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## Infectious Keratitis

Rochester Ophthalmology Conference  
March 18, 2016

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UNIVERSITY of ROCHESTER  
MEDICAL CENTER

### Case Presentation

**ID:** 35yo Female

**CC:** irritated, itching, discharge, tearing from the left eye

**HPI:** Several days of increasing irritation of the left eye. No recent injuries, although endorses rubbing for itching. Wears monthly contact lenses and takes them out "most nights."

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### Case Presentation

**POChx:** Refractive error - contact lens wearer for 10 years

**PMHx:** none

**SH:** Smokes socially

**FH:** non-contributory

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### Exam

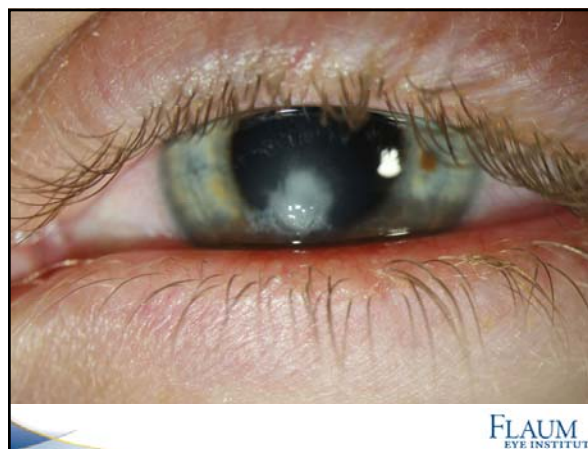
	OD	OS
Visual acuity (BCVA)	20/20	20/70
IOP	10	11
Pupils	PERRLA	PERRLA
EOM	Full	Full

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### Slit Lamp Exam

	OD	OS
Lids/Lashes	normal	Mild swelling and redness
Conjunctiva/Sclera	White and quiet	1+ injection
Cornea	Normal, contact lens in place	2mm x 3.5mm area of opacity with surrounding infiltrate just outside of visual axis inferiorly, underlying stromal edema, overlying 2mm area of epi defect
Anterior Chamber	Deep and quiet	1+ cell
Iris	Normal shape, size, morphology	Normal shape, size, morphology
Lens	clear	clear
Vitreous	clear	clear

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Diagnosis: **Infectious Keratitis**  
(Corneal Ulcer)

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## Epidemiology

US based studies in 1950s-1980s: 11.0 per 100,000 people

Recent studies: 20.9 to 27.6 per 100,000 person-years

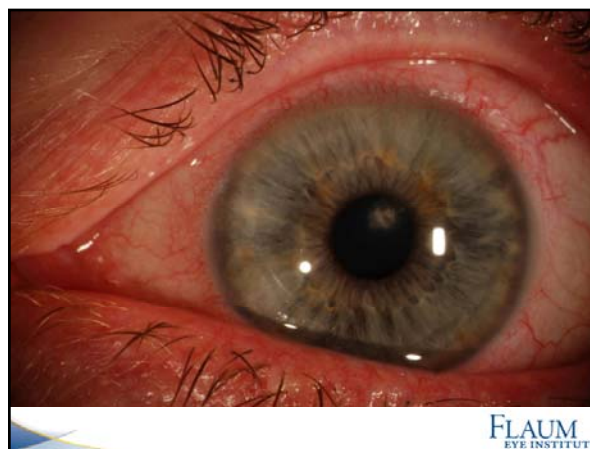
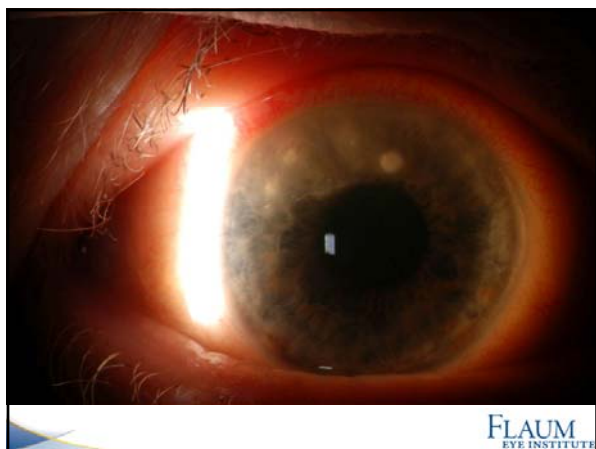
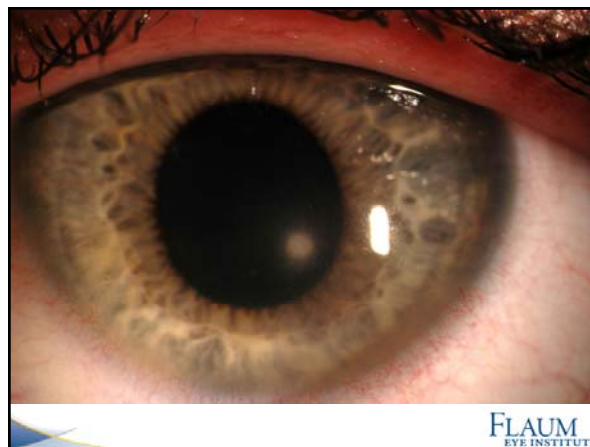
Contact lens wearers: 130.4 per 100,000 person-years

