



1



2

The typical story..

The contact lens wearer..

..who sometimes sleeps in their lenses..

..and who thinks their 2-week lens is a monthly-replacement..

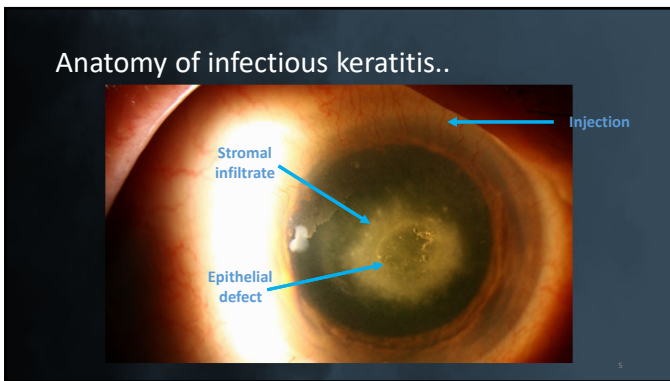
3

Incidence of infectious keratitis

- CDC estimated nearly 1 million annual visits to ophthalmology offices or ED for *keratitis* (2010)¹
- Population-based study (1998-1999)²
 - 27.6 per 100,000 person-years in non CL wearers
 - 130.4 per 100,000 person-years in CL wearers


1. Center for Disease Control. <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm9634a3.htm>. 2. Jang BH, Gritz DC, Kumar AS, Melickewitz DS, Powell TC, Smith SP, Whitcher JP, Margolis TP, Wong IG. Epidemiology of Ulcerative Keratitis in Northern California. *Arch Ophthalmol*. 2010;128(8):1022-1028. doi:10.1001/archophthol.128.8.1022

4



5

How do corneal ulcers occur?



1. Corneal defenses are violated
2. Opportunistic pathogen invades
 - Virulent invading organism
 - Normal ocular flora

6

Risk Factors

7

Risk Factors

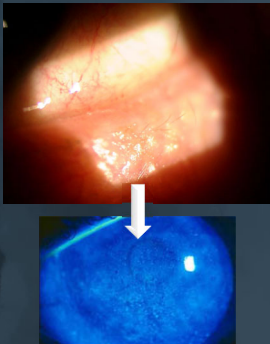
- Contact lens wear
 - Soft > rigid gas permeable
 - Extended > daily wear



8

Risk Factors

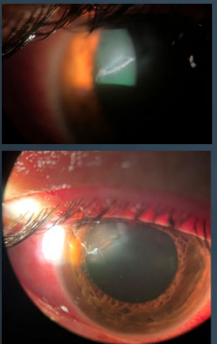
- Contact lens wear
- Epithelial breakdown
 - Dry eye
 - Bullous keratopathy
 - Hydrops
 - Neurotrophic keratitis



9

Risk Factors

- Contact lens wear
- Epithelial breakdown
- Trauma or corneal surgery
 - Corneal abrasions
 - Recurrent corneal erosion
 - Foreign body
 - Vegetative matter?
 - Etc



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Risk Factors

- Contact lens wear
- Epithelial breakdown
- Trauma or corneal surgery
- Eyelid disease
 - Trichiasis
 - Facial nerve palsy
 - Ectropion or entropion



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Risk Factors

- Contact lens wear
- Epithelial breakdown
- Trauma or corneal surgery
- Eyelid disease
- Systemic disease and immunocompromise
 - Rheumatologic disease
 - Iatrogenic (i.e. chemo)
 - HIV/AIDS
 - Diabetes

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Risk Factors

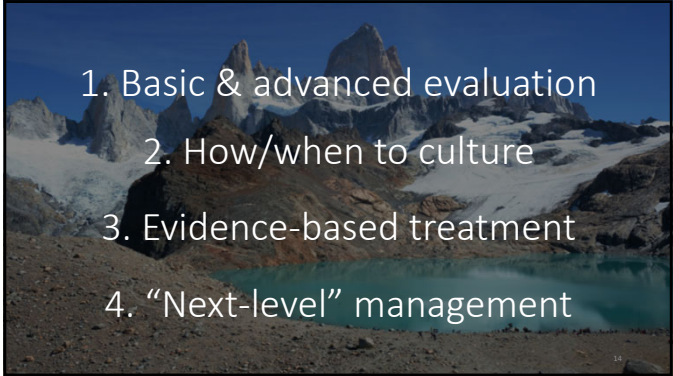
- Contact lens wear
- Epithelial breakdown
- Trauma or corneal surgery
- Eyelid disease
- Systemic disease and medical immunosuppression
- Geography
 - Hot/humid areas → fungal infections!

Rosa J RH, Miller D, Alfonso EC. The Changing Spectrum of Fungal Keratitis in South Florida. Ophthalmology 1994; 101(6): 1005-1012. Jafarzade S, Bahmani L, Chahk E. Fungal Keratitis: Changing patterns and risk factors. F1000 Res 2019; 8:1-10.


13

1. Basic & advanced evaluation
2. How/when to culture
3. Evidence-based treatment
4. "Next-level" management



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First things first:
The armchair quarterback




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Slit Lamp Examination



17

Pertinent Findings
Location
Epithelial defect
Presence of infiltrate(s)
Stromal edema
Stromal thinning
Anterior chamber
Keratic precipitates
Intraocular pressure
Perineuritis
Eye Pain
Eye Sensitivity

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Sterile vs **Infectious**

<p>Mild Pain Peripheral Small Multiple and arcuate Epithelium intact AC quiet No discharge and watery Mild injection</p>	<p>Moderate to Severe Pain Central Large Individual Full defect AC reaction Mucopurulent discharge Red, injected eye</p>
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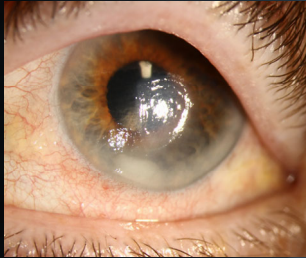
Location, location, location!

