Bacterial Keratitis
As a service to its members and the public, the American Academy of Ophthalmology has developed a series of guidelines called Preferred Practice Patterns™ that identify characteristics and components of quality eye care.

The Preferred Practice Patterns are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

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Innovation in medicine is essential to assure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients’ needs are the foremost consideration.

All Preferred Practice Patterns are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all Preferred Practice Patterns are current, each is valid for 5 years from the “approved by” date unless superseded by a revision.

Financial Disclosures:
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The Preferred Practice Patterns™ (PPP) series of guidelines has been written on the basis of three principles.

- Each Preferred Practice Pattern® guideline should be clinically relevant and specific enough to provide useful information to practitioners.
- Each recommendation that is made should be given an explicit rating that shows its importance to the care process.
- Each recommendation should be given an explicit rating that shows the strength of evidence that supports the recommendation and reflects the best evidence available.

In the process of revising this document, a detailed literature search of MEDLINE for articles in the English language was conducted on the subject of bacterial keratitis for the years 2000 to February 2005. The results were reviewed by the Cornea/External Disease Panel and used to prepare the recommendations, which they rated in two ways.

The panel first rated each recommendation according to its importance to the care process. This “importance to the care process” rating represents care that the panel thought would improve the quality of the patient’s care in a meaningful way. The ratings of importance are divided into three levels.

- Level A, defined as most important
- Level B, defined as moderately important
- Level C, defined as relevant but not critical

The panel also rated each recommendation on the strength of evidence in the available literature to support the recommendation made. The “ratings of strength of evidence” also are divided into three levels.

- Level I includes evidence obtained from at least one properly conducted, well-designed randomized controlled trial. It could include meta-analyses of randomized controlled trials.
- Level II includes evidence obtained from the following:
  - Well-designed controlled trials without randomization
  - Well-designed cohort or case-control analytic studies, preferably from more than one center
  - Multiple-time series with or without the intervention
- Level III includes evidence obtained from one of the following:
  - Descriptive studies
  - Case reports
  - Reports of expert committees/organizations (e.g., PPP panel consensus with peer review)

The evidence is that which supports the value of the recommendation as something that should be performed to improve the quality of care. The panel believes that it is important to make available the strength of the evidence underlying the recommendation. In this way, readers can appreciate the degree of importance the panel attached to each recommendation and they can understand what type of evidence supports the recommendation.

The ratings of importance and the ratings of strength of evidence are given in bracketed superscripts after each recommendation. For instance, "[A:II]" indicates a recommendation with high importance to clinical care [A], supported by sufficiently rigorous published evidence, though not by a randomized controlled trial [II].

The sections entitled "Orientation" and "Background" do not include recommendations; rather they are designed to educate and provide summary background information and rationale for the recommendations that are presented in the Care Process section. A summary of the major recommendations for care is included in Appendix 1.
ORIENTATION

ENTITY
Bacterial keratitis, which includes entities with the following ICD-9 classifications:
- Corneal ulcer (370.0)
- Corneal ulcer, unspecified (370.00)
- Marginal corneal ulcer (370.01)
- Ring corneal ulcer (370.02)
- Central corneal ulcer (370.03)
- Hypopyon ulcer (370.04)
- Perforated corneal ulcer (370.06)
- Corneal abscess (370.55)

DISEASE DEFINITION
Bacterial keratitis is a disease of the cornea caused by bacterial infection.

PATIENT POPULATION
Individuals of all ages who present with symptoms and signs suggestive of bacterial keratitis such as pain, redness, blurred vision, ocular discharge, corneal infiltrates, and ulcerations.

ACTIVITY
Diagnosis and management of the patient with bacterial infection of the cornea.

PURPOSE
The purpose of diagnosis and management of patients with bacterial keratitis is to minimize visual loss, relieve pain, eliminate the infectious agent, and minimize structural damage to the cornea.

GOALS
- Recognize and reduce risk factors that predispose patients to bacterial infection of the cornea.
- Establish the diagnosis of bacterial keratitis, differentiating it from other causes of keratitis.
- Utilize appropriate diagnostic tests.
- Deliver appropriate therapy.
- Relieve pain.
- Prevent complications, such as intraocular infection, cataract, perforation, and loss of vision.
- Educate patients and their families about treatment and ways to reduce risk factors in the future.

