Microbial Keratitis
Oh, how things have changed!

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Financial Disclosure Statement

- Associate Professor of Clinical Ophthalmology
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- Optometric Editor, Primary Care Optometry News
- Consultant, advisor, lecturer, investigator,
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- No financial disclosures to report today.

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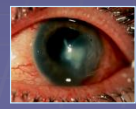
Microbial Keratitis
Oh, how things have changed!

Topics For Consideration …

Bacterial Keratitis
Non-bacterial Keratitis – Amoebic, Fungal, & Herpetic

- What today's bacterial keratitis looks like
- What surveillance data is telling us about microbial resistance
- How is it best diagnosed …clinical suspicion & diagnostic confirmation
- What is prudent first line therapy in bacterial keratitis
- What future bacterial keratitis treatment strategies look like
- How a certain OTC eye drop became public enemy #1

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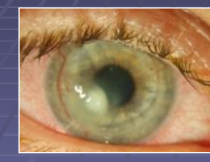
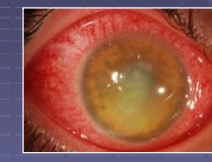
What today's microbial keratitis looks like …



44 yof teacher
Hx of KCN and DALK
Wears daily disposable / Rose K
Compliance breach
Failed fluoroquinolone monotherapy
Fortified Vancomycin + Tobramycin
S. epidermidis & S marcescens



33 yof health care worker
No pertinent history
Wears soft lenses & generic mps
No compliance breach
Failed aminoglycoside monotherapy
Moxifloxacin + Tobramycin +
Valacyclovir
No culture results

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What today's microbial keratitis looks like … across all demographics

Sand, etal Oph 2015
- All cultured cases of microbial keratitis from Doheny Eye (DEI) and LA County Medical Center (LAC) from 2008-2012.

- N = 290 cases from DEI -> 63% culture positive
- N = 186 cases from LAC -> 82% culture positive

- Gram (+) 69% with CoNS most common
- Gram (-) 31% with P. aeruginosa most common

Coagulase negative staphylococci commensal bacteria ?
- Newborns, catheters, implants, skin abrasions, ocular surface

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What today's microbial keratitis looks like …

Kowalski, etal Eye Cont Lens 2019
- N = 1,387 laboratory confirmed infectious keratitis isolates
- 72% bacterial
  - S. aureus (20%) and Strep species (9%)
  - P. aeruginosa (18%)
- 16% herpes simplex virus
- 7% fungal
- 5% acanthamoeba

Kase, etal Arq Bras Oftalmol 2023
- N = 4,810 corneal samples
- 70% bacterial
  - CoNS (45%) and S aureus (10%)
  - P aeruginosa (9%)
- 7% fungal
- 4% acanthamoeba

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What today's microbial keratitis looks like … for contact lens wearers

Ni, etal Cornea 2015
- *N = 323 infectious keratitis cases at Will's Eye Hospital (2009-2012)*
- *Contact lens wearers – P. aeruginosa and Fusarium*
- *Non-lens related – S. aureus and Candida*
- *38% CoNS & all MRSA resistant to fluoroquinolones*
- *Good susceptibility to tobramycin and vancomycin*
- *Voriconazole effective against all fungi*

Bennett, etal Eye Cont Lens 2019
- *N = 677 corneal ulcer cases at St Louis University (1999-2016)*
- *Contact lens wearers – P. aeruginosa*
- *Non-lens related – gram positive*
- *CoNS and ORSA comprised ~ 33% of all cases*

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What surveillance data is telling us about ocular microbial resistance

Bispot, etal Oph Ther 2022

Review of Medline, Biosis, Embase & ARMOR Surveillance
- *32 local / regional data sets compared with ARMOR (25 yr)*
- *S. aureus, CoNS, S. pneumoniae, P. aeruginosa, and H. influenza*

