# Severe, sight threatening microbial keratitis: aetiology, diagnosis and critical management considerations

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**To be read in conjunction with 2008 lecture**

**Assessing acute keratitis**

Relevant History
- Unilateral or bilateral
- Type of discharge
- Recurrent episodes
- Allergies/atopia
- Current Rx – including OTC
- Recent systemic symptoms
- Previous ocular surgery

Clinical assessment cont'd

- Predisposing factors
- Lid malposition
- Tear film
- Corneal sensation
- Ulcer dimensions
- Hypopyon
- Perforation

Carefully document appearance on presentation and daily thereafter by a plan and profile drawing with annotations and measurements
Consider slit-lamp Microphotography
+/- in vivo confocal microscopy

**DIAGNOSIS**

Conjunctival swabs little use
**Corneal scrape is paramount**
*Consider PCR*
Corneal biopsy
Culture contact lens
Culture contact lens cases

**Protect your patient (and yourself) by understanding the evidence-base**
**Levels of evidence**

Evidence constantly updated: 1980's important bacterial pathogens in microbial keratitis 87% of bacterial keratitis:
- Staphylococcus sp.
- Streptococcus sp.
- Pseudomonas sp.
- Enterobacteriaceae
  - proteus, klebsiella

**Differential diagnosis in presumed microbial keratitis**

Bacterial
Viral
Chlamydial
Acanthamoeba
Fungal
Non-infective

**Predisposition to severe keratitis**

Dry eye
Contact lens wear
Blepharitis
Lid malposition
Corneal exposure
Trauma
Previous surgery
Neurotrophic cornea

## The evidence base:

**1. Severe microbial keratitis leading to hospitalization in Western Australia**

| | |
|---|---|
| Prior ocular surgery | 23* |
| (5* Bullous keratopathy) | |
| Contact lens wear | 12 |
| Lid malposition | 9 |
| Trauma | 8 |
| HSV Keratitis | 7 |

**2. Aetiology of acute keratitis: prior ocular surgery**

Infectious keratitis post PRK Risk approximately 1:500 – 1:1000
Infective keratitis in 13 eyes/12 subjects
Final BSCVA 20/20 – 20/200
Bacterial Keratitis: predisposing factors, clinical & microbiological review of 300 cases
Bourcier T, Thomas F, Borderie et al. Br J Ophthal 2003:87;834-8

**3. National Ophthalmology Centre, Paris**

90.6% of 300 cases exhibited risk factors:
50% Contact Lens wear
21% Keratopathy
15% Trauma

**4. Contact lenses and infective keratitis in the 1990's:**

**Relative CL risk of bacterial keratitis**

| | |
|---|---|
| RGP CL annual risk is | 1:10,000 |
| Extended wear vs daily SCL | 3.9:1 |
| Overnight wear SCL | x10-15 risk |

(Acanthamoeba < 1% of keratitis but very strongly associated with contact lenses)

**5. Contact-lens-related microbial keratitis & morbidity**

- All ophthalmologists (440) in Netherlands
- 3 month period in 1996
- 92 cases of microbial keratitis
- 17 RGP, 63 DWSL, 12 EWSL
    - Annualized incidence:
    - RGP 1.1 per 10,000
    - DWSL 3.5 per 10,000
    - EWSL 20 per 10,000

**6. Severe microbial keratitis in a tertiary referral centre – is history useful?**
**88% had predisposing risk factors**

| | |
|---|---|
| Ocular surgery | 30% |
| Contact lens wear | 26% |
| Topical corticosteroids | 25% |
| Ocular trauma | 24% |
| Prior HSV | 11% |
| Dry Eye | 8% |
| Trichiasis/entropion | 6% |

**7. Bacterial Keratitis: predisposing factors, clinical & microbiological review of 300 cases.** Bourcier T, Thomas F, Borderie et al. Br J Ophthal 2003:87;834-8

National Ophthalmology Centre, Paris
Organisms identified in 68% of eyes

| | |
|---|---|
| 83% | Gram positive |
| 17% | Gram Negative |
| **2%** | **Polymicrobial** |

**8. Clinical characteristics of microbial keratitis in Taiwan: 10 yr x-sectional study 476 eyes**

**Organisms**

| | |
|---|---|
| Pseudomonas sp | 37.7% |
| Fungi | 13.5% |
| Staphylococci | 8.4% |
| Mycobacterium (non-TB) | 7.9% |
| Streptococci | 7.6% |
| Acanthamoeba | 4.4% |

**9. Clinical and Microbiological profile of infective keratitis in Switzerland**
**Risk factors**

- Contact lens wear 36%
- Blepharitis 21%
- Trauma 20%
- Xerophthalmia 15%
- Keratopathies 8%
- Eyelid abnormalities 6%

