Intraocular Antibiotics for Cataract Surgery Prophylaxis

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Injectable intracameral or intravitreal antibiotics appear to have advantages over topical eye drops in endophthalmitis prophylaxis for cataract surgery. However, without an approved, commercially prepared intraocular antibiotic formulation, the use of intraocular prophylactic treatment will likely remain debatable.

In cataract surgery, endophthalmitis prophylaxis has been and continues to be an important issue. Endophthalmitis occurs when the infecting organism—usually exogenous bacteria—gains access to the interior of the eye during or shortly after surgery.1 Though rare, postoperative endophthalmitis can have devastating visual consequences: even when treated aggressively with vitrectomy, only about half of affected patients achieve 20/40 or better vision.2

In the US, the vast majority of cataract surgeons routinely prescribe perioperative topical antibiotic drops for endophthalmitis prophylaxis.3 Alongside other prophylactic measures such as antiseptic preparation with povidone iodine and eyelid draping, drop therapy is purported to reduce floral colonization on the ocular surface and reduce the risk of infection; but its efficacy has not been confirmed by prospective studies.

Since the landmark European Society of Cataract & Refractive Surgeons (EscrS) endophthalmitis study, there is mounting evidence that intracameral antibiotic injection is an efficacious method of endophthalmitis prophylaxis.4,5 This raises the prospect of lessening or eliminating the need for drops by placing prophylactic antibiotics inside the eye during surgery. The intraocular approach is an attractive alternative because it can potentially help address issues associated with traditional drop therapy such as adherence and high cost.

Intracameral Antibiotics

Prophylactic intracameral antibiotic...
ics can be administered via a couple of routes. Some choose to mix the antibiotic into the irrigating fluid, though no reliable data exists to support the practice, and it is difficult to dose accurately with infusion. Alternatively, surgeons can directly inject a bolus of intracameral antibiotics at the end of cataract surgery.

The ESCRs Endophthalmitis Study Group reported a 5-fold reduction in endophthalmitis rates with intracameral injection of cefuroxime (0.07% vs 0.34% without intracameral cefuroxime). Since then, there has been a growing trend of adopting intracameral prophylaxis, and many observational studies have corroborated the finding that use of a direct intracameral bolus of cefuroxime at the end of cataract surgery can significantly reduce the occurrence of postoperative endophthalmitis. Other agents that have been used for intracameral injection include ceftazolin, moxifloxacin, and vancomycin, but their efficacy has not been established in prospective studies as cefuroxime has. The use of intracameral prophylaxis is now common in Europe but has lagged behind in the US. Until a few years ago, few US surgeons used any intracameral antibiotic. Only recently has there been increasing adoption of intracameral injection prophylaxis. According to the ASCRS member surveys, the percentage of surgeons using intracameral prophylaxis rose from 30% in 2007 to 50% in 2014. Of the 30% who were using intracameral antibiotics in 2007, half placed the antibiotic in the infusion bottle, while the other half injected directly. By 2014, surgeons who use intracameral bolus injection have outnumbered those mixing antibiotics into the irrigation solution (84% vs 16%).

The “Dropless” Approach

In the past two years, “dropless” cataract surgery has been introduced along with a new mode of endophthalmitis prophylaxis aimed at eliminating the need for postoperative drops. The procedure involves delivering a single dose of an antibiotic/corticosteroid combination into the anterior vitreous via transzonal or pars plana injection after intraocular lens (IOL) implantation. Two proprietary compounded formulations have been developed for use in dropless cataract surgery and are used on patients.

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available through US Food and Drug Administration (FDA)-registered compounding pharmacies: one containing triamcinolone and moxifloxacin (Tri-Moxi, Imprimus Pharmaceuticals, San Diego, CA) and the other triamcinolone, moxifloxacin, and vancomycin (Tri-Moxi-Vanc, Imprimus Pharmaceuticals, San Diego, CA).

Since intracameral prophylaxis has proved efficacious, it is reasonable to think that injecting antibiotics into the vitreous, where invading bacteria colonize and where drugs have a longer half-life, may be as effective, or potentially better. To date, no prospective head clinical studies have looked at the efficacy of intravitreal antibiotics compared to intracameral triamcinolone/moxifloxacin or triamcinolone/ moxifloxacin/vancomycin to date.

Other Practical Hurdles
In addition to compounding risks, there are other hurdles facing the dropless procedure. Compared with intracameral injection, transzonular intravitreal injection is a more challenging technique. Surgeons have to learn where and how to maneuver the cannula through the zonules without disrupting the zonules or injuring the ciliary body or iris, which can lead to intraocular hemorrhage. Performed with a 31-gauge needle, pars plana intravitreal injection carries its own risks, including vitreous hemorrhage, retinal tear, and retinal detachment. Because of their opaque nature, the triamcinolone/antibiotic formulations must be injected at the very end of the surgery (prior to viscoelastic removal), and patients may experience blurred vision and floaters immediately after surgery.