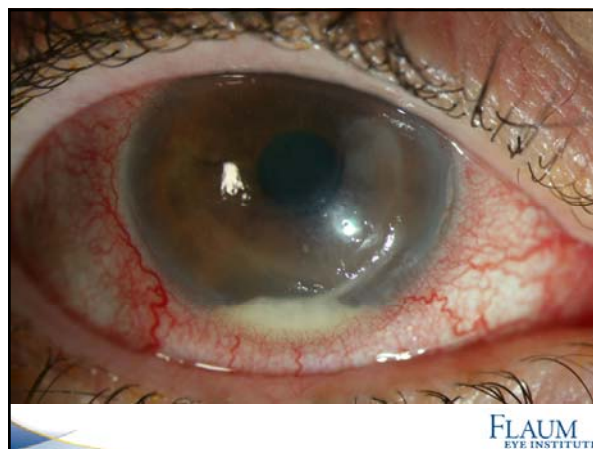
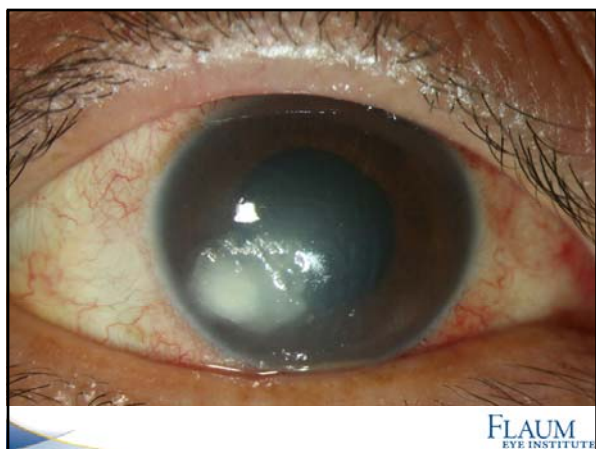
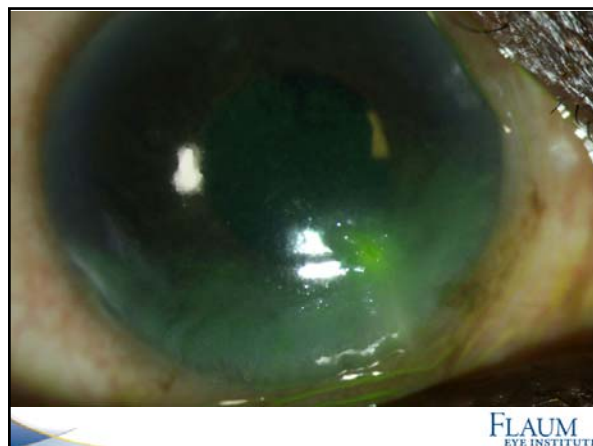
38.5 million contact lens wearers in the US

