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# Bacterial Keratitis Preferred Practice Pattern®


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Preferred Practice Pattern® guidelines are developed by the Academy's H. Dunbar Hoskins Jr., MD Center for Quality Eye Care without any external financial support. Authors and reviewers of the guidelines are volunteers and do not receive any financial compensation for their contributions to the documents. The guidelines are externally reviewed by experts and stakeholders before publication.

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# CORNEA/EXTERNAL DISEASE PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

The **Cornea/External Disease Preferred Practice Pattern® Panel** members wrote the Bacterial Keratitis Preferred Practice Pattern® guidelines (PPP). The PPP Panel members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in June 2018. The document was edited in response to the discussion and comments.

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The Bacterial Keratitis PPP was then sent for review to additional internal and external groups and individuals in July 2018. All those returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered. Members of the Cornea/External Disease Preferred Practice Pattern Panel reviewed and discussed these comments and determined revisions to the document.

# FINANCIAL DISCLOSURES

In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at www.cmss.org/codeforinteractions.aspx), relevant relationships with industry are listed. The Academy has Relationship with Industry Procedures to comply with the Code (available at www.aao.org/about-preferred-practice-patterns). A majority (70%) of the members of the Cornea/External Disease Preferred Practice Pattern Panel 2017–2018 had no financial relationships to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to October 2018 are available online at www.aao.org/ppp.

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# OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern® guidelines that **identify characteristics and components of quality eye care.** Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern® guidelines 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.

**These documents provide guidance for the pattern of practice, not for the care of a particular individual.** While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

**Preferred Practice Pattern® guidelines are not medical standards to be adhered to in all individual situations.** The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved US Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure 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 Pattern® guidelines are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the "approved by" date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at www.aao.org/about-preferred-practice-patterns) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Bacterial Keratitis PPP are ophthalmologists.

# METHODS AND KEY TO RATINGS

Preferred Practice Pattern® guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Quality, and the American College of Physicians.[3]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

| | |
|---|---|
| I++ | High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias |
| I+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| I- | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias |
| II++ | High-quality systematic reviews of case-control or cohort studies<br>High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal |
| II+ | Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal |
| II- | Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal |
| III | Nonanalytic studies (e.g., case reports, case series) |

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

| | |
|---|---|
| Good quality | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate quality | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Insufficient quality | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate<br>Any estimate of effect is very uncertain |

- Key recommendations for care are defined by GRADE[2] as follows:

| | |
|---|---|
| Strong recommendation | Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not |
| Discretionary recommendation | Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced |

- The Highlighted Findings and Recommendations for Care section lists points determined by the PPP Panel to be of particular importance to vision and quality of life outcomes.
- All recommendations for care in this PPP were rated using the system described above. Ratings are embedded throughout the PPP main text in italics.
- Literature searches to update the PPP were undertaken in February 2017 and June 2018 in PubMed and the Cochrane Library. Complete details of the literature searches are available at www.aao.org/ppp.

# HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

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The majority of community-acquired cases of bacterial keratitis resolve with empiric therapy and are managed without smears or cultures.[4,5] Smears and/or cultures are specifically indicated in the following circumstances: 1) a corneal infiltrate is central, large (>2 mm) and/or associated with significant stromal involvement or melting; 2) the infection is chronic in nature or unresponsive to broad-spectrum antibiotic therapy; 3) there is a history of corneal surgeries; 4) atypical clinical features are present that are suggestive of fungal, amoebic, or mycobacterial keratitis; or 5) infiltrates are in multiple locations on the cornea.[6]

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Topical antibiotics should be prescribed to prevent acute bacterial keratitis in patients presenting with a contact lens-related corneal abrasion.

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Patching the eye in a patient who wears contact lenses and has a corneal abrasion is not advised because of the increased risk of bacterial keratitis. Bandage contact lens use in the management of these epithelial defects remains controversial.

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The use of a cycloplegic agent is an often-overlooked adjunctive treatment and may decrease pain as well as synechia formation in bacterial keratitis. It is indicated when substantial anterior chamber inflammation is present.

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Corticosteroids may be considered after 24 to 48 hours when the causative organism is identified and/or infection is responding to therapy. Corticosteroids should be avoided in cases of infection involving organisms like *Acanthamoeba, Nocardia,* and fungus.

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Awareness of the increased resistance of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* to topical fluoroquinolones is important.

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# INTRODUCTION

## DISEASE DEFINITION

Bacterial keratitis is an infection of the cornea caused by bacteria.

## PATIENT POPULATION

The patient population includes individuals of all ages who present with symptoms and signs suggestive of bacterial keratitis such as pain, redness, blurred vision, discharge, corneal infiltrates, ulcerations, photophobia, and anterior chamber inflammation.

## CLINICAL OBJECTIVES

- Recognize and reduce risk factors that predispose patients to bacterial infection of the cornea
- Establish the diagnosis of bacterial keratitis and differentiate it from other causes of keratitis
- Utilize appropriate diagnostic tests
- Select appropriate therapy to resolve the keratitis
- Relieve pain
- Establish appropriate follow-up
- Prevent complications such as medication toxicity, intraocular infection, cataract, corneal perforation, and loss of vision due to corneal scarring
- Educate patients and their families about treatment and ways to reduce risk factors in the future

# BACKGROUND

## PREVALENCE

Approximately 71,000 cases of microbial keratitis (including bacteria, fungus, and *Acanthamoeba*) occur annually in the United States,[7] with an increasing incidence in recent years.[8] 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,[9,10] trauma, corneal surgery, ocular surface disease,[10] systemic diseases,[11] and immunosuppression, may alter the defense mechanisms of the ocular surface and permit bacteria to invade the cornea (see Risk Factors).

Although the most common pathogenic organisms identified in bacterial keratitis include staphylococci and gram-negative rods (*Pseudomonas* species), studies differ on the epidemiology of bacterial keratitis.[7,12-21] These differences could be associated with weather, rural vs. urban area, etiology of keratitis. A study of two hospitals in Los Angeles found that the majority of cases compromised gram-positive pathogens; coagulase-negative staphylococcus was the most common, and *Pseudomonas aeruginosa* was the most common gram-negative organism.[12] Another review found that gram-negative organisms were much more prevalent in southern US locations than in the northern United States, and south Florida had a higher rate than any other area of the country.[17] A high rate of gram-negative bacterial keratitis was also found in a large county hospital in Houston, Texas.[10]

It is common for multiple bacteria to be present in bacterial keratitis; one study reported that 43% of positive cultures yielded two or more bacterial organisms.[22] Polymicrobial keratitis can also occur. The most common causative organisms in polymicrobial keratitis are *Staphylococcus epidermidis* and *Fusarium* species. In these patients, the most common etiology is trauma.[23,24] The Steroids for Corneal Ulcers Trial (SCUT), a large, multicenter, international prospective treatment study comprising patients predominantly from Southern India, reported *Streptococcus pneumoniae* in 51.5% of cases, *P. aeruginosa* in 22.7%, and *Nocardia* species in 11.5%.[25] Two retrospective analyses from the United Kingdom and Italy found that contact lens use was the most common risk factor for bacterial keratitis.[26,27]

## RISK FACTORS

Risk factors that predispose patients to bacterial keratitis can be divided into two categories: presented below (Box 1 and Box 2). (For more details on risk factors associated with contact lens use, refer to the Refractive Errors & Refractive Surgery PPP.[28])

**Box 1. Extrinsic Factors**

The use of contact lenses, including bandage contact lenses,[10,29-36] is a risk factor for bacterial keratitis, especially when associated with the following:

- Overnight wear[37-41]
- Overnight orthokeratology[42-51]
- Overwear
- Inadequate disinfection of contact lenses (topping off solutions)
- Contamination of the contact lens storage case[39,41,52] (including rinsing of case with tap water[53])
- Ineffective or contaminated contact lens solution
- Storage or rinsing in tap water[54]
- Poor hygiene
- Use of unregulated lenses (cosmetic, Internet-based and over the counter purchases) without a doctor's prescription[40,55-60]
- Sharing of lenses[58]
- Swimming, using a hot tub, or showering while wearing contact lenses[30]
- Lack of supervision and follow-up (50% of asymptomatic patients during a routine visit presented with signs of complications[61])
- Trauma,[62] including chemical and thermal injuries,[63] foreign bodies, and local irradiation
- Previous ocular and eyelid surgery, including refractive surgery,[64,65] cataract surgery[66] and keratoplasty[67,68] (including keratoprosthesis[69,70])
- Medication-related factors (e.g., contaminated ocular medications, topical nonsteroidal anti-inflammatory drugs [NSAIDs], anesthetics, corticosteroids, preservatives, glaucoma medications)
- Immunosuppression (topical and systemic medications, medical conditions)
- Substance abuse[10]

**Box 2. Ocular Surface Disease**

Other risk factors for bacterial keratitis include local disease and system conditions.

