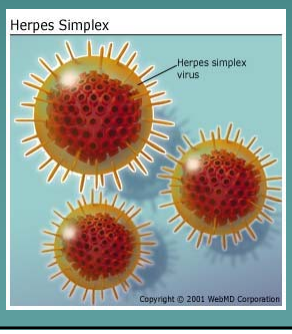
- Fungal Ulcers: ***Candida***
  - BB: OS: fungal ulcer urgent patch graft, subsequent endophthalmitis

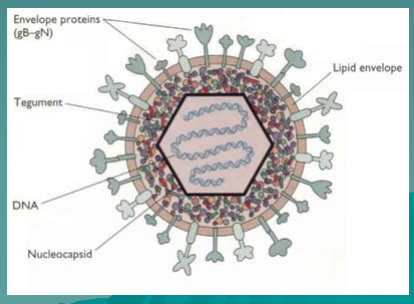


Infiltrative Keratitis: Infectious

- Fungal Ulcers: pigmented fungi

Viral Ulcers



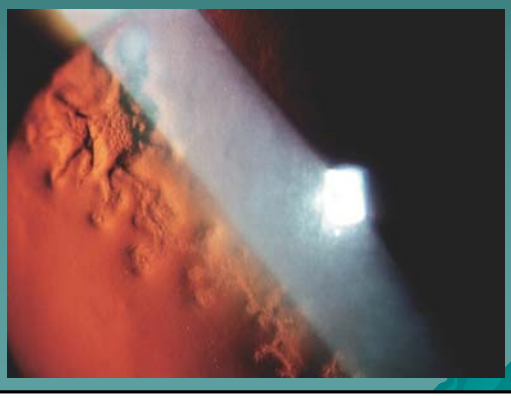


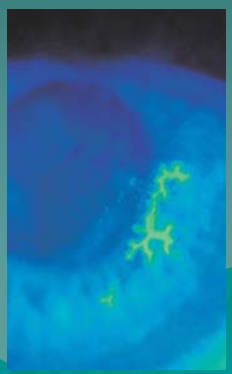
Infiltrative Keratitis: Infectious

Viral Ulcers: ***Herpes simplex***

Usually easy to distinguish from bacterial

- Epithelial dendrite



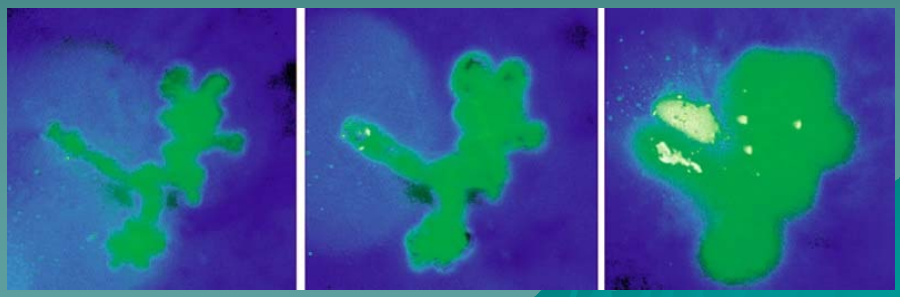


Infiltrative Keratitis: Infectious

Viral Ulcers: ***Herpes simplex***

Usually easy to distinguish from bacterial

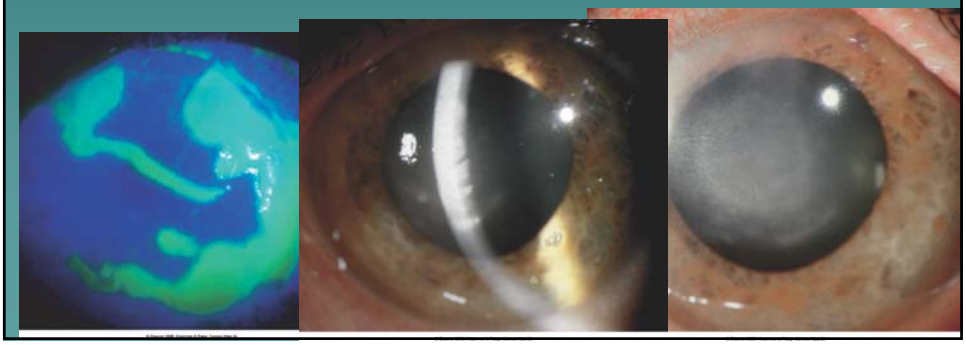
- Epithelial dendrite



Infiltrative Keratitis: Infectious

Viral Ulcers: ***Herpes simplex***

- Epithelial dendrite
- Geographic/ metaherpetic
- Subepithelial & stromal infiltrates



Infiltrative Keratitis: Infectious

Viral Ulcers: ***Herpes simplex***

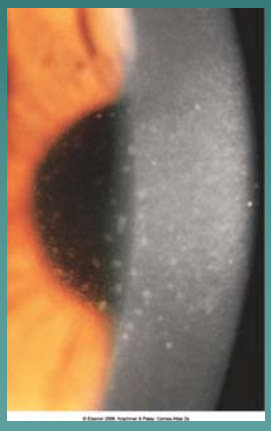
- Subepithelial & stromal scarring
- Disciform edema

