Bacterial Corneal Ulcers

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COS INSIGHT Cornea Planning Meeting
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Off label use of drugs/devices will be discussed.

I have/had an affiliation (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of my presentation(s).

<table>
<thead>
<tr>
<th>Financial Interest/ Affiliation</th>
<th>Name of Company(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Allergan, Bausch &amp; Lomb, Merck, Moria</td>
</tr>
<tr>
<td>Employment/Honoraria/Consulting Fees/Travel Expenses</td>
<td>Alcon, Allergan, Bausch &amp; Lomb, Labtician</td>
</tr>
<tr>
<td>Major Stock Shareholder</td>
<td>None</td>
</tr>
<tr>
<td>Member: Advisory Panel, Standing Committee, Board of Directors</td>
<td>Allergan, Bausch &amp; Lomb</td>
</tr>
<tr>
<td>Other Financial or Material Interest</td>
<td>None</td>
</tr>
</tbody>
</table>
This module will go over the management of a corneal ulcer including initial management, choice of antibiotics, decision-making during the healing phase, and medical/surgical treatment options for various stages of ulcers.
Learning Objectives

To be able to describe work-up and initial management of a corneal ulcer

To be able to gauge the healing of a corneal ulcer and know when a referral is needed

To be able to describe surgical options a cornea specialist may offer
Contact Lens Wearer Presents at 3pm on a Friday Afternoon...

• What would you want to know about patient on history?

• What key exam findings do you look for?

• What treatment would you start?
Contact Lens Wearer Presents at 3pm on a Friday Afternoon...

- **History**
  - Contact lens wear habits
    - Sleeping in contact lenses, home-made saline
    - Swimming, hot tub
  - Trauma
    - Foreign body, vegetative matter

- **Exam**
  - Size, depth, location of epithelial defect and infiltrate
  - Anterior chamber reaction

- **Treatment**
  - Cycloplegic drops
  - Topical antibiotics (drops, ointment)
  - ? NSAID drops
Patient Returns 2 Days Later Like This...

How did this become an ulcer?
Development and Worsening of Ulcer

- Bad Bug
- Bad Drug
- Bad Surface
- Bad Patient
Healing Issues

What comments do you have regarding:

• How long should it take for the epithelium to heal?
• How long should antibiotics be continued?
• What is the role of epithelial debridement?
• How does diagnosis and management of marginal keratitis differ from that of corneal ulcer?
Why Would We Consider Referring This Patient to a Cornea Specialist?

- Option 1: Access to fortified antibiotics
- Option 2: Access to cultures and stains
- Option 3: Steroid drops
- Option 4: Not comfortable managing on my own
- Option 5: I would not refer and manage this patient in my office initially
Key Points

To summarize, I want to remind you of the following lessons to keep in mind when initially managing an ulcer:

- Follow patient closely and emphasize compliance
- Support the ocular surface
- Be prepared to change management approach if ulcer worsens: fortified drops, re-culture
- Build relationships with microbiology lab and compounding pharmacy
- Low threshold for referral to corneal specialist
What Would a Cornea Specialist Do?

• Option 1: Anterior Segment OCT / Collagen Crosslinking
• Option 2: Re-culture
• Option 3: Fortified antibiotic drops
• Option 4: Gluing
• Option 5: Therapeutic graft on a “hot” eye and consider re-grafting later if needed
These patients’ bacterial ulcer have healed, but have left a visually significant corneal scar. What have you usually done in situations like this?