**Local:**

- Loose corneal sutures[71]
- Tear-film deficiencies
- Abnormalities of the eyelid anatomy and function (including exposure)
- Misdirection of eyelashes
- Adjacent infection/inflammation (including gonococcal conjunctivitis, blepharitis, canaliculitis, dacryocystitis)[72]
- Neurotrophic keratopathy (e.g., trigeminal neuropathy)
- Disorders predisposing to recurrent erosion of the cornea
- Corneal abrasion or epithelial defect
- Viral keratitis (herpes simplex virus [HSV] or varicella zoster virus [VZV] keratitis)
- Corneal epithelial edema, especially bullous keratopathy

**Systemic conditions:**

- Diabetes mellitus[73]
- Debilitating illness, especially malnourishment and/or respirator dependence[74]
- Connective tissue disease
- Dermatological/mucous membrane disorders (e.g., Stevens-Johnson syndrome,[63] ocular mucous membrane pemphigoid)
- Immunocompromised status[11]
- Atopic dermatitis/blepharoconjunctivitis
- Vitamin A deficiency
- Acoustic neuroma or neurological surgery causing damage to the Vth and/or VIIth cranial nerves
- Graft-versus-host disease

## NATURAL HISTORY

Loss of vision can frequently occur due to corneal scarring or topographic irregularity. Untreated or severe bacterial keratitis may result in corneal perforation, and it has the potential to develop into endophthalmitis and result in loss of the eye.[10,11] 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, timely institution of therapy, and appropriate follow-up. Bacterial keratitis can occur in any region of the cornea, but infections involving the central or paracentral cornea are of paramount importance. Scarring in this location has the potential to cause substantial visual loss, even if the infecting organism is successfully eradicated.[75] Although some bacteria (e.g., *Neisseria gonorrhoeae*) can invade an intact corneal epithelium, most cases of bacterial keratitis develop 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*, *Streptococcus pneumoniae*, or *Neisseria gonorrhoeae* cause rapid tissue destruction, whereas other organisms such as nontuberculous mycobacteria and *Streptococcus viridans* species are usually associated with a more indolent course. Some bacteria that are considered to be normal conjunctival flora (e.g., *Corynebacterium*) may become opportunistic pathogens in the compromised eye.

There is a higher risk of polymicrobial keratitis in patients who have systemic and/or multiple risk factors for keratitis, and there are a higher number and duration of infiltrates in polymicrobial keratitis than in monomicrobial keratitis.[76]

# CARE PROCESS

## PATIENT OUTCOME CRITERIA

Outcome criteria for treating bacterial keratitis include the following:

- Reducing pain
- Resolving discharge as well as corneal and anterior chamber inflammation
- Reducing secondary intraocular damage from inflammation such as cataract formation and glaucoma
- Resolving epithelial defect
- Restoring corneal integrity and minimizing scarring and vascularization
- Restoring visual function

# DIAGNOSIS

Evaluation of the patient with presumed bacterial keratitis includes a careful assessment of elements from the comprehensive medical eye evaluation[77,78] 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 (e.g., degree of pain, redness, discharge, blurred vision, photophobia, duration of symptoms, circumstances surrounding the onset of symptoms)
  - Contact lens history[29,30] (e.g., wearing schedule; overnight wear; type of contact lens; contact lens solution; contact lens hygiene protocol; tap-water rinsing of contact lenses; swimming, using a hot tub, or showering while wearing contact lenses; method of purchase, such as over the Internet; and decorative contact lens use)
- Review of other ocular history, including risk factors such as HSV keratitis, VZV keratitis, previous bacterial keratitis, trauma, dry eye, and previous ocular surgery, including refractive and facial (including laser cosmetic) surgery
- Review of other medical problems, including immune status, systemic medications, and history of methicillin-resistant *Staphylococcus aureus* (MRSA) or other multidrug-resistant infections
- Current and recently used ocular medications
- Medication allergies

## Physical 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
- Globe position
- Eyelids and eyelid closure
- Conjunctiva
- Nasolacrimal apparatus
- Corneal sensation testing could be considered if appropriate

### Slit-Lamp Biomicroscopy

Clinical features suggestive of bacterial keratitis include suppurative stromal infiltrates (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 and an anterior chamber reaction is often seen.

Slit-lamp biomicroscopy should include evaluation of the following:

- Eyelid margins
  - Inflammation
  - Ulceration
  - Meibomian gland dysfunction/anterior blepharitis
  - Eyelash abnormalities, including trichiasis/distichiasis
  - Lagophthalmos
  - Lacrimal punctal anomalies
  - Ectropion/entropion
- Conjunctiva
  - Discharge
  - Inflammation
  - Morphologic alterations (e.g., follicles, papillae, cicatrization/symblephara, scarring, keratinization, membrane, pseudomembrane, ulceration, evidence of prior surgery)
  - Ischemia
  - Foreign body
  - Filtering bleb, tube erosion
  - Loss of tissue or of the epithelium
- Sclera
  - Inflammation (e.g., infectious versus immune)
  - Ulceration

- Thinning
- Nodule
- Ischemia

- Cornea
  - Epithelium, including defects and punctate keratopathy, edema, epithelial movement patterns
  - Stroma, including ulceration, thinning, perforation, and infiltrate (location [central, peripheral, inferior, perineural, surgical, or traumatic wound], density, size, shape [ring], number [satellite], depth, character of infiltrate margin [suppuration, necrosis, feathery, soft, crystalline], color), edema
  - Endothelium (endothelial plaque)
  - Foreign body, including sutures[66,79]
  - Signs of corneal dystrophies (e.g., epithelial basement membrane dystrophy)
  - Previous corneal inflammation (thinning, scarring, or neovascularization)
  - Signs of previous corneal or refractive surgery

Fluorescein or rose bengal/lissamine green staining of the cornea is usually performed and may provide additional information about other factors, such as the presence of dendrites, pseudodendrites, loose or exposed sutures, foreign body, and any epithelial defect. Staining of epithelium must be differentiated from pooling of stain in an area of corneal thinning.

- Anterior chamber for depth and the presence of inflammation, including cell and flare, hypopyon, fibrin, hyphema
- Anterior vitreous for the presence of inflammation
- Contralateral eye for clues to etiology as well as possible similar underlying pathology

## 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.[4,5] Smears and/or cultures are specifically indicated in the following circumstances: 1) a corneal infiltrate is central, large, and/or is associated with significant stromal involvement or melting; 2) the infection is chronic or unresponsive to broad-spectrum antibiotic therapy; 3) there is a history of corneal surgeries; or 4) atypical clinical features are

present that are suggestive of fungal, amoebic, or mycobacterial keratitis; or 5) infiltrates are in multiple locations on the cornea.[6]

Smears and/or cultures are often helpful for eyes that have an unusual history (e.g., if there has been trauma with vegetable matter or if the patient wore contact lenses while in a hot tub). Specialized studies may be indicated to identify atypical organisms. 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, such as following an intraocular surgery, perforating trauma, or sepsis. Before initiating antimicrobial therapy, cultures are indicated in sight-threatening or severe keratitis of suspected microbial origin. See Table 1 for additional details.

TABLE 1 RECOMMENDATIONS FOR DIAGNOSTIC TESTS: VITAL STAINS AND CULTURE

| Factors | Culture | Vital Stain Dyes |
|---|---|---|
| Small, peripheral, no stromal melting | Culture optional | Gram, Giemsa stain optional |
| Large, central, stromal melting, chronic, atypical appearance, sight threatening | Culture | Gram, Giemsa stain |

A study that surveyed 15 cornea specialists by showing them photographs of culture-proven bacterial keratitis and smear-proven fungal keratitis found that they correctly differentiated bacterial and fungal keratitis by chance, but in fewer than 70% of cases.[80] This study highlights the importance of using cultures to correctly identify the etiology of infectious ulcers.