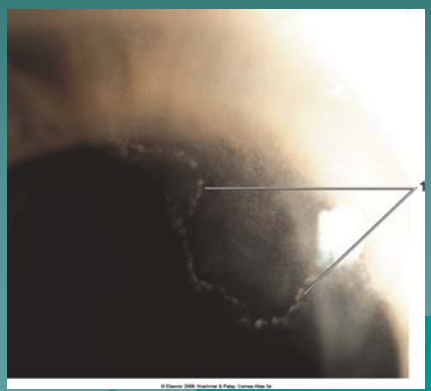
Wessely ring

Infiltrative Keratitis: Infectious

Viral Ulcers: ***Herpes simplex***

- Endotheliitis





Infiltrative Keratitis: Infectious

Note on Endotheliitis

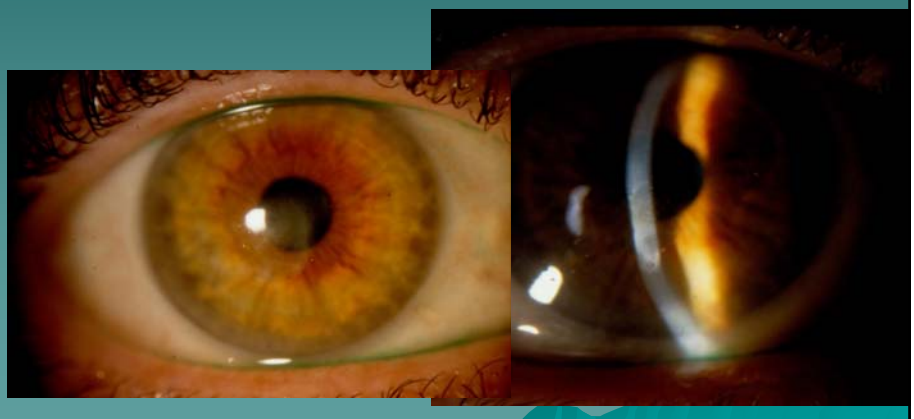
Cytomegalovirus

- 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

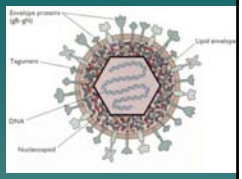


Infiltrative Keratitis: Infectious

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

Infiltrative Keratitis: Infectious

Viral Ulcers: ***Herpes simplex***



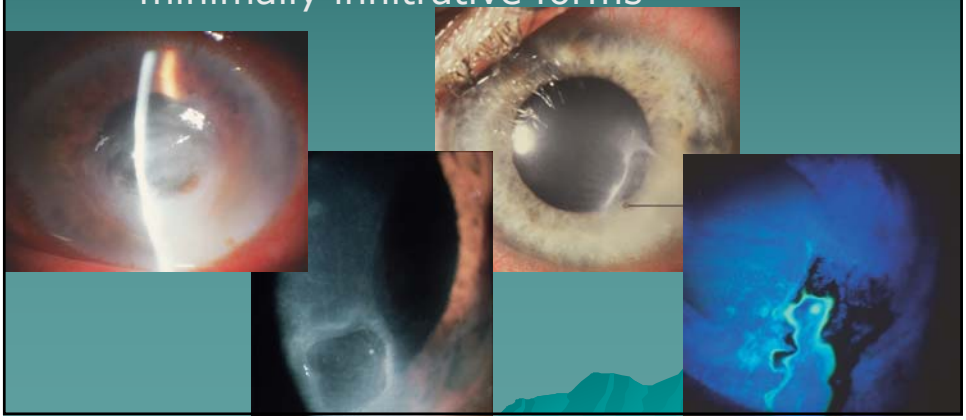
Necrotizing keratitis less common

- 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***

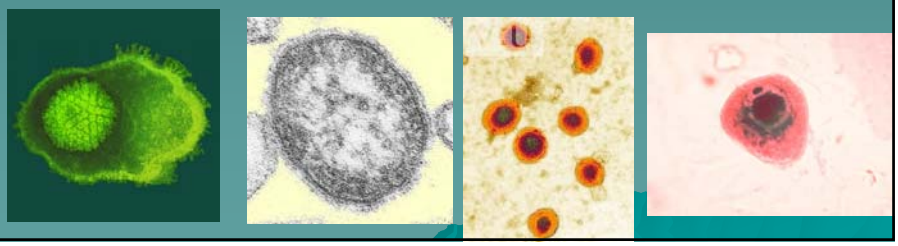
Necrotizing keratitis: dense infiltrative vs minimally infiltrative forms



Infiltrative Keratitis: Infectious

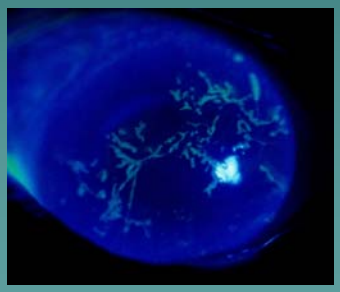
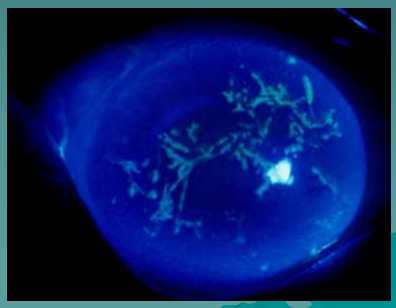
Less common Viral Ulcers:

- Herpes Zoster (VZV varicella/ chickenpox)
- Measles (Kwashiorkor, vit A deficiency)
- Mumps
- CMV (newborns with disseminated disease/ immunosuppressed host)



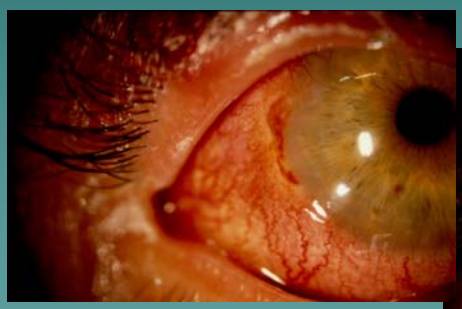
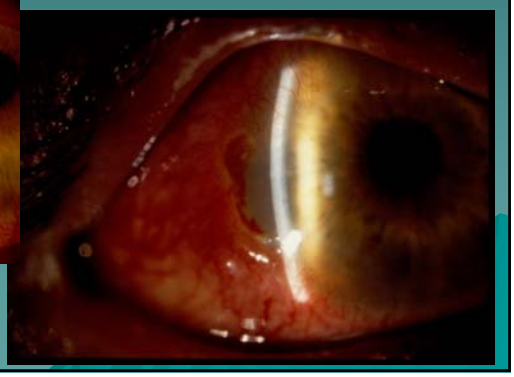
Infiltrative Keratitis: Infectious

