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Bacterial Keratitis Preferred Practice Pattern®

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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.

Cornea/External Disease Preferred Practice Pattern Panel 2022–2023
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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in June 2023. The document was edited in response to the discussion and comments.

Preferred Practice Patterns Committee 2023
David K. Wallace, MD, MPH, Chair
Christina J. Flaxel, MD
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The Bacterial Keratitis PPP was sent for review in July 2023 to improve the quality of the guideline, to gather feedback on the draft recommendations and to assess feasibility for and applicability to the target audience, including assessing the facilitators and barriers to implementing recommendations (e.g., U.S. ophthalmologists and other important groups, including patients, other physicians, international ophthalmologists, research organizations, ophthalmological organizations, and experts in the field). The PPP was sent for review to the following patient organizations to solicit the views and preferences of patients and the public: Consumers United for Evidence-Based Healthcare, American Foundation for the Blind, Foundation Fighting Blindness, Lighthouse Guild, National Federation of the Blind, and Prevent Blindness. All those who were returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered (indicated with an asterisk below). Members of the Cornea/External Disease Preferred Practice Pattern Panel reviewed these comments and determined revisions to the document.

<u>Academy Reviewers</u>
Board of Trustees and Committee of Secretaries*
Council
General Counsel*
Ophthalmic Technology Assessment Committee
Cornea/External Disease Panel
Basic and Clinical Science Course Section 8 Subcommittee*
Practicing Ophthalmologists Advisory Committee for Education*

<u>Invited Reviewers</u>
American College of Surgeons, Advisory Council for Ophthalmic Surgery

American Foundation for the Blind
American Ophthalmological Society*
American Society of Cataract & Refractive Surgery
American Uveitis Society*
Asia Cornea Society*
Association for Research in Vision and Ophthalmology
Association of University Professors of Ophthalmology
Canadian Ophthalmological Society
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Foundation Fighting Blindness
International Council of Ophthalmology
International Society of Refractive Surgery
Lighthouse Guild
National Eye Institute
National Federation of the Blind
National Medical Association, Ophthalmology Section
Ocular Microbiology and Immunology Group
Prevent Blindness
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This guideline will be formally re-evaluated and updated on a 5-year cycle in 2028. A Summary Benchmark is a resource to facilitate application of the guideline and to provide criteria that could be used to measure the application of recommendations, which will be available to all at www.aao.org/ppp.

FINANCIAL DISCLOSURES

There is no external funding, including industry/commercial support, for the development of this PPP or for the distribution of the guidelines. The Academy has fully funded the development of this PPP, and the views or interests of the Academy has not influenced the final recommendations which are based on evidence from systematic reviews. All those individuals significantly involved in the guideline development process, including guideline panel members, PPP Committee members, Secretary for Quality of Care, and Academy staff, have declared competing/financial interests through a financial interest disclosure process as well as an assessment of the Open Payments website (available at https://openpaymentsdata.cms.gov/). The interests of the guideline panel members are provided at the beginning of each meeting and those with competing interests in a guideline topic do not participate in voting on areas of disagreement. In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at https://cmss.org/code-for-interactions-with-companies/), relevant relationships with industry are listed. As per CMSS code, direct financial relationships with companies do not include food and beverage, research funds paid to the institution and relationships outside of the topic of the PPP. The Academy has Relationship with Industry Procedures to comply with the Code (available at www.aao.org/about-preferred-practice-patterns). A majority (82%) of the members of the Cornea/External Disease Preferred Practice Pattern Panel 2022–2023 had no direct 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 2023 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 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 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 on March 3, 2022 and June 7, 2023 in PubMed. Complete details of the literature searches are available at www.aao.org/ppp.

- Recommendations are based on systematic reviews, as per the Institute of Medicine (Clinical Practice Guidelines We Can Trust, 2011). In formulating the recommendations, the health benefits, side effects/harms/risks, and the balance of benefits and risks are reviewed and considered. Final decisions are arrived at through informal consensus techniques. If there are areas of disagreement, a vote will be conducted among the members of the guideline panel. If there are individuals with direct financial relationships in the area of disagreement, these individuals will refrain from the vote.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

The majority of community-acquired cases of bacterial keratitis that are small noncentral ulcers resolve with topical empiric therapy.[4, 5] However, smears and/or cultures are specifically indicated in certain circumstances.[6, 7]

Contact lens wear is the number-one risk factor for microbial keratitis in the United States. Overnight wear (including orthokeratology) is a major risk factor for infection. In many other parts of the world, trauma is the leading risk factor for bacterial keratitis.

Topical antibiotics should be prescribed to prevent acute infection in patients with a corneal abrasion who wear contact lenses or suffered trauma. In these patients, patching the eye early on is not advised because these increase the risk of secondary bacterial keratitis.

When treating microbial keratitis, corticosteroids may be considered after 48 hours of antibiotic therapy when the causative organism is identified and/or the infection has responded to therapy. Corticosteroids should be avoided in cases of suspected *Acanthamoeba, Nocardia,* or fungus. The efficacy of the therapeutic regimen is judged primarily by the clinical response. In *Pseudomonas* and other gram-negative keratitis, there may be increased inflammatory signs during the first 24 to 48 hours despite appropriate therapy.

From 2005 to 2015 there was increased resistance of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* to topical fluoroquinolones.[8, 9]

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, photophobia, discharge, corneal infiltrates, ulcerations, and anterior chamber inflammation.