- Central –likely more virulent pathogen
- Peripheral – more likely staph marginal



20

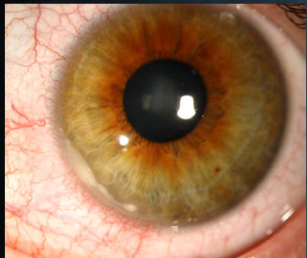
Infiltrate



- Presence or absence!
- What do the borders look like?
 - Hazy/feathered → think fungal
- Multiple infiltrates may be seen in satellite, atypical, or staph species

21

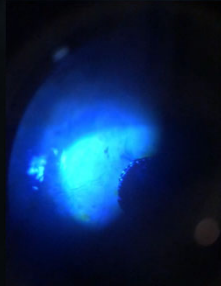
Epithelial defect



- Relative size compared to infiltrate?
- Monitor for response to treatment

22

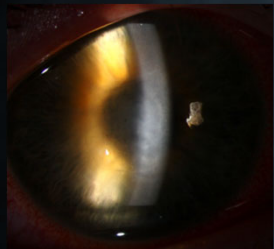
Stromal thickness



- Corneal edema is common
- Watch areas of thinning very closely

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Stromal thickness



- Corneal edema is common
- Watch areas of thinning very closely
- Excessive edema?
 - Think HSV!

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Case in point: 44 yo Hispanic male

Always keep HSV in the back of your mind!

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Anterior chamber

- AC reaction \neq infection
- Hypopyon may be present in severe cases
- Granulomatous KPs could suggest herpetic
- Grade at each visit

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Pain / Sensation

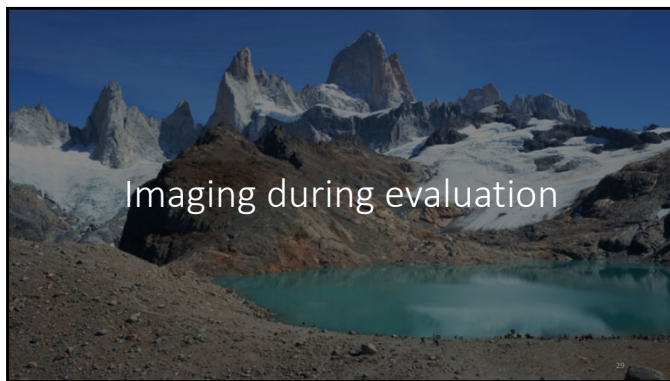
- Critical question!!
- Less than expected?
 - Check sensitivity in clinic!
 - Consider neurotrophic or herpetic
- More than expected?
 - Consider acanthamoeba

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Perineuritis

- Uncommon finding
- Hallmark of acanthamoeba

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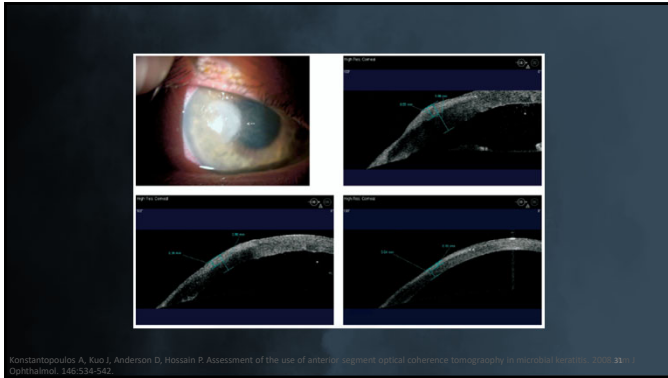
29

Anterior segment OCT

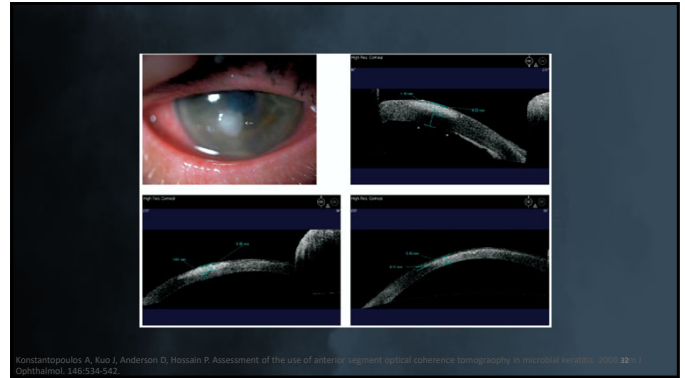
- Supportive tool in diagnosis and management, including objective treatment response, of microbial keratitis^{1,2}
- Best results with high resolution

1. Konstantopoulos A, Kuo J, Anderson D, Hossain F. Assessment of the use of anterior segment optical coherence tomography in microbial keratitis. 2018. *Am J Ophthalmol*. 146:534-542. 2. Soliman W, Farhat A, El-Sedaily D, Al-Hussaini A. Spectral domain anterior segment optical coherence tomography in acute. *Arab Clin Exp Ophthalmol*. 2011; 2(1):49-55.