Obtaining a corneal culture is a means of identifying the causative organism(s) and the only method to determine antibiotic sensitivity. Cultures are helpful to guide modification of therapy in patients with a poor clinical response to treatment and to decrease toxicity by eliminating unnecessary medications. Microbial pathogens are categorized by examining stained smears from corneal scrapings[4] and may increase yield of identification of the pathogen, especially if the patient is on antibacterial therapy. The material for smear is applied to clean glass microscope slides in an even, thin layer (see Appendix 3 for specific diagnostic stains). Polymerase chain reaction and immunodiagnostic techniques may be useful,[81-85] but they are not widely available in the office setting.

Corneal material is obtained by instilling a topical anesthetic agent (tetracaine should be avoided because of antimicrobial effect) and using a heat-sterilized

platinum (Kimura) spatula, blade, jeweler's forceps, or other similar sterile instrument to obtain scrapings of material from the advancing borders of the infected area of the cornea. Culture yield may be improved by avoiding anesthetics with preservatives.[86] Obtaining only purulent material usually results in inadequate yield. A thiol or thioglycolate broth-moistened calcium alginate or sterile cotton swab may also be used to obtain material. This is most easily performed using slit-lamp biomicroscope magnification. When using transport media, similar methods are used to obtaining corneal material. The material is then transferred to the cotton or calcium alginate swab, which is then placed in the tube.

Corneal scrapings for culture should be inoculated directly onto appropriate culture media to maximize culture yield (see Appendix 4).[87] If this is not feasible, specimens should be placed in transport media.[88,89] In either case, cultures should be immediately incubated or taken promptly to the laboratory. One study found that adding liquid culture media increased the chance of isolating bacterial species compared with solid culture media alone.[90] Cultures of contact lenses, the lens case, and contact lens solution may provide additional information to guide therapy.

A newer, simplified collection device using a nylon-tipped swab with a flocked tip arrangement has been shown have a similar culture-positivity rate when compared with traditional collection methods.[22] Increased capillary action and hydraulic liquid uptake of the device allows for improved sample collection. The swab is placed in 1 ml of modified Amies medium and then aliquoted in the laboratory for further culture and analysis. Collection is more cost-effective and less time consuming because there is no need to maintain fresh culture media.

It may be helpful to obtain cultures from eyes treated empirically that were not first cultured and in which the clinical response is poor; however, a delay in pathogen recovery may occur, so keeping cultures for longer may be helpful.[11,91] If the cultures are negative, the ophthalmologist may consider stopping antibiotic treatment for 12 to 24 hours and then reculturing the corneal ulcer.

### Corneal Biopsy and Deep Stromal Culture Techniques

Corneal biopsy may be indicated if the response to treatment is poor or if repeated cultures have been negative and the clinical picture continues to strongly suggest an infectious process. In one study, organisms were identified by culture in 42% of corneal biopsies and identified on histopathological examination in 40% of cases.[92] Corneal biopsy may also be indicated if the infiltrate is located in the mid or deep

stroma with overlying uninvolved tissue.[93,94] With a cooperative patient, corneal biopsy may be performed at the slit-lamp biomicroscope or operating microscope. Using topical anesthesia, a small trephine (e.g., a 2- to 3-mm dermatic punch) or blade is used to excise a small piece of stromal tissue at the edge of the infiltrate (as far from the center of the cornea as possible) that is large enough to allow bisection so that one portion can be sent for culture and the other for histopathology.[95] A corneal biopsy taken from the center of the cornea may result in a significant refractive error from the irregular surface. Taking the biopsy from the edge of the infiltrate will increase the yield of viable pathogen, whereas a biopsy from the center of an infiltrate may only yield nonviable pathogen and debris. A femtosecond laser can also be used to excise a lamellar disc of tissue, although this is a more costly alternative. The biopsy specimen should be delivered to a pathologist in a timely fashion for formal evaluation.

If an infiltrate surrounds a preexisting suture, the suture should be removed and sent for culture. An option for culturing a deep corneal abscess may be to use a suture that can be passed through the abscess without disturbing the overlying intact corneal epithelium and stroma. A 7-0 or 8-0 vicryl or silk suture can be passed through the abscess. The pathogen may attach to the fibers of the suture, and the suture can then be cultured. Another option in cases of a deep corneal abscess with overlying clear cornea is to take the biopsy from below a lamellar flap. An additional set of smears and cultures can be obtained from the deep stroma after the biopsy is performed.

### Corneal Imaging

Scanning laser confocal microscopy is used to image the various levels of the cornea from the epithelium through stroma to the endothelium in vivo. Initially, confocal microscopy had been used to examine endothelial cells to help clinicians manage endothelial conditions, as well as ex vivo to examine the quality of potential corneal donor tissue. With the recent advances in confocal technology to enhance the resolution and microscopic power, its use as a diagnostic tool has broadened. Confocal technology has been shown to be of some use in the diagnosis of infectious keratitis, including bacterial, fungal, and, most notably, parasitic (e.g., *Acanthamoeba*).[96-99] Optical coherence tomography may also be helpful in determining depth of involvement.

### Differential Diagnosis

The 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 an infiltrative keratitis. An increase in the incidence of *Acanthamoeba* and fungal keratitis since 2004 has been noted.[8,100-109] Viruses including HSV, VZV, and Epstein-Barr virus produce immunologically mediated corneal infiltrates that may resemble a bacterial, fungal, or *Acanthamoeba* keratitis. Bacterial and fungal keratitis have fewer differentiating characteristics than *Acanthamoeba* keratitis.[110] Eyes with viral keratitis are also prone to microbial superinfection, but this generally occurs in patients with larger epithelial defects or more severe viral disease, who are older or who are immunosuppressed. When there is clinical uncertainty regarding the etiology, initial management of such cases with bacterial superinfection should include empiric antibiotics. Viruses can also cause a true suppurative keratitis without superinfection, as in cases noted to have necrotizing stromal disease.

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 connective tissue disease (e.g., rheumatoid arthritis, systemic lupus erythematosus), vasculitic disorders (e.g., polyarteritis nodosa, granulomatosis with polyangiitis), and other inflammatory disorders such as sarcoidosis may produce an infiltrative keratitis. Other causes of infection include dermatologic disorders (e.g., severe ocular rosacea) and allergic conditions (e.g., vernal keratoconjunctivitis and atopic keratoconjunctivitis). Atopy is also a risk factor for HSV ocular disease.[111] 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 noninfectious.

## MANAGEMENT

### Prevention

Avoiding or correcting predisposing factors may reduce the risk of bacterial keratitis. Screening patients for predisposing factors and educating them about the risks of overnight wear of contact lenses[29,37,47] and proper contact lens care[112] may reduce the incidence of bacterial keratitis in those who wear contact lenses. (See Appendix 5 for

recommendations on contact lens care.) For those patients who require a therapeutic bandage contact lens, many clinicians prefer to use topical antibiotic prophylaxis. Although studies have not been done to test or prove an optimal dose and no topical antibiotics have been approved for bacterial keratitis prophylaxis, some authors recommend twice-daily antibiotic dosing.[113] Some clinicians prefer not to use antibiotics in this setting because of the risks of bacterial resistance, drug or preservative toxicity, and cost. The use of topical antibiotics does not eliminate the risk of infectious keratitis, and this risk may be greater in patients with chronic ocular surface disease.[32] Opinions vary on the use of a topical antibiotic when a bandage contact lens is used and on how frequently such lenses should be changed. Patients should be informed of the risk of infectious keratitis when wearing a bandage contact lens, and of the need to contact their treating ophthalmologist if redness, pain, or increased photophobia develops. They should also be informed that they are still at risk for infection, despite the use of antibiotics. Ideally, bandage contact lenses should be used for a finite treatment period; however, in many cases, their use may be protracted. In this situation, periodic exchange of the contact lens is advised. Regular follow-up is necessary under these circumstances to reassess the contact lens, to look for changes in the patient's ocular status, and to re-emphasize the need for patient vigilance. Most ocular trauma can be avoided by using protective eyewear for sports and other high-risk activities.[114]

Early detection and appropriate treatment are important to minimize permanent visual loss.[115] Patients with risk factors predisposing them to bacterial keratitis should be educated about their increased risk, acquainted with the signs and symptoms of infection, and informed that they need to consult an ophthalmologist promptly if they experience such warning signs or symptoms. Ocular surface disease such as corneal epithelial defects, severe tear deficiency, or lagophthalmos should be treated. Prophylactic antibiotics can be considered for patients with chronic epithelial defects; however, the routine use of prophylactic topical antibiotics in this setting is controversial. Since efficacy has not been established, chronic use may promote growth of resistant organisms. Prophylactic topical antibiotics following corneal abrasion may prevent ulceration when treatment is started within 24 hours of the abrasion.[116] For patients who wear contact lenses and develop a traumatic abrasion, it is advisable to avoid pressure patching and perhaps the use of a bandage contact lens, since there is a higher risk of secondary infectious keratitis.