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

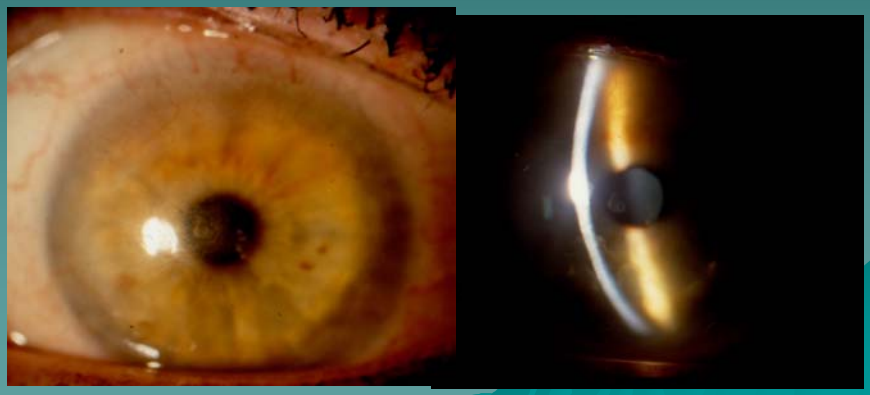
Infiltrative Keratitis: Infectious

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

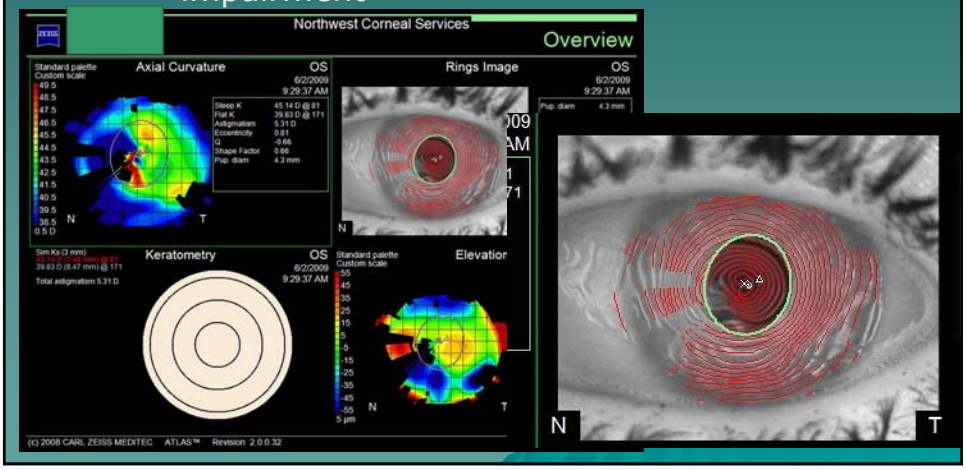
Infiltrative Keratitis: Infectious

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



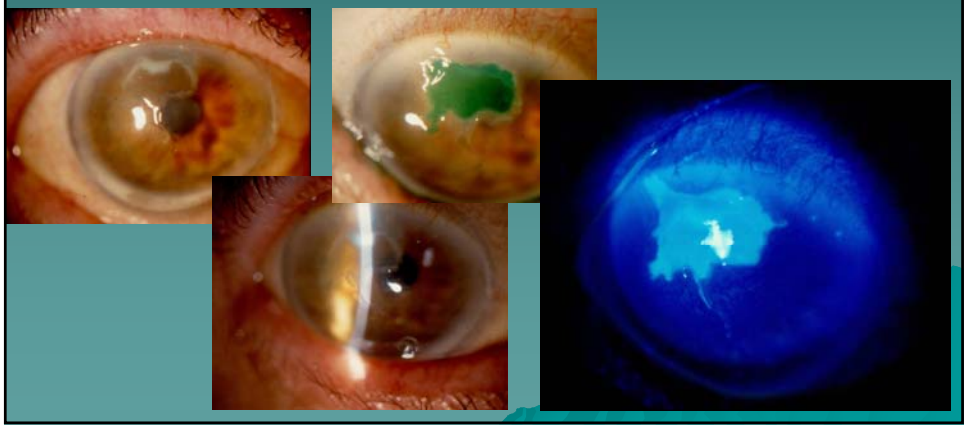
Infiltrative Keratitis: Infectious

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



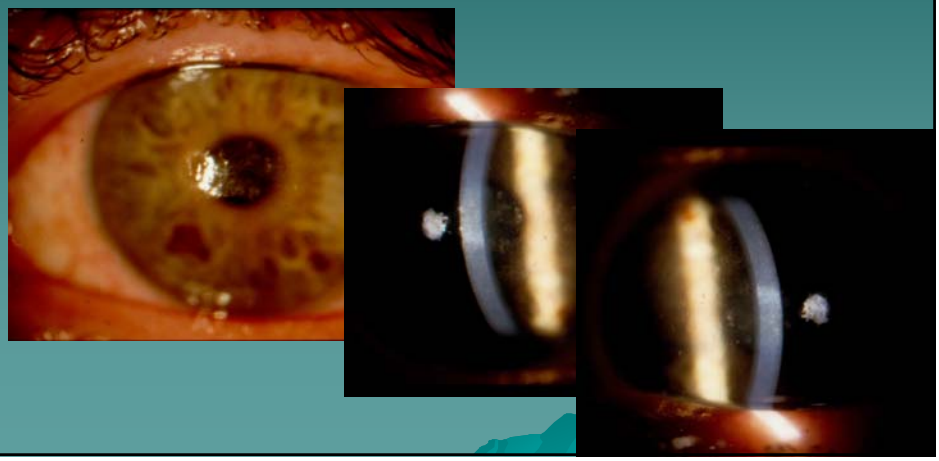
Infiltrative Keratitis: Infectious

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



Infiltrative Keratitis: Infectious

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

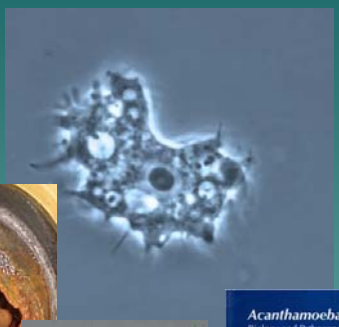


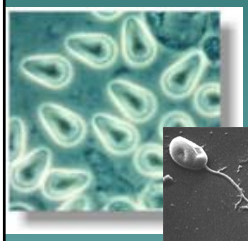
Parasites

Infiltrative Keratitis: Infectious

Parasites

- Acanthamoeba spp
- Microsporidia



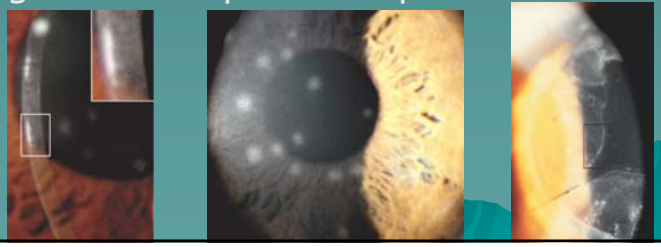


Infiltrative Keratitis: Infectious

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