30



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TABLE. Summary of Corneal Infiltrate Characteristics

Case No.	Patient Age (yrs)	Risk Factor	Location	Presentation AS OCT Infiltrate Thickness (µm)	Presentation AS OCT Corneal Thickness at Infiltrated Area (µm)	Final AS OCT Infiltrate Thickness (µm)	Final AS OCT Corneal Thickness at Infiltrated Area (µm)
1	29	CL wear	ST	190	800	110	650
2	63	CL wear	Inferior	130	670	120	590
3	35	RCES	IT	370	910	250	610
4	57	CL wear	Central	530	1180	170	450
5	60	CL wear	Temporal	590	1590	160	540
6	72	Trichiasis, lagophthalmos	Central	3640*	NP*	0*	190
7	61	CL wear	Central	370	800	630	630

AS OCT = anterior segment optical coherence tomography; CL = contact lens; IT = inferior temporal; RCES = recurrent corneal erosion syndrome; ST = superior temporal; yrs = years.
 *In Case 6, measurements refer to AS OCT inflammatory plaque width; infiltrate thickness could not be measured.
 *In Case 6, measurement of corneal thickness was not possible at presentation, because the endothelium could not be distinguished clearly from the endothelial inflammatory plaque.

Konstantopoulos A, Kuo J, Anderson D, Hossain P. Assessment of the use of anterior segment optical coherence tomography in microbial keratitis. 2008; 33: 1. Ophthalmol. 146:534-542.

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Example OCT findings:

1. Stromal infiltrate
2. Epithelial defect
6. Small stromal cystic spaces*
7. Full thickness cystic spaces* (necrosis)
9. Desmetocele
10. Stromal scar

*Cystic spaces were found to be present for fungal etiologies

Soliman W, Fathalla A, El-Sebasty D, Al-Hussaini A. Spectral domain anterior segment optical coherence tomography in microbial keratitis. Arch Clin Exp Ophthalmol. 2013; 25(1):546-553.

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May help differentiate residual scarring from active infection.

- Intact epithelium
- Anterior stromal hyperreflectivity without stromal thickening
- Hyperreflectivity with compact stroma and mild thinning

Soliman W, Fathalla A, El-Sebasty D, Al-Hussaini A. Spectral domain anterior segment optical coherence tomography in microbial keratitis. Arch Clin Exp Ophthalmol. 2013; 25(1):546-553.

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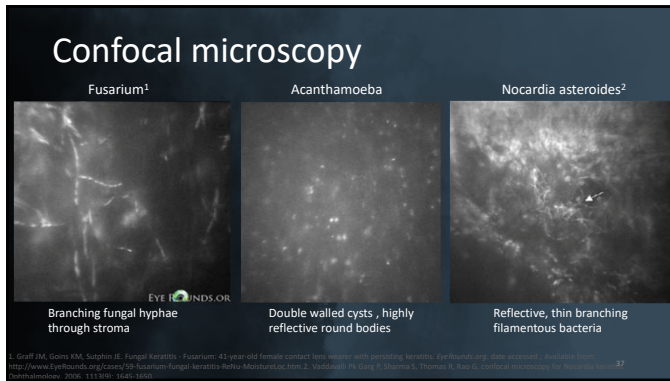
Confocal microscopy

Supportive tool in diagnosis of **atypical** microbial keratitis

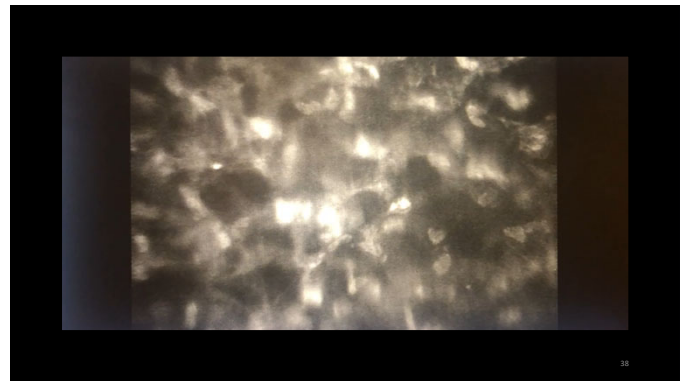
- Pros:
 - Excellent magnification allows in vivo visualization of corneal planes
- Cons:
 - Acquiring and interpreting images is challenging and requires experience

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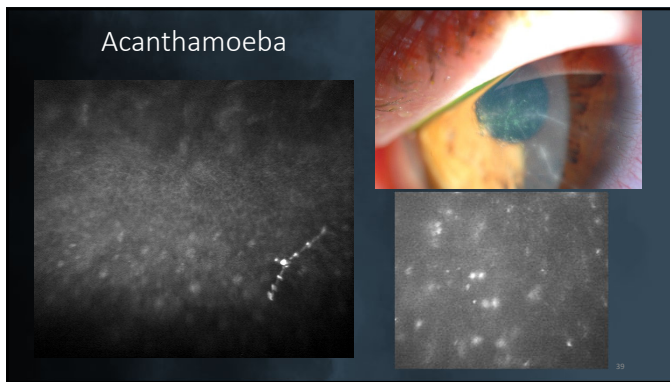
36



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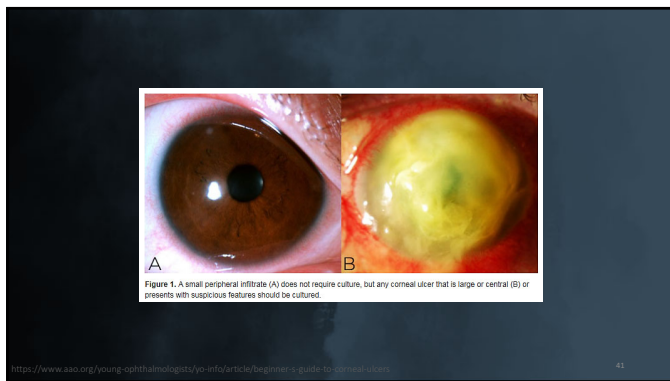
38