More importantly, no head-to-head clinical studies have looked at the efficacy of intravitreal antibiotics compared to intracameral antibiotics such as cefuroxime, moxifloxacin, or vancomycin. The pharmacokinetics of intravitreal triamcinolone/moxifloxacin or triamcinolone/moxifloxacin/vancomycin are yet to be studied. Currently, it is unclear whether the duration of coverage is adequate with these combination compounds placed in the anterior vitreous. There is also the risk of elevated intraocular pressure (IOP) and glaucoma associated with corticosteroids. Topical corticosteroid drops are known to induce ocular hypertension, especially in responders, but can easily be discontinued should that occur. Transzonular triamcinolone, on the other hand, would require vitrectomy to remove if pressure elevation occurs as a result.

Since vancomycin remains the first-line therapy for gram-positive endophthalmitis, the use of prophylactic vancomycin during routine cataract surgery has been controversial due to concerns about emergence of bacterial resistance. There have also been reports of severe retinal toxicity with the use of intraocular vancomycin. A recent case series report has associated
the use of intracameral vancomycin with the development of hemorrhagic occlusive retinal vasculitis (HORV) after uncomplicated cataract surgery. The visual outcome of affected eyes was poor despite aggressive treatment, with final visual acuity less than 20/100 in most cases.

Conclusions

Intracameral antibiotics has proven highly effective in reducing endophthalmitis rates after cataract surgery, with cefuroxime and moxifloxacin emerging as the preferred medications. What has limited the use of intracameral antibiotics in the US is the risk of compounding errors. Transzonal or pars plana intravitreal injection of combined antibiotic/steroid is a promising prophylaxis technique, but it is also not without drawbacks due to the delivery of this medication into the vitreous. Surgeons must balance the potential benefits vs the potential risks when deciding whether or not to offer this during surgery. For intraocular antibiotic injection to become more widely accepted as a routine practice in cataract surgery prophylaxis, access to an approved commercial antibiotic preparation would be extremely helpful.

REFERENCES

Keratoconjunctivitis and Blepharokeratoconjunctivitis

Raj K. Goyal, MD, MPH

Because it is vision-threatening, keratitis is the most critical component of keratoconjunctivitis (KC) and blepharokeratoconjunctivitis (BKC). However, risk factors including blepharitis, extremes of age, and contact lens wear must also factor in to the KC and BKC workup and management.

Keratoconjunctivitis (KC) and blepharokeratoconjunctivitis (BKC) are prevalent within the general population. In my private practice of adult, mostly general ophthalmology, KC and BKC account for about 10% and 5% of clinic visits, respectively. And it will be my experience that KC is underdiagnosed in many eye care practices: patients with KC often have undetected blepharitis, which is highly prevalent among eye care patients and is not always obvious on physical examination.1

Presentation

KC is most commonly bacterial in origin and is typically acute. Patients may present with symptoms typical of bacterial conjunctivitis, eg, ocular itchiness, redness, or mucopurulent discharge. Pain or decreased vision may accompany keratitis.

BKC, which may be acute or chronic, follows a bimodal age distribution, with children and elderly adults predominating. In preverbal and young children, blepharoconjunctival signs or symptoms—discharge, redness, or crust—may go unnoticed and be overlooked by parents and can lead to mild to severe corneal involvement.2

Among seniors, BKC often starts with bacterial (commonly Staphylococcus species) overload or infection of the eyelids and lid margins, which causes flaking around the eyelashes (collarettes) that can fall onto the ocular surface. In turn, an ocular surface antibody reaction to bacterial toxins can lead to keratitis.

Less commonly, adult KC or BKC may present as a presumed allergic conjunctivitis that is unresponsive to treatment (over-the-counter or prescription). Patients with longstanding ocular surface symptoms can grow tolerant of them, thus allowing a mild ocular infection to progress to keratitis.

Etiology

Infectious KC may be viral, bacterial, fungal, or parasitic in etiology. The most common viral source is adenovirus, which causes epidemic keratoconjunctivitis (EKC). Patients with EKC typically present with symptoms and signs common to most forms of acute viral conjunctivitis: redness, tearing, discomfort, follicular reaction on the lower tarsal conjunctiva, and sometimes photophobia. Patients may have a history of exposure to someone with conjunctivitis (“pinkeye”).