CLINICAL OBJECTIVES

- Recognize and reduce risk factors that predispose patients to bacterial infections of the cornea
- Establish the diagnosis of bacterial keratitis and differentiate it from other causes of keratitis
- Utilize appropriate diagnostic tests
- Select appropriate therapy
- 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 options 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,[10] with an increasing incidence.[11] 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,[12, 13] trauma, corneal surgery, ocular surface disease,[10] systemic diseases,[14] and immunosuppression, may alter the defense mechanisms of the ocular surface and permit bacteria to invade the cornea (see Risk Factors). Two retrospective analyses from the United Kingdom and Italy found that contact lens use was the most common risk factor for bacterial keratitis.[15, 16]

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.[10, 17-26] These differences could be associated with climate, rural versus urban area, or the etiology of keratitis. A study of two hospitals in Los Angeles found that the majority of cases comprised gram-positive pathogens; coagulase-negative staphylococcus was the most common, and *Pseudomonas aeruginosa* was the most common gram-negative organism.[17] Another review found that gram-negative organisms were much more prevalent in the southern United States than in the northern United States, and south Florida had the highest rate.[22] A high proportion of gram-negative bacterial keratitis was also found in a large county hospital in Houston, Texas.[13]

It is common for multiple species to be present in bacterial keratitis; one study reported that 43% of positive cultures yielded two or more bacterial organisms.[27] Polymicrobial keratitis can also occur with the most common causative organisms, which are *Staphylococcus epidermidis* and the *Fusarium* species. The most common etiology of polymicrobial keratitis is trauma.[28, 29] 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%.[30]

RISK FACTORS

Risk factors that predispose patients to bacterial keratitis can be divided into two categories, described in Table 1 and Table 2. (For more details on risk factors associated with contact lens use, refer to the Refractive Errors PPP[31] and the Refractive Surgery PPP.[32])

Table 1. Extrinsic Risk Factors Related to Contact Lens Wear

The use of contact lenses, including therapeutic contact lenses,[13, 33-40] is a risk factor for bacterial keratitis, especially when associated with the following:

- Overnight wear[41-45]
- Overnight orthokeratology[46-55]
- Overwear beyond FDA-approved replacement schedule
- Inadequate disinfection of contact lenses (topping off solutions)
- Contamination of the contact lens storage case[43, 45, 56] (including rinsing the case with tap water[57])
- Ineffective or contaminated contact lens solution
- Storing or rinsing in tap water[58]
- Poor contact lens hygiene practices (hand washing, lens case use, storage location and replacement frequency, contact lens soaking duration)
- Using a damaged lens
- Poor fitting lens
- Using unregulated lenses (decorative, Internet-based and over-the-counter purchases) without a doctor's prescription[44, 59-64]
- Sharing lenses[62]
- Swimming, using a hot tub, or showering while wearing contact lenses[34]
- Lack of supervision and routine follow-up (50% of asymptomatic patients during a routine visit presented with signs of complications[65])

Table 2. Ocular Surface Disease Risk Factors

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

Local disease

- Trauma,[66] including chemical and thermal injuries,[67] foreign bodies, and local irradiation
- Previous ocular and eyelid surgery, including glaucoma surgery,[68] refractive surgery,[69, 70] cataract surgery[71] and keratoplasty[72, 73] (including keratoprosthesis[74, 75])
- Loose corneal sutures[76]
- Tear-film deficiencies
- Abnormalities of the eyelid anatomy and function (including exposure)
- Misdirection of eyelashes (including trachomatous trichiasis)
- Adjacent infection/inflammation (including gonococcal conjunctivitis, blepharitis, canaliculitis, dacryocystitis)[77]
- Neurotrophic keratopathy (e.g., trigeminal neuropathy)
- Disorders predisposing to recurrent erosion of the cornea
- Corneal abrasion or epithelial defect

Systemic

- Diabetes mellitus[78]
- Critical illness, especially malnourishment and/or respirator dependence[79]
- Connective tissue disease
- Dermatological/mucous membrane disorders (e.g., Stevens-Johnson syndrome,[67] ocular mucous membrane pemphigoid)
- Immunosuppression (topical and systemic medications, medical conditions)[14]
- Atopic dermatitis/blepharoconjunctivitis
- Vitamin A deficiency
- Damage to cranial nerves V and VII (e.g., acoustic neuroma, neurological surgery)
- Graft-versus-host disease
- Substance abuse[13]

◆ Medication-related factors (e.g., contaminated ocular medications, topical nonsteroidal anti-inflammatory drugs [NSAIDs], anesthetics, corticosteroids, preservatives, glaucoma medications) ◆ Viral keratitis (herpes simplex virus [HSV] or varicella zoster virus [VZV]) ◆ Corneal epithelial edema, especially bullous keratopathy ◆ Environmental contamination (e.g., workplace)	

NATURAL HISTORY

Loss of vision resulting from bacterial keratitis can frequently occur due to corneal scarring or contour irregularity. Untreated or severe bacterial keratitis may result in corneal perforation and has the potential to develop into endophthalmitis and result in loss of the eye.[13, 14] Because this process of corneal tissue loss can take place rapidly (within 24 hours when the infection is caused by a virulent organism), optimal management requires prompt 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 can cause substantial visual loss, even if the infecting organism is successfully eradicated.[80] Although some bacteria (e.g., *Neisseria gonorrhoeae, P. aeruginosa*) 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 depends 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 *N. 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, whether from local ocular disease or systemic immune compromise.