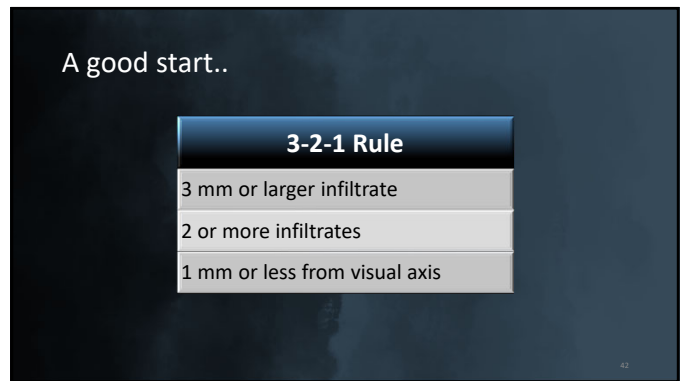
39



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Realistic recommendations

1. Central lesions that threaten vision
2. Risk of perforation
3. Scleral tissue involvement
4. Lesion is not responding to treatment
5. Infiltrate after injury with vegetative matter
6. Institutionalized patients where MRSA is possible
7. Atypical features suggestive of fungal, amoebic, or mycobacterial

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How do I culture?

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Single Sample

Multiple Sample

Biopsy

Also known as "Quick Culture"

1. Use swab to inoculate transport media
2. Send to pre-specified lab
3. Lab inoculates multiple plates



No significant difference in growth compared to direct plating¹
May be less cumbersome for small practices²


Michelle SD, Kumar A, Cavallio V, Srivastava M, Whitcher J. Reliability of transport medium in the laboratory evaluation of corneal ulcers. Am J Ophthalmol. 2005 Dec; 140(6): Pg 1007-1011. 2. Pankaj S, Saini R, Laxmi S, et al. The comparative one-touch study: a simplified microbiologic specimen collection method. Am J Ophthalmol. 2023; 258: 1-12.

45

Single Sample

Multiple Sample

Biopsy



Blood
Most bacteria
Aerobic
Fungi

Chocolate
Haemophilus
Neisseria
G (-)

Sabouraud
(or potato dextrose)
Fungi

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Single Sample

Multiple Sample

Biopsy

PCR
Acanthamoeba
HSV

Thioglycollate
Anaerobic
bacteria

Slides
Gram stain
Fungal

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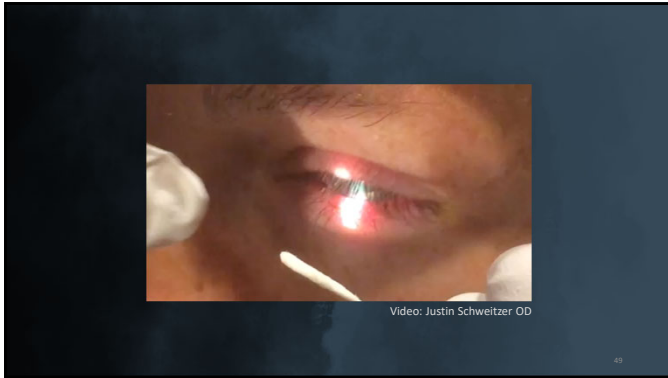
Single Sample

Multiple Sample

Biopsy

- Pathology specimen gathered by ophthalmologist via
 - Blade or trephine
 - Suture pass
- Reserved for treatment-unresponsive
- Examination done by **pathology** laboratory

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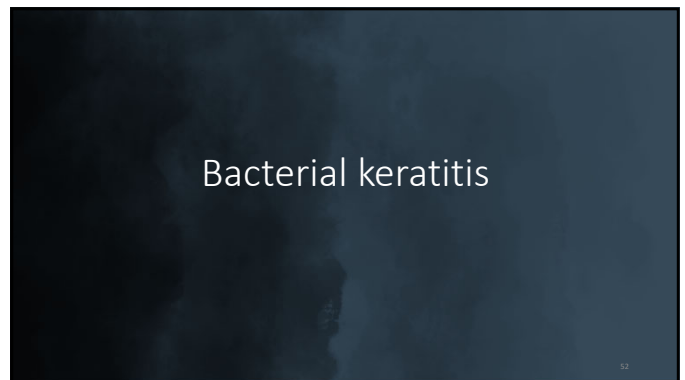
49



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Bacterial keratitis

- The most common pathogens we will see!
- North America: staphylococcus aureus (G+)
- Contact lens: pseudomonas aeruginosa (G-)

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Bacterial keratitis

This process can be:


- Directly related to the pathogen
- Mediated by the host immunogenic response

54

How does the literature guide our management of bacterial keratitis?

55

Resistance is on the rise



Early generation fluoroquinolones
Especially for G (+)

↑

1. Schaefer F, Bruttin O, et al. Bacterial keratitis: a prospective clinical and microbiological study. Br J Ophthalmol. 2001;2. Alkharji H, et al. Trends in resistance to ciprofloxacin....J Ocul Pharmacol Ther. 2008.

56

Prospective Surveillance Studies

- TRUST 2008^{1,2,3}
(Ocular Tracking Resistance in the US Today)
- ARMOR 2009-2018⁴
(Antibiotic Resistance Monitoring in Ocular Microorganisms)

1. Ashbell PA, Colby KA, Deng S, et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. Am J Ophthalmol. 2008;145(6):951-958. 2. Ashbell PA, Sahm DE. Longitudinal nationwide antimicrobial susceptibility surveillance in ocular isolates: results from Ocular TRUST 3. Presented at: American Society of Cataract and Refractive Surgery Annual Meeting; April 26, 2008; San Diego, CA. 3. Ashbell PA, Sahm DE, Shadron A. Ocular TRUST 3: ongoing longitudinal surveillance of antimicrobial susceptibility in ocular isolates. Presented at: American Society of Cataract and Refractive Surgery Annual Meeting; April 7, 2009; San Francisco, CA. 4. Ashbell PA, Sahm DE, Sahm DE, DeCory JH. Trends in antibiotic resistance among ocular microorganisms in the United States from 2009 to 2018. JAMA Ophthalmol. 2020;138(11):438-450.