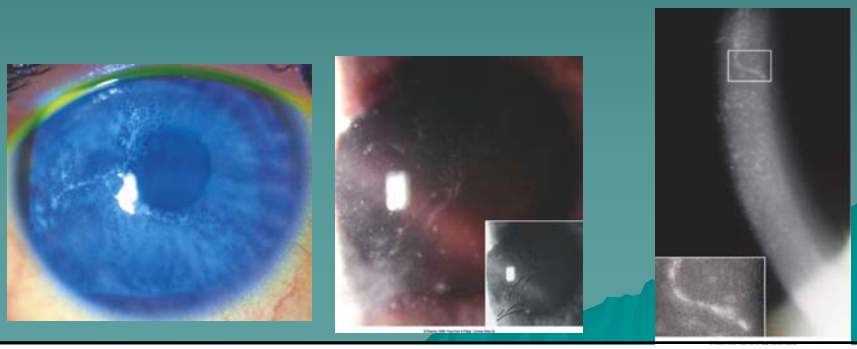


Infiltrative Keratitis: Infectious

Protozoal Infections:

Acanthamoeba keratitis

- Pseudodendrites (trophozoites)
- Radial keratoneuritis infiltrates

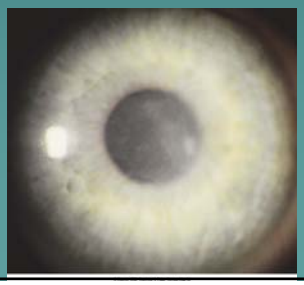


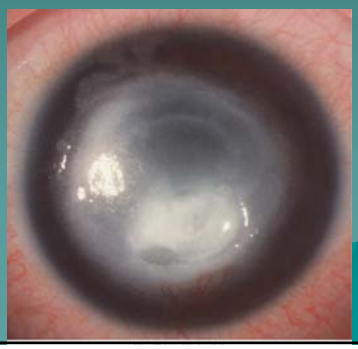
Infiltrative Keratitis: Infectious

Protozoal Infections:

Acanthamoeba keratitis

- Diffuse or sectoral stromal keratitis
- Ring infiltrates & ulceration
- Adjacent scleritis





Infiltrative Keratitis: Infectious

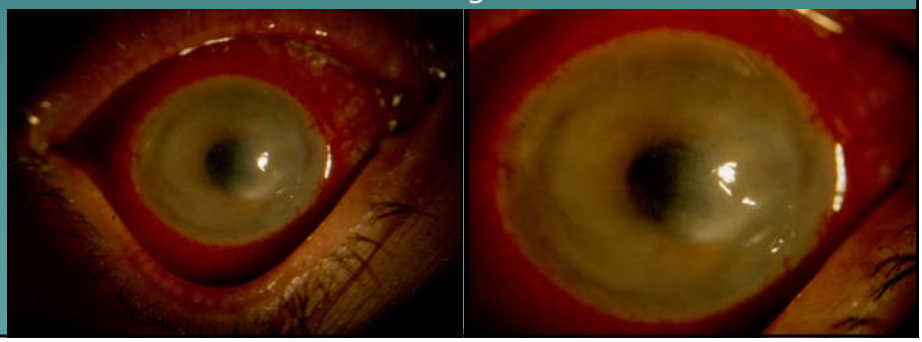
Protozoal Infections:

Acanthamoeba keratitis

- Diffuse/ sectoral stromal keratitis
- Ring infiltrates
- 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

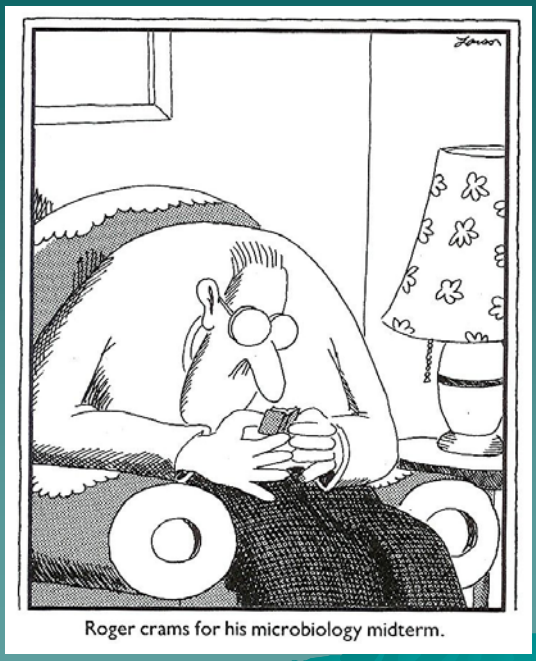


Infiltrative Keratitis: Infectious

Microsporidiosis (Nosema, Brachiola algerae) parasites:

- Not uncommon in India (mosquitoes)
- Consider immunosuppressed host

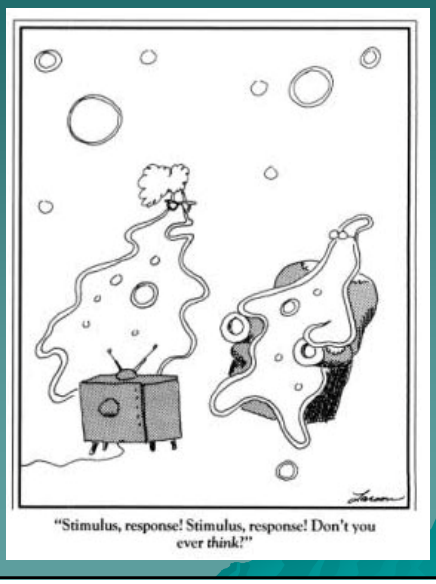
spores



Roger crams for his microbiology midterm.