- *Trends to date …*
- *overall, increased in-vitro resistance to fluoroquinolones*
- *slight decrease in MRSA, but increase in CoNS*
- *MRSA effectively doubles likelihood of multi-drug resistance*

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What surveillance data is telling us about ocular microbial resistance

Always be mindful of MRSA

- *4.6% health care workers harbor MRSA (Albrich 2008)*
- *8 – 13% contact sports athletes harbor MRSA (Karanika 2016)*
- *Ocular MRSA no longer post-op complication only!*
- *High % of MRSA demonstrate multi-drug resistance (Asbell 2019)*
  - *Increasing resistance to FQ's*
  - *Fortified vancomycin and aminoglycosides effective*
- *Think MRSA if …*
  - *Non-responsive to first line therapy*
  - *History of compromised immunity and debilitating systemic disease*
  - *Chronic ocular surface disease*

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What surveillance data is telling us about ocular microbial resistance

And MRSE

- *S. epidermidis are ubiquitous inhabitants*
- *Well established ocular virulence*
  - *50+% of S. epidermidis ocular isolates are MRSE*
  - *S. epidermidis associated endophthalmitis*
- *Biofilm shields from innate-acquired immunity and renders AB's ineffective*
  - *Increasing resistance against FQ's*
- *Effective agents*
  - *Besifloxacin (Schecter, etal Oph Ther 2020)*
  - *Ceftazidine, Vancomycin, Tobramycin (Oliver, etal Rev Esp 2022)*
- *2* therapy including*
  - *Quorum sensing inhibition*
  - *Anti-biofilm immunotherapy*

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What surveillance data is telling us about ocular microbial resistance

CoNS is a legitimate concern

Asbell, ARMOR 2019
- *Increasing % of isolates*
- *Resistance to fluoroquinolones (Ni 2015)*

Cabrea-Aguas, etal Clin Exp Oph 2020
- *5 yr surveillance study involving 711 culture (+) corneal scrapings*
- *CoNS most common isolate – 46%*

Romanowski, etal Antibioitics 2021
- *Speciated 50 isolates of CoNS related keratitis. S. epidermidis #1*
- *Moxifloxacin reasonable first line therapy*
- *Fortified cefazolin, tobramycin, or vancomycin*

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What surveillance data is telling us about ocular microbial resistance

P aeruginosa remains a formidable foe

- *Secretory toxins enhance transepithelial migration (Fleiszig 2006)*
- *Contact lens ideal biofilm substrate (Wu 2017)*
- *Mobile genetic elements translate resistance (Subedi 2017)*
- *Mutations in resistance determining regions of FQ targeting genes (Thirumalmuthu 2019)*

- *Consistently top gram (-) isolate in ARMOR (Asbell 2019)*

- *Fluoroquinolone & Fortified Tobramycin*
- *Topical Colistin (polymyxin E) (Jain, etal Cornea 2014)*

- *Beware of Green Nail Syndrome (Nowakowska, etal Ped Derm 2023)*

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What surveillance data is telling us about ocular microbial resistance

Polymicrobial infections are more common than we think

Steger, etal Ophthalmologe 2014
- *Medical University of Innsbruck*
- *123 cases of microbial keratitis 2010 – 2012*
- *59% gram (+) and 51% gram (-) and 7% fungal*
- *30% polymicrobial*

Blondeau, etal ARVO Abstract IOVS 2019
- *Meta-analysis of 3 trials*
- *17% of cases had polymicrobial infection*
- *H. influenza and S. aureus most common isolates*

Besifloxacin & fortified tobramycin

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How is it best diagnosed …clinical suspicion & diagnostic confirmation

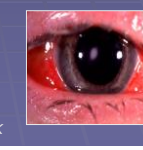
What are the relative risks for corneal infiltrative events (CIE's)?