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Ocular TRUST (2005-2008)

Ocular Tracking Resistance in the US Today

1. *S. aureus* methicillin resistance up to 50%
 - Concurrent resistance to other antibiotic classes, as well
2. Coagulase-negative staphylococci (CoNS) methicillin resistance as high as 62%

Ashbell PA, Colby KA, Deng S, et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. Am J Ophthalmol. 2008;145(6):951-958.

58

ARMOR (2009-2018)

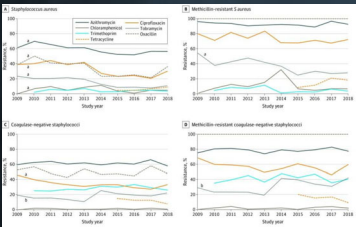
Antibiotic Resistance Monitoring in Ocular Microorganisms

1. *S. aureus* and Coagulase-negative staphylococci (CoNS) have high rates (nearly 30-50%) of methicillin resistance
2. These methicillin-resistant organisms *also* showed higher resistance to fluoroquinolones, aminoglycosides, and macrolides
3. Fluoroquinolones: Besifloxacin >> alternate 4th gen > 2nd or 3rd gen
4. Vancomycin still with high susceptibility
5. *S. pneumoniae*, *P. aeruginosa*, *H. influenzae* appeared pan-sensitive (yay!)

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ARMOR (2009-2018)

Antibiotic Resistance Monitoring in Ocular Microorganisms




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What antibiotics *should* we use?

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Gatifloxacin (Zymar, Zymaxid)




Pros:

1. ? Equivalent efficacy to fortified therapy¹
2. G (+) and G (-)

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Moxifloxacin (Vigamox, Moxeza)



Pros:

1. Preservative Free
2. Better tolerability
3. G (+) and G (-)

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Besifloxacin (Besivance)



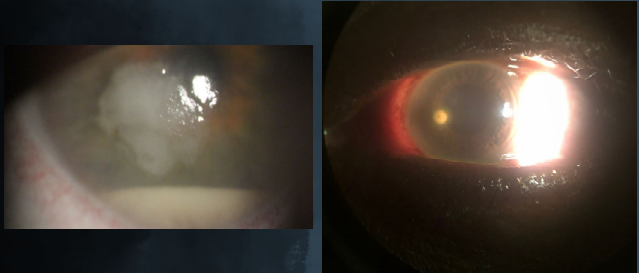
Pros:

1. Only available as an ophthalmic suspension
2. Strong G (+) and G (-)
3. Good for MRSA

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How do you decide when to use fortified antibiotics?

65



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Fortified antibiotics

Gram (+)	Vancomycin 50mg/mL or Cefazolin 50mg/mL
Gram (-)	Tobramycin 14mg/mL

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Treatment Schedule

Fortified example dosage schedule:

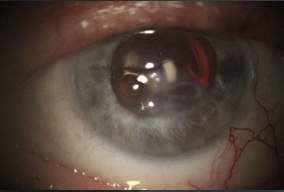
- Every 1-2 hours around the clock
- Improvement?
 - Every 2-4 hours while awake
- Resolution
 - Discontinue

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What *else* do we have to combat microbial keratitis?

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Doxycycline and Vitamin C



Justin Schweitzer OD

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Steroids for Corneal Ulcers Trial (SCUT study)

0.5% moxifloxacin q1h for 48 hours

500 patients with bacterial keratitis

SCUT 1 3 mo eval → SCUT 2 12 mo eval


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Steroids for Corneal Ulcers Trial (SCUT I)

1. Steroid group required more time to re-epithelialize
2. 4 adverse events in the placebo group and none in the steroid group
3. No statistically significant difference in VA at 3 months
4. No statistically significant difference in scar size at 3 months

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Steroids for Corneal Ulcers Trial (SCUT study)



Trend was..

- Better VA
- Less scarring

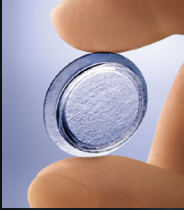
..in the steroid group

1. Srinivasan M, Mascarenhas J, Rajaraman R, et al. Corticosteroids for bacterial keratitis: the Steroids for Corneal Ulcers Trial (SCUT). Arch Ophthalmol. 2012;130(12):1642-50. 2. Kim M, Mascarenhas J, Rajaraman R, et al. The steroid for corneal ulcer trial (SCUT): comparing 1% methyl-prednisolone acetate of a randomized controlled trial. Ophthalmology. 2014;121(12):2303-10.


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Amniotic Membranes

Cryo-preserved



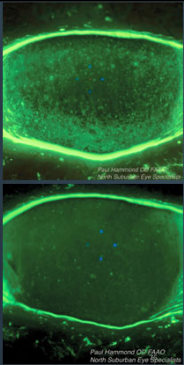
Dehydrated



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Amniotic membrane actions

1. Reduce inflammation
2. Inhibit scarring
3. Inhibit angiogenesis
4. Promote epithelialization
5. Possess anti-microbial properties
6. Restore lost corneal thickness*

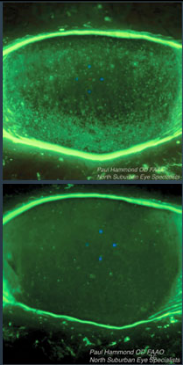


Paul Hammond DVM, PhD, North Carolina Eye Specialists

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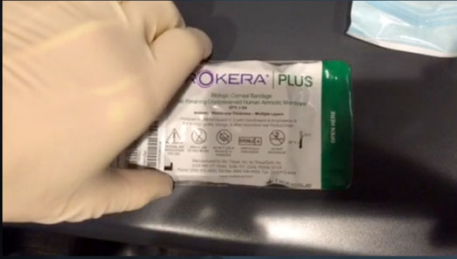
Amniotic membrane indications

- Corneal ulcer
- Neurotrophic defect
- Corneal burn (chem or thermal)
- Dry eye / filamentary keratitis
- Acute SJS
- Etc..