## Treatment

### Initial Treatment

Topical antibiotic eye drops are capable of achieving high tissue levels and are the preferred method of treatment in most cases.[117] (See Table 2 for recommendations about antibiotic therapy.) Ocular ointments may be useful at bedtime in less severe cases and may be useful for adjunctive therapy. Ointments lack solubility and therefore the therapeutic agents are not able to penetrate into the cornea significantly for optimum therapeutic benefit.

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.[118] 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 efficacy and the potential risk for inducing drug toxicity and corneal epithelial hypoxia.[119-121] 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. A higher minimum inhibitory concentration to the treating antibiotic is associated with worse clinical outcomes, including slower re-epithelialization and more lines of visual acuity lost at 3 months.[122]

For central or severe keratitis (e.g., deep stromal involvement or an infiltrate larger than 2 mm with extensive suppuration), a loading dose such as every 5-15 minutes followed by frequent applications such as every hour is recommended. Cycloplegic agents may be used to decrease synechiae formation and decrease pain from bacterial keratitis, and they are indicated when substantial anterior chamber inflammation is present.

TABLE 2 ANTIBIOTIC THERAPY FOR BACTERIAL KERATITIS

| Organism | Antibiotic | Topical Concentration | Subconjunctival Dose |
|---|---|---|---|
| No organism identified or multiple types of organisms | Cefazolin or vancomycin | 25–50 mg/ml | 100 or 25 mg in 0.5 ml |
| | with | | |
| | Tobramycin or gentamicin | 9–14 mg/ml | 20 mg in 0.5 ml |
| | or | | |
| | Fluoroquinolones* | Various† | |
| Gram-positive cocci | Cefazolin | 50 mg/ml | 100 mg in 0.5 ml |
| | Vancomycin‡ | 10–50 mg/ml | 25 mg in 0.5 ml |
| | Bacitracin‡ | 10,000 IU | |
| | Fluoroquinolones* | Various† | |
| Gram-negative rods | Tobramycin or gentamicin | 9–14 mg/ml | 20 mg in 0.5 ml |
| | Ceftazidime | 50 mg/ml | 100 mg in 0.5 ml |
| | Fluoroquinolones | Various† | |
| Gram-negative cocci§ | Ceftriaxone | 50 mg/ml | 100 mg in 0.5 ml |
| | Ceftazidime | 50 mg/ml | 100 mg in 0.5 ml |
| | Fluoroquinolones | Various† | |
| Gram-positive rods (Nontuberculous mycobacteria) | Amikacin | 20–40 mg/ml | 20 mg in 0.5 ml |
| | Clarithromycin | 10 mg/ml | |
| | Azithromycin‖ | 10 mg/ml | |
| | Fluoroquinolones | Various† | |
| Gram-positive rods (*Nocardia*) | Sulfacetamide | 100 mg/ml | |
| | Amikacin | 20–40 mg/ml | 20 mg in 0.5 ml |
| | Trimethoprim/sulfamethoxazole: | | |
| | trimethoprim | 16 mg/ml | |
| | sulfamethoxazole | 80 mg/ml | |

Modified with permission from the American Academy of Ophthalmology Basic and Clinical Science Course Subcommittee. Basic Clinical and Science Course. External Disease and Cornea: Section 8, 2017–2018. Table 10-6. San Francisco: American Academy of Ophthalmology, 2017.

* Fewer gram-positive cocci are resistant to gatifloxacin, moxifloxacin, and besifloxacin than other fluoroquinolones.

† Besifloxacin 6 mg/ml; ciprofloxacin 3 mg/ml; gatifloxacin 3 mg/ml; levofloxacin 15 mg/ml; moxifloxacin 5 mg/ml; ofloxacin 3 mg/ml, all commercially available at these concentrations.

‡ 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.

‖ Data from Chandra NS, Torres MF, Winthrop KL. Cluster of *Mycobacterium chelonae* keratitis cases following laser in-situ keratomileusis. *Am J Ophthalmol*. 2001;132(6):819-30.

Single-drug therapy using a fluoroquinolone has been shown to be as effective as combination therapy utilizing antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics.[117,123-128] [I+, Good, Strong] Fortified topical antibiotics should be considered for large and/or visually significant corneal infiltrates, especially if a hypopyon is present. (See Appendix 6 for instructions on preparing fortified topical antibiotics.) Ciprofloxacin 0.3%, ofloxacin 0.3%, and levofloxacin 1.5% have been approved by the Food and Drug Administration (FDA) for the treatment of bacterial keratitis.[129-131] Compared with ofloxacin 0.3%, levofloxacin 1.5% demonstrated equal efficacy in the endpoints of complete re-epithelialization and no progression of infiltrate for two consecutive visits.[105] Some pathogens (e.g., *Streptococci*, anaerobes) reportedly have variable susceptibility to fluoroquinolones,[124,132] and the prevalence of resistance to the fluoroquinolones appears to be increasing.[15,25,133,134] The increasing resistance may be associated with recent fluoroquinolone use, hospitalization, and recent ocular surgery.[135] A study of over 3200 ocular isolates collected from 2009 to 2013 found methicillin resistance in 42% of staphylococcal isolates, with a high concurrent resistance to fluoroquinolone; however, an increased resistance overall during the study period was not observed.[136] However, two separate 20-year reviews found increasing methicillin-resistant *S. aureus* keratitis from 1993 to 2012[137] and from 1996 to 2015.[138] Gatifloxacin and moxifloxacin have been reported to have better coverage of gram-positive pathogens than earlier generation fluoroquinolones in head-to-head in vitro studies.[139] Although widely used, the fourth-generation fluoroquinolones are not FDA-approved for the treatment of bacterial keratitis. However, in studies including some randomized controlled trials, both moxifloxacin and gatifloxacin performed at least as well as standard therapy, fortified cefazolin/tobramycin combination therapy, and potentially better than an earlier-generation fluoroquinolone, ciprofloxacin.[123,126,127,140-143] In southern India, there has been a sharp increase in resistance of *Pseudomonas aeruginosa* to moxifloxacin, from 19% in 2007 to 52% in 2009.[144] A 20-year study in San Francisco found increasing overall resistance of organisms to moxifloxacin from 1996 to 2015.[138] An in vitro study showed no empiric coverage advantage of either cefazolin/tobramycin, cefuroxime/gentamicin, or moxifloxacin over several gram-positive and gram-negative organisms.[145]

Besifloxacin 0.6% is a topical fluoroquinolone that was approved by the FDA in 2009 for bacterial conjunctivitis, and it has a potency against ocular pathogenic bacteria that is similar to the fourth-generation agents.[146] Several industry-

sponsored in vitro and in vivo rabbit studies have shown potential utility in the management of acute bacterial keratitis.[147-149] One in vitro study found that besifloxacin had better coverage over ciprofloxacin- and methicillin-resistant staphylococci than other fluoroquinolones did, including moxifloxacin.[150] Another study has shown efficacy of besifloxacin in bacterial keratitis in clinical use.[151] A Cochrane review found no evidence of difference in corneal perforation rates between any classes of topical antibiotics.[128] [I+, Good, Strong]

Combination fortified-antibiotic therapy is an alternative to consider, especially for severe infection and for eyes unresponsive to initial treatment.[5,10,125,145] Fortified antibiotics should be prepared by a compounding pharmacy that is a member of the Pharmacy Compounding Accreditation Board[152] and designated by the FDA as a 503A and/or 503B facility. Treatment with more than one agent may be necessary for nontuberculous mycobacteria; infection with this pathogen has been reported in association with LASIK.[153,154]