Sterile Infiltrative Keratitis

Sterile Infiltrative Keratitis



Infiltrative Keratitis: Sterile

Often in contact lens wearers

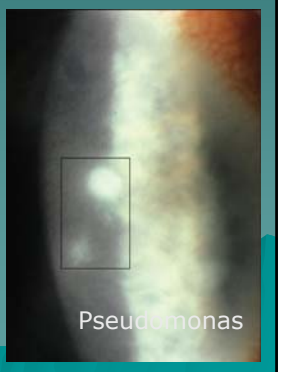
- Tend to be smaller (<1mm)
- Multiple
- Arcuate, mid peripheral or peripheral
- Minimal pain, photophobia, discharge, epithelial defect, or anterior chamber reaction

Infiltrative Keratitis: Sterile

- Not possible to be certain any infiltrate is sterile

sterile

Sterile culture



Pseudomonas

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

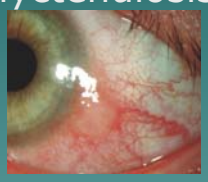
Infiltrative Keratitis: Sterile

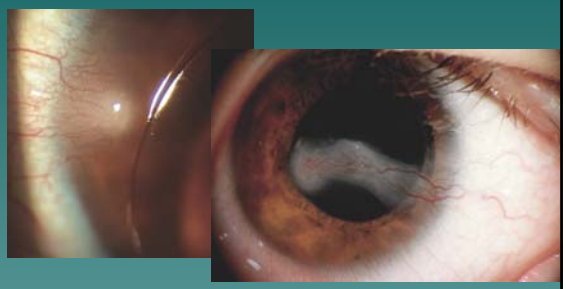
Rosacea keratitis/ ulcer

- Responds to lid hygiene, steroids and tetracyclines, ± antibiotic

Infiltrative Keratitis: Sterile

Phlyctenulosis

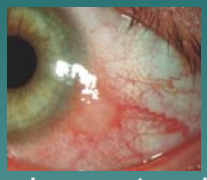


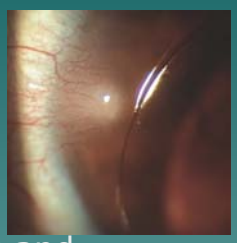


- May involve conjunctiva or cornea
- Cell mediated hypersensitivity to various infectious antigens
- Small ulcers central to areas of superficial vascularization

Infiltrative Keratitis: Sterile

Phlyctenulosis

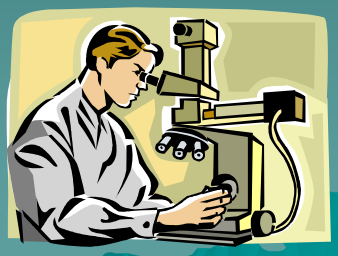




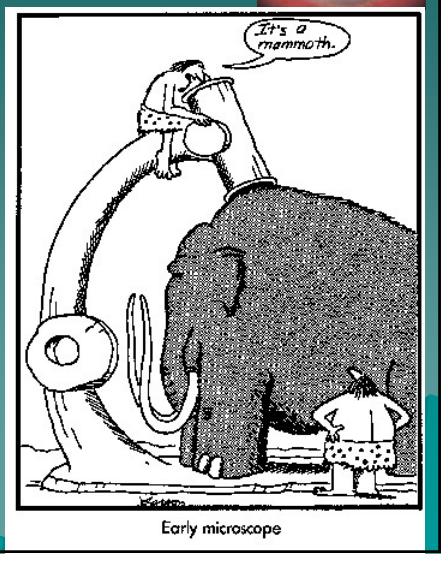
Etiology:

- Staph
  - Responds to lid hygiene, steroids and tetracyclines, ± antibiotic
- Mycobacteria
- TB
- Coccidioides
- Candida

Laboratory Evaluation

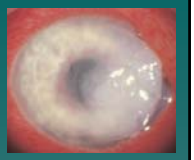


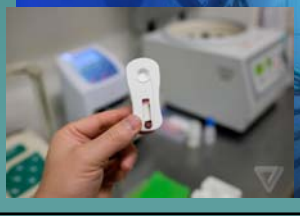
Laboratory Evaluation



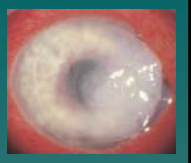
Early microscope

Laboratory Evaluation





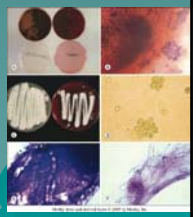
Laboratory Evaluation of Corneal Ulcers



Can one predict proper treatment without cultures?

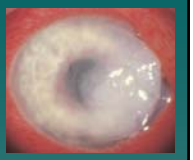
Prospective study of 15 ophthalmologists

- 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

Kimura platinum spatula

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

Laboratory Evaluation

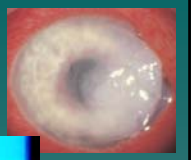
Inoculated media

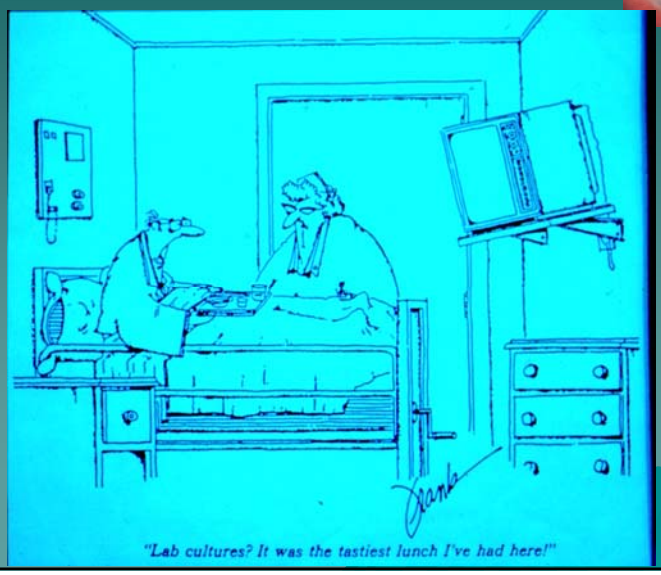
- Blood, chocolate agar, thioglycolate (bacteria)
- Lowenstein-Jensen optimal for AFB (NTM)
- Sabouraud's dextrose agar (fungus)
- M-4 medium (Herpes simplex, zoster for culture or DNA (PCR))
- Sterile saline (acanthameba—transferred to E coli or similar plated medium in lab)