Chalmers (2013)
- *Reusing Daily Disposable = 4x*
- *Overnight wear of SiHy = 2-5x*
- *< 25 yoa or > 50 yoa = 2x*

Wilcox (2010), Shovlin (2011), Merchea (2012) & Kilvington (2013)
- *Increased risk with PQ-1 / Aldox MPS*
- *Delftia, Stenotrophomonas, Achromobacter, Serratia*

Szczotka-Flynn (2010)
- *CIE's statistically more likely in CL bioburden & smoking*
- *No correlation between corneal staining and CIE's*

Szczotka-Flynn (2024)
- *153 BK vs 158 'high risk' controls.*
- *BK older, male, and history of smoking*
- *Compliant daily disposables protective against severe BK*



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How is it best diagnosed …clinical suspicion & diagnostic confirmation

"Historical" clinical features of bacterial keratitis …

Gram (+) organisms
- *round, gray-white infiltrate*
- *localized with distinct borders*
- *minimal surrounding edema*

Gram (–) organisms
- *large, less defined infiltrate*
- *increased suppuration*
- *adherent exudate in ulcer bed*

Wilcox (2011)
- *Gram (+) carriers: 3x risk of CLPU.*
- *Gram (-) carriers: 5x risk of CLARE.*

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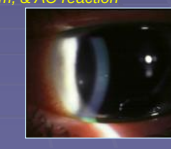
Oh, how things have changed!

How is it best diagnosed … clinical suspicion & diagnostic confirmation

Stein, etal AJO 1988.
Infectious keratitis correlated with
Patient Symptoms: Dull pain & purulent discharge
Clinical findings: Epithelial defect, infiltration, & AC reaction

Aasuri, etal Eye Cont Lens 2003
Patient Symptoms: Severe pain
Clinical exam: lid edema, irregular infiltrate > 2mm, & AC reaction



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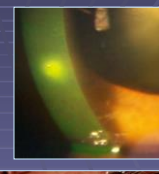
Is it imperative we culture?

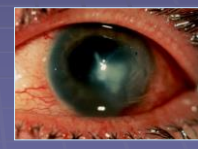
Miller, etal ICAAC Conf 2015

N = 176 cases microbial keratitis
- *U of Miami Hospital ER in 2014*
- *52% treated without cultures*
- *44% those cultured were (+)*

- *Ultimately, combination therapy in 27%*
  - *MRSA and Fusarium*

Are we good antimicrobial stewards?





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Is it imperative we culture?

- *Culturing*

Mini-tip culturette (thioglycolate)

Agar plates
- *Blood agar – aerobic organisms & saprophytic fungi*
- *Chocolate agar – Neisseria, Moraxella, Haemophilus*
- *Lowenstein-Jensen – Nocardia & Mycobacterium*

Epley, etal Cornea 1998
Compared direct plating vs mini-tip culturette
Sensitivity & specificity similar between techniques

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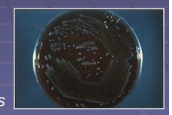
Oh, how things have changed!

Is it imperative we culture?

Konda, etal Opt & Vis Sci 2013

- *Cultured 125 eyes with presumed microbial keratitis*
- *Cultures (+) in 40% of corneas / 80% of CL cases / 92% of CL's*
- *94% of cornea & CL cultures agreed*
- *77% of cornea & case cultures agreed*



Martins etal CLAO 2002

- *113 ewscl wearers with presumed microbial keratitis*
- *29% bandage lenses / 71% cosmetic lenses*
- *Concordance between corneal and contact lens / case cultures*
  - *Fungal 100%*
  - *Amoebic 80%*
  - *Bacterial 75% (Pseudomonas most common)*

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Oh, how things have changed!

Can we predict whether a culture will be positive?