**10. Clinical and Microbiological profile of infective keratitis in Switzerland**

Organisms

- Staph epidermidis 40%
- Staph aureus 22%
- Strept species 13%
- Pseudomonas sp 9%

Sensitivities (resistance to drug)

- to fluoroquinolones 1-15%
- to aminoglycosides 13-22%
- to cefazolin 37%

**11. Case Control Study of Microbial keratitis in Hong-Kong**

223 new cases of presumed MK over 18 months

- 26% wore contact lenses
- **Overall 35% of scrapes yielded +ve results**
- Pseudomonas sp predominant, 5 acanthamoeba

Annual incidence of Microbial keratitis

- 0.63 per 10,000 population
- 3.40 per 10,000 CLW
- 9.30 per 10,000 EW CLW

Of 90 cultured isolates

- **Gram-positive 37 (41%)**
  - Staphylococcus Aureus - 9
- **Gram-negative 42 (47%)**
  - Pseudomonas Aeruginosa - 28
- **Fungi 5 (5.4%)**
  - Fusarium Species - 3
- **Protozoan 6 (6.6%)**
  - Acanthamoeba Species - 6

## Always be prepared to reconsider the diagnosis in microbial keratitis

**The varied manifestations of HSV**

Punctate
Dendritic
Disciform
Endotheliitis
Stromal
Geographic/amoeboid
Metaherpetic/trophic

**Herpes Zoster Ophthalmicus**

- Ophthalmic division of trigeminal nerve
- Approximately 15% of Herpes Zoster
- Usually in elderly
- Rare under 45 but as young as 2
- Consider immuno-suppression /AIDS if two separate dermatomes involved

**HZO: Ocular involvement**

- Lid oedema/rash
- Conjunctivitis
- Episcleritis
- Scleritis
- Acute epithelial keratitis
- Nummular keratitis
- Disciform keratitis
- Neurotrophic keratitis
- Anterior uveitis

**Adenoviral kerato-conjunctivitis**

- Clinical presentation – mild to severe conjunctivitis / keratitis
- **Highly contagious !**
- Occupational hazard of ophthalmologists & optometrists

**Always Consider Global Differences**

*Epidemiology of suppurative Keratitis*

- Multicentre study: Ghana & India 99-01
- 1090 patients recruited
- Organisms
    - Filamentous fungi (42%)
        - Fusarium and Aspergillus
    - Bacterial Organisms
        - Ghana: Pseudomonas
        - India: Streptoccoci

**Consider Global Differences Fungal Keratitis**

- E.g. Fusarium Species with B&L ReNu
    - Topical Rx
        - Natamycin
        - Amphotericin
    - Systemic Rx
        - Voriconazole / itraconazole

**Centres for Disease Control (CDC) Acanthamoeba update 2007**

Typically AK is a rare disease - 1-2 cases/million contact lens PA in USA, based on analysis of cases identified during an outbreak of AK 1985–1987
With estimated 30 million in USA wearing SCL, this would equate to approx 30 to 60 cases of AK per year.

**Treatment of bacterial keratitis**

Once it was easy! First line antibiotic therapy 1990's
*NB only after obtaining microbiology specimens*

**Fortified duo-therapy**

| | |
|---|---|
| Cephalosporin | e.g. cefuroxime 5.0% |
| Aminoglycoside | e.g. tobramycin 1.25 - 1.5% |

**Monotherapy**

| | |
|---|---|
| Fluoroquinolone | e.g. ciprofoxacin/ofloxacin |

**Is there still a role for fortified duotherapy in 2008?**

**Cephalosporins – principally for Gram +ve bacteria**
Fortified 5% solution for Rx of severe bacterial keratitis as *duotherapy Rx*
No commercial ocular preparations – unpreserved – made up by hospital pharmacy

***Sensitivity 1997-2000****

| | |
|---|---|
| –Staph Aureus | 94% |
| –Staph (coag. neg.) | 98% |
| –Strept. Pneumoniae | 94% |

**Aminoglycosides – principally for Gram –ve bacteria**
Tobramycin or gentamicin, as part of fortified duotherapy (1.2-1.5%)
Active against spectrum Gram +ve and –ve bacteria, *including pseudomonas*

***Sensitivity 1997-2000 Tobramycin****

| | |
|---|---|
| –Pseudomonas aer. | 94% |
| –Staph Aureus | 83% |
| –Staph (coag. neg.) | 78% |
| –Strept. Pneumoniae | 48% |

**Fluoroquinolones as monotherapy in severe bacterial keratitis**
Ciprofloxacin inately more potent but penetration of Ofloxacin is x4 greater than ciprofloxacin
*Cekic O et al, Ophthal Surg 1999*
However, all gram positive bacteria equally susceptible to corneal concentrations obtained by ofloxacin & ciprofloxacin
*Kowalski RP et al, Cornea 1998*
Both drugs excellent against common gram +ve and gram –ve bacteria, less good against strept pneumonia & pseudomonas aeruginosa