**Contact lens wear is the single greatest risk factor for developing keratitis in the United States**

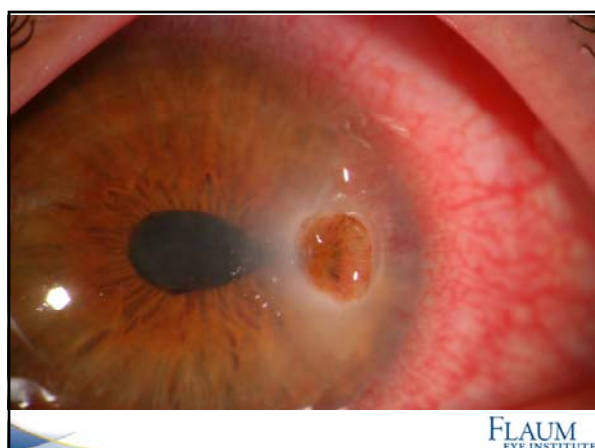
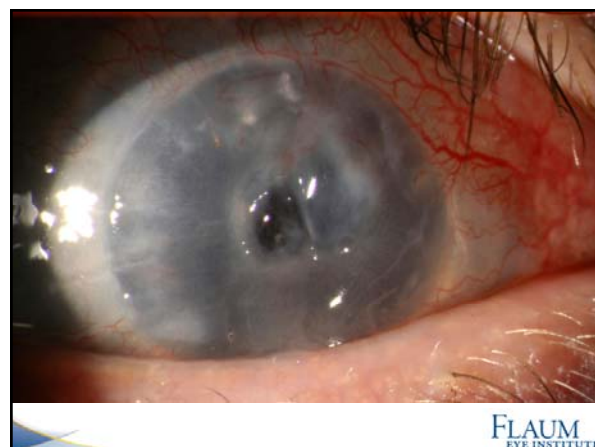
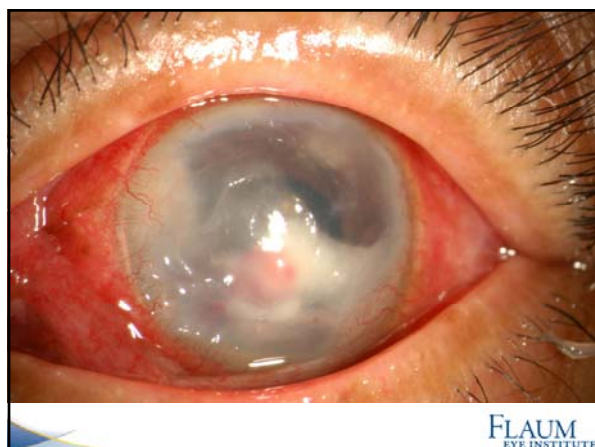
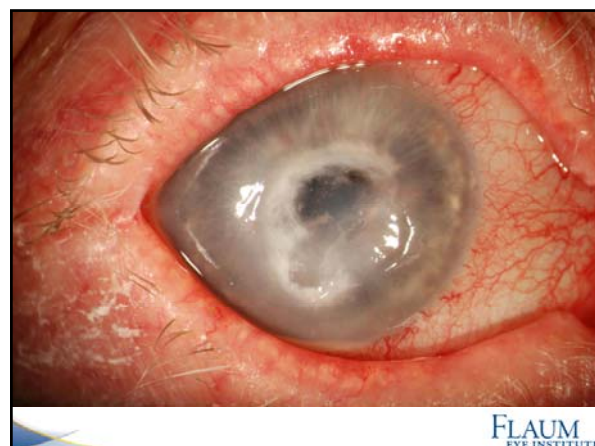
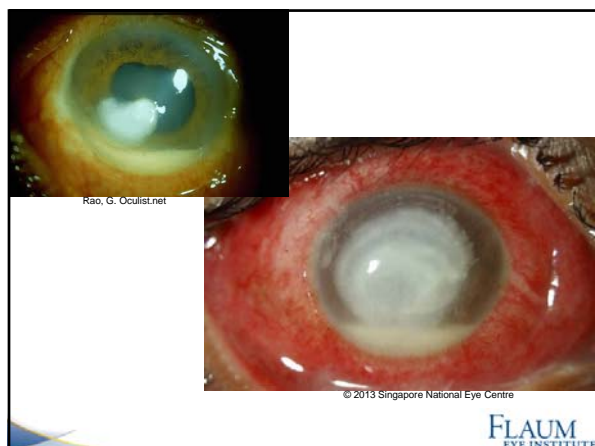
Erie, J. C., Nevitt, M. P., Hodge, D. O. & Ballard, D. J. Incidence of ulcerative keratitis in a defined population from 1950 through 1988. *Arch. Ophthalmol.* 111, 1665-71 (1993).  
Jeng, B. H. et al. Epidemiology of ulcerative keratitis in Northern California. *Arch. Ophthalmol.* 128, 1022-8 (2010).  
Ibrahim, Boase & Cree. Incidence of Infectious Corneal Ulcers, Portsmouth Study, UK. *J Clin Exp Ophthalmol* (2012). Doi 10.4172/2155-9570.56-001  
Dart, J. K., Stapleton, F. & Minassian, D. Contact lenses and other risk factors in microbial keratitis. *Lancet* 338, 650-3 (1991)