Bhadange, etal Br J Ophth 2014

- *N = 60 cases of microbial keratitis at LV Prasad Eye Institute*
- *Retrospectively compared culture (-) with culture (+)*
  - *Infiltrate size or history of trauma no association with culture result*
  - *Prior topical antibiotic use & duration correlate with culture (-)*
  - *Major ocular surgery correlate with culture (+)*

Ting, etal Front Med 2021

- *Nottingham (UK) microbial keratitis positive cultures associated with*
  - *Older age*
  - *Prior steroid use*
  - *Poor presenting visual acuity*
  - *Larger epithelial defect & infiltrate*
  - *Central ulcer location*
  - *hypopyon*

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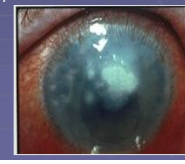
Is it imperative we culture?

- *Ulcer within 2mm of visual axis and …*
- *Epithelial defect > 2mm and...*
- *Ulcer depth > 20% corneal thickness and...*
- *AC reaction > grade 2*

Additional considerations …

- *Infiltrate involving visual axis and/or 25% depth*
- *History of vegetative trauma*
- *Atypical ulcer features*
- *Corneal melting and/or scleral extension*
- *Hospitalized or immunocompromised*
- *Non-responsive to first line therapy*

AAO Preferred Practice Patterns 2018



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What other diagnostic tests may be beneficial?

- *Polymerase chain reaction (PCR)*
  Tuft, etal Eye (Lond) 2023
  used 'decision to tx' as definition for microbial keratitis
  'presumed' 2021 BK, 365 AK, 226 FK
  added benefit of PCR to culture? 1.4% BK, 24.4% AK, 5.8% FK
- *In Vivo Confocal Microscopy (IVCM)*
  Wang, etal Int Oph 2019
  N = 46 cases of microbial keratitis with IVCM
  good sensitivity & specificity in Fungal, Viral, Acanth, & Bacterial
  especially valuable in atypical / mixed cases
  Hoffman, etal Eye (Lond) 2022
  IVCM most sensitive for amoebic and fungal keratitis
  cultures remain 'gold standard' for bacterial keratitis

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What other diagnostic tests may be beneficial?

- *Does AI potentially play a role here?*

Sarayar, etal Front Public Health 2023

- *PubMed, Google Scholars, Proquest, Science Direct, Cochrane, and Scopus*
- *11 articles with data set of 34,500 images*
- *All studies used convolutional neural network algorithm (DL)*

Most AI models outperformed human counterparts with a collective accuracy of 96.6% in differentiating IK from non-IK

But, collective accuracy of 64% in differentiating BK from FK

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What is prudent first line therapy in microbial keratitis

Principles of Treatment (Shovlin)

- *Broad spectrum agent (s)*
- *Rapid, intensive topical dosing*
- *Avoid aggressive pain medications and topical steroids early on*
- *Daily evaluation until significant improvement*
- *Tailor antibiotic choice by clinical response and culture results*
- *If using multiple agents, discontinue only one at a time*
- *Avoid abrupt cessation of all medications*

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Oh, how things have changed!

What is prudent first line therapy in microbial keratitis

Is monotherapy acceptable?

- *Ciprofloxacin (Eifferman 1996) & Ofloxacin (O'Brien 1997) Study Groups*

Then gram (+) resistance developed

- *Fluoroquinolone resistant s. aureus up to 28% (Alexandrakis 2000)*
- *Gram (-) : Gram (+) shifted to 51%:49% (Goldstein 1999)*

Resulting in the development of the C8-methoxy (4th generation) fluoroquinolones
Eventually even C8-methoxy fluoroquinolones found vulnerable

- *Gatifloxacin resistant CoNS epidermidis (Jhanji 2007)*
- *Moxifloxacin resistant P. aeruginosa (Moshifar 2006)*
- *Gatifloxacin resistant MRSA (Moshifar 2006)*

All susceptible to fortified vancomycin or fortified tobramycin

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Oh, how things have changed!