Contact lens cases:

- Consider culturing

Laboratory Evaluation





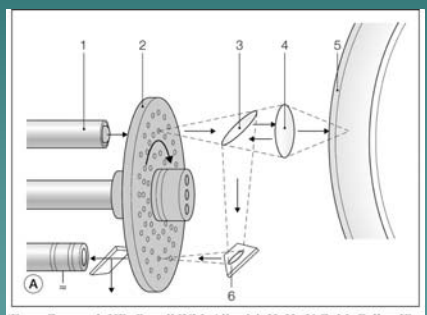
Laboratory Evaluation

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

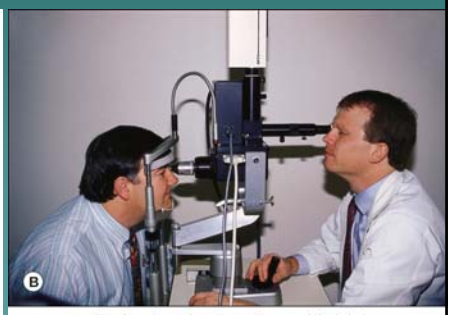
M-4 viral transport media

Laboratory Evaluation

Confocal Specular Microscopy



(From Cavanagh HD, Petroll WM, Alizadeh H, He Y-G, McCulley JP, Jester JV: Clinical and diagnostic use of in vivo confocal microscopy in patients with corneal disease, *Ophthalmology* 100:1444–1454, 1993.)

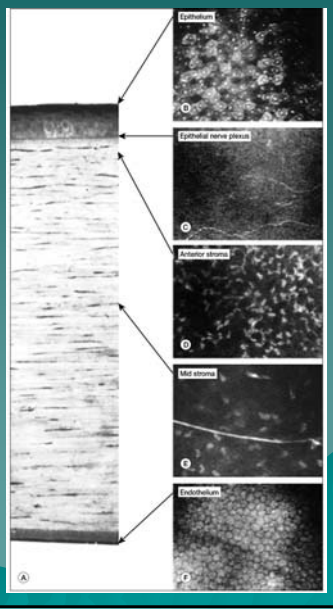


(Tandem Scanning Corp., Reston, Virginia.)

Laboratory Evaluation

Confocal Specular Microscopy

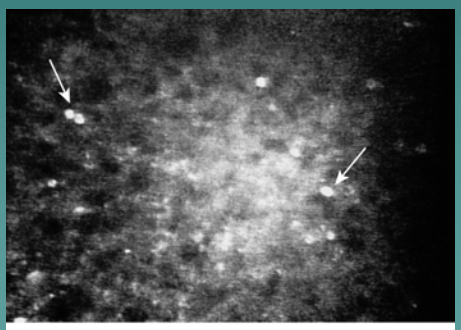
- Histological analysis of all corneal layers
- Image:
  - Bacteria
  - Fungus
  - Amebas
  - Microsporidia
  - Viral (Langerhans' cells)



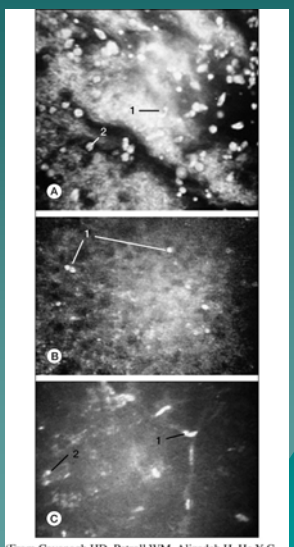
Laboratory Evaluation

Confocal Specular Microscopy

- Acanthameba



(Courtesy of W.M. Petrol, PhD, Dallas, Texas.)

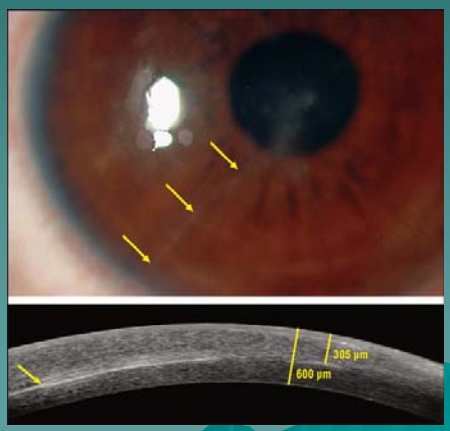


(From Cavanagh HD, Petroll WM, Alizadeh H, He Y-G, McCulley JP, Jester JV: Clinical and diagnostic use of in vivo confocal microscopy in patients with corneal disease. *Ophthalmology* 100:1444–1454, 1993.)