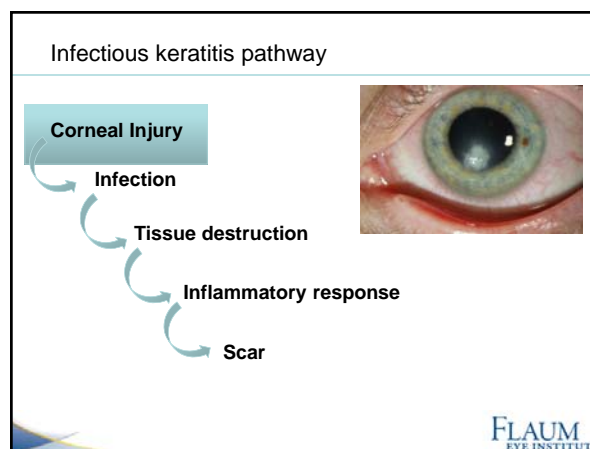
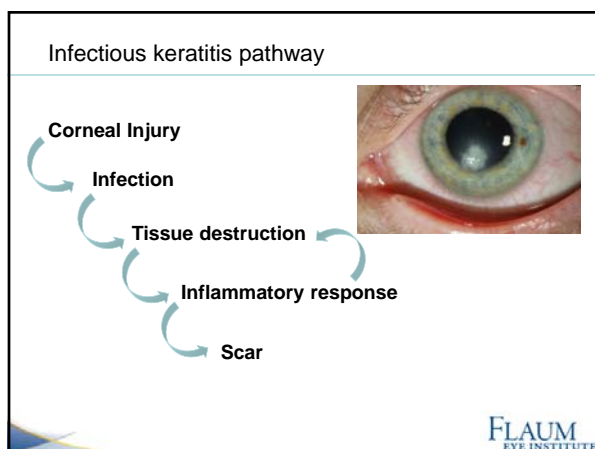
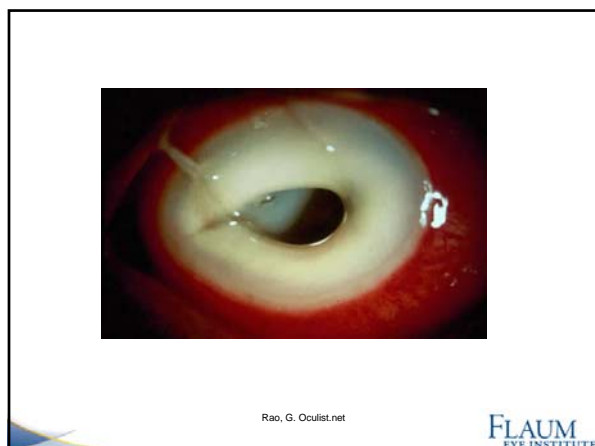
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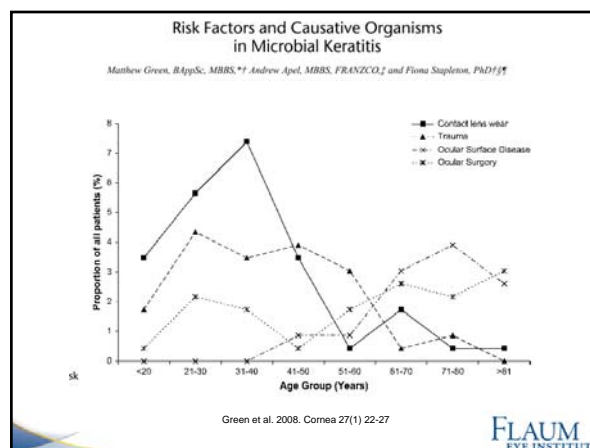


**Healthy eyes do not develop spontaneous keratitis!**

**Need to have a compromised ocular surface:**

- Direct injury (trauma, surgery)
- Any eye disease that leads to breakdown of the surface
  - Dry eye
  - Recurrent erosions
  - Corneal dystrophies
  - Corneal edema
  - Herpetic infections
- Patients who don't heal well
  - Diabetics
  - Immunocompromised
  - Elderly

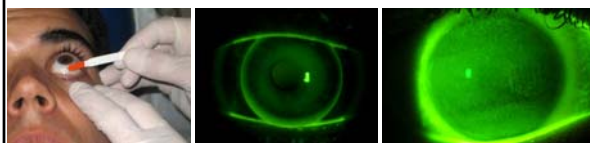
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## Why are contact lens wearers at higher risk?

What does contact lens wear do to the eye?

- Dry eye
- Micro-trauma
- Allergy
- Inflammation
- Brings microorganisms to the surface for prolonged periods of time



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## Infectious keratitis pathway

Corneal Injury

Infection

Tissue destruction

Inflammatory response

Scar



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Bacterial



www.nesta.org.uk



Nocamels.com

Fungal



Photo by Alena Kubatova www.microbeworld.org



Viral

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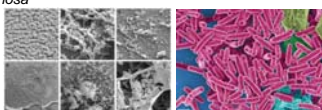
## Bacterial Causative Agents

Often reflect the **normal flora** of the ocular surface (gram-positive)

- coagulase-negative *Staphylococci*
- Staphylococcus aureus*
- Streptococcus* sp.
- Corynebacterium*

If gram-negative organisms are identified:

- Pseudomonas aeruginosa*
- Serratia marcescens*
- Moraxella* sp.