Paul Hammond DVM, PhD, North Carolina Eye Specialists

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Video: Justin Schweitzer OD

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Tape tarsorrhaphy

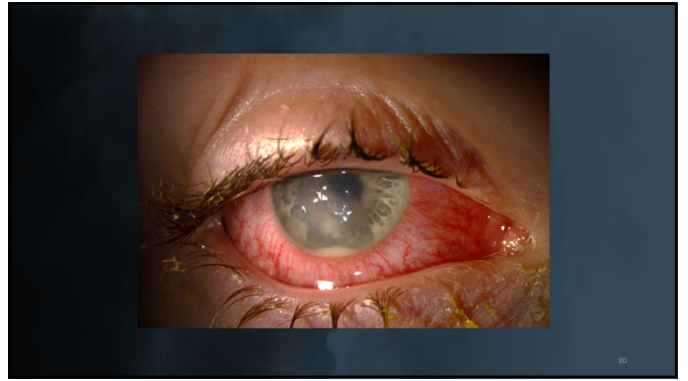


1. Mimouni M, Liu ES, Din N, et al. Tape suture tarsorrhaphy for persistent corneal epithelial defects. Am J Ophthalmol. 2021;237:235-240.

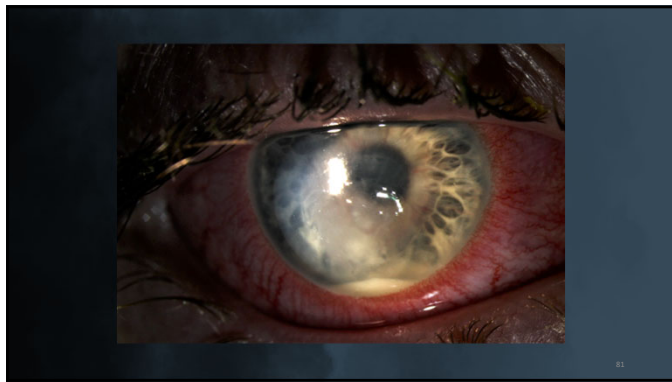
78



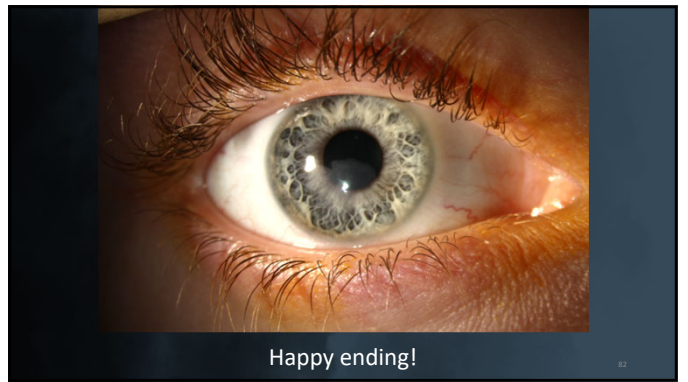
79



80



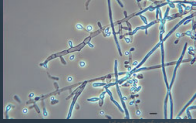
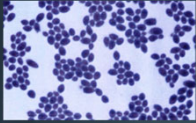
81



82

Who gets fungal keratitis?

- Contact lens wear (37%)
- Ocular surface disease (29%)
- Ocular trauma (25%)

Kay LJ, Gower EW, Iovieno A, et al. Clinical and microbiological characteristics of fungal keratitis in the United States, 2001-2007: a multicenter study. *Cornea*. 2011;30(11):1484-1490.

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Types of fungal keratitis^{1,2}

Filamentous fungi

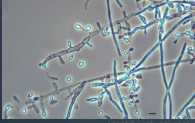
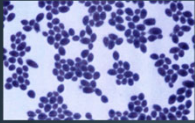
- Ocular trauma (78%)
- Contact lens wear (86%)

Non-filamentous fungi

- Ocular surface disease (53%)
- Cooler climates

Candida and *Aspergillus* are most common

- *Fusarium* more common in South Florida





1. Kay LJ, Gower EW, Iovieno A, et al. Clinical and microbiological characteristics of fungal keratitis in the United States, 2001-2007: a multicenter study. *Cornea*. 2011;30(11):1484-1490.
2. Amari Z, Miller O, Galor A. Current Thoughts in Fungal Keratitis: Diagnosis and Treatment. *Surv Ophthalmol*. 2013;58(2):104-114.

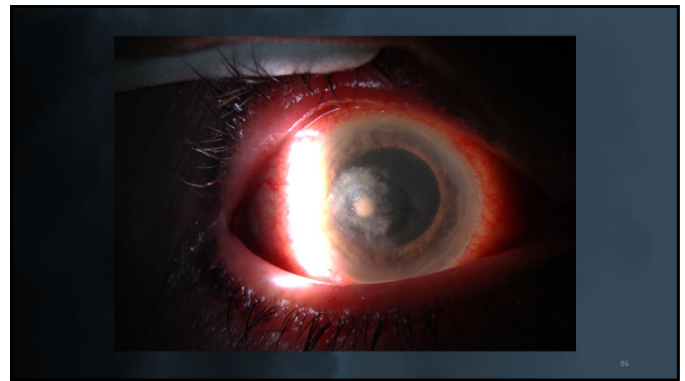
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Features of fungus (vs bacteria)

- Less painful, less inflammation
- Satellite lesions common
- Feathered infiltrate edges
- Deeper stromal involvement
- Take longer to worsen
- Co-infections can be common



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Management

Starts with culturing!