Laboratory Evaluation

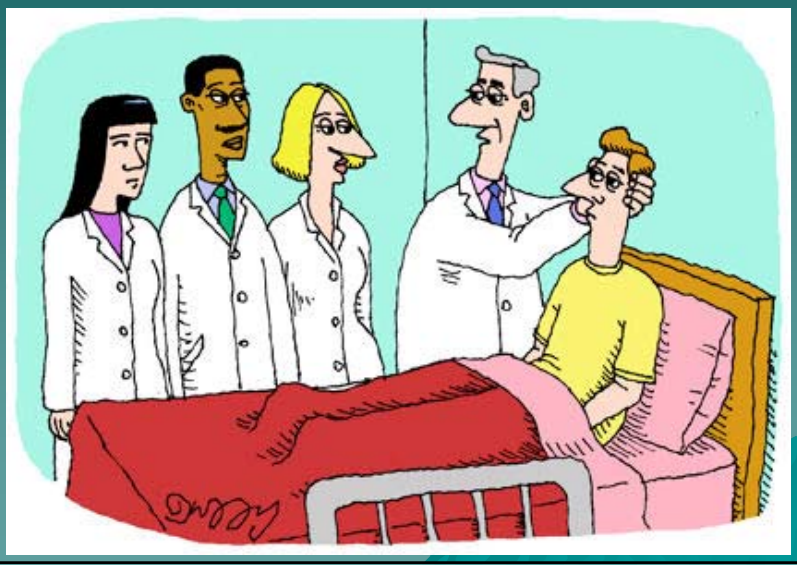
OCT/ Corneal module

- Acanthameba



TREATMENT OF INFILTRATIVE KERATITIS

The Corneal Ulcer Patient circa -1980's



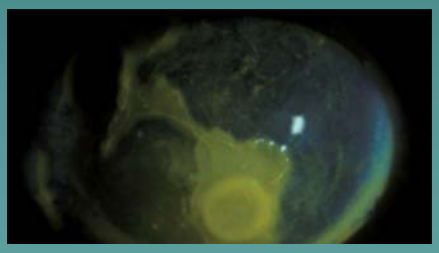
Goals of Treatment

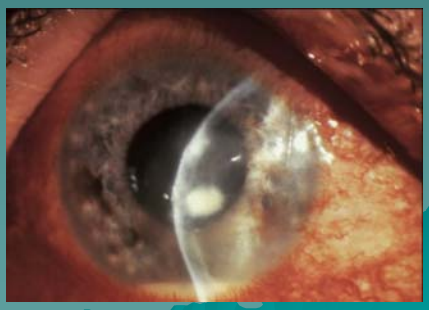
- Rapidly stop replication of organisms
- Prevent host tissue/ collagen destruction
- Get epithelium to heal (stops corneal melting)
- Reduce scarring
- Avoid neovascularization
- Preserve vision

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

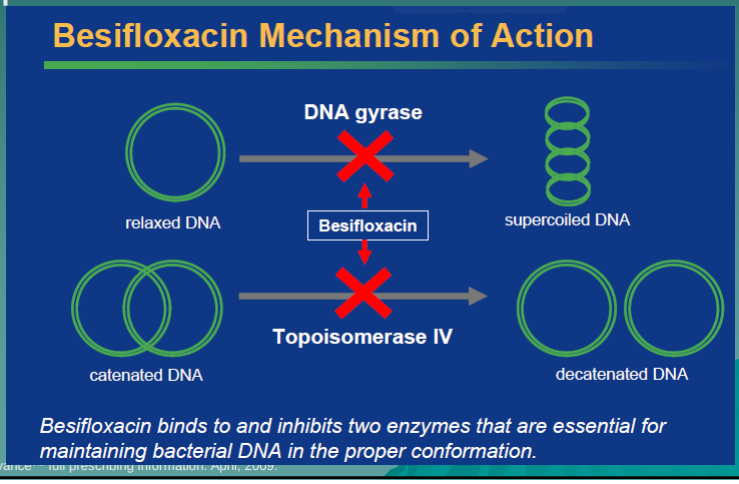
MBC = Minimum bactericidal concentration; MIC = Minimum inhibitory concentration

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

Besivance besifloxacin ophthalmic suspension, 0.6%

Besivance™ Microbiologic Activity

- Balanced inhibition of bacterial reproduction



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

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**

Pseudomonas

Efficacy against MRSA

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

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

Antibiotic Resistance

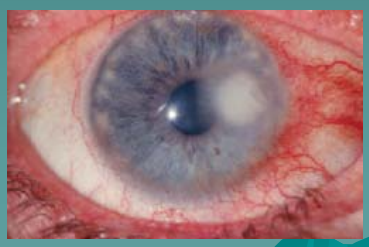
- ARMOR STUDY (Antibiotic Resistance Monitoring in Ocular Microorganisms surveillance study)
  - US Nationwide ongoing study examples:
  - *S pneumonia* non-susceptibility doubled for PCN, Azith and Chloro 2013-2014
  - *S. aureus* more susceptible to Oxacillin, Cipro and Azith 2013-1014
  - Coag Neg *Staph* more non-susc to Tobramycin
  - 25% *S aureus*, 50% CoagNS were methicillin resistant, many multidrug resistant
  - Some *Pseudomonas a.* non-susc to polyB, imipinem, cipro

Asbell et al ARVO 2015

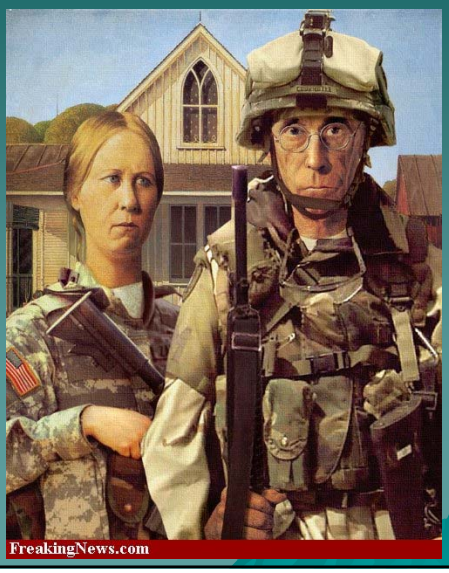
Antibiotic Resistance

- 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***

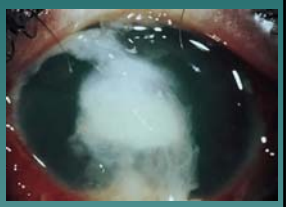
Steroid Treatment

- 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

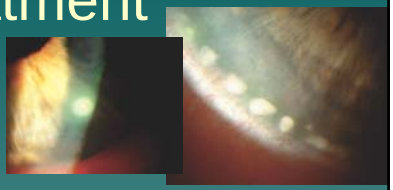


- Corticosteroids allow pseudomonas organisms to "smolder"
- Organisms can live inside PMN's for up to 4-6 weeks
- Require concomitant antibiotic treatment 4-6 weeks

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:

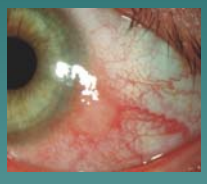
Catarrhal related to staph:

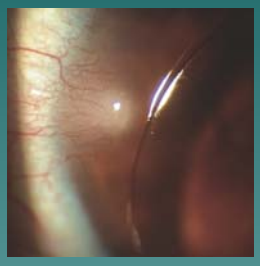
- Responds well to topical antibiotic/ steroid combination, e.g. Tobradex, or Zylet
- If in doubt, try 48 hours of antibiotic and if not worsening or slowly improving, then add loteprednol or fluorometholone
- Start lid hygiene ~1 week later, after infiltrate/ ulceration resolved
- Follow for recurrences

Empiric Treatment

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 antiotics used:
  - Tobramycin 14 mg/ml
  - Vancomycin 25 mg/ml

Culture Driven Treatment: Compounding Pharmacy Peril

- Gov't regulation of "big guns"

"Figured I better get one before they crack down on the tank shows."

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

Rajaramman et al Asia Pac J Ophthalmol (Phila) 2015 May-June 4(3):146-50
Other similar studies

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

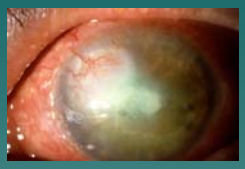
- Ganciclovir 0.15% FDA approved for HSV keratitis 2009 (Zirgan)
- Tube/ gel form
- 1 application 5x/day until ulcer heals, then tid for 7 days
- Targets only replication of HSV DNA
- Little toxicity, similar to acyclovir ointment (unlike TFT)

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:

HSV/Infiltrative Keratitis Update



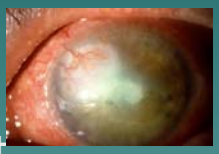
Stromal keratitis treatment

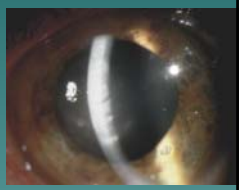
- Disciform edema & stromal keratitis:
  - poor response to antivirals alone
  - primarily immunologic mediated
- Herpetic Eye Disease Study (HEDS)
  - TFT + steroids do not increase early or late recurrences of HSV or cause other complications

HSV/Infiltrative Keratitis Update

Stromal keratitis treatment

- Disciform edema & stromal keratitis:





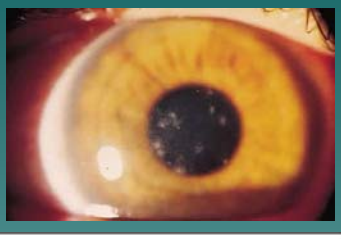
- Long-term treatment
  - ~3 months drop for drop steroid+TFT or GCV *or* steroid+oral ACV
  - long-term advantage with oral ACV and topical steroids (no topical antiviral)
  - At least 2 years oral ACV in my practice

(400mg bid)

ADENOVIRUS TREATMENT UPDATE

Adenovirus Treatment Update

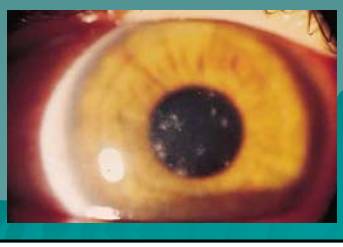
- Prompt diagnosis and treatment reduce likelihood of subepithelial infiltrates (SEI's)
- Adenovirus DNA in-office dx aid (AdenoPlus)
  - Immunochromatography assay
  - Detects adenoviral Hexon protein in tear fluid



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

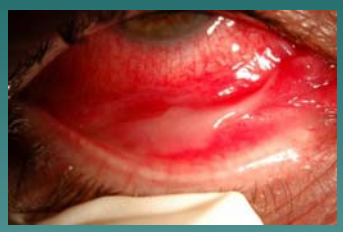


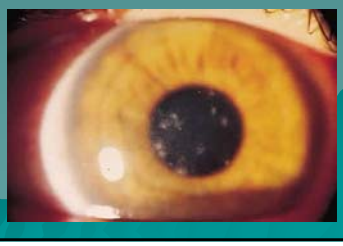
Adenovirus Treatment Update

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

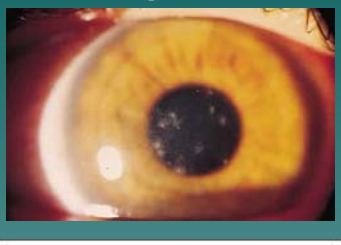
Arq Bras Oftalmol 2011 Nov-Dec;74(6):417-21





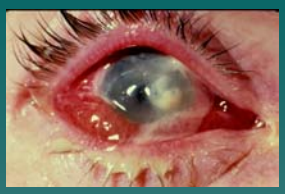
Adenovirus Treatment Update

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

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THANK YOU ALL!
&
PACIFIC UNIVERSITY
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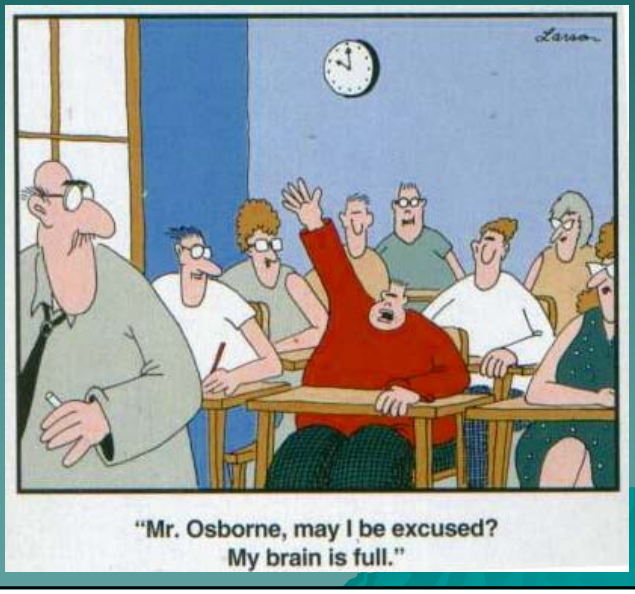
25TH ANNIVERSARY
VICTORIA CONFERENCE!

Questions

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