BACKGROUND

EPIDEMIOLOGY
It is estimated that 30,000 cases of microbial keratitis (including bacteria, fungus, and acanthamoeba) occur annually in the United States. Bacterial keratitis rarely occurs in the normal eye because of the human cornea's natural resistance to infection. However, predisposing factors including contact lens wear; trauma; corneal surgery; ocular surface disease including tear deficiencies and corneal abnormalities; systemic diseases, and immunosuppression may alter the defense mechanisms of the ocular surface and permit bacteria to invade the cornea (see Risk Factors).
Causes of bacterial keratitis are listed in Table 1. The most common pathogenic organisms identified in bacterial keratitis include gram-negative rods (Pseudomonas species), Staphylococci and Streptococci. Studies differ regarding the epidemiology of bacterial keratitis. A review of 30 years of cultures for suspected infectious keratitis in Miami showed that gram-positive isolates remained relatively stable and gram-negative isolates declined. A review of 5 years of bacterial isolates from cases of bacterial keratitis in Pittsburgh showed gram-positive isolates decreasing while gram-negative isolates remained relatively stable. A review of 15 years of bacterial isolates from cases of keratitis in London showed that the Pseudomonas species increased in proportion to organisms identified, but there was no overall increase in the proportion of gram-negative isolates. In bacterial keratitis associated with the use of cosmetic contact lenses, Pseudomonas is the most commonly identified etiologic agent, accounting for up to two-thirds of cases. A review from Florida found that Serratia marcescens was as commonly isolated as Pseudomonas aeruginosa in contact lens-associated keratitis. Pseudomonas is also a common pathogen in bacterial keratitis that occurs in hospitalized infants and in adults who are respirator dependent.

<table>
<thead>
<tr>
<th>Class/Organism</th>
<th>Common Isolates*</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-Positive Isolates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive Cocci</td>
<td>Staphylococcus aureus</td>
<td>4–30</td>
</tr>
<tr>
<td></td>
<td>Coagulase negative Staphylococci</td>
<td>5-40</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pneumonia</td>
<td>1-25</td>
</tr>
<tr>
<td></td>
<td>Streptococcus viridans group</td>
<td>1-15</td>
</tr>
<tr>
<td>Gram-positive Bacilli</td>
<td>Corynebacterium species</td>
<td>1-5</td>
</tr>
<tr>
<td></td>
<td>Propionibacterium species</td>
<td>1-12</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium species</td>
<td>1-2</td>
</tr>
<tr>
<td>Gram-Negative Isolates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative Bacilli</td>
<td>Pseudomonas aeruginosa</td>
<td>5-45</td>
</tr>
<tr>
<td></td>
<td>Serratia marcescens</td>
<td>1-12</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis</td>
<td>1-5</td>
</tr>
<tr>
<td></td>
<td>Enteric gram-negative bacilli, other</td>
<td>1-10</td>
</tr>
<tr>
<td>Gram-negative Coccobacillary organisms</td>
<td>Haemophilus influenzae, other Haemophilus species</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td>Moraxella species and related species</td>
<td>1-5</td>
</tr>
<tr>
<td>Gram-negative Cocci</td>
<td>Neisseria species</td>
<td>1</td>
</tr>
</tbody>
</table>

*R* Regional differences may affect the order and percentage of pathogens.

Ranges are derived from the following sources:


RISK FACTORS

There are four categories of risk factors that predispose patients to bacterial keratitis.

Exogenous Factors
- Use of contact lenses, especially on an extended-wear basis. (High prevalence of inadequate contact lens disinfection, contact lens storage-case contamination, and contaminated contact lens solutions among contact lens users have been reported. However, bacterial keratitis has occurred in patients with apparently good compliance with contact lens care regimens.)
- Trauma, including chemical and thermal injuries, foreign bodies, and local irradiation
- Previous ocular and eyelid surgery
- Loose sutures
- Previous corneal surgery, including refractive surgery and penetrating keratoplasty
- Medication related and medicamentosa (e.g., contaminated ocular medications, topical nonsteroidal anti-inflammatory drugs, anesthetics, steroids, antimicrobials, preservatives, glaucoma medications)
- Immunosuppression (topical and systemic)
- Factitious disease, including anesthetic abuse

Ocular Surface Disease
- Misdirection of eyelashes
- Abnormalities of eyelid anatomy and function (including exposure)
- Tear film deficiencies
- Adjacent infection: conjunctivitis including gonococcal, blepharitis, canalliculitis, dacryocystitis

Corneal Epithelial Abnormalities
- Neurotrophic keratopathy (neuropathy of cranial nerve V, herpes keratitis)
- Disorders predisposing to recurrent erosion of cornea
- Viral keratitis (herpes simplex or zoster keratitis)
- Corneal epithelial edema, especially bullous keratopathy

Systemic Conditions
- Diabetes mellitus
- Debilitating illness, especially malnourishment and/or respirator dependence
- Collagen vascular disease
- Substance abuse
- Dermatological/mucous membrane disorders (e.g., Stevens-Johnson syndrome, ocular cicatrical pemphigoid)
- Immunocompromised status
- Atopic dermatitis/blepharoconjunctivitis
- Gonococcal infection with conjunctivitis
- Vitamin A deficiency

NATURAL HISTORY

While some forms of bacterial keratitis may not result in corneal scarring and visual loss, most are associated with corneal scarring or tissue alteration and the risk of subsequent loss of vision. Untreated bacterial keratitis may result in corneal perforation, with the potential for development of endophthalmitis and loss of the eye. Because this process of destruction can take place rapidly (within 24 hours when the infection is caused by a virulent organism), optimal management requires rapid recognition and timely institution of therapy. Bacterial keratitis can occur in any part of the cornea, but infections involving the central cornea are of paramount importance. Scarring in this location has the potential to cause significant visual loss, even if the infecting organism is successfully eradicated. While some bacteria (e.g., gonococcus) can invade an intact corneal
epithelium, most bacterial keratitis develops at the site of an abnormality or defect in the corneal surface.