What is prudent first line therapy in microbial keratitis

- *Prescribe aggressively*
  - *Moxifloxacin, gatifloxacin, or besifloxacin*
  - *Loading dose with frequent dosing*
- *Cover with an adjunct agents*
  - *Gram (-): Fortified Aminoglycoside (Kowalski 2019)*
  - *Gram (+): Polytrim (Chang, 2015)*
- *Compounding Considerations*
  - *Gram (-): Tobramycin (14mg/ml), Amkacin (20mg/ml), Colistin (0.19%)*
  - *Gram (+): Vancomycin (20-30mg/ml), Ceftazidine (50mg/ml), Lysostaphin (0.28%)*

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What is prudent first line therapy in microbial keratitis

- *Combinations for consideration*
  - *Besifloxacin & Polytrim*
  - *Moxifloxacin & Tobramycin 14mg/ml*
  - *Tobramycin 1.5% / Vancomycin 5% (Imprimis Tobra-Vanc)*
- *Consider alternative routes of administration*
  - *Subconjunctival injection*
  - *IV / Oral*
  - *Sub-palpebral lavage*
- *Minimize collateral tissue damage*
  - *Oral doxycycline*
  - *Topical azithromycin*
  - *Topical corticosteroid*
  - *Amniotic membrane*

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Oh, how things have changed!

When does topical steroid use make sense?

Wilhemus Oph 2002

- *50 yr literature review – Avoid steroid use in microbial keratitis*

Srinivasan Arch Oph 2011 (SCUT)

- *No difference in perforation, scarring or BCVA between groups*
- *Benefits? Severe keratitis and earlier intervention (w/in 2-3 days)*

Blair, etal Can J Oph 2011

- *Healing rate same, though smaller residual ulcer size in steroid group*

Ray, etal JAMA Oph 2014 (SCUT)

- *Steroid may improve vision in severe BMK, especially if used early*

Green, etal Cornea 2019

- *High dose steroids result in better visual outcome*

Bottom Line? Do we want to suppress neutrophil extracellular traps (NET)?
Who should NOT get steroids? Suspected fungal, acanthamoeba, nocardia

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Oh, how things have changed!

What is the role of amniotic membrane therapy in microbial keratitis?

Mohammadpour & Sabet J OphVis Res 2016

- *N = 6 eyes with infectious keratitis & descemetocele non-responsive to AB's*
- *Amniotic Membrane Therapy for 3 months resulted in BCVA 20/30-20/50*

Tabatabaei, etal Oc Surf 2017

- *N = 49 eyes AB + AM vs 50 eyes AB gtt alone*
- *AB+AM group better VA and smaller residual scar*

Cheng & Tseng Cornea 2017

- *4 eyes with HSV keratitis treated with Prokera AM and oral acyclovir*
- *Reduced inflammation, rapid re-epithelialization, and symptom relief in 1 week*

Memmi, etal Cornea 2022

- *N = 50 patients with infectious corneal ulceration*
- *No difference between cryopreserved and dehydrated AM's*

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Oh, how things have changed!

What future bacterial keratitis treatment strategies look like

New antimicrobial therapies – are the quinolones no longer viable?

Re-visiting earlier generation quinolones

- *Trovafloxacin – urinary tract infections … hepatotoxicity*
- *Temafloxacin – respiratory infections … kidney, liver, clotting*
- *Gemifloxacin – respiratory infections – kidney, liver, tendons*

Herbert, etal BMJ Open Oph 2022

- *MIC's, solubility, penetration, and corneal binding*
- *Potential for bacterial keratitis application*
  - *Avarofloxacin*
  - *Delafloxacin*
  - *Finafloxacin*
  - *Levonadifloxacin*
  - *Nemonofloxacin*
  - *Zabofloxacin*

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What future bacterial keratitis treatment strategies look like

New antimicrobial therapies – blasts from the past?