Green, M., Apel, A., & Stapleton, F. Risk factors and causative organisms in microbial keratitis. *Cornea* 27, 22-7 (2008)  
 Ni, W. et al. Seasonal, geographic, and antimicrobial resistance patterns in microbial keratitis: 4-year experience in eastern Pennsylvania. *Cornea* 34, 296-302 (2015)  
 Stapleton, F. & Carmi, N. Contact lens-related microbial keratitis: how have epidemiology and genetics helped us with pathogenesis and prophylaxis. *Eye (Lond)* 26, 185-93 (2012).  
 Alexandrakis, G., Alfonso, E. C. & Miller, D. Shifting trends in bacterial keratitis in south Florida and emerging resistance to fluoroquinolones. *Ophthalmology* 107, 1487-92 (2000).  
 Pandita, A. & Murphy, C. Microbial keratitis in Waikato, New Zealand. *Clin. Experiment. Ophthalmol.* 39, 393-7 (2011)

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## Infectious keratitis pathway

Corneal Injury

Infection

Tissue destruction

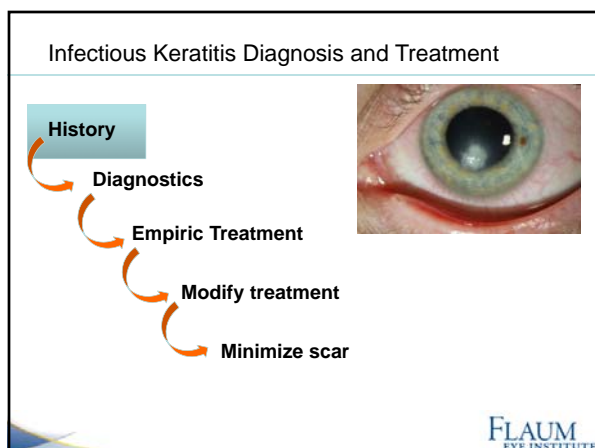
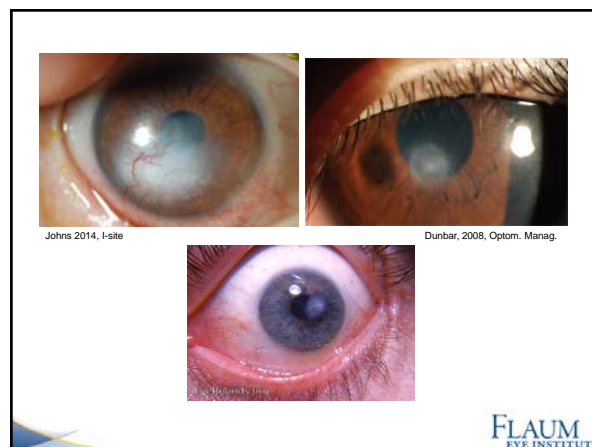
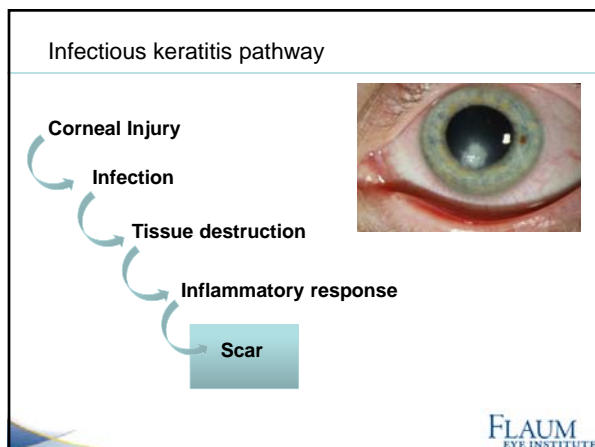
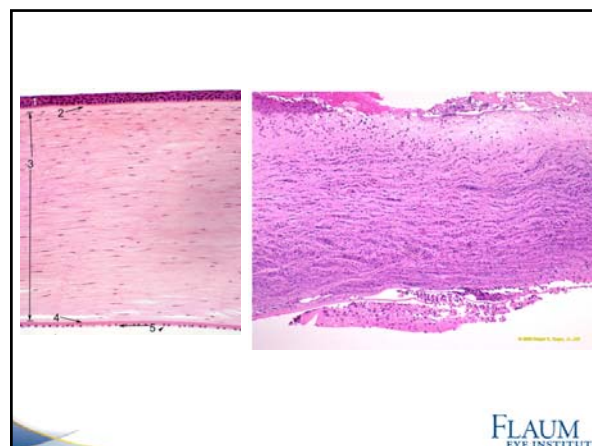
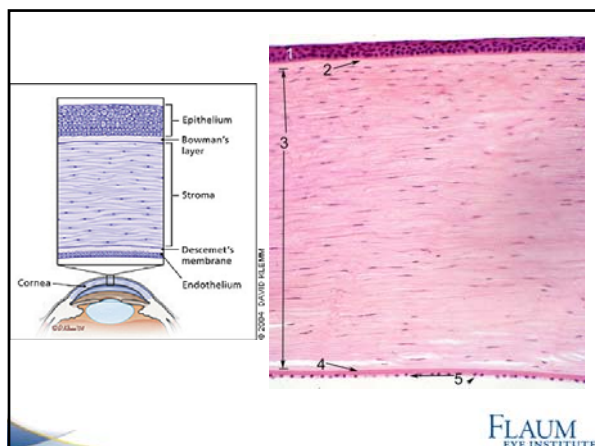
Inflammatory response