Patients who have systemic and/or multiple risk factors for keratitis have a higher risk of polymicrobial keratitis, and there are a greater number and longer duration of infiltrates in polymicrobial keratitis than in monomicrobial keratitis.[81]

CARE PROCESS

PATIENT OUTCOME CRITERIA

Treatment goals for bacterial keratitis include the following:

- Eradicating microorganisms from corneal tissues
- Reducing pain
- Resolving discharge as well as corneal and anterior chamber inflammation
- Minimizing secondary intraocular damage from inflammation including cataract formation, glaucoma, and corneal edema
- Limiting stromal infiltration and tissue loss
- Healing epithelial defect
- Restoring corneal integrity, and minimizing scarring and vascularization
- Optimizing visual function

DIAGNOSIS

Evaluation of the patient with presumed bacterial keratitis includes a careful assessment of elements from the comprehensive medical eye evaluation[82, 83] specifically relevant to bacterial keratitis, as described below.

History

- Ocular symptoms (e.g., degree of pain, redness, discharge, blurred vision, photophobia) including duration of symptoms and circumstances surrounding the onset of symptoms
- Contact lens history[33, 34] (e.g., wearing schedule; overnight wear; type of contact lens; contact lens solution; homemade saline; 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) (See Table 1)
- Review of other ocular history, including risk factors such as herpes simplex virus (HSV) keratitis, varicella zoster virus (VZV) keratitis, previous bacterial keratitis, trauma, dry eye, recurrent corneal erosion, and previous ocular surgery, including refractive and facial (including laser cosmetic and blepharoplasty) surgery
- Review of other medical problems, including immune status, rosacea, atopy, diabetes, systemic medications, and history of methicillin-resistant *Staphylococcus aureus* (MRSA) or other multidrug-resistant infection
- Current and recently used ocular and systemic medications
- Medication allergies

Physical Examination

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 if 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, hands, and overall hygiene
- Facial examination (rosacea, herpes zoster)
- Globe position
- Eyelids and eyelid closure
- Conjunctiva (injection, chemosis)
- 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 more 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. Periodic slit-lamp biomicroscopy in contact lens wearers is essential; 50% of asymptomatic patients during a routine visit presented with signs of complications of contact lens wear, most commonly papillae and/or giant papillary conjunctivitis.[65]

Slit-lamp biomicroscopy should include evaluation of the following:

- Eyelid
  - Inflammation
  - Ulceration
  - Meibomian gland dysfunction/anterior blepharitis
  - Eyelash abnormalities, including trichiasis/distichiasis
  - Lagophthalmos
  - Floppy eyelid
  - Lacrimal punctal anomalies
  - Ectropion/entropion
  - Upper eyelid eversion
  - Punctal ectropion

- Conjunctiva
  - Discharge
  - Inflammation
  - Morphologic alterations (e.g., follicles, papillae, cicatrization, symblephara, scarring, keratinization, membrane, pseudomembrane, ulceration, loss of epithelial tissue, evidence of prior surgery, chalasis)
  - Evert eyelid to inspect tarsal conjunctiva
  - Ischemia
  - Foreign body
  - Filtering bleb, tube erosion
- Sclera
  - Inflammation (e.g., infectious versus immune)
  - Ulceration
  - Thinning
  - Nodule
  - Ischemia
- Cornea
  - Epithelium, including defects and punctate keratopathy, edema, epithelial basement membrane dystrophy
  - Stroma, including ulceration, thinning, perforation, edema, 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)
  - Endothelium (endothelial plaque)
  - Foreign body, including sutures[71, 84]
  - Signs of corneal dystrophies (e.g., epithelial basement membrane dystrophy)
  - Evidence of 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 epithelial defect. Staining of epithelium must be differentiated from pooling of stain in an area of corneal thinning with intact epithelium. Pooling can be wicked away with a cotton swab or by irrigating the cornea.
- Anterior chamber for depth and the presence of inflammation, including cell and flare, fibrin, hyphema, and hypopyon. Hypopyon may present as a blunting of the inferior angle or present at 3:00 or 9:00 if the patient had recently been lying down.
- 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 and cultures.[4, 5] However, smears and cultures are specifically recommended prior to initiating antimicrobial therapy in the following circumstances:[6, 7]

- A central, large corneal infiltrate (within 3 mm of the corneal center and ≥2 mm in size,) and/or presence of ≥2 adjacent lesions and/or associated with significant stromal involvement or melting
- There are ≥1+ cells in the anterior chamber
- There is a history of corneal surgery
- Atypical clinical features present that are suggestive of fungal, amoebic, or mycobacterial keratitis

- There are multiple corneal infiltrates[85]

Smears and cultures are also often helpful for patients with additional risk factors (e.g., trauma with organic matter, contact lens wear while in a hot tub, postoperative infiltrates in surgical wounds or lamellar interfaces, chronic infection, or poor response to broad-spectrum antibiotic therapy). 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. See Table 3 for additional details.

TABLE 3 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
Post-surgery infiltrates	Culture	Gram, Potassium hydroxide, Calcofluor white and acid fast

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 in less than 70% of cases.[86] This study highlights the importance of using cultures to correctly identify the etiology of microbial keratitis.