- Option 1: Observe, scar may get better
- Option 2: Use steroid drops
- **Option 3: Contact lens**
- **Option 4: Refer for corneal surgery**
To summarize, I want to remind you of the following lessons when thinking of how to improve vision in a resolved ulcer patient:

- What is potential for vision?
- Be aggressive with epithelial defects in neurotrophic corneas: punctal cautery, tarsorrhaphy, serum tears
- Be aware of surgical options and refer to cornea specialist for consideration
THANK YOU!
## Bugs

**Refractory due to incorrect diagnosis: ?Fungal, viral, acanthamoeba**

### TABLE 1 COMMON CAUSES OF BACTERIAL KERATITIS IN THE UNITED STATES

<table>
<thead>
<tr>
<th>Class/Organism</th>
<th>Common Isolates*</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive Isolates</strong></td>
<td></td>
<td>29–75.1</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td><em>Staphylococcus aureus</em></td>
<td>4–27.6</td>
</tr>
<tr>
<td></td>
<td>MRSA</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Coagulase negative <em>Staphylococci</em></td>
<td>1–45.5</td>
</tr>
<tr>
<td></td>
<td>MRSE</td>
<td>43.1</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus pneumoniae</em></td>
<td>0–3.4</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus viridans group</em></td>
<td>1–6.9</td>
</tr>
<tr>
<td>Gram-positive bacilli</td>
<td><em>Propionibacterium</em> species</td>
<td>4–7</td>
</tr>
<tr>
<td></td>
<td><em>Mycobacterium</em> species</td>
<td>3</td>
</tr>
<tr>
<td><strong>Gram-Negative Isolates</strong></td>
<td></td>
<td>31–50</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>3–33</td>
</tr>
<tr>
<td></td>
<td><em>Serratia marcescens</em></td>
<td>3–13.5</td>
</tr>
<tr>
<td></td>
<td><em>Proteus mirabilis</em></td>
<td>3.4–4</td>
</tr>
<tr>
<td></td>
<td>Moraxella species and related species</td>
<td>1–20.7</td>
</tr>
<tr>
<td></td>
<td>Enteric and other gram-negative bacilli</td>
<td>1–10</td>
</tr>
<tr>
<td>Gram-negative cocccobacillary organisms</td>
<td><em>Haemophilus influenzae, other Haemophilus species</em></td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Source: Bacterial Keratitis Preferred Practice Pattern, AAO, 2013.*
## Drugs

### TABLE 3  ANTI-BACTERIAL THERAPY FOR BACTERIAL KERATITIS

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Topical Concentration</th>
<th>Subconjunctival Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No organism identified or multiple types of organisms</strong></td>
<td>Cefazolin with Tobramycin or gentamicin or Fluoroquinolones&lt;sup&gt;+&lt;/sup&gt;</td>
<td>50 mg/ml</td>
<td>100 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td>Vancomycin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>15–50 mg/ml</td>
<td>25 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td>Bacitraion&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10,000 IU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Various&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Gram-positive cocci</strong></td>
<td>Cefazolin</td>
<td>50 mg/ml</td>
<td>100 mg in 0.5 ml</td>
</tr>
<tr>
<td><strong>Gram-negative rods</strong></td>
<td>Tobramycin or gentamicin</td>
<td>9–14 mg/ml</td>
<td>20 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td>Cefazidime</td>
<td>50 mg/ml</td>
<td>100 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>Various&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Gram-negative cocci&lt;sup&gt;3&lt;/sup&gt;</strong></td>
<td>Ceftriaxone</td>
<td>50 mg/ml</td>
<td>100 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td>Cefazidime</td>
<td>50 mg/ml</td>
<td>100 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>Various&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Nontuberculous mycobacteria</strong></td>
<td>Amikacin</td>
<td>20–40 mg/ml</td>
<td>20 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>10 mg/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azithromycin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>10 mg/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>Various&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Nocardia</strong></td>
<td>Sulfacetamide</td>
<td>100 mg/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>20–40 mg/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trimethoprim/sulfamethoxazole: trimethoprim</td>
<td>16 mg/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>sulfaemethoxazole</td>
<td>80 mg/ml</td>
</tr>
</tbody>
</table>

*Source: Bacterial Keratitis Preferred Practice Pattern, AAO, 2013.*
Monotherapy vs Fortified Antibiotics

**Randomized clinical study for comparative evaluation of fourth-generation fluoroquinolones with the combination of fortified antibiotics in the treatment of bacterial corneal ulcers.**

Shah VM¹, Tandon R, Satpathy G, Nayak N, Chawla B, Agarwal T, Sharma N, Titiyal JS, Vajpayee RB.