Scar



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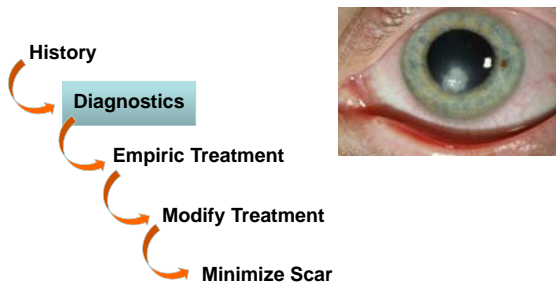
### History

*Spontaneous keratitis in a healthy eye does not occur!*

- Contact lens use?
- Trauma? (accidental or surgical)
- Underlying ocular history
  - Herpetic disease
  - ABMD/corneal erosions
  - dry eye
  - neurotrophic cornea
- Underlying medical history
  - Diabetes
  - immune status
  - recent illness
- Tempo of disease
  - rapidly evolving vs indolent
  - pain
  - degree of vision loss

The FLAUM EYE INSTITUTE logo is at the bottom right.

### Infectious Keratitis Diagnosis and Treatment



**History**

**Diagnostics**

**Empiric Treatment**

**Modify Treatment**

**Minimize Scar**

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### To culture or not to culture...

Many cases in the community are treated empirically without culture

**AAO guidelines:**

- Large ulcer
- Centrally located,
- Involving mid or deep stroma
- Infection that has not been responsive to initial treatment
- Atypical features which may indicate fungal, amoebic or mycobacterial keratitis

Hsu, H. Y. et al. Community opinions in the management of corneal ulcers and ophthalmic antibiotics: a survey of 4 states. Eye Contact Lens 26, 195-200 (2010). American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Bacterial Keratitis. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp

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### Culture Options

- Gram stain (slide)
- Aerobic culture
  - Tryptan soy broth
  - Blood agar
  - Chocolate: Neisseria, haemophilus
- Aerobic culture: Thioglycolate broth
- Fungal: potato dextrose plate and smear
- Mycoplasma (TB): agar in a tube (Middlebrook/Lowenstein)
- Acanthamoeba: e coli overlay plate on agar
- Viral culture: UTM (universal transport media)

**Yield of cultures 40-60%**

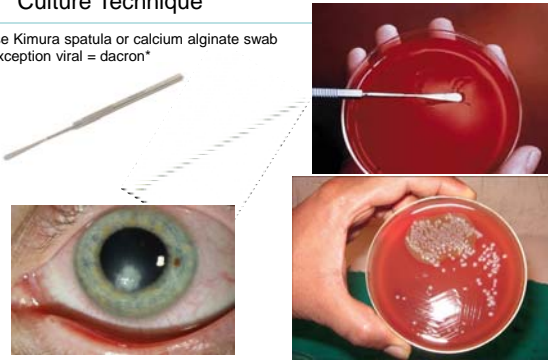
Delayed cultures does NOT decrease yields – may take longer to recover pathogens

Ni, N. et al. Seasonal, geographic, and antimicrobial resistance patterns in microbial keratitis: 4-year experience in eastern Pennsylvania. Cornea 34, 298-302 (2015). Levey, S. B., Katz, H. R., Abrams, D. A., Hirschbein, M. J. & Marsh, M. J. The role of cultures in the management of ulcerative keratitis. Cornea 16, 383-6 (1997).