The rate of disease progression is dependent on the virulence of the infecting organism and on host factors (see Risk Factors, and Prevention and Early Detection). For example, highly virulent organisms such as Pseudomonas or gonococcus cause rapid tissue destruction, while other organisms such as nontuberculous mycobacteria and viridans-type Streptococcus are usually associated with a more indolent course. Some bacteria, which are considered to be normal conjunctival flora (e.g., Corynebacteria), may become opportunistic pathogens in the compromised eye.

**PREVENTION AND EARLY DETECTION**

Avoiding or correcting predisposing factors may reduce the risk of bacterial keratitis. For example, screening patients for predisposing factors and educating them about the risks of extended-wear lenses\(^\text{20}\) and proper contact lens care\(^\text{13}\) may reduce the incidence of bacterial keratitis in those who wear contact lenses. Most ocular trauma can be avoided by using protective eyewear for sports and other high-risk activities.\(^\text{21}\)

Early detection and treatment are imperative to prevent permanent visual loss. Patients with risk factors predisposing them to bacterial keratitis should be educated as to their relative risk and acquainted with the symptoms of the condition. Patients should be informed that if they experience such warning signs, they should consult an ophthalmologist promptly. Ocular surface disease such as corneal epithelial defects, severe tear deficiency, or lagophthalmos should be treated. In patients with acute or chronic epithelial defects, prophylactic antibiotics can be considered; however, the routine use of prophylactic topical antibiotics in this setting is controversial because their efficacy has not been established and use may promote growth of resistant organisms.

**CARE PROCESS**

**PATIENT OUTCOME CRITERIA**

Outcome criteria for treating bacterial keratitis include the following:

- Resolved corneal inflammation
- Reduced pain
- Resolved infection
- Restored corneal integrity and minimal scarring and vascularization
- Restored visual function

**DIAGNOSIS**

Evaluation of the patient with presumed bacterial keratitis includes those features of the comprehensive medical eye evaluation\(^\text{22, 23}\) specifically relevant to bacterial keratitis as listed below.

**History**

Obtaining a detailed history is important in evaluating patients with bacterial keratitis. Pertinent information includes the following:

- Ocular symptoms\(^\text{A,III}\) (e.g., degree of pain, redness, discharge, blurred vision, photophobia, duration of symptoms, circumstances surrounding the onset of symptoms)
Review of prior ocular history, including risk factors such as contact lens wear, swimming or using a hot tub while wearing contact lenses, herpes simplex virus keratitis, herpes zoster virus keratitis, previous bacterial keratitis, previous ocular surgery including refractive surgery, trauma, and dry eye

Review of other medical problems

Current ocular medications and medications recently used

Medication allergies

Examination

The physical examination includes measurement of visual acuity, an external examination, and slit-lamp biomicroscopy.

Visual Acuity

In many cases, patient discomfort, tearing, and inflammation will compromise visual acuity. It is useful, however, to document baseline visual acuity and to ascertain that it is consistent with the anterior segment examination.

External Examination

An external examination should be performed with particular attention to the following:

- General appearance of the patient including skin conditions
- Facial examination
- Eyelids and eyelid closure
- Conjunctiva
- Nasolacrimal apparatus
- Corneal sensation

Slit-Lamp Biomicroscopy

Slit lamp biomicroscopy should include evaluation of the following:

- Eyelid margins: inflammation, ulceration, eyelash abnormalities including trichiasis, irregularities, lacrimal punctal anomalies
- Conjunctiva: discharge, inflammation, morphologic alterations (e.g., follicles, papillae, cicatrization, keratinization, membrane, pseudomembrane, ulceration, prior surgery), ischemia, foreign bodies, filtering blebs
- Sclera: inflammation (e.g., infectious versus autoimmune), ulceration, scarring/thinning, nodules, ischemia
- Cornea: epithelium, including defects and punctate keratopathy, edema; stroma, including ulceration, thinning, perforation, and infiltrate (location [central, peripheral, perineural, surgical, or traumatic wound], density, size, shape [ring], number [satellite], depth, character of infiltrate margin [suppurative, necrosis, feathery, soft, crystalline], color), edema; endothelium; foreign bodies, including sutures; signs of corneal dystrophies (e.g., epithelial basement membrane dystrophies); previous corneal inflammation (thinning, scarring, or neovascularization); signs of previous corneal surgery (e.g., corneal transplantation, radial keratotomy, astigmatic keratotomy or limbal relaxing incision, LASIK, or other refractive surgery)

Fluorescein or rose bengal staining of the cornea is usually performed and may provide additional information, such as presence of dendrites, pseudo-dendrites, and any epithelial defect.