Obtaining a corneal culture is a means of identifying the causative organism(s) and determining 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 may be 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 (PCR) and immunodiagnostic techniques may be useful and are now more widely available in the office setting.[87-92] Of note, PCR may fail to distinguish between antigenic material and live organisms.

Corneal material is obtained by instilling a topical anesthetic agent, preferably proparacaine 0.5% (tetracaine should be avoided because of its antimicrobial effect), then using a sterile single-use blade, sterile spatula, or similar instrument to obtain scrapings of material from the base or periphery of the suspected infection. Culture yield may be improved by avoiding anesthetics with preservatives.[93] 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. When using transport media, similar methods are used to obtain corneal material. The material is then transferred to the cotton or calcium alginate swab, which is then placed in the transport media tube.

Corneal scrapings for culture should be inoculated directly onto appropriate culture media to maximize culture yield (see Appendix 4).[94] If this is not feasible, specimens should be placed in transport media.[95, 96] 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.[97] Cultures of contact lenses, the lens case, and contact lens solution may provide additional information to guide therapy.

A simplified collection device using a nylon-tipped swab with a flocked tip arrangement has been shown to have a similar culture positivity rate when compared with traditional collection methods.[27] 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 initially 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.[14, 98] If the cultures are negative, the ophthalmologist may consider stopping antibiotic treatment for 12 to 24 hours and then reculturing the corneal ulcer.

In cases that are not responding to treatment as expected, consideration should be given to using special culture media (e.g., Löwenstein-Jensen media for mycobacteria or non-nutrient agar seeded with *E. coli*).

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.[99] Corneal biopsy may also be indicated if the infiltrate is located in the mid or deep stroma with overlying uninvolved tissue.[100, 101] 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 dermal 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 for histopathology.[102] 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 corneal biopsy taken from the center of the cornea may result in a significant refractive error from the resultant irregular surface. It is helpful to discuss the case with the pathologist prior to the biopsy to ensure that the specimen is properly prepared for maximum yield and delivered promptly. Based on culture results, antibiotic therapy should be tailored as indicated in Table 4.

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 can 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 microbial keratitis, including bacterial, fungal, and, most notably, parasitic (e.g., *Acanthamoeba*).[103-106] Individual bacteria cannot be identified through confocal microscopy. However, epithelial and stromal bullae in confocal microscopy have been noted in patients with bacterial keratitis.[107] Challenges associated with confocal microscopy include access to the confocal microscopes and dependence on technical expertise in obtaining and interpreting the images. Anterior segment optical coherence tomography may also be helpful in determining the depth of involvement. Ultrasound biomicroscopy can help characterize the status of intraocular structures when severe keratitis precludes the use of alternative devices. Clinical photography is also helpful in assessing the treatment response.[108]

Differential Diagnosis

The differential diagnosis includes infectious and noninfectious causes of infiltrates. Nonbacterial corneal pathogens, including fungi (both yeast and mold), parasites (including microsporidia and protozoa such as *Acanthamoeba*), and nematodes (such as *Onchocerca*) may cause a microbial keratitis.[109] An increase in the incidence of *Acanthamoeba* and fungal keratitis since 2004 has been noted.[11, 110-119] Fungal ulcers may have a dry rather than suppurative appearance, a feathered edge, satellite lesions, or a posterior plaque. A ring infiltrate is commonly seen in both fungal ulcers and *Acanthamoeba* keratitis. Inflammation along corneal nerves, radial keratoneuritis, is more typical of *Acanthamoeba* keratitis, as well as severe pain in excess of the findings. Viruses including HSV, VZV, and Epstein-Barr 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.[120] 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, and patients who are older or immunosuppressed. When there is clinical uncertainty about 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, such as phlyctenular keratitis, staphylococcus-associated marginal keratitis, or peripheral ulcerative keratitis secondary to autoimmune disease.

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 risk factors for 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.[121] 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 these factors and educating them about the risks of overnight wear of contact lenses[33, 41, 51] and proper contact lens care[122] may reduce the incidence of bacterial keratitis in those who wear contact lenses. (See Appendix 5 for recommendations on contact lens care.) For patients who require a therapeutic contact lens, some authors recommend 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.[123] Other 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 microbial keratitis, and this risk may be greater in patients with chronic ocular surface disease.[36] 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 microbial keratitis when wearing bandage contact lenses and of the need to contact their treating ophthalmologist if redness, pain, or increased photophobia develops. These patients 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.

Early detection and appropriate treatment are important to minimize permanent visual loss.[124] 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, entropion, 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. Topical antibiotics should be prescribed to prevent acute bacterial keratitis in patients who wear contact lenses and present with a corneal abrasion. Similarly, a broad-spectrum topical antibiotic is recommended for any patient presenting with corneal abrasion following trauma. This strategy helps prevent not only bacterial infection but fungal infection as well.[125] Prophylactic topical antibiotics following corneal abrasion has been shown to prevent ulceration when treatment is started within 24 hours of the abrasion.[125, 126] *(I+, Moderate, Strong)* In patients with contact-lens associated abrasion, patching the eye or using a therapeutic contact lens is not advised due to concerns for increased risk of secondary bacterial 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 of bacterial keratitis.[127] The majority of community-acquired cases of small noncentral ulcers resolve with topical empiric therapy.[4, 5] (See Table 4 for recommendations about antibiotic therapy.) In selected cases, the initial treatment choice 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.[128]

Ocular ointments lack solubility and therefore the therapeutic agents are not able to penetrate into the cornea significantly for optimum therapeutic benefit. However, ointments may be useful at bedtime in less severe cases and may be useful for adjunctive therapy.