**Fluoroquinolones: 2nd gen. fluoroquinolones equivalence in MK**
Efficacious against Gram positive and Gram negative bacteria, esp. staphylococci,
Less effective against certain streptococci
Variable effectiveness against pseudomonas
Low toxicity and good ocular penetration

**Risk of Perforation in keratitis (ofloxacin)**
Royal Victorian Eye and Ear Hospital, Melbourne 1991-1999
Retrospective review of 277 cases hospitalized for bacterial keratitis

| Corneal perforation | |
|---|---|
| Fluroquinolone Rx | 12.7% (18/142) |
| Fortified AB's Rx | 0.7% (1/135) |

"Fourth" generation fluoroquinolones

- Second generation
  - Ciprofloxacin
  - Ofloxacin
- Third generation
  - Levofloxacin
- Fourth generation
  - Gatifloxacin
  - Moxifloxacin

**USA trends in microbial keratitis and fluoroquinolone resistance 1990-00**

**Bascom Palmer Eye Institute (2920 cultures)**
Fluoroquinolone resistance increased 11 to 28%
Aminoglycoside resistance unchanged

**Eye & Ear Institute Pittsburgh (1053 isolates)**
Gram +ve decreased from 81.8% to 51.4%
Staph Aureus fluoroquinolone resistance increased
to ciprofloxacin 5.8% to 51.4%

**Antibiotic resistance Fourth Generation fluoroquinolones**
For most isolates no susceptibility difference between the ***five*** fluoroquinolones
The MICs for 4th generation statistically lower for gram positive bacteria
Fourth generation show greater susceptibility of Staph aureus resistant to 2nd and 3rd
However, Ciprofloxacin demonstrated lowest MICs for gram negative bacteria

**Fourth generation fluoroquinolones: mechanism of action**
Bactericidal
Inhibit two enzymes involved in Bacterial DNA Synthesis
DNA Gyrase (topoisomerase I)
Topoisomerase IV

**Antibiotic resistance to fourth generation fluoroquinolones?**
**Alteration in target enzymes:**
DNA Gyrase & Topoisomerase IV
**Alteration in access to target:**
Expression of membrane efflux pumps

**Resistance to 4th gen. fluoroquinolones**
2 cases of keratitis post PRK/LASIK
6% of 100 isolates of Ps. aeruginosa

**Efficacy of moxifloxacin in the treatment of bacterial keratitis: a randomised controlled trial, Melbourne, Australia**
229 patients – 83% culture positive
Randomised to:
fortified tobramycin & cephazolin
Or ofloxacin
Or moxifloxacin
*No statistical difference in groups in relation to time to cure, healing rate, or complications*

**Duo therapy or monotherapy ?**

| **Monotherapy** | **Duotherapy** |
|---|---|
| Small lesions | Large lesions |
| Peripheral lesions | Central Lesions |
| Previous Duotherapy | Previous FluorQ |
| Culture sensitivity | Culture sensitivity |
| Limited Compliance | Suspected |
| Patient cost | Pseudomonas** |

**Second line antibiotic therapy**

Modify antibiotic regime based only upon cultures and sensitivities

## Treat aggressively

**Outcome & morbidity of severe keratitis in Western Australian tertiary centre**
**Severe microbial keratitis (N=53)**

70% < 20/200 on admission
39% < 20/200 latest review

**Management of severe microbial keratitis in NZ tertiary referral centre (Auckland)**
**Severe end of MK spectrum**

49% central, 20% paracentral,
40% of eyes <20/200
Median lesion 2.4mm

**Pathogens identified in 75% of 1st and 50% 2nd scrapes**
**with *33% being polymicrobial***

Staphylococcus – coagulase negative
Propionibacterium acnes
Staphylococcus epidermidis
Streptococcus pneumoniae
Staphylococcus aureus
Pseudomonas aeruginosa

**Management of severe microbial keratitis in NZ tertiary referral centre**
**NB: 33% polymicrobial**

62% Rx fortified Kefzol & tobramycin
31% Rx ciprofloxacin
Mean hospital stay 5.2 days (1-31 days)
Median final BCVA 20/40, however, 33.8% had 20/100 or poorer vision at discharge

## Brief Summary - Antibacterial Rx severe keratitis (RED FLAG)

1. Always attempt to identify organism by a corneal scrape and culture

2. Make a decision duo or mono Rx
   Site, severity, susceptibility, compliance

3. Minimise resistance
   High frequency no tapering of fluoroquinolones

4. Definitive management
   Always consider scrape/re-scrape to identify organisms

5. As a rule you should never use corticosteroids in infective keratitis

**Acanthamoeba - a plague on both our houses**

*Acanthamoeba* is a protozoan that causes a rare but devastating corneal infection
1973 first reported in keratitis
1980's profile raised with public and eye care professions, since contact lens related "epidemic" of *acanthamoeba* keratitis