- Anterior chamber: depth; inflammation, including cell and flare, hypopyon, fibrin, hyphema
- Anterior vitreous: presence of inflammation

Clinical features suggestive of bacterial keratitis include dense suppurative stromal infiltrate (particularly those greater than 1 mm in size) with indistinct edges, edema, and white cell infiltration in surrounding stroma. An epithelial defect is typically present. An anterior chamber reaction is often seen.
**Diagnostic Tests**

**Cultures and Smears**

The majority of community-acquired cases of bacterial keratitis resolve with empiric therapy and are managed without smears or cultures. Smears and cultures are indicated, however, in cases with a corneal infiltrate that is large and extends to the middle to deep stroma, that are chronic in nature or unresponsive to broad spectrum antibiotic therapy, or that have clinical features suggestive of fungal, amoebic, or mycobacterial keratitis. Smears and cultures are often helpful in eyes with an unusual history, e.g., trauma with vegetable matter or using a hot tub while wearing contact lenses. The hypopyon that occurs in eyes with bacterial keratitis is usually sterile, and aqueous or vitreous taps should not be performed unless there is a high suspicion of microbial endophthalmitis. Prior to initiating antimicrobial therapy, cultures are indicated in sight-threatening or severe keratitis of suspected microbial origin.

A culture is a means of identifying the causative organism(s) and the only means of determining sensitivity to antibiotics. Cultures are helpful to guide modification of therapy in patients with a poor clinical response to treatment and to decrease toxicity by eliminating unnecessary drugs. In eyes treated empirically without first obtaining cultures in which the clinical response is poor, obtaining cultures then may be helpful, although a delay in pathogen recovery may occur. If the cultures are negative, the ophthalmologist may consider stopping antibiotic treatment for 12 to 24 hours and then reculturing. Microbial pathogens may be categorized by examining stained smears of corneal scrapings; this may increase yield of identification of pathogen, especially if the patient is on antibacterial therapy. Polymerase chain reaction (PCR) and immunodiagnostic techniques may be useful but are not currently widely available.

Corneal material is obtained by instilling a topical anesthetic agent and using a heat-sterilized platinum (Kimura) spatula, blade, or other similar sterile instrument to obtain scrapings of material from the advancing borders of the infected area of the cornea. A thiol or thioglycollate broth-moistened dacron/calcium alginate or sterile cotton swab may also be used to obtain material. This is most easily performed with slit-lamp magnification.

Corneal scrapings for culture should be inoculated directly onto appropriate culture media in order to maximize culture yield (see Appendix 2). If this is not feasible, specimens should be placed in transport media. In either case, cultures should be immediately incubated or taken promptly to the laboratory. Cultures of contact lenses, lens case, and solution may be useful in situations where acanthamoeba is suspected or corneal cultures are negative. The material for smear is applied to clean glass microscope slides in an even, thin layer (see Appendix 3 for specific diagnostic stains).

**Corneal Biopsy**

Corneal biopsy may be indicated if there has been a lack of response to treatment or if cultures have been negative on more than one occasion and the clinical picture continues to strongly suggest an infectious process. It may also be indicated if the infiltrate is located in the mid or deep stroma with overlying uninvolved tissue. In a cooperative patient, corneal biopsy may be performed while at the slit-lamp or operating microscope. Using topical anesthesia, a small trephine or blade is used to excise a small piece of stromal tissue, which is large enough to allow bisection so that one portion can be sent for culture and the other for histopathology. The biopsy specimen should be delivered to the laboratory in a timely fashion. In cases of a deep corneal abscess with overlying clear cornea, the method should be modified and the biopsy taken from below a lamellar flap.

**Differential Diagnosis**

Differential diagnosis includes infectious and noninfectious causes of infiltrates. Nonbacterial corneal pathogens, including fungi (both yeast and mold), parasites (including protozoa such as acanthamoeba), and nematodes (such as Onchocerca) may cause infiltrative keratitis. Viruses including herpes simplex, varicella zoster, and Epstein-Barr virus produce immunologically mediated cornea infiltrates that may resemble supplicative keratitis. Noninfectious stromal
infiltration may be associated with contact lens wear (particularly extended-wear contact lenses) or antigens from local and systemic bacterial infections. Systemic diseases, such as collagen vascular disorders (rheumatoid arthritis, systemic lupus erythematosus), vasculitic disorders (periarteritis nodosa, Wegener's granulomatosis), and other inflammatory disorders such as sarcoidosis may produce infiltrative keratitis. Other causes include dermatologic disorders (severe rosacea) and allergic conditions (vernal keratoconjunctivitis and atopic keratoconjunctivitis). Corneal trauma, including chemical and thermal injury, and corneal foreign bodies, including exposed or loose sutures, may also lead to infiltrative keratitis, which may be infectious or non-infectious in nature.