**Abstract**

**PURPOSE:** Comparative evaluation of efficacy of monotherapy with moxifloxacin (0.5%) or gatifloxacin (0.3%) with combination therapy of cefazolin (5%) and tobramycin (1.3%) in treatment of bacterial corneal ulcers.

**METHODS:** Patients diagnosed with bacterial keratitis (ulcer diameter 2-8 mm) were randomized to 1 of the 3 treatment groups (tobramycin 1.3% and cefazolin 5%, gatifloxacin 0.3%, or moxifloxacin 0.5%). After obtaining corneal scrapings, assigned study medication was instilled hourly for 48 hours and tapered as per clinical response. Healing of ulcer, duration to cure, adverse reactions, antibiogram profile, treatment failures, final visual acuity, and corneal opacity size were evaluated.

**RESULTS:** A total of 61 patients were enrolled [cefazolin and tobramycin (n = 20), gatifloxacin (n = 21), and moxifloxacin (n = 20)]. Overall, 57 patients (93%) healed on treatment. On comparison of the mean time taken to heal, no statistically significant difference was found among all the 3 treatment groups (P = 0.98). Positive bacterial culture was obtained in only 38 patients (62%). There was no significant difference in the bacterial isolates in each treatment group. There were 4 (7%) treatment failures (perforation or nonhealing ulcer): 1 (5%) each in moxifloxacin and gatifloxacin group and 2 (10%) in fortified antibiotics group. All regimens were well tolerated.

**CONCLUSION:** The study failed to find a difference in the efficacy of monotherapy with fourth-generation fluoroquinolones in the treatment of bacterial corneal ulcers of 2-8 mm size when compared with combination therapy of fortified antibiotics.

Criticism of study: Insufficient power to make their conclusion
Surface

Ocular Surface Support

- Preservative-free lubrication
- Doxycycline
- Vitamin C
- Punctal plugs
- Autologous serum tears
- Tarsorrhaphy
- Amniotic membrane
- Oculoplastics input if lid is abnormal
Fortified Antibiotics

- Alternating hourly for first 36 hours, then taper off fortified drops within 1-2 weeks
- Do you have access to a compounding pharmacy?
- Other considerations: subconjunctival and intrastromal antibiotic injections; systemic

### Fortified Antibiotics

**Cefazolin 50 mg/ml or Ceftazidime 50 mg/ml**
1. Add 9.2 ml of artificial tears to a vial of cefazolin, 1 g (powder for injection).
2. Dissolve. Take 5 ml of this solution and add it to 5 ml of artificial tears.
3. Refrigerate and shake well before instillation.

**Tobramycin 14 mg/ml or Gentamicin 14 mg/ml**
1. Withdraw 2 ml from an injectable vial of intravenous tobramycin or gentamicin (40 mg/ml).
2. Add the withdrawn 2 ml to a 5 ml bottle of tobramycin or gentamicin ophthalmic solution to give a 14 mg/ml solution.
3. Refrigerate and shake well before instillation.

**Vancomycin 15 mg/ml, Vancomycin 25 mg/ml, or Vancomycin 50 mg/ml**
1. To a 500 mg vial of vancomycin:
   a. Add 33 ml of 0.9% sodium chloride for injection USP (no preservatives) or artificial tears to produce a solution of 15 mg/ml.
   b. Add 20 ml of 0.9% sodium chloride for injection USP (no preservatives) or artificial tears to produce a solution of 25 mg/ml.
   c. Add 10 ml of 0.9% sodium chloride for injection USP (no preservatives) or artificial tears to produce a solution of 50 mg/ml.
2. Refrigerate and shake well before instillation.

Source: Bacterial Keratitis Preferred Practice Pattern, AAO, 2013.
How Many Would Do Stains/Cultures Themselves? How? In Which Cases?