***Acanthamoeba* is free-living amoeba**

Relatively common in the environment.
Has been isolated from water including:
natural & treated water in pools/hot tubs
drinking water systems - shower heads, taps sewage systems
soil
air in association with cooling towers, heating, ventilation and air conditioner systems

**Opportunistic bacteria & fungal hunters**

Most people will be exposed to *Acanthamoeba* during their lifetime
Generally will not get sick as most species are bacteriovores
Some are opportunists that can cause infections in humans & animals

**Acanthamoeba: incidence, outcome and risk factors: England/Wales 97-99**

106 cases, 88% CL wearers
1.1 & 1.3 / million adult population
17.5 & 21.4 / million CL wearers
CL wearers: south vs north – x 9 risk
Hard vs soft domestic $H_2O$ - x 3 risk

**<u>Diverse presentation of acanthamoeba keratitis</u>**

Common **symptoms** include:
- Redness
- watering
- Disproportionate pain
- Severe photophobia
- Foreign body sensation
- Decreased visual acuity

Common **signs** include:
- Punctate staining
- epithelial defects
- stromal infiltrates
- ring infiltrate
- **radial keratoneuritis**
- decreased sensation

**Clinical Presentation - Have a high index of suspicion**

Careful history should raise suspicion
Often a delay in making diagnosis, frequently mistaken for HSV keratitis
Treatment aggressive & extensive – therefore must achieve microbiological diagnosis prior to Rx

**Reduced time to diagnosis**

Time to diagnosis 1985 - mean 180 days 1992 - mean 9.3 days
70-75% misdiagnosed HSV

**Establishing the diagnosis 2**
Diagnosis - culture and via polymerase chain reaction (PCR) of corneal scrapings
Useful to culture contact lenses/cases
*in vivo* confocal microscopy has been utilized to detect the amoeba or *acanthamoeba* cysts

**Treatment of *acanthamoeba* Successful treatment requires**
Early diagnosis
Aggressive medical & surgical therapies
Medical treatment with topical antimicrobial agents
As cyst form may be highly resistant a combination of drugs used
Therapeutic agents
Combination therapy incorporating 2 of the 3 following topical agents:
**Chlorhexidine**
**Propamidine Isethionate** [Brolene]
**Polyhexamethylene biguanide** [PHMB]

**Prognosis**
*Acanthamoeba* keratitis has a good outcome if detected and treated early
Late diagnosis has poor prognosis for vision & disastrous outcomes including:
Ongoing infection,
Permanently reduced vision
Need for corneal transplantation.

**Centres for Disease Control (CDC) Acanthamoeba update 2007**
08/01/07 recall of AMO solution product
COMPLETE MoisturePLUS Multi-purpose Contact Lens Solution
Of 102 people with AK included in the preliminary analysis of June 2007

## Corticosteroids & microbial keratitis

1. May mask presentation & delay appropriate management of severe keratitis, particularly acanthamoeba

2. Topical steroids shown to be a significant risk factor in severe keratitis requiring hospitalization

**The evidence-based literature on corticosteroids & microbial keratitis**

Experimental models suggest possible advantages

However, clinical studies show no significant effect!

Prior use of corticosteroids predisposes:

| | |
|---|---|
| Eyes with corneal disease to MK | Odds Ratio 2.63 |
| Eyes with MK to treatment failure | Odds Ratio 3.75 |

**Using steroids wisely (and extremely rarely) – *red flag***

As a general rule steroids should be avoided in microbial keratitis
Be certain of diagnosis – do not simply use because no response to Rx
Always consider re-scrape
Identify drug sensitivities
*Only consider if infective agent identified and specificity of Rx confirmed and in conjunction with an ophthalmologist*
Observe 3-4 days of definite response to anti-microbials
Introduce as weak potency limited regimen - watch for corneal thinning

**Poor prognostic features of microbial keratitis**

Severe dry eye
Neurotrophic cornea
Central or paracentral location
3mm or greater diameter ulcer
Fungal ulcer
Prior use of steroids
Late referral

**Surgical interventions in severe microbial keratitis**

Remove involved sutures
Diagnostic biopsy
Lid surgery
Punctal occlusion
Penetrating keratoplasty
Evisceration/enucleation

**Prevention of severe microbial keratitis**

Appropriate contact lens care
Avoidance of steroid missuse
Management of epithelial trauma
Patient education post surgery
Routine corneal suture removal
Intensive attempts to isolate organism
Intensive early anti-microbial therapy