Methicillin-resistant and oxacillin-resistant *S. aureus* has been isolated with increasing frequency from patients with bacterial keratitis[12,155-160] and has been reported following keratorefractive surgery.[161] Fluoroquinolones are generally poorly effective against MRSA ocular isolates.[11,136,137,162] Methicillin-resistant *S. aureus* isolates generally are susceptible to vancomycin.[163,164] (See Appendix 6 for instructions for preparing fortified topical antibiotics.) A case series of vancomycin-resistant enterococcus demonstrated that topical linezolid can be used,[156] with no ocular surface toxicity.[157] Keratitis from multidrug-resistant *Pseudomonas aeruginosa* has been reported, with high morbidity.[165,166] Topical colistin 0.19% may be considered in such cases.[167] A special note should be made for *Moraxella* keratitis, which is usually susceptible to fluoroquinolones and aminoglycosides yet requires a more prolonged treatment duration (mean, 41.9 days).[168]

Recurrent bacterial keratitis is more likely to be caused by *S. aureus*.[169] Colonization of the nasopharynx, oropharynx, and ocular surface with *S. aureus* may be the source of recurrent infection. Treatments to decolonize *S. aureus* could be considered in patients with recurrent disease to prevent further infection.

Systemic antibiotics are rarely needed, but they 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.[170]

Frequency of reevaluation of the patient with bacterial keratitis depends on the extent of disease. Severe cases (e.g., deep stromal involvement or stroma larger than 2 mm with extensive suppuration) should be followed daily initially, at least until stable or once clinical improvement is confirmed.

### Corticosteroid Therapy

Topical corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis. Much of the literature shows no difference in clinical outcome with the addition of corticosteroids.[171-174] [I+, Good, Strong] The potential advantage is the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss. Potential disadvantages include recrudescence of infection, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting, and increased intraocular pressure (IOP). The SCUT treatment study found no benefit of concurrent topical corticosteroid therapy using prednisolone phosphate 1% in conjunction with broad-spectrum topical antibiotic.[175] However, this study did not find an increase of adverse events associated with corticosteroid use in bacterial keratitis therapy. In a subgroup analysis of SCUT data, there was a potential benefit for using corticosteroids in *Pseudomonas* keratitis and in more severe cases of bacterial keratitis. The same study found that treatment of *Nocardia* keratitis with corticosteroids resulted in poor visual outcomes,[176] and a subsequent follow-up found that these results were similar at 12-months follow-up.[177] A second subgroup analysis found that the addition of topical corticosteroids within 2 to 3 days of antibiotic therapy (rather than after 4 or more days) resulted in a 1-line better visual acuity at 3 months compared with placebo.[178]

The objective of topical corticosteroid therapy is to use the minimum amount required to achieve control of inflammation. Successful treatment requires optimal timing, careful dose regulation, use of adequate concomitant antibacterial medication, and close follow-up. Optimal use of corticosteroids and antibiotics is largely determined by the clinician's experience and the individual patient's response to therapy. A conservative approach would avoid prescribing corticosteroid treatment for presumed bacterial ulcers until the organism has been identified, the epithelial defect is healing, and/or the ulcer is consolidating. If the ulcer is associated with *Nocardia* or fungus, the outcomes of corticosteroid therapy are likely to be poor; for most bacteria other than Nocardia, the risk is low and may be beneficial.[179] Although a small, retrospective study that included fungal

keratitis[180] found the use of corticosteroids in the initial treatment of corneal ulcers to be a risk factor for requiring a penetrating keratoplasty, a more recent clinical trial has shown that corticosteroids may not have this direct correlation.[175] Therefore, judicious use with close follow-up would be prudent.[175,180,181]

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, typically after identification of the pathogen (and after fungal infection has been ruled out).

Patient compliance is essential, and IOP must be monitored. The patient should be examined within 1 to 2 days after initiation of topical corticosteroid therapy. Risks of long-term topical corticosteroid therapy including cataract and glaucoma should be discussed with the patient.

Despite the controversy, many experts believe that the judicious use of topical corticosteroids can reduce morbidity.[175] 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. Inflammation and symptoms (e.g., decreased vision, photophobia, lacrimation, injection, and hyperemia) may temporarily increase as corticosteroids are reduced because of the lack of local immune suppression. The increase in inflammation may not be due to worsening of the infection and, therefore, patients should be advised of possible increased symptoms. Chronic topical immunotherapy, such as use of corticosteroids, increases the risk of infectious crystalline keratopathy, which has the striking appearance of a snowflake or ice crystals in the stroma of the cornea. These can often be seen associated with sutures in the cornea or surgical or traumatic junctions within the stroma (e.g., graft-host junction of a penetrating keratoplasty).[182] Management of these infections often requires discontinuation of the topical immunotherapy and the addition of long-term therapy with topical antimicrobial agents to eradicate the typically encapsulating bacteria. These infections are extremely difficult to manage and often require surgical intervention to achieve successful treatment. Typically, these patients complain of only mild symptoms, such as blurred vision, and have a relatively asymptomatic course prior to diagnosis, most likely due to the topical immunotherapy and sequestration of organisms in biofilm.

## Modification of Therapy

The efficacy of the therapeutic regimen is judged primarily by the clinical response. The results of cultures and sensitivity testing may have an impact on therapeutic decision making, especially if the patient is not responding to initial therapy. When the patient is improving, 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. 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:[183]

- Reduced 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 cells, 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.

Topical therapy is tapered according to the 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, owing to wide variability in the severity of the infectious process in individual cases. Because prolonged use of topical antibiotics causes toxicity, they should be tapered as the infection improves. Medication toxicity can cause worsening inflammation or even corneal melting. If there is a persistent epithelial defect and the infection is under control, adjunctive therapies to rehabilitate the surface should be instituted, such as lubrication, antibiotic ointment, bandage contact lens, amniotic membrane coverage, or tarsorrhaphy. More prolonged therapy may be mandated by the

presence of virulent or indolent organisms or for immunocompromised patients. Most antibiotic eye drops should not be tapered below 3 to 4 times a day because low doses are subtherapeutic and may increase the risk of developing antibiotic resistance.

### 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 corticosteroid 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. Also, preserved solutions such as anesthetic or cycloplegic agents should be avoided. Selected media capable of supporting the growth of atypical microorganisms may also increase culture yield and can be considered, such as Löwenstein-Jensen media for atypical mycobacteria. (See Appendix 4 for a list of culture media for bacterial keratitis.) Other atypical organisms to consider are fungi or parasites such as *Fusarium* and *Acanthamoeba*, which are of particular concern because of a rise in the incidence of keratitis associated with these pathogens. Although these infections can be diagnosed using appropriate staining of corneal smears, confocal microscopy can also be helpful in identifying the organisms in the tissue.

### Therapy for Complicated Cases

Coexisting risk factors, such as eyelid abnormalities, should be corrected for optimal results. Additional treatment is necessary in cases where the integrity of the eye is compromised, such as when there is an extremely thin cornea, impending or frank perforation, progressive or unresponsive disease, or endophthalmitis. Oral antibiotics in the tetracycline class (including doxycycline and minocycline) could be used to counteract corneal stromal thinning by inhibiting matrix metalloproteinases, but there are limited data on their use for the management of their infectious component.[184,185] Application of tissue adhesive, penetrating keratoplasty, and lamellar keratoplasty are among the other treatment options for progressive corneal stromal thinning. The application of an amniotic membrane could be considered to decrease inflammation and stabilize the ocular surface to avoid an emergent keratoplasty and improve prognosis of an elective keratoplasty.[186-190] One randomized controlled trial found that double-layer amniotic membrane transplantation 2 to 5 days after initiation of topical antibiotics

improved visual acuity at 6 months but did not improve corneal healing time, hypopyon size or duration, or depth of corneal opacity.[188] Another controlled study applied single-layer amniotic membrane after 2 to 3 days of antibiotic therapy in culture-proven *Pseudomonas* keratitis; it found decreased pain postoperatively, decreased density of corneal opacity, and better uncorrected visual acuity compared with a control group who received only antibiotics.[189] Amniotic membrane transplantation and conjunctival flap may be used in cases refractory to medical treatment.[190] These treatments can offer support for corneal epithelial healing, but keratoplasty should be applied in cases of large corneal perforation. When corneal tissue is removed, it should be sent for pathologic and microbiologic analysis. Bacterial keratitis carries more favorable outcome measures than fungal keratitis.[191] Results from the SCUT were compared with those from the Mycotic Ulcer Treatment Trial (MUTT) and found that at 3 months, fungal keratitis cases had a larger infiltrate/scar, a slower re-epithelialization rate, and a higher perforation rate than bacterial keratitis cases.