In cases where adherence is questionable or a delay in obtaining fortified antibiotics is anticipated, subconjunctival antibiotic injections may be helpful. Systemic therapy may be useful in cases of scleral or intraocular extension of infection or systemic infection such as *N. gonorrhoeae*. Collagen shields or soft contact lenses soaked in antibiotics may be considered to enhance drug delivery but have the potential risk of inducing drug toxicity and corneal epithelial hypoxia.[129-132] Collagen shields and soft contact lenses may also become displaced or lost, leading to unrecognized interruption of drug delivery.

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 to 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 anterior segment inflammation associated with bacterial keratitis.

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.[127, 133-138] 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 FDA for the treatment of bacterial keratitis.[139-141] 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.[115] Some pathogens (e.g., *Streptococci*, anaerobes) reportedly have variable susceptibility to fluoroquinolones,[134, 142] and the prevalence of resistance to the fluoroquinolones appears to be increasing.[20, 30, 143, 144] Individual risk factors for fluoroquinolone resistance include recent fluoroquinolone use, hospitalization, age, and recent ocular surgery.[145, 146] A study of over 3,200 ocular isolates collected from 2009 to 2013 found methicillin resistance in 42% of *Staphylococcal* isolates, with a high concurrent resistance to fluoroquinolone; however,

an increase in drug resistance overall during the study period was not observed.[8] In a systematic review over multiple decades, the prevalence of methicillin-resistant *Staphylococcal* isolates peaked from 2005 to 2015, with a possible decreasing trend over recent years.[9] 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.[147] 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.[133, 136, 137, 148-151] In southern India, there has been a sharp increase in resistance of *P. aeruginosa* to moxifloxacin, from 19% in 2007 to 52% in 2009.[152] A 20-year study in San Francisco found increasing overall resistance of organisms to moxifloxacin from 1996 to 2015.[153] 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.[154] Besifloxacin 0.6% is a topical fluoroquinolone that has been established as a potent treatment for bacterial conjunctivitis and possibly bacterial keratitis, with a potency against ocular pathogenic bacteria similar to the fourth-generation agents.[155, 156] A Cochrane review found no evidence of difference in corneal perforation rates between any classes of topical antibiotics.[138]

Combination fortified-antibiotic therapy is an alternative to consider, especially for severe infection and for eyes unresponsive to initial treatment.[5, 13, 135, 154] Fortified antibiotics should be prepared by a compounding pharmacy that is a member of the Pharmacy Compounding Accreditation Board[157] and designated by the FDA as a 503A and/or 503B facility. (See Appendix 6 for guidelines for preparation of fortified topical antibiotics.) Treatment with more than one agent may be necessary for nontuberculous mycobacteria; infection with this pathogen has been reported in association with LASIK.[158, 159]

Methicillin-resistant and oxacillin-resistant *S. aureus* have been isolated with increasing frequency from patients with bacterial keratitis[17, 160-165] and have been reported following keratorefractive surgery.[166] Fluoroquinolones are generally poorly effective against MRSA ocular isolates.[8, 14, 167, 168] Methicillin-resistant *S. aureus* isolates generally are susceptible to vancomycin.[169, 170] 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 *P. aeruginosa* has been reported, with high morbidity.[171, 172] Topical colistin 0.19% may be considered in such cases.[173] Of note *Moraxella* keratitis is usually susceptible to fluoroquinolones and aminoglycosides, but requires a more prolonged treatment duration (mean, 41.9 days).[174]

Recurrent bacterial keratitis is more likely to be caused by *S. aureus*.[175] 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 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.[176]

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

TABLE 4 ANTIBIOTIC THERAPY FOR BACTERIAL KERATITIS

Organism	Antibiotic	Topical Dose	Subconjunctival Dose
Gram-positive cocci	Cefazolin	50 mg/mL	100 mg in 0.5 mL
	Vancomycin	25–50 mg/mL	25 mg in 0.5 mL
	Moxifloxacin, gatifloxacin, levofloxacin, besifloxacin	5–6 mg/mL	Not available
Gram-negative rods	Tobramycin	9–14 mg/mL	20 mg in 0.5 mL
	Ceftazidime	50 mg/mL	100 mg in 0.5 mL
	Ciprofloxacin, ofloxacin, moxifloxacin, gatifloxacin, levofloxacin, besifloxacin	3–6 mg/mL	Not available
None or multiple types of organisms	Fortified cefazolin	50 mg/mL	100 mg in 0.5 mL
	with		
	Fortified tobramycin	9–14 mg/mL	20 mg in 0.5 mL
	or		
	Fluoroquinolones	3–6 mg/mL	Not available
Gram-negative cocci	Ceftriaxone	50 mg/mL	100 mg in 0.5 mL
	Ceftazidime	50 mg/mL	100 mg in 0.5 mL
	Ciprofloxacin, ofloxacin, moxifloxacin, gatifloxacin, levofloxacin, besifloxacin	3–6 mg/mL	Not available
Mycobacteria	Clarithromycin	10 mg/mL 0.03%	
	Moxifloxacin, gatifloxacin, besifloxacin	5–6 mg/mL	Not available
	Amikacin		
		20–40 mg/mL	20 mg in 0.5 mL
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, 2022–2023. Table 10-6. San Francisco: American Academy of Ophthalmology, 2022.