Polytrim – Rifampin combination

Chojnacki & Wozniak J of Antimicrob & Chemo Ag 2018
- *Effective in 70% of S. aureus & P. aeruginosa isolates in murine model*

Povidone–Iodine (povidone + hydrogen iodine + iodine)

Isenberg, etal AJO 2017
- *studied time to presumed cure in 172 cases of bacterial keratitis*
- *povidone-iodine 1.25% non-inferior to antibiotic treatment*
- *antibiotics were neo-poly-gram (Philippines) or ciprofloxacin (India)*

Bodin A J Case Rep 2020
- *61 yom with corneal ulcer resistant to antibiotic and antiviral treatment*
- *resolution with 0.66% nanoemulsion povidone-iodine tid x 3 wks*

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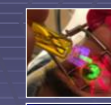
What future microbial keratitis treatment strategies look like

Corneal Collagen Cross-linking (CCXL)

Liberation of reactive oxygen species (disinfection)
Increased collagen resistance to proteolytic enzymes



Randleman, etal OSN 2012
- *N = 16 culture positive bacterial keratitis*
- *Single treatment with CCXL and .01% riboflavin*
- *86% eyes successfully treated*

Rose Bengal Photodynamic Antimicrobial Therapy (RB-PDTAT)

Free radical stromal oxidation without collateral damage

Naranjo etal AJO 2019
- *RB-PDT in 18 eyes non-responsive to anti-microbial therapy*
- *Acanthamoeba, Fusarium, & Pseudomonas most common isolates*
- *Successful in 72% of cases. Average time to resolution 46 days*

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Oh, how things have changed!

What future microbial keratitis treatment strategies look like … now!

How about a little bio-inspiration ?

Antimicrobial Peptides (AMP's)
- *Small peptides as part of innate immune system of many organisms*

Tam, etal J Clin Inv 2012
- *Synthesized keratins bacteriocidal against S pyogenes, E coli, S aureus, & P aeruginosa*

Dutta, etal IOVS 2016
- *Melamine coated contact lenses inhibited P aeruginosa & S aureus*

Casciaro, etal Biopolymers 2017
- *Esculentin-1a (frog AMP) bacteriocidal against P aeruginosa*

Clemens, etal IOVS 2017
- *"Designed" HDP's bacteriocidal against P aeruginosa*

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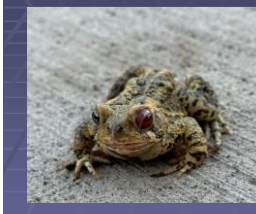
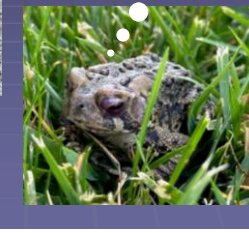
Perhaps, bioinspiration is the answer?



…medicine consists in amusing the patient while nature cures …. Voltaire



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Oh, how things have changed!

How a certain OTC eye drop become public enemy #1

The backdrop
- *uptick in severe corneal ulcers non-responsive to conventional tx*
- *multidrug-resistant strain of p. aeruginosa*
- *devastating outcomes in 80+ cases*

The culprit
- *P. aeruginosa strain producing Verona integron mediated metallo-B-lactamase & Guiana extended spectrum B-lactamase.*
- *strains traced back to EzriCare & Delsam OTC artificial tears*

The Treatment
- *IV cefiderocol, topical imipenem-cilistatin, & topical polytrim*
- *on 2-1-2023 CDC issues Health Alert Network Advisory*
- *Fortified topical cefiderocol (Romanowski, etal ARVO 2024)*

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Microbial Keratitis
Oh, how things have changed!

Topics For Consideration …

Bacterial Keratitis
Non-bacterial Keratitis – Amoebic & Fungal Infections

- *What today's bacterial keratitis looks like*
- *What surveillance data is telling us about microbial resistance*
- *How is it best diagnosed …clinical suspicion & diagnostic confirmation*
- *What is prudent first line therapy in bacterial keratitis*
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Thank you for attending!

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