Microbial and Parasitic Infections Of the Cornea and Sclera
- Contact Lens–Related Infectious Keratitis
- Bacterial keratitis
- Atypical Mycobacteria
- Fungal Keratitis
- Acanthamoeba Keratitis
- Corneal Stromal Inflammation Associated With Systemic Infections
- Microsporidiosis
- Loiasis
- Microbial Scleritis
CONTACT LENS–RELATED INFECTIOUS KERATITIS
PATHOGENESIS

- Contact lens wear: *most common risk factor in developed countries*

- Why?
  - Introduction of a contaminated foreign body to the corneal surface
  - Interruption of normal tear flow, essential to corneal immunity
  - Induction of corneal epithelial micro trauma
  - Alteration of ocular surface immunity
  - Induction of corneal hypoxia
  - Hygiene-related factors
MANAGEMENT

- **Patching** of any corneal epithelial defect or corneal infiltrate in a contact lens wearer: **absolutely contra indicated**

- **Bacteria** are most the common pathogen

- **Coverage for the most common** bacterial pathogen in contact lens–related keratitis, *Pseudomonas aeruginosa*

- *Acanthamoeba and fungal* pathogens should be **suspected** if the clinical presentation or **clinical course is atypical**.
BACTERIAL KERATITIS
GENERAL

- **Common** sight-threatening condition.
- May have **explosive onset** and rapidly progressive stromal inflammation.
- **Untreated**, it often leads to progressive tissue destruction with corneal perforation or extension of infection to adjacent tissue.
- Epidemiologic studies in Australia have estimated the **annual incidence** of cosmetic contact lens–related ulcerative keratitis at 0.21% for individuals using extended-wear soft lenses and 0.02% for patients using daily-wear soft lenses.
RISK FACTORS

- Contact lens wear
- Trauma
- Contaminated ocular medications
- Impaired defense mechanisms
- Altered structure of the corneal surface
PATHOGENESIS

- First **adhesion** to the cornea

- **Proliferation and invasion** corneal stroma, often with the aid of bacteria-specific proteases

- Reactive host inflammation begins, leading to characteristic **corneal necrosis**

- Reduction of bacterial loads and, potentially, direct control of the inflammatory response may reduce keratolysis.
CLINICAL PRESENTATION

- **Rapid onset** of
  - pain
  - conjunctival injection
  - photophobia
  - decreased vision

- **Bacterial** corneal ulcers are typically a **single infiltrate** and show a sharp epithelial demarcation with underlying dense, **suppurative stromal inflammation** that has indistinct edges and is surrounded by stromal edema
  - *P. aeruginosa* typically produces **stromal necrosis** with a shaggy surface and adherent mucopurulent exudate
Infections caused by slow-growing, fastidious organisms such as mycobacteria or anaerobes may have a non supplicative infiltrate and intact epithelium.

Infectious crystalline keratopathy presents as densely packed, white, branching aggregates of organisms in the virtual absence of a host inflammatory response, shielded by the bacterial biofilm coating.

Risk factors:
- corticosteroid use
- contact lens wear,
- previous corneal surgery

Bacterial species, most commonly α-hemolytic *Streptococcus* species

Fungal species
LABORATORY EVALUATION

- The **prevalence** of a particular causative organism depends on the **geographic location and risk factors**

- **Clinical appearance** of the infection is an **unreliable guide** in determining the causative pathogen

- In addition to culturing the cornea, it may be helpful to **culture contact lenses, contact lens cases, solutions**, and any other potentially contaminating sources, such as inflamed eyelids.

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**Table 5-5 Causes of Bacterial Keratitis**

<table>
<thead>
<tr>
<th>Common Organisms</th>
<th>Uncommon Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td><em>Neisseria</em> spp</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td><em>Moraxella</em> spp</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> and other <em>Streptococcus</em> spp</td>
<td><em>Mycobacterium</em> spp</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> (most common organism in soft contact lens wearers)</td>
<td><em>Nocardia</em> spp</td>
</tr>
<tr>
<td>Enterobacteriaceae (<em>Proteus, Enterobacter, Serratia</em>)</td>
<td>Non-spore-forming anaerobes</td>
</tr>
<tr>
<td></td>
<td><em>Corynebacterium</em> spp</td>
</tr>
</tbody>
</table>
MANAGEMENT

- Initial therapy: empiric, topical broad-spectrum coverage

- Therapy must be initiated before definitive diagnosis is obtained in order to rapidly reduce the bacterial load and minimize later visual disability

- Routine corneal ulcers: monotherapy with topical fluoroquinolones provides outcomes equivalent to those of combination therapy, because of the excellent penetration achieved with commercially available concentrations of fluoroquinolones

  - Every 30–60 minutes and then tapered in frequency according to the clinical response
  - In severe cases, administration of antibiotics every 5 minutes for 30 minutes
  - Third- and fourth-generation fluoroquinolones have improved gram-positive and atypical mycobacterial coverage but limited activity against MRSA.
MANAGEMENT

- Alternatively, topical combination therapy with an agent active against gram-positive bacteria and another agent active against gram-negative bacteria can be used as initial therapy.