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Management

Filamentous (*Fusarium, Aspergillus*)

- Natamycin 5%
- Voriconazole 1%
- Ketoconazole 1%

Non-filamentous / Yeast (*Candida*)

- ? Natamycin 5%*
- Amphotericin B 0.15%
- Voriconazole 1%
- Fluconazole 0.2%
- Capsogfungin 0.5%



Oral antifungals may require systemic drug monitoring during use (i.e. q2week LFTs)

Ansari Z, Miller D, Galor A. Current Thoughts in Fungal Keratitis: Diagnosis and Treatment. Curr Fungal Infect Rep. 2013;7(3):209-218.
Al-Badriyeh D, Neoh CD, Stewart K, Kong DC. Clinical utility of voriconazole eye drops in ophthalmic fungal keratitis. Clin Ophthalmol. 2010;4:393-400.

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Mycotic Ulcer Treatment Trials (MUTT I and II)

Take home points:


- Natamycin outperformed voriconazole¹ * All cases were filamentous
 - Better VA, smaller scars, fewer perforations or TKPs
- Added oral voriconazole did not improve outcomes²
 - Rate of perforation equal, need for PKP same, more adverse effects with vori

1. Pragna NV, Krishnan T, Mascarenhas J, et al. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. JAMA Ophthalmol. 2013;31(4):422-9. 2. Pragna NV, Krishnan T, Rajaraman R, et al. Effect of Oral Voriconazole on Fungal Keratitis in the Mycotic Ulcer Treatment Trial (MUTT II): A Randomized Clinical Trial. JAMA Ophthalmol. 2016;34(12):1365-1372.

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What else might these need?

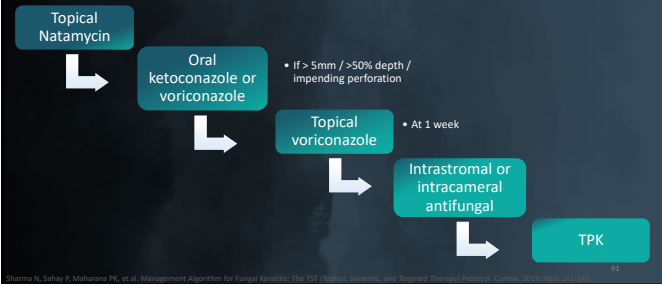
- Topical antibiotics
- Oral anti-fungal
 - 400 mg voriconazole BID
 - 200 mg fluconazole
- Intrastromal (or intracameral) anti-fungal
- Topical steroids??



Youtube / Dr. Mallikarjun MH

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“Topical, Systemic, Targeted” Management Algorithm for Fungal Keratitis

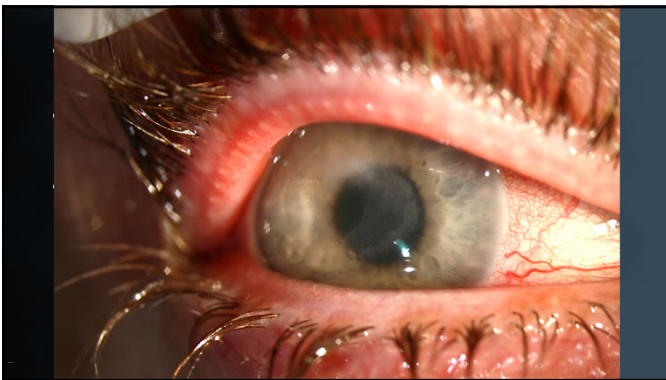


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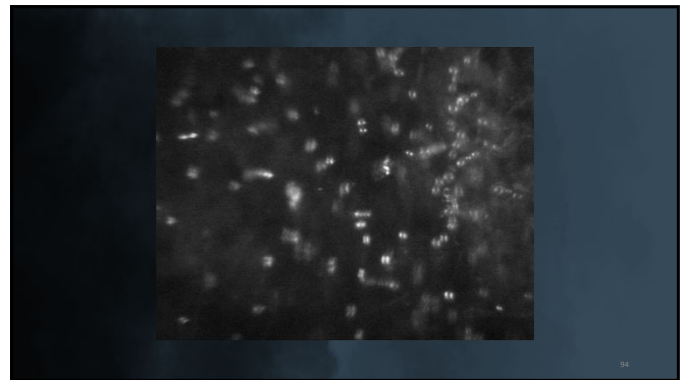
Fungal keratitis: in summary

- Cultures can be difficult to obtain
- Buckle up for the long haul...
Fungal keratitis treatment can last MONTHS!
- Aggressive (hourly) treatment
- Follow daily until improvement

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Acanthamoeba keratitis

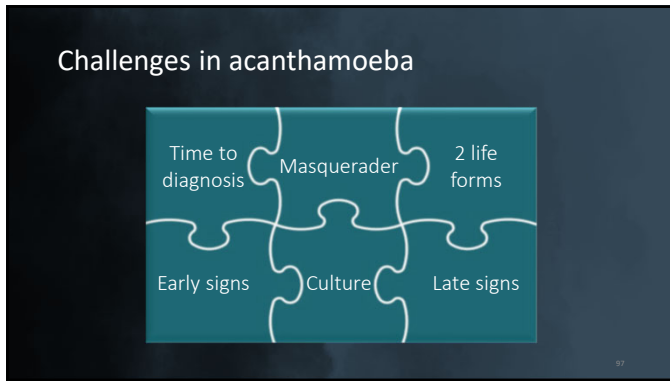
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Diagnosing acanthamoeba

“The most important step in AK diagnosis is to think of it.”