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### Culture Technique

Use Kimura spatula or calcium alginate swab  
\*exception viral = dacron\*




Indian Journal of Medical Microbiology, Vol. 27, No. 2, April-June, 2009, pp. 159-161

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### Tissue biopsy

Advantages: tissue for culture and histopathology  
Disadvantages: risk of procedure (perforation)



**Microbiologic and Histopathologic Assessment of Corneal Biopsies in the Evaluation of Microbial Keratitis**

JARED R. YOUNGER, R. DUNCAN JOHNSON, GARY N. HOLLAND, JON P. PAGE, RICHARD L. NEPOMUCENO, BEN J. GLASGOW, ANTHONY J. ALDAYE, FEE YU, JASON LITAK, AND BARTLY J. MONDINO, ON BEHALF OF THE UCLA CORNEA SERVICE

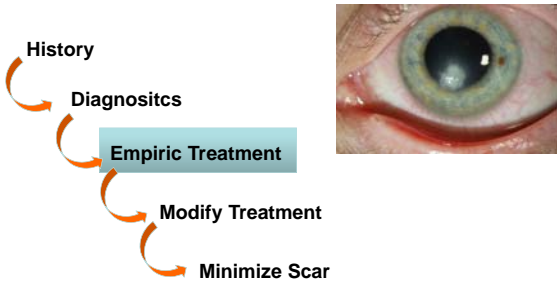
Causal agent was identified in 42% of cases either with culture or histopathologic examination

44% of patients had initial negative cultures from corneal scrapings

Complication rate: 3/53 perforation (6%)

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### Infectious Keratitis Diagnosis and Treatment



**History**

**Diagnostics**

**Empiric Treatment**

**Modify Treatment**

**Minimize Scar**

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## Empiric Treatment

Don't wait for culture data/gram stain

### Empiric treatment: BROAD SPECTRUM

Fluoroquinolones: well tolerated, good ocular penetration

Currently use: **FOURTH GENERATION (Vigamox)**  
Excellent gram-negative, including Pseudomonas  
Good gram-positive

Initial treatment regimen is INTENSE:  
every 30min-every 1 hour AROUND THE CLOCK

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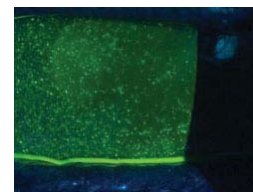
## Fortified antibiotics

### Gram negative coverage:

-Tobramycin  
-Gentamycin

### Gram-positive coverage:

-Vancomycin  
-Cefazolin

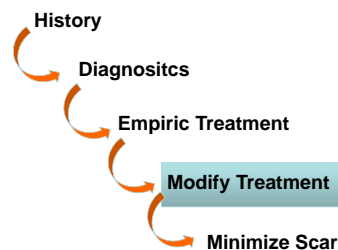


**Advantages:** Better coverage

**Disadvantages:** difficult to obtain, limited shelf life, ocular toxicity

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## Infectious Keratitis Diagnosis and Treatment



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## Resistance

2008 Ocular Tracking Resistance in US Today (TRUST)  
2009 Antibiotic Resistance Monitoring in ocular Microorganisms (ARMOR)

Across early fluoroquinolones:  
Methicillin-sensitive *S. aureus* (MSSA) susceptibility 80%  
Methicillin-resistant *S. aureus* (MRSA) susceptibility 15%

Ophthalmology Volume 107, Number 8, August 2003

Table 5. In Vitro Resistance of Tested Bacterial Isolates to Fluoroquinolones (Ofloxacin and Ciprofloxacin)

	1990		1991		1992		1993		1994		1995		1996		1997		1998		Total
	% Resistant		% Resistant		% Resistant		% Resistant		% Resistant		% Resistant		% Resistant		% Resistant		% Resistant		% Resistant
Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total	Total
Neophthia/acetaminophen	27	11	26	7	20	15	27	7	27	8	27	8	32	16	37	33	32	28	262
Pseudo	51	0	53	2	44	2	32	0	41	0	33	3	50	0	27	0	32	0	145

Asbell, P. A. et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. *Am. J. Ophthalmol.* 145, 951-958 (2008).  
Haas, W., Pillar, C. M., Torres, M., Morris, T. W. & Sahm, D. F. Monitoring antibiotic resistance in ocular microorganisms: results from the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) 2009 surveillance study. *Am. J. Ophthalmol.* 152, 567-574.e3 (2011).  
Alexandrakis, G., Haimovici, R., Miller, D. & Alfonso, E. C. Corneal biopsy in the management of progressive microbial keratitis. *Am. J. Ophthalmol.* 129, 571-6 (2000).