<table>
<thead>
<tr>
<th>Culture Not Needed</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Small (&lt;2mm)</td>
<td>• Large (&gt;2mm)</td>
</tr>
<tr>
<td>• Peripheral</td>
<td>• Central</td>
</tr>
<tr>
<td>• Superficial</td>
<td>• Mid to deep stroma</td>
</tr>
<tr>
<td>• No thinning</td>
<td>• Stromal thinning</td>
</tr>
<tr>
<td>• Typical</td>
<td>• Atypical</td>
</tr>
<tr>
<td></td>
<td>• Unresponsive to treatment</td>
</tr>
<tr>
<td></td>
<td>• Have relationship with microbiology lab!</td>
</tr>
</tbody>
</table>
## Stains

### TABLE A4  Stains Used To Identify Common Causes of Bacterial Keratitis in the United States

<table>
<thead>
<tr>
<th>Type of Stain</th>
<th>Organisms Visualized</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram stain*</td>
<td>Best for bacteria; can also visualize fungi; amoeba</td>
<td>Distinguishes gram-positive from gram-negative organisms; widely available; rapid (5 minutes)</td>
</tr>
<tr>
<td>Giemsa stain*</td>
<td>Bacteria, fungi; <em>Chlamydia, Acanthamoeba</em></td>
<td>Basis for Aema-color and Diff-Quik tests; widely available; rapid (2 minutes)</td>
</tr>
<tr>
<td>Acid fast</td>
<td><em>Mycobacterium, Nocardia</em></td>
<td>Widely available; takes 1 hour; reliable stain for Mycobacteria</td>
</tr>
<tr>
<td>Acridine orange*</td>
<td>Bacteria, fungi; † Acanthamoeba</td>
<td>Requires use of epifluorescent microscope; rapid (2 minutes)</td>
</tr>
<tr>
<td>Calcofluor white</td>
<td>Fungi; ‡ Acanthamoeba</td>
<td>Requires use of epifluorescent microscope; rapid (2 minutes)</td>
</tr>
</tbody>
</table>

* Most useful stains for screening purposes.
† PAS (periodic acid-Schiff) and GMS (Gomori methenamine silver) also can be used to identify fungi.
‡ H&E (hematoxylin and eosin) and PAS also can be used to identify *Acanthamoeba.*

Source: Bacterial Keratitis Preferred Practice Pattern, AAO, 2013.
# Cultures

## TABLE A5  
**CULTURE AND TRANSPORT MEDIA FOR BACTERIAL KERATITIS**

<table>
<thead>
<tr>
<th>Media</th>
<th>Common Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard</strong></td>
<td></td>
</tr>
<tr>
<td>Blood agar</td>
<td>Aerobic and facultatively anaerobic bacteria, including <em>P. aeruginosa</em>, <em>S. aureus</em>, <em>S. epidermidis</em>, and <em>S. pneumoniae</em></td>
</tr>
<tr>
<td>Chocolate agar</td>
<td>Aerobic and facultatively anaerobic bacteria, including <em>H. influenzae</em>, <em>N. gonorrhea</em>, and <em>Bartonella</em> species</td>
</tr>
<tr>
<td>Thioglycollate broth</td>
<td>Aerobic and facultatively anaerobic bacteria</td>
</tr>
<tr>
<td>Sabouraud dextrose agar</td>
<td>Fungi</td>
</tr>
<tr>
<td><strong>Supplemental</strong></td>
<td></td>
</tr>
<tr>
<td>Anaerobic blood agar (CDC, Schaedler, Brucella)</td>
<td><em>P. acnes</em>, <em>Peptostreptococcus</em></td>
</tr>
<tr>
<td>Löwenstein-Jensen medium</td>
<td><em>Mycobacterium</em> species, <em>Nocardia</em> species</td>
</tr>
<tr>
<td>Middlebrook agar</td>
<td><em>Mycobacterium</em> species</td>
</tr>
<tr>
<td>Thayer-Martin agar</td>
<td>Pathogenic <em>Neisseria</em> species</td>
</tr>
<tr>
<td><strong>Transport</strong></td>
<td></td>
</tr>
<tr>
<td>BHI (brain heart infusion [Oxoid]) medium</td>
<td>Aerobic and facultatively anaerobic bacteria</td>
</tr>
<tr>
<td>Amies medium without charcoal</td>
<td>Aerobic and facultatively anaerobic bacteria; Fungi</td>
</tr>
</tbody>
</table>

**NOTE:** Fungi and *Acanthamoeba* can be recovered on blood agar. However, more specific media are available (fungi: Sabouraud dextrose agar, brain-heart infusion agar, *Acanthamoeba*: buffered charcoal yeast extract, non-nutrient agar with *E. coli* overlay).