**TREATMENT**

**Initial**

Topical antibiotic eye drops are capable of achieving high tissue levels and are the preferred method of treatment in most cases.[A:III] Ocular ointments may be useful at bedtime in less severe cases and also may be useful for adjunctive therapy.

Subconjunctival antibiotics may be helpful where there is imminent scleral spread or perforation or in cases where adherence to the treatment regimen is questionable. Systemic therapy may be useful in cases of scleral or intraocular extension of infection or systemic infection such as gonorrhea. Collagen shields or soft contact lenses soaked in antibiotics are sometimes used and may enhance drug delivery. They may also be useful in cases where there is an anticipated delay in initiating appropriate therapy, but these modalities have not been fully evaluated in terms of the potential risk for inducing drug toxicity. In addition, collagen shields and soft contact lenses can become displaced or lost, leading to unrecognized interruption of drug delivery. In selected cases, the choice of initial treatment may be guided by the results obtained from smears that are diagnostic.

Topical broad-spectrum antibiotics are used initially in the empiric treatment of bacterial keratitis [A:III] (see Table 2). For severe keratitis (e.g., deep stromal involvement or a defect larger than 2 mm with extensive suppuration), a loading dose every 5 to 15 minutes for the first hour, followed by applications every 15 minutes to 1 hour around the clock, is recommended.[A:III] For less severe keratitis, a regimen with less frequent dosing is appropriate. Cycloplegic agents may be used to decrease synechia formation and to decrease pain in more severe cases of bacterial keratitis and are indicated when significant anterior chamber inflammation is present.

Single-drug therapy using a fluoroquinolone (e.g., ciprofloxacin, ofloxacin) has been shown to be as effective as combination therapy utilizing antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics. Some pathogens (e.g., Streptococci, anaerobes) reportedly have variable susceptibility to fluoroquinolones, and the prevalence of resistance to the fluoroquinolones appears to be increasing. Gatifloxacin and moxifloxacin (fourth-generation fluoroquinolones) have been reported to have better coverage of gram-positive pathogens than earlier generation fluoroquinolones in head-to-head in vitro studies. The fourth-generation fluoroquinolones are not yet FDA-approved for the treatment of bacterial keratitis. Although there have been some concerns of increased perforation when utilizing fluoroquinolones in the management of severe bacterial keratitis compared to traditional fortified topical antibiotics (cefazolin and tobramycin), these reports are retrospective, not randomized, and will need confirmation in future studies.

Combination fortified-antibiotic therapy is an alternative to consider for severe infection and for eyes unresponsive to treatment. Treatment with more than one agent may be necessary for non-tuberculous mycobacteria; infection with this pathogen has been reported in association with LASIK. Table 2 contains recommendations for antibiotic therapy and instructions for preparing fortified topical antibiotics.

Systemic antibiotics are rarely needed, but may be considered in severe cases where the infectious process has extended to adjacent tissues (e.g., the sclera) or when there is impending or frank perforation of the cornea. Systemic therapy is necessary in cases of gonococcal keratitis.
<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
<th>Topical Concentration</th>
<th>Subconjunctival Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>No organism identified or multiple types of organisms</td>
<td>Cefazolin with Tobramycin/Gentamicin or Fluoroquinolones</td>
<td>50 mg/ml</td>
<td>100 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9–14 mg/ml</td>
<td>20 mg in 0.5 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 or 5 mg/ml</td>
<td></td>
</tr>
<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>15–50 mg/ml</td>
<td>25 mg in 0.5 ml</td>
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<tr>
<td></td>
<td>Bacitracin*</td>
<td>10,000 IU</td>
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<tr>
<td></td>
<td>Moxifloxacin or Gatifloxacin</td>
<td>3 or 5 mg/ml</td>
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</tr>
<tr>
<td>Gram-negative rods</td>
<td>Tobramycin/Gentamicin</td>
<td>9–14 mg/ml</td>
<td>20 mg in 0.5 ml</td>
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<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 or 5 mg/ml</td>
<td></td>
</tr>
<tr>
<td>Gram-negative cocci†</td>
<td>Ceftriaxone</td>
<td>50 mg/ml</td>
<td>100 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 or 5 mg/ml</td>
<td></td>
</tr>
<tr>
<td>Non-tuberculous mycobacteria</td>
<td>Amikacin</td>
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<td>20 mg in 0.5 ml</td>
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<td>Clarithromycin†</td>
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<td></td>
<td>Fluoroquinolones</td>
<td>3 or 5 mg/ml</td>
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<td>Amikacin</td>
<td>20–40 mg/ml</td>
<td>20 mg in 0.5 ml</td>
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<tr>
<td></td>
<td>Trimethoprim/sulfamethoxazole:</td>
<td>16 mg/ml</td>
<td></td>
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<td></td>
<td></td>
<td>80 mg/ml</td>
<td></td>
</tr>
</tbody>
</table>

* For resistant Enterococcus and Staphylococcus species and penicillin allergy. Vancomycin and bacitracin have no gram-negative activity and should not be used as a single agent in empirically treating bacterial keratitis.
† Systemic therapy is necessary for suspected gonococcal infection.
‡ Dosage for oral systemic therapy in adults is 500 mg every 12 hours. Topical therapy has had some success but the medication is irritating and clinical experience is limited.