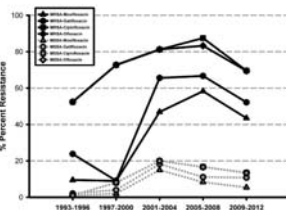
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## Antibiotic Resistance in the Treatment of *Staphylococcus aureus* Keratitis: a 20-Year Review

Victoria S. Chang, MD, Deepinder K. Dhalwani, MD, LAc, Leela Raju, MD, and  
Regis P. Kowalski, MS, M(ASCP)

TABLE 2. Resistance Rates of MSSA and MRSA to Commonly Used Topical Ophthalmic Antibiotics From 1993 to 2012

Antibiotic	MSSA	MRSA	P (χ <sup>2</sup> )
Bacitracin	2.2%	16.7%	0.0001
Cefazolin	0.7%	33.6%	0.0001
Gentamicin	2.2%	13.9%	0.0001
Polymyxin B	97.5%	100.0%	0.076
Sulfamethoxazole	1.1%	5.7%	0.008
Tobramycin	7.6%	60.7%	0.0001
Trimethoprim	1.1%	11.5%	0.0001
Ciprofloxacin	10.1%	73.8%	0.0001
Ofloxacin	11.2%	74.6%	0.0001
Moxifloxacin	5.9%	35.2%	0.0001
Gatifloxacin	4.3%	45.9%	0.0001
Vancomycin	0.0%	0.0%	—



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## Emerging Pseudomonas Resistance

### Draft Genome Sequences of Two Drug-Resistant Isolates of *Pseudomonas aeruginosa* Obtained from Keratitis Patients in India

Ramesh K. Aggarwal,\* Chhavi Dawar,\* Satrupa Das,\* Savitri Sharma\*

Centre for Cellular & Molecular Biology (CCMB), Hyderabad, India; \*Indian Eye Research Centre, Hyderabad Eye Research Foundation, L.V. Prasad Eye Institute (LVPEI), L.V. Prasad Marg, Banjara Hills, Hyderabad, India\*

### Rational treatment strategies:

Double coverage? – using a multidrug approach similar to HIV or TB

Adding better gram+ coverage

Vigamox with fortified vancomycin/cefazolin

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## Infectious Keratitis Diagnosis and Treatment

### History

### Diagnostics

### Empiric Treatment

### Modify Treatment

### Minimize Scar



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## Steroids in Corneal Ulcers

**Benefits:** suppressing inflammation → reduce scarring

**Disadvantages:** increase in infection burden, increase risk of corneal melting, elevated IOP

Meta-analysis of existing trials (including SCUT):

**No benefit nor disadvantage with respect to:**

- Visual acuity
- re-epithelialization
- quality of life
- adverse affects

Herretes, S., Wang, X. & Reyes, J. M. Topical corticosteroids as adjunctive therapy for bacterial keratitis. *Cochrane Database Syst Rev* 10, CD005430 (2014).

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### Original Investigation

## Early Addition of Topical Corticosteroids in the Treatment of Bacterial Keratitis

Kathryn J. Ray, MA; Muthiah Srinivasan, MD; Jeena Mascarenhas, MD; Revathi Rajaraman, MD; Meenakshi Ravindran, MD; David V. Glidden, PhD; Catherine E. Oldenburg, MPH; Catherine Q. Sun, BS; Michael E. Zegans, MD; Stephen D. McLeod, MD; Nisha R. Acharya, MD; Thomas M. Lietman, MD

Sub-analysis of SCUT trial data:

3 month best spectacle-corrected acuity

**Steroids: 3 days within diagnosis vs 4 or more days**

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### Severe ulcers:

- 3 line improvement if administered within 2-3 days ( $p=.02$ )
- 2 line improvement if administered after 4 days ( $p=.17$ )

### Moderate ulcers:

- 1 line improvement if administered with 2-3 days ( $p=.09$ )
- 2 lines worse if administered after 4 days ( $p=.01$ )

### Mild ulcers:

- No significant improvement compare to placebo
- 2 lines worse if administered after 4 days ( $p=.01$ )

Severe: CF vision  
Moderate: 20/40-20/800  
Mild: <20/40

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## Conclusions

- Corneal ulcers require prompt evaluation and treatment
- Obtain thorough history – remember healthy eyes do not develop keratitis
- Cultures and smears should be obtained, even if treatment has started
- Antibiotic resistance is prevalent – fortified antibiotics give the broadest coverage, particularly for gram positive organisms
- Steroids may provide some benefit with respect to scarring if initiated early

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## Thank You



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