### Emerging Treatments

Topical povidone-iodine 1.25% has been shown to be as effective as topical antibiotics for bacterial keratitis in a randomized, controlled clinical trial performed in Philippines and India.[192] Povidone-iodine is available at substantially lower cost than topical antibiotics. The lower concentration of povidone-iodine was chosen to reduce stinging and may be an effective alternative treatment for use in developing countries where antibiotics may be a scarce commodity.

Corneal cross-linking has been used successfully in the treatment of moderate bacterial ulcers.[193] A randomized controlled study with 32 patients found that patients who received a single cross-linking treatment in addition to standard medical therapy had faster reepithelialization and shorter treatment duration than the control group receiving standard medical therapy alone. Cross-linking may be beneficial in cases of bacterial keratitis refractory to medical therapy alone.[194-196] A meta-analysis of 12 articles found that corneal cross-linking is potentially effective for treatment of bacterial keratitis and can block corneal melting, especially in bacterial keratitis.[197] As ultraviolet energy is absorbed within the first 100 µm, cross-linking has been proposed to have a greater effect in more shallow infiltrates.[198] One small study found that cross-linking alone, without antibiotic therapy, can resolve bacterial keratitis in 14 out of 16 cases.[199] Cross-linking has

more evidence of success with more anterior infections as an adjunct with standard antibiotic therapy, especially in difficult cases.[200,201] [I+, Good, Discretionary]

## PROVIDER AND SETTING

The diagnosis and management of patients with bacterial keratitis require the clinical training and experience of an ophthalmologist and vary, especially with concomitant pathology, because the disease has the potential to cause visual loss or blindness. If the diagnosis or treatment is in question, or if the condition is severe or refractory to treatment, consultation with or referral to an ophthalmologist who has expertise and experience in the management of bacterial keratitis is desirable. Corneal specialists are more likely than noncorneal specialists to gram stain and culture cases of bacterial keratitis and to prescribe fortified antibiotics for severe corneal ulcers.[5] However, cornea specialists outside of the United States are less likely to treat initially with fortified antibiotics than corneal specialists in the United States and are less concerned with resistant organisms.[202]

The majority of patients with bacterial keratitis are 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. Hospitalization may also be considered in cases where compliance is doubtful, since frequent instillation of eye drops is required. Some patients are unable to instill the eye drops in an outpatient setting because of age, mental, or physical disability, or because of an inadequate support system.

## COUNSELING AND REFERRAL

Patients and care providers should be educated about severe visual impairment from bacterial keratitis and the need for strict adherence to the therapeutic regimen. The possibility of permanent visual loss and need for future visual rehabilitation should be discussed. Patients who wear contact lenses should be educated about the risk for infection associated with contact lens wear, overnight wear, and the importance of adherence to techniques that promote contact lens hygiene[40,52] (see Appendix 5). The risks and timing of resuming contact lens wear following bacterial keratitis should be discussed with the patient, and the lens choice and fitting should be reassessed by the eye care professional. Adverse events related to FDA-approved products (i.e., contact lenses and care products) should be reported to MedWatch (www.fda.gov/medwatch), the Safety Information and Adverse Reporting Program for drugs and other medical products regulated by the FDA.

Visual rehabilitation improves functional ability,[203] and patients with substantial visual impairment should be referred for vision rehabilitation and social services if they are not

candidates for surgery.[204] More information on vision rehabilitation, including materials for patients, is available at www.aao.org/low-vision-and-vision-rehab.

## SOCIOECONOMIC CONSIDERATIONS

Bacterial keratitis is a major cause of visual disability because it can lead to corneal opacification. The World Health Organization (WHO) recognizes it as a silent epidemic.[205] Developing countries have a much higher incidence of bacterial keratitis compared with developed countries. For example, Olmsted County, Minnesota, had an incidence of microbial keratitis of 11 per 100,000[206] compared with an incidence of 113 per 100,000 in India[207] and 799 per 100,000 in Nepal.[116] The largest risk factor for bacterial keratitis in the United States is contact lens use,[29,208] whereas trauma is the largest risk factor in Southeast Asia[116,209] and South India.[62] Infectious keratitis is the leading cause of blindness in China.[210]

There have been successful attempts to prevent bacterial keratitis in developing countries. In the Bhaktapur Eye Study, patients with corneal abrasions confirmed by clinical examination who presented within 48 hours of the injury without signs of corneal infection were enrolled and given chloramphenicol ointment 1% three times a day for 3 days.[116] Only 18 of 442 patients went on to develop corneal ulcers. The WHO applied the Bhaktapur Eye Study model in Bhutan.[211] Volunteer health workers were trained to follow the inhabitants of 55 villages and to use the same chloramphenicol ointment regimen for corneal abrasions. There were 115 corneal abrasions during the study period, and no cases of keratitis developed. Those districts not using topical antibiotics outside of the 55-village Bhutan study zone had an unchanged rate of corneal ulcers of 339 per 100,000. This effort is being expanded to other countries and may be a cost-effective method of preventing the morbidity and further health care costs of bacterial keratitis.[212]

The incidence of infectious keratitis has been shown in multiple studies to be higher in patients of lower socioeconomic status, than in patients of higher socioeconomic status.[210,213] There is a significant financial burden of bacterial keratitis that results from direct costs due to medications, visits to ophthalmologists, and diagnostic testing and from indirect costs due to loss of income, assistance from caregivers, and eyeglass purchases.[214] A study on contact-lens-associated microbial keratitis performed in Australia found that associated costs (including costs of hospital-bed days, outpatient and emergency department visits, drugs, pathology testing, and indirect costs such as lost productivity for patients and caregivers) were AU$5515 for severe cases with vision loss, AU$1596 for severe cases without vision loss, and AU$795 for mild keratitis.[214] The estimated cost of contact-related microbial keratitis in the United States in 2010 was approximately $58 million.[215] Higher

socioeconomic status in the United States was associated with more serious contact-lens-related corneal infections.[41]

When topical antibiotics are considered specifically, the cost of fortified antibiotics can be much higher than commercially available antibiotics because of the costs associated with compounding pharmacies. As mentioned earlier, use of a topical second-generation fluoroquinolone (e.g., ofloxacin and ciprofloxacin) has been shown to be comparable to fortified antibiotics.[216] However, no randomized controlled study comparing the outcomes of fluoroquinolones with the outcomes of fortified antibiotics in severe cases of bacterial keratitis has been performed. Topical povidone-iodine 1.25% may become a cost-effective alternative to topical antibiotics.[192]

# APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

*Providing quality care*
*is the physician's foremost ethical obligation, and is*
*the basis of public trust in physicians.*
*AMA Board of Trustees, 1986*

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual, and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients, and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual, and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced, and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
  - The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
  - The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
  - When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
  - The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.
  - The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn they respond in an adequate and timely manner.

  - The ophthalmologist maintains complete and accurate medical records.
  - On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
  - The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
  - The ophthalmologist and those who assist in providing care identify themselves and their profession.
  - For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.
- Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices, or procedures.
- The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

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Approved by: Board of Trustees
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4th Printing: July 2005

# APPENDIX 2. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES

Bacterial keratitis includes entities with the following ICD-10 classifications:

| | ICD-10 CM |
|---|---|
| Corneal ulcer, unspecified | H16.00- |
| Marginal corneal ulcer | H16.04- |
| Ring corneal ulcer | H16.02- |
| Central corneal ulcer | H16.01- |
| Hypopyon ulcer | H16.03- |
| Perforated corneal ulcer | H16.07- |
| Unspecified corneal edema | H18.20 |
| Corneal infiltrate | H18.20 |
| Contact lens keratitis | H18.82- |
| Contact lens infiltrate | H18.21-, H18.82- |
| Bacterial keratitis | H16.8 |

CM = Clinical Modification used in the United States; ICD = International Classification of Diseases; (–) = 1, right eye; 2, left eye; 3, bilateral

Additional information:

- Certain ICD-10 CM categories have applicable 7th characters. The applicable 7th character is required for all codes within the category, or as the notes in the Tabular List instruct. The 7th character must always be the 7th character in the data field. If a code that requires a 7th character is not 6 characters, a placeholder X must be used to fill in the empty characters.
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, separate codes for both the left and right side should be assigned. Unspecified codes should only be used when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4th digit, 5th digit, or 6th digit):
  - Right is always 1
  - Left is always 2
  - Bilateral is always 3

# APPENDIX 3. DIAGNOSTIC STAINS

Table 3-1 lists diagnostic stains that are used in cultures to identify causes of bacterial keratitis.