**NOTES FOR TABLE 2: PREPARATION OF FORTIFIED TOPICAL 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 of tobramycin or gentamicin injectable vial (40 mg/ml).
2. Add 2 ml to a tobramycin or gentamicin ophthalmic solution (5 ml) to give a 14 mg/ml solution.

**Vancomycin 15 mg/ml, Vancomycin 25 mg/ml or Vancomycin 50 mg/ml**
1. Add 33 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 15 mg/ml. Add 20 ml of 0.9% sodium chloride for injection USP (no preservatives) or artificial tears to produce a solution of 25 mg/ml. 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.

**Amikacin**
Intravenous formulation can be used (80 mg/2 cc ampules).

**Trimethoprim/sulfamethoxazole**
16 mg/ml and 80 mg/ml commercial preparation can be used.

Adapted from Basic Clinical and Science Course 2005-2006, Section 8, External Disease and Cornea. Table 7-6. San Francisco: American Academy of Ophthalmology.
Frequency of re-evaluation of the patient with bacterial keratitis depends on the extent of disease, but severe cases (e.g., deep stromal involvement or larger than 2 mm with extensive suppuration) initially should be followed at least daily until clinical improvement or stabilization is documented.\[A:III\]

**Modification of Therapy**

The efficacy of the therapeutic regimen is judged primarily by the clinical response. The results of cultures and sensitivity testing may impact therapeutic decision making, especially if the patient is not responding to initial therapy. If the patient is improving, however, therapy need not be adjusted solely on the basis of laboratory studies. Dual antibiotic treatment designed to achieve broad spectrum coverage may become unnecessary once the causative organism has been isolated.

In general, the initial therapeutic regimen should be modified when the eye shows a lack of improvement or stabilization within 48 hours.\[A:III\] Keratitis due to Pseudomonas and other gram-negative organisms may exhibit increased inflammation during the first 24 to 48 hours despite appropriate therapy. Several clinical features suggest a positive response to antibiotic therapy:  
- Reduction in pain
- Reduced amount of discharge
- Lessened eyelid edema or conjunctival injection
- Consolidation and sharper demarcation of the perimeter of the stromal infiltrate
- Decreased density of the stromal infiltrate in the absence of progressive stromal loss
- Reduced stromal edema and endothelial inflammatory plaque
- Reduced anterior chamber cell, fibrin, or hypopyon
- Initial re-epithelialization
- Cessation of progressive corneal thinning

Modification of therapy may mean a change in the type, concentration, or frequency of antibiotic treatment. Adjunctive therapy such as a temporary or permanent tarsorrhaphy may also be considered.

Topical therapy is tapered according to clinical response, taking into account the severity of the initial clinical picture and the virulence of the pathogen. Specific tapering recommendations are difficult to make, due to wide variability in the severity of the infectious process in individual cases. Factors that may mandate more prolonged therapy include the presence of virulent or indolent organisms or presence of immunocompromise.

**Indications for Reculture**

Lack of a favorable clinical response, particularly in the setting of negative culture results, suggests the need for reculture and/or biopsy. Toxicity from medications or steroid withdrawal may be confused with antibiotic failure, and medicamentosa may be a potential cause of an apparent lack of clinical improvement. Discontinuation of antibiotics for 12 to 24 hours prior to reculture may increase culture yield. Selected media capable of supporting the growth of atypical microorganisms may also increase culture yield and can be considered, e.g., Löwenstein-Jensen media for atypical mycobacteria. (See Appendix 2.)

**Corticosteroid Therapy**

Topical corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis. The potential advantage is the probable suppression of inflammation and reduction of subsequent corneal scarring, which can cause visual loss. Potential disadvantages include recrudescence of infection, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting, and increased intraocular pressure. There is no conclusive scientific evidence indicating that steroids alter clinical outcome. Despite the risks involved, many experts believe that the judicious use of topical corticosteroids in the treatment of bacterial keratitis can reduce morbidity. Patients being treated with ocular topical corticosteroids at the time of presentation of...
suspected bacterial keratitis should have their corticosteroid regimen reduced or eliminated until the infection has been controlled.\textsuperscript{[A:III]}

The objective in topical corticosteroid therapy is to use the minimum amount of corticosteroid required to achieve control of inflammation. Successful treatment requires optimal timing, careful dose regulation, use of adequate concomitant antibacterial medication, and close follow-up. Patient compliance is essential, and the intraocular pressure must be monitored frequently. The patient should be examined within 1 to 2 days after initiation of topical corticosteroid therapy.\textsuperscript{[A:III]}

In cases where the corneal infiltrate compromises the visual axis, topical corticosteroid therapy may be added to the regimen following at least 2 to 3 days of progressive improvement with topical antibiotic treatment. Topical antibiotics, which are generally administered more frequently than corticosteroids during treatment of active infection, are continued at high levels with gradual tapering.