Corticosteroid Therapy

Topical corticosteroid therapy may have a beneficial role in treating some cases of microbial keratitis. Much of the literature shows no difference in clinical outcome with the addition of corticosteroids.[177-180] The potential advantage is the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss. Potential disadvantages include recurrence of infection, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting, and increased intraocular pressure (IOP). The Steroids for Corneal Ulcer Trial (SCUT) found no benefit of concurrent topical corticosteroid therapy using prednisolone phosphate 1% in conjunction with broad-spectrum topical antibiotic.[181] 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 (ulcers completely covering the central 4-mm pupil or vision of counting fingers or worse) cases of bacterial keratitis. The same study found that treatment of *Nocardia* keratitis with corticosteroids resulted in poor visual outcomes,[182] and a subsequent follow-up found that these results were similar at the 12-month follow-up.[183] A second subgroup analysis of non-*Nocardia* keratitis 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.[184]

A consideration in 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 the addition of corticosteroids may be beneficial.[185] Although a small, retrospective study that included fungal keratitis[186] 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.[181] Therefore, judicious use with close follow-up would be prudent.[181, 186, 187]

In cases where the corneal infiltrate compromises the central cornea, topical corticosteroid therapy may be added to the treatment 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).

The IOP must be monitored, and 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.[181] 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).[188] 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 does not respond 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:[109]

- Reduced pain
- Reduced amount of discharge
- Reduced 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. However, most antibiotic eye drops should not be tapered below subtherapeutic dosing as it may increase the risk of developing antibiotic resistance. 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.

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) and N-acetylcysteine could be used to counteract corneal stromal thinning by inhibiting matrix metalloproteinases, but there are limited data on their use for the management of infectious keratitis.[189-191] 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 urgent keratoplasty and improve prognosis of an elective keratoplasty.[192-196] 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.[194] 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.[195] Amniotic membrane transplantation and conjunctival flap may be used in cases refractory to medical treatment.[196] Tenons patch graft[197] with cyanoacrylate glue can be an effective option for the management of larger perforations. More recently, tectonic Descemet's stripping endothelial keratoplasty has been an alternative to tectonic penetrating or lamellar keratoplasty for perforation.[198-200] When

corneal tissue is removed, it should be sent for pathologic and microbiologic analysis. Bacterial keratitis has more favorable outcomes than fungal keratitis.[201] 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. There is variable evidence on the efficacy of intrastromal injection of antifungals.[202, 203]

Corneal Cross-Linking for Microbial Keratitis

Corneal cross-linking has been used successfully in the treatment of moderate bacterial ulcers.[204] 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 re-epithelialization 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.[205-207] A meta-analysis of 12 articles found that corneal cross-linking is potentially effective for treatment of bacterial keratitis and can inhibit corneal melting, especially in bacterial keratitis.[208] Another meta-analysis of 59 eyes showed variable results.[209] Cross-linking has been proposed to have a greater effect in more shallow infiltrates because ultraviolet energy is absorbed within the anterior cornea.[210] One small study found that cross-linking alone, without antibiotic therapy, can resolve bacterial keratitis in 14 out of 16 cases.[211] Cross-linking has more evidence of success with more anterior infections as an adjunct with standard antibiotic therapy, especially in difficult cases.[212-215] Although cross-linking has been used off-label for the treatment of microbial keratitis, it is not FDA approved for this indication.

PROVIDER AND SETTING

The diagnosis and management of patients with bacterial keratitis requires the clinical training and experience of an ophthalmologist, especially in the setting of 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 and are less concerned with resistant organisms than corneal specialists in the United States.[216]

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 unlikely, or if pain is severe. Some patients are unable to instill 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 the risk of 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 (including orthokeratology),[217] and the importance of adherence to techniques that promote contact lens hygiene[44, 56] (see Appendix 5). The incidence of microbial keratitis is as high as 20 per 10,000 wearers per year for extended wear compared with 1 to 2 per 10,000 wearers per year for daily wear.[43] The risks and timing of resuming contact lens wear following bacterial keratitis should be discussed with the patient, and the lens choice and fit and mode of wear should be reassessed, including switching the patient to daily disposable lens wear, which has a lower rate of complications than daily wear of reusable lenses. Adverse events related to FDA-regulated products (e.g., contact lenses and care products) are encouraged to be reported to MedWatch (www.fda.gov/medwatch), the Safety Information and Adverse Reporting Program. Although the FDA acknowledges the higher risk of extended-wear contact lenses by its class III medical-device designation (which is the same class as intraocular lenses), it is not clear to patients that this distinction exists. One way to influence additional labelling of risk is for doctors and patients to report all corneal infiltrative events and contact lens-related infections to MedWatch.[218]

Visual rehabilitation improves functional ability,[219] and patients with substantial visual impairment should be referred for vision rehabilitation and social services if they are not candidates for surgical rehabilitation.[220] 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 and irregularity. The World Health Organization (WHO) recognizes it as a silent epidemic.[221] The largest risk factor for bacterial keratitis in the United States is contact lens use,[33, 222] whereas trauma is the largest risk factor in Southeast Asia[125, 223] and South India.[66] Low- to middle-income countries have a much higher incidence of bacterial keratitis compared with high-income countries. For example, Olmsted County, Minnesota, had an incidence of microbial keratitis of 11 per 100,000[224] compared with an incidence of 113 per 100,000 in India[225] and 799 per 100,000 in Nepal.[125] Microbial keratitis is the leading cause of corneal blindness in China.[226]