- **Combination therapy** may be warranted if monotherapy fails or if at initial presentation the ulcer is large, vision threatening, or atypical in nature.

- Effectively treated, most infectious keratitis is culture-negative after 48–72 h, but treatment should be continued until substantial control of the infection is seen.

- Thereafter, a prophylactic broad-spectrum antibiotic (not a fortified antibiotic) may be given at a therapeutic dose until the corneal epithelium is healed.
### Table 5-6 Initial Therapy for Bacterial Keratitis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Topical Dose</th>
<th>Subconjunctival Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive cocci</td>
<td>Cefazolin</td>
<td>50 mg/mL</td>
<td>100 mg in 0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Vancomycin*</td>
<td>25–50 mg/mL</td>
<td>25 mg in 0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin or</td>
<td>5 or 3 mg/mL</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>gatifloxacin</td>
<td>respectively</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>9–14 mg/mL</td>
<td>20 mg in 0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime</td>
<td>50 mg/mL</td>
<td>100 mg in 0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>3 mg/mL</td>
<td>Not available</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td>Cefazolin</td>
<td>50 mg/mL</td>
<td>100 mg in 0.5 mL</td>
</tr>
<tr>
<td>No organism or multiple types of organisms</td>
<td>with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>9–14 mg/mL</td>
<td>20 mg in 0.5 mL</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>3 or 5 mg/mL</td>
<td>Not available</td>
</tr>
<tr>
<td>Gram-negative cocci</td>
<td>Ceftriaxone</td>
<td>50 mg/mL</td>
<td>100 mg in 0.5 mL</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>gatifloxacin</td>
<td>respectively</td>
<td></td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Clarithromycin</td>
<td>10 mg/mL 0.03%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin or</td>
<td>5 or 3 mg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gatifloxacin</td>
<td>respectively</td>
<td></td>
</tr>
</tbody>
</table>

*For resistant *Staphylococcus* species.
MANAGEMENT

Preparation of topical antibiotics

**Cefazolin 50 mg/mL**
1. Add 9.2 mL of artificial tears to a vial of cefazolin in 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.

**Vancomycin 50 mg/mL**
1. Add 10 mL of 0.9% sodium chloride for injection USP (no preservatives) or artificial tears to a 500-mg vial of vancomycin to produce a solution of 50 mg/mL.
2. Refrigerate and shake well before instillation.

**Ceftazidime 50 mg/mL**
1. Add 9.2 mL of artificial tears to a vial of ceftazidime 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**
1. Withdraw 2 mL of tobramycin injectable vial (40 mg/mL).
2. Add 2 mL to a tobramycin ophthalmic solution (5 mL) to give a 14 mg/mL solution.
3. Refrigerate and shake well before instillation.
MANAGEMENT

- **Systemic antibiotics** and intensive topical antibiotics are indicated in cases with suspected **scleral and/or intraocular extension** of infection.

- If cultures are performed, initial broad-spectrum therapy should continue until an organism is recovered.

- Once the microbe is **identified**, or the clinical response suggests the change, **appropriate** monotherapy may be considered.

- Parameters useful to **monitor clinical response** to therapy:
  - Blunting of the perimeter of the stromal infiltrate
  - Decreased density of the stromal infiltrate
  - Reduction of stromal edema endothelial inflammatory plaque
  - Reduction in anterior chamber inflammation
  - Re-epithelialization
  - Cessation of corneal thinning
Corticosteroid therapy for bacterial keratitis remains **controversial**

Corticosteroids are effective at modifying inflammatory response, but they also **inhibit the host response** to infection.

As there is still significant risk associated with corticosteroid use in patients with bacterial or other forms of infectious keratitis not appropriately treated, following are **recommended criteria** for instituting corticosteroid therapy for bacterial keratitis:

- Corticosteroids should **not be used in the absence of appropriate antibiotic therapy**.
- The patient must be able to return for **frequent follow-up** examinations and demonstrate adherence to appropriate antibiotic therapy.
- No other associated virulent or difficult-to-eradicate organism is found or suspected.
MANAGEMENT

- Penetrating keratoplasty (PK)
  - Progression despite the therapy
  - Descemetocoele formation or perforation
  - No response to antimicrobial therapy
  - **Interrupted sutures** are recommended as peripheral iridectomies
ATYPICAL MYCOBACTERIA
GENERAL

- Important pathogens in post-LASIK infections

- The most common pathogens are *Mycobacterium fortuitum* and *Mycobacterium chelonei*, which may be found in soil and water

- Delayed-onset post-refractive infections, classically with recalcitrant, non-suppurative infiltrates.