**Therapy for Complicated Cases**

Additional treatment is necessary in cases where the integrity of the eye is compromised, such as an extremely thin corneal surface, or impending or frank perforation, or where there is progressive or unresponsive disease or endophthalmitis. Application of tissue adhesive, lamellar keratoplasty, and penetrating keratoplasty are among the treatment options.

**PROVIDER AND SETTING**

The diagnosis and management of patients with bacterial keratitis require the clinical training and experience of an ophthalmologist because the disease has the potential to cause visual loss or blindness and because the ophthalmologist is familiar with medical conditions associated with bacterial keratitis.\textsuperscript{[A:III]} Severe cases, or those that fail to respond to treatment, may be best managed by an ophthalmologist who has extensive expertise with bacterial keratitis.

The majority of patients with bacterial keratitis can be treated on an outpatient basis. Hospitalization may be necessary if the keratitis is severe or vision threatening, if compliance is impractical, or if pain is severe. Compliance may be impractical due to the requirement for frequent instillation of eyedrops (such as every 15 to 30 minutes around the clock), the patient's inability to instill the eyedrops because of age, mental or physical disability, or the lack of an adequate support system at home.

**COUNSELING/REFERRAL**

Patients and care providers should be educated about the destructive nature of bacterial keratitis and the need for strict adherence to the therapeutic regimen.\textsuperscript{[A:III]} The possibility of permanent visual loss and need for future visual rehabilitation should be discussed.\textsuperscript{[A:III]} Patients who wear contact lenses should be educated about the increased risk of infection associated with contact lens wear, overnight wear, and the importance of adherence to techniques that promote contact lens hygiene.\textsuperscript{[A:III]} If the diagnosis or treatment is in question, or if the condition is refractory to treatment, consultation with or referral to an ophthalmologist who has expertise and experience in the management of bacterial keratitis may be desirable. Patients with significant visual impairment or blindness should be referred for vision rehabilitation if they are not candidates for surgical visual rehabilitation.\textsuperscript{[A:III]} A social service referral is also appropriate in cases of severe visual impairment or blindness.
APPENDIX 1. SUMMARY OF MAJOR RECOMMENDATIONS FOR CARE

DIAGNOSIS

History
- Ocular symptoms\textsuperscript{[A:III]}
- Review of prior ocular history\textsuperscript{[A:III]}
- Review of other medical problems\textsuperscript{[A:III]}
- Current ocular medications and medications recently used\textsuperscript{[A:III]}
- Medication allergies\textsuperscript{[A:III]}

Examination
- Visual acuity\textsuperscript{[A:III]}
- General appearance of the patient including skin conditions\textsuperscript{[B:III]}
- Facial examination\textsuperscript{[B:III]}
- Eyelids and eyelid closure\textsuperscript{[A:III]}
- Conjunctiva\textsuperscript{[A:III]}
- Nasolacrimal apparatus\textsuperscript{[B:III]}
- Corneal sensation\textsuperscript{[A:III]}

\textbf{Slit-Lamp Biomicroscopy}
- Eyelid margins\textsuperscript{[A:III]}
- Conjunctiva\textsuperscript{[A:III]}
- Sclera\textsuperscript{[A:III]}
- Cornea\textsuperscript{[A:III]}
- Anterior chamber\textsuperscript{[A:III]}
- Anterior vitreous\textsuperscript{[A:III]}

Diagnostic Tests: Cultures and Smears

Smears and cultures are indicated in cases with a corneal infiltrate that is large and extends to the middle to deep stroma, that are chronic in nature or unresponsive to broad spectrum antibiotic therapy, or that have clinical features suggestive of fungal, amœbic, or mycobacterial keratitis.\textsuperscript{1} [A:III] The hypopyon that occurs in eyes with bacterial keratitis is usually sterile, and aqueous or vitreous taps should not be performed unless there is a high suspicion of microbial endophthalmitis.\textsuperscript{[A:III]}

Prior to initiating antimicrobial therapy, cultures are indicated in sight-threatening or severe keratitis of suspected microbial origin.\textsuperscript{[A:III]}

Corneal scrapings for culture should be inoculated directly onto appropriate culture media in order to maximize culture yield (see Appendix 2).\textsuperscript{2} [A:III] If this is not feasible, specimens should be placed in transport media.\textsuperscript{3} [A:III] In either case, cultures should be immediately incubated or taken promptly to the laboratory.\textsuperscript{[A:III]}

Management recommendations are described in the main body of the text.