TABLE 3-1 STAINS USED TO IDENTIFY COMMON CAUSES OF BACTERIAL KERATITIS IN THE UNITED STATES

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

* 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*.

Data from:

Infections of the eyes, ears, and sinuses. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:832-841.

Laboratory methods for diagnosis of parasitic infections. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:543-627.

Laboratory methods in basic mycology. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:629-716.

Role of microscopy. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:78-92.

Murray PR, Shea VR. In: *Pocket Guide to Clinical Microbiology*. Washington, DC: ASM; 2004:131-181.

# APPENDIX 4. CULTURE AND TRANSPORT MEDIA

Table 4-1 lists culture and transport media that are used in the management of bacterial keratitis.

TABLE 4-1 CULTURE AND TRANSPORT MEDIA FOR BACTERIAL KERATITIS

| Media | Common Isolates |
|---|---|
| Standard | |
| Blood agar | Aerobic and facultatively anaerobic bacteria, including *P. aeruginosa*, *S. aureus*, *S. epidermidis*, and *S. pneumoniae* |
| Chocolate agar | Aerobic and facultatively anaerobic bacteria, including *H. influenzae*, *N. gonorrhea*, and *Bartonella* species |
| Thioglycollate broth | Aerobic and facultatively anaerobic bacteria |
| Sabouraud dextrose agar | Fungi |
| Mannitol salt agar | *Staphylococcus* isolates |
| Supplemental | |
| Anaerobic blood agar (CDC, Schaedler, Brucella) | *P. acnes*, *Peptostreptococcus* |
| Löwenstein-Jensen medium | *Mycobacterium* species, *Nocardia* species |
| Middlebrook agar | *Mycobacterium* species |
| Thayer-Martin agar | Pathogenic *Neisseria* species |
| Transport | |
| BHI (brain heart infusion [Oxid]) medium | Aerobic and facultatively anaerobic bacteria |
| Amies medium without charcoal | Aerobic and facultatively anaerobic bacteria; fungi |

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

References:


Laboratory methods for diagnosis of parasitic infections. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:543-627.

Laboratory methods in basic mycology. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:629-716.

Mycobacteria. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:478-509

Overview and general considerations. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:455-477.

Traditional cultivation and identification. In: Forbes BA, Sahm DF, Weissfeld AS, eds. *Bailey and Scott's Diagnostic Microbiology*. St. Louis, MO: Mosby; 2007:93-119.

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Kaye SB, Rao PG, Smith G, et al. Simplifying collection of corneal specimens in cases of suspected bacterial keratitis. *J Clin Microbiol*. 2003;41(7):3192-3197.

McLeod SD, Kumar A, Cevallos V, et al. Reliability of transport medium in the laboratory evaluation of corneal ulcers. *Am J Ophthalmol*. 2005;140(6):1027-1031.

Murray PR, Shea VR. In: Pocket Guide to Clinical Microbiology. Washington, DC: ASM; 2004:131-81, 269-270.

# APPENDIX 5. CONTACT LENS CARE

The following recommendations have been excerpted from the Refractive Errors and Refractive Surgery PPP.[28]

PATIENT EDUCATION AND CONTACT LENS CARE

The United States Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) have made recommendations for contact lens wearers regarding proper lens care practices, which are incorporated into the recommendations below[217,218]:

- Wash hands with soap and water, and dry (lint-free method) before handling contact lenses every time.
- Do not sleep in your contact lenses unless instructed by your eye doctor.
- Never store your contact lenses in water.
- Keep water away from your contact lenses. Take contact lenses out before showering, swimming, or using a hot tub.
- Rub and rinse contact lenses in disinfecting solution each time you remove them.
- Rub and rinse the case with contact lens solution, dry it with a clean tissue, and store it upside down with the caps off after each use.
- Do not top off solution. Use only fresh contact lens disinfecting solution in your case—never mix old and new solutions.
- Wear and replace contact lenses according to the schedule prescribed by your doctor.
- Follow the specific contact lens cleaning and storage guidelines from your doctor and the solution manufacturer.
- Keep the contact lens case clean and replace it every 3 months.
- Remove the contact lenses and consult your doctor immediately if you experience symptoms such as redness, pain, tearing, increased light sensitivity, blurry vision, discharge, or swelling.
- See your eye doctor yearly or as often as he or she recommends for contact lens examination.

These recommendations apply to contact lenses prescribed for refractive error and for contact lenses that alter the appearance of the eye.[219,220] All contact lenses, even decorative and costume contact lenses are medical devices. Doctors, patients, and consumers should be aware that there is a federal statute stating that a contact lens seller cannot provide contact lenses to its customer without a valid prescription.[221] Stores or websites selling any contact lenses without requiring a prescription are engaging in business activity that is subject to federal law enforcement.

When contact lenses are initially prescribed and dispensed, patients should be trained and supervised in contact lens insertion and removal. Patients should be aware that all contact lenses, even decorative and costume contact lenses, are medical devices and require a physician's prescription and supervision. Stores or websites may sell contact lenses without requiring a prescription; these lenses are unregulated and may be counterfeit. Contact lens cleaning and disinfection should be carefully explained, because improper care may be associated with complications of contact lens wear.[41,105,222,223]

Hydrogen peroxide systems may be superior to preserved disinfecting solutions in reducing pathogen binding and cysticidal disinfection, but they require more complex care regimens.[30,224-226] Patients should be instructed to use only sterile products that are commercially prepared specifically for contact lens care and to replace these at the intervals recommended by the manufacturers.[227] Specifically, patients should be instructed not to rinse contact lenses or lens cases with water (e.g., tap water, bottled water).[41] Patients should also be instructed to clean and replace contact lens cases at least every 3 months, because they can be a source of lens contamination.[228-230] Patients should be instructed to replace the solution in contact lens cases each time the lenses are disinfected.[217,231] Contact lens wearers should also use only fresh contact lens disinfecting solution in their case, and never mix old and new solutions (e.g., "topping off" solution).[232]

Patients should be made aware that using contact lenses can be associated with the development of ocular problems, including corneal infections that may threaten vision, and that overnight wear of contact lenses is associated with a fivefold relative risk of these corneal infections compared with daily wear.[37-39,233-235] Even occasional overnight wear has risks[236] and is discouraged. The increased risk of corneal infections with overnight contact lens wear should be discussed with patients who are considering this modality of vision

correction. If patients choose overnight wear, they should be instructed to use only lenses specifically approved for extended wear.

Swimming with contact lenses has been associated with the development of *Acanthamoeba* keratitis,[235] and showering with lenses seems to be part of a pattern of risk.[105] Patients should be instructed to minimize water contact when wearing contact lenses and informed of the risks of wearing contact lenses while swimming, sitting in a hot tub, showering, bathing, and washing hair.

Patients should be advised to have regularly scheduled examinations to monitor the fit of the contact lens; to monitor ocular health, including pannus, scarring, inflammation and ectasia; and to reinforce proper lens care and hygiene.[61]

# APPENDIX 6. PREPARATION OF FORTIFIED TOPICAL ANTIBIOTICS

Preparation of fortified topical antibiotics should be performed using sterile techniques. The use of antibiotics in the treatment of post-LASIK bacterial keratitis is discussed in the Refractive Errors and Refractive Surgery PPP.[28] Instructions for preparing fortified topical antibiotics used in treating bacterial keratitis are as follows:

**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.

**Amikacin 40 mg/ml**

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

**Trimethoprim/sulfamethoxazole**

A 16-mg/ml / 80-mg/ml commercial preparation can be used.