There have been successful attempts to prevent bacterial keratitis in low- to middle-income 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.[125] Only 18 of 442 patients went on to develop corneal ulcers. The WHO applied the Bhaktapur Eye Study model in Bhutan.[227] 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.[228]

The estimated cost of contact lens-related microbial keratitis in the United States in 2010 was approximately $135 million.[229] Higher socioeconomic status in the United States was associated with more serious contact lens-related corneal infections.[45] The estimated wholesale cost of medication in the treatment of bacterial keratitis in the United States is $933 USD per patient.[230] In other parts of the world, the incidence of microbial keratitis has been shown in multiple studies to be higher in patients of lower socioeconomic status.[226, 231] There is a significant financial burden of bacterial keratitis that results from direct costs due to medications, visits to ophthalmologists, and diagnostic testing, and also from indirect costs due to loss of income, assistance from caregivers, and eyeglass purchases.[232] 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$5,515 for severe cases with vision loss, AU$1,596 for severe cases without vision loss, and AU$795 for mild keratitis.[232]

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. Use of a topical second-generation fluoroquinolone (e.g., ofloxacin and ciprofloxacin) has been shown to be comparable in efficacy to fortified antibiotics,[233] 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.

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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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 A3-1 lists diagnostic stains that are used in cultures to identify causes of bacterial keratitis.

TABLE A3-1 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 A4-1 lists culture and transport media that are used in the management of bacterial keratitis.

TABLE A4-1 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.

APPENDIX 5. CONTACT LENS CARE

The following recommendations have been excerpted from the Refractive Errors PPP[31] and Refractive Surgery PPP.[32]

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[234, 235]:

- 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.[236, 237] 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.[238] Stores or websites selling any contact lenses without requiring a prescription are engaging in business activity that is subject to federal law enforcement; these lenses are unregulated and may be counterfeit.

When contact lenses are initially prescribed and dispensed, patients should be trained and supervised in contact lens insertion and removal. Contact lens cleaning and disinfection should be carefully explained, because improper care may be associated with complications of contact lens wear.[45, 115, 239, 240]

Hydrogen peroxide systems may be superior to preserved disinfecting solutions in reducing pathogen binding and cysticidal disinfection, but they require more complex care regimens.[34, 241-243] 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.[244] Specifically, patients should be instructed not to rinse contact lenses or lens cases with water (e.g., tap water, homemade saline, or bottled water).[45] 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.[45, 245, 246] Patients should be instructed to replace the solution in contact lens cases each time the lenses are disinfected.[234, 247] 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).[248]

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.[41-43, 249-251] Even occasional overnight wear has risks[252] 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,[251] and showering with lenses seems to be part of a pattern of risk.[115] 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.[65]

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 Surgery PPP.[32] 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 or ceftazidime, 1 g (powder for injection).
2. Dissolve. Take 5 ml of this solution and add it to 5 ml of artificial tears.
3. Refrigerate and shake well before instillation.

Tobramycin 14 mg/ml 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.[173]

Povidone-iodine 1.25%

Prepare by dilution of povidone-iodine 5% or 10% with balanced salt solution.[253]

Linezolid 2 mg/ml (0.2%)

Intravenous solution 2 mg/ml[254]

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 8,2022-2023. Table 10-6. San Francisco: American Academy of Ophthalmology, 2022.

LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed database were conducted on March 3, 2022; the search strategies are listed below. Specific limited update searches were conducted on June 7, 2023. The searches had added filters for human, English-language randomized controlled trials and systematic reviews and date limiters to capture literature published since June 27, 2018. The panel analyzed 563 studies of which 26 were included in the PPP. The literature searches with the disease condition and the search terms patient values and patient preferences didn't yield results. The literature searches for economic evaluation and treatment cost yielded 1 study which was provided to the panel and the article did not merit inclusion in the PPP.

Search 1: (eye infections, bacterial[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab])

Search 2: ("eye infections, bacterial/epidemiology"[MeSH Terms] OR "eye infections, bacterial/ethnology"[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab])

Search 3: ("eye infections, bacterial/drug therapy"[MeSH Terms] OR "eye infections, bacterial/therapy"[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab])

Search 4: ("eye infections, bacterial/microbiology"[MAJR]) AND (keratitis[tiab] OR ulcer*[tiab])

Search 5: ("eye infections, bacterial/etiology"[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab])

Search 6: ("eye infections, bacterial"[MAJR]) AND ("contact lenses"[MAJR])

Search 7: ("drug resistance"[MAJR]) AND ("eye infections, bacterial"[MAJR])

Search 8: ("eye infections, bacterial"[MeSH Terms]) AND ("risk factors"[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab])

Search 9: ("eye infections, bacterial/diagnosis"[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab]) NOT (Case Reports[PT])

Search 10: ("keratitis"[MeSH Terms] OR Corneal Ulcer[MeSH Terms]) AND (bacteria*[tiab])

Search 11: (bacteria*[tiab]) AND ((bacteria*[ti] AND keratitis[ti]) OR (cornea*[ti] AND ulcer*[ti]) OR (ulcer*[ti] AND keratitis[ti])) NOT (Case Reports[PT])