– Lorenzo-Morales et al¹

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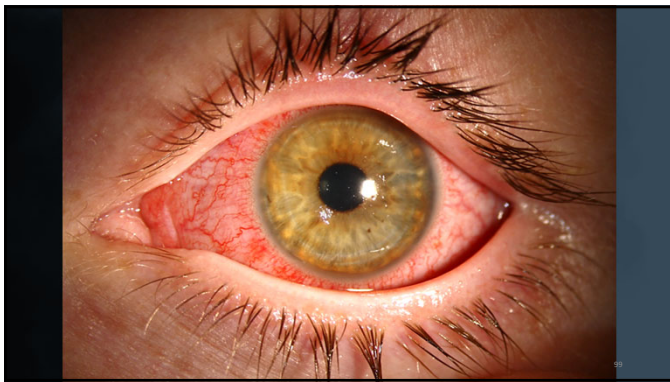


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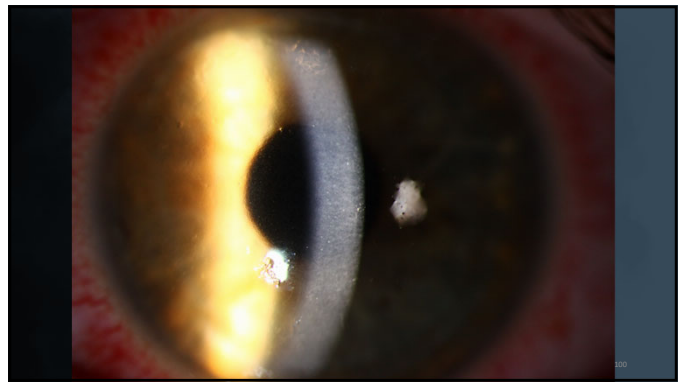
Clinical signs of acanthamoeba

- Early**
 - Nonspecific superficial keratopathy (may be “dendritic”)
 - +/- perineuritis
 - Pain >> findings
- Mid stage**
 - Anterior stromal infiltration (often multifocal)
- Late stage**
 - Deep stromal infiltration
 - Ring infiltrate

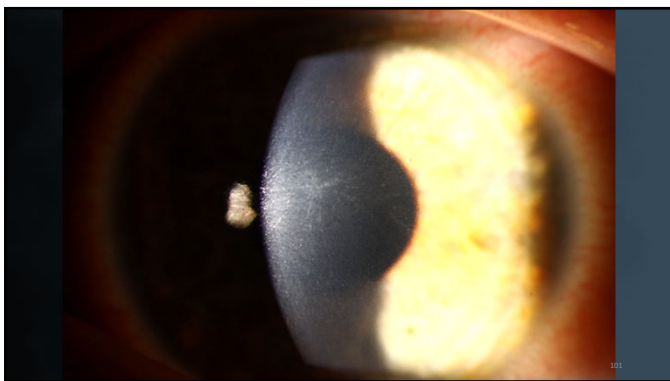
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Treatment for acanthamoeba

- There is no silver bullet 
- Current strategies employ multi-drug regimen (hourly) and long taper

Biguanide Chlorhexidine Polyhexamethylene (PHMB)	Diamide Propamidine (Brolene®) Hexamidine	IV Pentamidine? Adjunct antifungal (-azole)? Aminoglycoside? Topical steroid? Miltefosine®?
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The big guns

- Therapeutic penetrating keratoplasty
- Photodynamic therapy



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Steroids for Corneal Ulcers Trial II (SCUTII study)

- Culture or gram stain proven bacterial keratitis
- Three arms, prospective multicenter study
 1. Antibiotics
 2. Antibiotics + early steroids
 3. Antibiotics + early steroids + corneal cross linking

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Photodynamic antimicrobial therapy

Why does it work??

1. Inhibit microbial growth
2. Induce oxidative damage to pathogens
3. Strengthens stroma to reduce susceptibility to enzymatic digestion

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Cross-Linking Corneal Ulcers

Ultraviolet (UVA) with Riboflavin

- First non-infectious corneal melt (2000)¹
- First infectious microbial keratitis (2008)²
- Meta-analysis (2016)³
 - 96 bacteria, 32 fungi, 11 acanthamoeba, 2 herpes simplex, 13 co-infections, 21 inconclusive etiology
 - Stronger evidence for effectiveness in bacterial cases vs fungal or protozoan

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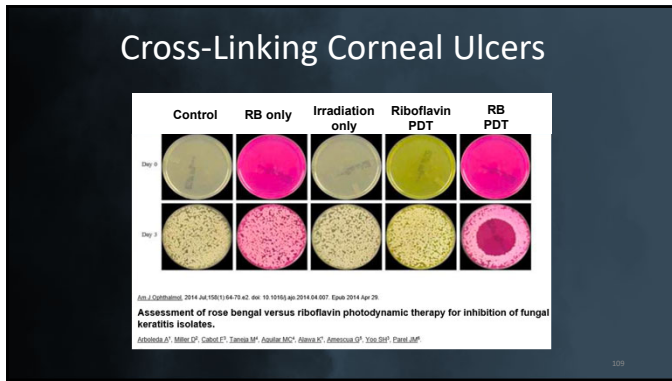
Cross-Linking Corneal Ulcers

Green light with Rose Bengal

- Inhibition of fungal keratitis isolates (2014)^{1*}
- Inhibition of MRSA keratitis isolates (2016)^{2*}
- Successful treatment of resistant fusarium keratitis (2017)³
- Reduces rate of therapeutic PK (2019)⁴

*Denotes in vitro study

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In conclusion..

- Infectious keratitis is COMMON
- Less virulent organisms are more common than the bad ones..
- We should manage infectious keratitis to the extent of our comfort and ability
- Know when to treat and when to refer

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ALL_THINGS_EYE

Scan this nametag on Instagram to follow all_things_eye.

Thank you!

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