**Colistin 0.19%**

Intravenous colistimethate sodium powder 1 million IU/75 mg to 10 ml of distilled water to produce 7.5 mg/ml (0.75%). Add 1 ml of this solution to 3 ml of distilled water.[167]

**Povidone-iodine 1.25%**

Prepare by dilution with balanced salt solution.[192]

**Linezolid 2mg/ml (0.2%)**

Intravenous solution 2 mg/ml[237]

Modified with permission from the American Academy of Ophthalmology Basic and Clinical Science Course Subcommittee. Basic Clinical and Science Course. External Disease and Cornea: Section 8,2017–2018. Table 10-6. San Francisco: American Academy of Ophthalmology, 2017.

# LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed and Cochrane databases were conducted in February 2017; the search strategies were as follows. Specific limited update searches were conducted after June 2018.

**Bacterial Keratitis:**

(eye infections, bacterial[MeSH Terms]) OR (“eye infections, bacterial/epidemiology"[MeSH Terms] OR ("eye infections, bacterial/ethnology"[MeSH Terms]) OR ("eye infections, bacterial/microbiology"[MAJR]) OR ("eye infections, bacterial/diagnosis"[MeSH Terms]) OR ("eye infections, bacterial/pathology"[mh:noexp] OR "eye infections, bacterial/physiopathology"[mh:noexp] OR "eye infections, bacterial/physiology"[mh:noexp]) OR (bacteria*[tiab]) AND (keratitis[tiab])

OR ((cornea*[tiab] AND (keratitis[tiab] OR ulcer*[tiab])) OR (("keratitis"[MeSH Terms] OR Corneal Ulcer[MeSH Terms]) AND (bacteria*[tiab]) OR (bacteria*[tiab])) OR (cornea*[ti] AND ulcer*[ti]) OR (ulcer*[ti] AND keratitis[ti])) OR (eye infections, bacterial[MeSH Terms]) AND (keratitis[tiab] OR (ulcer*[tiab]) AND (Disease Progression[MeSH Terms]) OR (bacterial keratitis[tiab])

**Epidemiology:**

("Eye Infections, Bacterial/epidemiology"[mh]) AND “bacterial keratitis” [tiab]) OR (“bacterial keratitis” [tiab] AND epidemiology) OR ("eye infections, bacterial/ethnology"[mh] AND (keratitis[tiab])

**Etiology:**

((“bacterial keratitis” [tiab]) AND (etiology OR “etiologic agents” OR "gram-positive isolates" OR "gram-positive cocci" OR "staphylococcus aureus" OR "Coagulase negative Staphylococci" OR "Streptococcus pneumoniae" OR "Streptococcus viridans group" OR "Gram-positive Bacilli" OR "Corynebacterium species" OR "Propionibacterium species" OR "Mycobacterium species" OR "Gram-Negative Isolates" OR "Gram-negative Bacilli" OR "Pseudomonas aeruginosa" OR "Serratia marcescens" OR "Proteus mirabilis" OR "Enteric gram-negative bacilli") OR (("bacterial keratitis"[tiab] AND (etiology OR “etiologic agents” OR "gram-negative coccobacillary" OR haemophilus OR moraxella OR "gram-negative cocci" OR neisseria)) OR ("Eye Infections, Bacterial/etiology"[mh] AND "bacterial keratitis"[tiab])

**Risk:**

("eye infections, bacterial"[MeSH Terms]) AND ("risk factors"[MeSH Terms]) OR ulcer*[tiab])

**Risk - Exogenous factors:**

(("Contact Lenses"[Mesh] OR orthokeratology [All Fields] OR "Wounds and injuries"[Mesh] OR "Ophthalmologic Surgical Procedures"[Mesh] OR "Pharmaceutical Preparations"[Mesh] OR "Drug Eruptions"[Mesh] OR "Immunosuppression"[Mesh] OR "Sutures"[Mesh] OR "Factitious

Disorders"[Mesh])) AND (("Risk Factors"[Mesh] AND "bacterial keratitis"[TIAB]) OR ("eye infections, bacterial"[MAJR]) AND ("contact lenses"[MAJR]))

**Risk - Ocular Surface Disease:**

("Eyelashes"[Mesh] OR "Eyelids"[mh] OR "Eyelid Diseases"[Mesh] OR "Tears"[mh] OR "Conjunctivitis"[mh]) AND "bacterial keratitis"[tiab]

**Risk - Corneal Epithelial Abnormalities:**

("Trigeminal Nerve Diseases"[mh] OR "Keratitis, Herpetic"[mh] OR "Cornea/abnormalities"[mh] OR "Corneal Edema"[mh] OR "Epithelium, Corneal"[mh] OR "Cornea/pathology"[mh] OR "Corneal Diseases"[mh]) AND ("bacterial keratitis"[tiab])

**Risk - Systemic Conditions:**

("Diabetes Mellitus"[Mesh] OR "Diabetes Complications"[Mesh] OR "Malnutrition"[Mesh] OR "Ventilators, Mechanical"[Mesh] OR "Vascular Diseases"[Mesh] OR "Substance-Related Disorders"[Mesh] OR "Skin Diseases"[Mesh] OR "Mucus"[Mesh] OR "Immunocompromised Host"[Mesh] OR "Dermatitis, Atopic"[Mesh] OR "Neisseriaceae Infections"[Mesh] OR "gonococcal"[All Fields] OR "Vitamin A Deficiency"[Mesh]) AND ("bacterial keratitis"[All Fields])

**BK and sterile hypopyon:**

(hypopyon AND "bacterial keratitis")

**Cultures and smears in the management of BK:**

("Culture Techniques"[Mesh] OR smear*) AND "bacterial keratitis"

**Culture yield improvement:**

"Culture Techniques"[Mesh] AND "Anesthetics"[Mesh] AND "Preservatives, Pharmaceutical"[Mesh]

**Treatment:**

("Therapeutics"[Mesh] OR "therapy "[Subheading] OR treatment* OR "Treatment Outcome"[Mesh] OR "Disease Management"[Mesh]) AND "bacterial keratitis") OR (("eye infections, bacterial/drug therapy"[MeSH Terms] OR "eye infections, bacterial/therapy"[MeSH Terms]) AND (keratitis[tiab])) OR (ulcer*[tiab]) OR (besifloxacin[tiab]) AND (“bacterial keratitis”[tiab])

**Drug Resistance:**

("Fluoroquinolones"[Mesh] AND "bacterial keratitis" AND ("Drug Resistance"[Mesh]) OR (("drug resistance"[MAJR]) AND ("eye infections, bacterial"[MAJR]))

**Increased risk of perforation:**

"Fluoroquinolones/adverse effects"[Mesh] AND "Corneal Ulcer"[Mesh]

**Keratitis due to Pseudomonas**

"Pseudomonas"[Mesh] AND "Keratitis"[Mesh] AND "Inflammation/prevention and control"[Mesh]

**Prolonged use of topical antibiotics – toxicity:**

"Anti-Bacterial Agents/toxicity"[Mesh] AND "Administration, Topical"[Mesh] AND "bacterial keratitis"

**Adjunctive therapies for BK:**

"Complementary Therapies"[Mesh] AND "bacterial keratitis"

**Corticosteroids in the management of BK:**

Corticosteroid* AND "bacterial keratitis"

**Correcting co-existing factors:**

("Comorbidity"[Mesh] OR "Eyelids/abnormalities"[Mesh]) AND "bacterial keratitis"

**Cost analysis:**

(eye infections, bacterial[MeSH Terms]) AND ("cost of illness"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab])

**Socioeconomic:**

("eye infections, bacterial"[MESH Terms]) AND (keratitis[tiab] OR ulcer*[tiab]) AND (economics[MeSH Terms] OR cost[MeSH Terms] OR "quality of life"[MeSH Terms])

# RELATED ACADEMY MATERIALS

**Basic and Clinical Science Course**

External Disease and Cornea (Section 8, 2018–2019)

**Focal Points**

Antibiotic Use in Corneal and External Eye Infections (2011)

**Preferred Practice Pattern® Guidelines – Free download available at www.aao.org/ppp.**

Comprehensive Adult Medical Eye Evaluation (2015)

Pediatric Eye Evaluations (2017)

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