Search 12: ("eye infections, bacterial/pathology"[mh:noexp] OR "eye infections, bacterial/physiopathology"[mh:noexp] OR "eye infections, bacterial/physiology"[mh:noexp]) AND (keratitis[tiab] OR ulcer*[tiab]) NOT (case reports[pt])

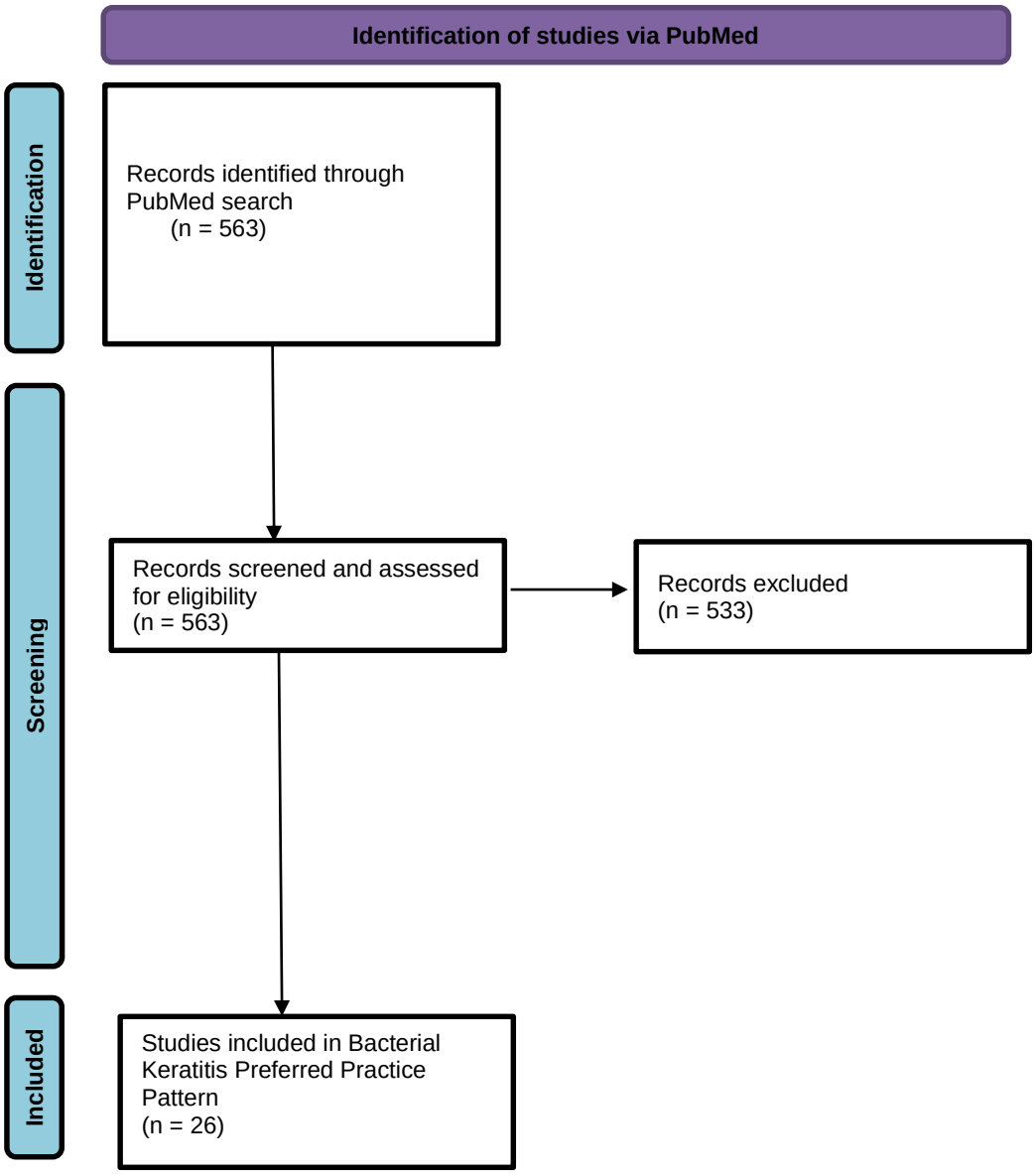
Search 13: (eye infections, bacterial[MeSH Terms]) AND ("cost of illness"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab])

Search 14: (eye infections, bacterial[MeSH Terms]) AND (keratitis[tiab] OR ulcer*[tiab]) AND (Disease Progression[MeSH Terms])

Search 15: (besifloxacin[tiab]) AND (keratitis[tiab])

Search 16: (bacterial keratitis[tiab]) OR (bacteria*[tiab]) AND (keratitis[tiab] OR (cornea*[tiab] AND ulcer*[tiab]) OR (keratitis[tiab] AND ulcer*[tiab]))

Search 17: (bacterial keratitis[tiab] AND (patient values[tiab] OR patient preferences[tiab])



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

RELATED ACADEMY MATERIALS

Basic and Clinical Science Course
External Disease and Cornea (Section 8, 2023–2024)

Preferred Practice Pattern® Guidelines – Free download available at www.aao.org/ppp**.**
Comprehensive Adult Medical Eye Evaluation (2020)
Pediatric Eye Evaluations (2022)
Vision Rehabilitation (2022)

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