FOLLOW-UP EVALUATION

Frequency of re-evaluation of the patient with bacterial keratitis depends on the extent of disease, but severe cases (e.g., deep stromal involvement or larger than 2 mm with extensive suppuration) initially should be followed at least daily until clinical improvement or stabilization is documented.\textsuperscript{[A:III]} In general, the initial therapeutic regimen should be modified when the eye shows a lack of improvement or stabilization within 48 hours.\textsuperscript{[A:III]}
PROVIDER AND SETTING

The diagnosis and management of patients with bacterial keratitis require the clinical training and experience of an ophthalmologist because the disease has the potential to cause visual loss or blindness and because the ophthalmologist is familiar with medical conditions associated with bacterial keratitis. \(^{[A:III]}\) The majority of patients with bacterial keratitis can be treated on an outpatient basis.

COUNSELING/REFERRAL

Patients and care providers should be educated about the destructive nature of bacterial keratitis and the need for strict adherence to the therapeutic regimen. \(^{[A:III]}\) The possibility of permanent visual loss and need for future visual rehabilitation should be discussed. \(^{[A:III]}\) Patients who wear contact lenses should be educated about the increased risk of infection associated with contact lens wear, overnight wear, and the importance of adherence to techniques that promote contact lens hygiene. \(^{4,5}\) \(^{[A:III]}\) Patients with significant visual impairment or blindness should be referred for vision rehabilitation if they are not candidates for surgical visual rehabilitation. \(^{6}\) \(^{[A:III]}\)

REFERENCES

## APPENDIX 2. CULTURE MEDIA

### TABLE 1 CULTURE MEDIA FOR BACTERIAL KERATITIS

<table>
<thead>
<tr>
<th>Standard Media</th>
<th>Common Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood agar</td>
<td>Aerobic and facultatively anaerobic bacteria, including P. aeruginosa, S. aureus, S. epidermidis, S. pneumoniae</td>
</tr>
<tr>
<td>Chocolate agar</td>
<td>Aerobic and facultatively anaerobic bacteria, including H. influenzae, N. gonorrhea, and Bartonella species</td>
</tr>
<tr>
<td>Thioglycollate broth</td>
<td>Aerobic and facultatively anaerobic bacteria</td>
</tr>
</tbody>
</table>

### Supplemental Media

<table>
<thead>
<tr>
<th>Anaerobic blood agar (CDC, Schaedler, Brucella)</th>
<th>P. acnes, Peptostreptococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Löwenstein-Jensen medium</td>
<td>Mycobacteria species, Nocardia species</td>
</tr>
<tr>
<td>Middlebrook agar</td>
<td>Mycobacteria species</td>
</tr>
<tr>
<td>Thayer-Martin agar</td>
<td>Pathogenic Neisseria species</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, blood agar with E. coli overlay).

**References:**
# APPENDIX 3. DIAGNOSTIC STAINS

## TABLE 1 DIAGNOSTIC STAINS FOR BACTERIAL KERATITIS

<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,† amœbæ</td>
<td>Distinguishes gram-positive from gram-negative organisms; widely available; rapid (5 minutes)</td>
</tr>
<tr>
<td>Giemsa stain*</td>
<td>Bacteria, fungi,† chlamydia Acanthamoeba</td>
<td>Basis for Aema-color and Diff-Quik tests; widely available; rapid (2 minutes)</td>
</tr>
<tr>
<td>Acid fast</td>
<td>Mycobacteria, Nocardia</td>
<td>Widely available; takes 1 hour; reliable stain for Mycobacteria</td>
</tr>
<tr>
<td>Acidine orange*</td>
<td>Bacteria, fungi,† acanthamoeba</td>
<td>Requires use of epifluorescent microscope; rapid (2 minutes)</td>
</tr>
<tr>
<td>Calcoflur 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.

References:
RELATED ACADEMY MATERIALS

Basic and Clinical Science Course
   External Disease and Cornea (Section 8, 2005-2006)

Eye Fact Sheets
   Herpes Simplex Eye Disease (2004)
   Herpes Zoster (2004)

Information Statement
   Extended Wear of Contact Lenses (2004)

LEO Clinical Update Course CD-ROM
   Cornea & External Disease (2003)

Patient Education Brochure
   Contact Lenses (2005)

Preferred Practice Patterns
   Comprehensive Adult Medical Eye Evaluation (2005)
   Pediatric Eye Evaluations (2002)

To order any of these materials, please call the Academy’s Customer Service number, 415.561.8540 or visit www.aao.org/store.
REFERENCES


55. American Academy of Ophthalmology. Basic Clinical and Science Course, 2005-2006; Section 8, External Disease and Cornea, pg 172.