Source: Bacterial Keratitis Preferred Practice Pattern, AAO, 2013.
Steroids

Corticosteroids for Bacterial Keratitis:

The Steroids for Corneal Ulcers Trial (SCUT)

Muthiah Srinivasan, MD, Jeena Mascarenhas, MD, Revathi Rajaraman, MD, Meenakshi Ravindran, MD, Prajna Lalitha, MD, David V. Glidden, PhD, Kathryn J. Ray, MA, Kevin C. Hong, BA, Catherine E. Oldenburg, MPH, Salena M. Lee, OD, Michael E. Zegans, MD, Stephen D. McLeod, MD, Thomas M. Lietman, MD, Nisha R. Acharya, MD, MS, and for the Steroids for Corneal Ulcers Trial Group


The Steroids for Corneal Ulcers Trial (SCUT): Secondary 12-Month Clinical Outcomes of a Randomized Controlled Trial

MUTHIAH SRINIVASAN, JEENA MASCARENHAS, REVATHI RAJARAMAN, MEENAKSHI RAVINDRAN, PRAJNA LALITHA, KIERAN S. O’BRIEN, DAVID V. GLIDDEN, KATHRYN J. RAY, CATHERINE E. OLDENBURG, MICHAEL E. ZEGANS, JOHN P. WHITCHEER, STEPHEN D. MCLEOD, TRAVIS C. PORCO, THOMAS M. LIETMAN, AND NISHA R. ACHARYA, FOR THE STEROIDS FOR CORNEAL ULCERS TRIAL GROUP

Steroids

- On initial presentation, may consider stopping or tapering steroid and/or NSAID drops!
- Use steroids with caution
- SCUT trial
  - Topical corticosteroid vs placebo therapy (500 patients)
  - At 3 months:
    - No difference in BSCVA
    - Data suggests Nocardia ulcers fared worse with steroids
    - No harm overall
  - At 12 months:
    - Steroids may be associated with improved long-term visual outcomes among ulcers not caused by Nocardia
When do you feel patient is better off being managed by a cornea specialist rather than by you in the office?

- Central location of ulcer
- Increasing pain
- Enlarging epithelial defect and/or infiltrate
- Adjacent or involving sclera (add systemic antibiotic)
- Stromal thinning, desmetocele
- Lack of improvement on fluoroquinolone monotherapy (?MRSA)
- Monocular patients
- Anterior chamber inflammation, hypopyon
- Non-compliance
- Perforation
- Risk factors for poor healing (e.g., diabetes, poor lid function, etc.)
CXL for Infectious Keratitis

- Perform anterior segment OCT first, then crosslink infected cornea

(Cornea 2006;25:1057–1059)
CXL for Infectious Keratitis
Gluing

- Fibrin glue (Tisseel, Evicel, Artiss) can be used to seal perforations (less than 2-3 mm)
- Can also be used for areas of impending perforation
- Several techniques
- Glue video (coming...
Contact Lens

- Soft contact lens
- Rigid gas permeable lens
- Hybrid lens
- Piggyback lens system
- Semi-scleral or scleral lens
- Prosthetic Replacement of Ocular Surface Ecosystem (PROSE)
Surgical Options

- Phototherapeutic Keratectomy (PTK)
- Keratoplasty
  - Lamellar: Deep Anterior Lamellar Keratoplasty (DALK)
  - Full-thickness: Penetrating Keratoplasty (PK)
- Keratoprosthesis (KPro)
  - Lamellar: KeraKlear KPro
  - Full thickness: Boston KPro
Artificial Corneas
THANK YOU!