- Diagnosis with acidfast stain or culture on Lowenstein-Jensen media

- Treatments include oral and topical clarithromycin, moxifloxacin, and gatifloxacin.
FUNGAL KERATITIS
PATHOGENESIS

- **Less common** than bacterial, 5-10% in US
- **Trauma** with plant or vegetable leading risk factor
- Other risk factors:
  - Contact lens wear
  - Topical corticosteroids
  - Immunocompromised hosts
  - Systemic corticosteroid and immunosuppressant
  - Corneal surgery
CLINICAL PRESENTATION

- Fewer inflammatory signs and symptoms during the initial period than bacterial keratitis and may have little or no conjunctival injection upon initial presentation.

- Pain can be out of proportion to the relatively uninflamed cornea

- Filamentous fungal: a gray-white, dry-appearing infiltrate that has irregular feathery or filamentous margins

- Occasionally, multifocal or satellite infiltrates may be present

- Deep stromal infiltrate and hypopyon may occur

- As the keratitis progresses, intense suppuration may develop
LABORATORY EVALUATION

- The fungal cell wall stains with Gomori methenamine silver but, except for Candida, does not take up Gram stain.

- **Blood, Sabouraud’s, and brain–heart** infusion media: preferred media for fungal culture.

- Confocal microscopy **useful** in detecting branching filaments in the cornea.
MANAGEMENT

- **Natamycin 5% suspension:**
  recommended for treatment of most cases of *filamentous* fungal keratitis

- **Topical amphotericin B (0.15%–0.30%):**
  most efficacious agent available to treat *yeast* keratitis and *Aspergillus* species

- **Topical voriconazole 1%:**
  effective in treating some cases of fungal keratitis *unresponsive to other therapy*
MANAGEMENT

- **Systemic administration**: more severe keratitis or keratitis with intracameral extension
  - ketoconazole (200–600 mg/day)
  - fluconazole (200–400 mg/day)
  - itraconazole (200 mg/day)
  - voriconazole (200–400 mg/day)
  - posaconazole (800 mg/day)

- Alternatively, **intrastromal administration** of aqueous-soluble amphotericin B (5–10 mcg/0.1 cc) or voriconazole (50–100 mcg/0.1 cc)

- **Mechanical debridement** may be beneficial for cases of superficial fungal keratitis
ACANTHAMOEBA KERATITIS
PATHOGENESIS

- Ubiquitous protozoa found in **freshwater and soil**
- May exist as motile trophozoites or dormant cysts
- Associated with **contact lens use**
- **Resistant** to killing by freezing and desiccation
CLINICAL PRESENTATION

- Severe ocular pain, photophobia
- Mildly symptomatic, diffuse punctate epitheliopathy or dendritic epithelial lesion
- Stromal infection typically occurs in the central cornea
- Centered, partial or complete ring infiltrate in the central cornea is frequently observed
- Inflamed corneal nerves, called radial perineuritis or radial keratoneuritis
- Bilateral in 7%–11%
LABORATORY EVALUATION

- Culture
  - Non nutrient agar
  - Characteristic trails form as the motile trophozoites travel across the surface of the culture plate

- Lamellar corneal biopsy may be required

- Confocal microscopy

In vivo confocal microscopy image of Acanthamoeba cysts. (Courtesy of Elmer Y. Tu, MD.)
MANAGEMENT

- **Early diagnosis** is the most important prognostic indicator of a successful treatment outcome.

- The presence of **deep stromal inflammation, a ring infiltrate**, or extracorneal manifestations significantly **worsens the prognosis**.

- Clinical features for Acanthamoeba keratitis rather than HSV:
  - **noncontiguous or multifocal pattern** of granular epitheliopathy and subepithelial opacities (unlike the contiguous, dendritic pattern in HSV keratitis).
  - **disproportionately severe pain** (unlike disproportionately mild pain secondary to trigeminal nerve involvement in HSV).
  - Presence of **epidemiologic risk factors** such as contact lens use or exposure to possibly contaminated freshwater.
  - **Failure to respond** to initial antiviral therapy.
MANAGEMENT

Agents used for **topical administration** include

- **Diamidines**: propamidine, hexamidine
- **Biguanides**: polyhexamethylene biguanide (polyhexanide), chlorhexidine
- **Aminoglycosides**: neomycin, paromomycin
- **Imidazoles/triazoles**: voriconazole, miconazole, clotrimazole, ketoconazole, itraconazole

The mainstay of pharmacologic treatment: biguanide, with a diamidine sometimes used early in the course of therapy, although successful resolution can be achieved with a biguanide alone. When compared, chlorhexidine 0.02% and polyhexamethylene biguanide (PHMB) 0.02% did not show any difference. Single-agent systemic voriconazole treatment has been shown to be efficacious in some recalcitrant cases.

Corticosteroid use has not been shown to improve or worsen clinical outcomes.

The judicious use of topical and systemic immunosuppressants in selected cases seem to be valuable after the patient has been treated for a period of at least 2 weeks.

**Keratoplasty:**
- cases that are progressing despite maximal medical therapy
- vision rehabilitation after completion of treatment
CORNEAL STROMAL INFLAMMATION ASSOCIATED WITH SYSTEMIC INFECTIONS
MANAGEMENT

- Nonsuppurative stromal keratitis can be caused by:
  - Reactive arthritis
  - Congenital or acquired syphilis
  - Lyme disease
  - Tuberculosis
  - Leprosy (Hansen disease)
  - Onchocerciasis
MICROSPORIDIOSIS
GENERAL

- Intracellular protozoa

- Increasingly reported as the cause of infection in immunocompetent persons in Southeast Asia

- 2 clinical presentations depending on the immune status:
  - In **immunocompetent** individuals
    - corneal stromal keratitis
  - In patients with **AIDS**
    - conjunctivitis and an epithelial keratopathy
    - possible dissemination the sinuses, respiratory tract, GI tract

- **Detection**: light microscopy, transmission electron microscopy, immunofluorescence antibody techniques
MANAGEMENT

- Restoration of immune function
- Topical fumagillin
- PK in severe cases of corneal thinning
- Recurrence common after treatment discontinuation
- More recent cases self-limited or responsive to a wide array of commercially available topical ophthalmic antibiotics.
LOIASIS
GENERAL

- Filarial nematode (e.g., Loa loa)
- Conjunctivitis, dermatologic manifestations
- From human to human by the bite of an infected female deer fly from West and Central Africa
- A migrating worm moves under the skin (under the periocular skin or bulbar conjunctiva)
GENERAL

- **Extraction of the filarial** worm cures the conjunctivitis

- Antiparasitic treatment for disseminated infestation
  - Diethylcarbamazine is generally given 2 mg/kg 3 times a day for 3 weeks and repeated as necessary
  - Concurrent administration of corticosteroids and/or antihistamines may be necessary to minimize allergic reactions.
MICROBIAL SCLERITIS
PATHOGENESIS

- **Very rare**: extension of microbial keratitis involving the peripheral cornea

- **Trauma and contaminated foreign bodies** are possible risk factors, as well as pterygium surgery

- Can also be a feature of
  - Syphilis,
  - Tuberculosis
  - Leprosy or
    - *Acanthamoeba species*, *Nocardia* species, atypical mycobacteria

- Diffuse or nodular scleritis is an occasional complication of VZV
LABORATORY EVALUATION

- Evaluating suppurative scleritis is similar to evaluating microbial keratitis.
- **Smears and cultures** are obtained before antimicrobial therapy is begun.
- If the overlying epithelium is intact, a scleral or episcleral biopsy should be performed.
MANAGEMENT

- **Topical antimicrobial therapy** is begun just as for microbial keratitis.

- Because of the **difficulty in controlling** microbial scleritis, subconjunctival injections and intravenous antibiotics may also be used.

- **Long-term oral therapy** shows promise.
CONCLUSIONS

- Contact lens wear: most common risk factor of infectious keratitis in developed countries

- **Patching** of any corneal epithelial defect or corneal infiltrate in a contact lens wearer: absolutely contra indicated

- When bacteriical keratitis is suspected, **therapy must be initiated** before definitive diagnosis is obtained

- Initial therapy consists of **empiric, topical broad-spectrum coverage**

- Corticosteroid therapy for bacterial keratitis remains **controversial**
CONCLUSIONS

- Infections caused by slow-growing, fastidious organisms such as mycobacteria or anaerobes may have a non suppurative infiltrate and intact epithelium.

- In case of fungal keratitis, fewer inflammatory signs and symptoms and little or no conjunctival injection are typical.

- Acanthamoeba keratitis can be mildly symptomatic, with diffuse punctate epitheliopathy or dendritic epithelial lesion simulating HSV.

- Early diagnosis is the most important prognostic indicator of a successful treatment outcome in Acanthamoeba keratitis.