In addition to the signs mentioned above, physical examination may reveal pseudomembranes, subconjunctival hemorrhages, subepithelial infiltrates, or pre-auricular adenopathy. Generally self-limited, EKC infection usually resolves on its own within several weeks. Some patients, however, develop serious vision-threatening complications—including scarring of the conjunctiva or cornea—that can persist far longer.3

Bacteria are the most common causative agents in KC and BKC; Staphylococcus, Pseudomonas, and Streptococcus predominate. Other bacteria, including Propionibacterium, Corynebacterium, and Acinetobacter—and lesser known genera including Brevundimonas, Aquabacterium, Sphingomonas, Streptophyta, Bradyrhizobium, and Methylobacterium—have been shown to be present on the healthy ocular surface and may cause infection if the ocular surface is disrupted.4 A Korean study by Lee and coworkers revealed a relative abundance of staphylococci, acinetobacteria, and corynebacteria in the ocular microbiome of blepharitis patients compared with unaffected subjects, suggesting that a higher bacterial load of certain species within the normal eyelid flora might contribute to pathogenesis.4

Fungal KC is relatively rare, oc-

CORE CONCEPTS

➤ Look for evidence of blepharitis in patients with KC: BKC is most common in pediatric and geriatric patients.

➤ KC may be bacterial (most common), viral, fungal, or parasitic.

➤ Contact lens wear predisposes to KC; Pseudomonas is a leading cause of contact lens-associated keratitis.

➤ Adenovirus KC is self-limited but may cause serious ocular surface damage; in-office testing is available.

➤ Checking the eyes, lids, and lashes should be a routine part of preventive care for disabled and elderly patients.

➤ Treatment of bacterial BKC and KC should cover for Staphylococcus, Streptococcus, and Pseudomonas.

An article on the same subject was published in 2013. This version has been updated by the author.

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TOPICS IN OCULAR ANTIINFECTIVES 5
Contact lens wear is the leading risk factor for the development of bacterial, fungal, and amoebic KC. Rates of contact lens-associated microbial keratitis continues to rise, despite the introduction and high uptake of daily disposable varieties. Contact lenses limit the tear film’s natural ability to wash and enzymatically clean the ocular surface, induce hypoxia, increase corneal temperature, and provide a nidus for infection, particularly in association with inadequate lens and lens case cleaning.

Overnight wear, particularly for weeks at a time, remains a major risk factor for contact-lens associated keratitis. Patients who are in the habit of sleeping in their lenses may lose the ability to feel infection-associated pain and thus delay seeking treatment.

The most commonly isolated pathogen in cases of contact lens-related infections is the Gram negative bacterial pathogen *Pseudomonas aeruginosa*. *P. aeruginosa* is a common contaminant of lens care solutions and lens cases, where it forms biofilms that are not removed by simple rinsing of the case. *P. aeruginosa* corneal ulcers are particularly concerning because they tend to progress rapidly and may be recalcitrant to first line treatments. Ocular surface infection can quickly involve the entire cornea and can elicit an acute, destructive inflammatory response that, if not adequately treated, may lead to poor outcomes, with stromal thinning or perforation, and, ultimately, significant scarring.

Additional risk factors include Asian race—which may allow for lashes to rub against the ocular surface—and redundant periorcular skin, which is typical in elderly patients and can contribute to dryness, scaling, or eyelash inversion; this can seed the ocular surface with bacteria, setting the stage for BKC. In addition, nasolacrimal duct obstruction is a risk factor for KC.

### Diagnosis

Patients with an acute or chronic red eye with or without discharge warrant evaluation for KC and BKC. A careful history should include sequence of signs and symptoms (eg, whether redness and discharge began in one or both eyes), presence or absence of periocular or systemic symptoms (including lid symptoms), and recent exposures.

Typically, bacterial infections are characterized by purulent discharge and a papillary reaction, as opposed to the serous discharge and follicular reaction found in viral infections. Distinguishing among different viral infections is more difficult because of the similarity in symptoms, but characteristic signs may provide diagnostic clues. A corneal dendrite, for instance, is indicative of a herpes virus infection. One feature that distinguishes EKC from other forms of viral conjunctivitis is its corneal involvement and potential to impair vision. Slit lamp findings can vary from punctate erosions to a large hypopyon in the anterior chamber. The presence of pre-auricular nodes can help raise the suspicion of EKC, but is not diagnostic.

### Managing EKC

Accurate and timely diagnosis of EKC is important for optimal management and containment. Clinical diagnosis of EKC, however, can be challenging because of its nonspecific presentation. Indeed, using only signs and symptoms for guidance, up to 50% of conjunctivitis cases may be misdiagnosed. When adenovirus is suspected, point-of-care testing via the AdenoPlus™ (Nicox/RPS)—which offers 90% sensitivity and 96% specificity—may be employed to help confirm the diagnosis.

Since there are no FDA-approved antiviral treatments for adenovirus infection, preventing it from spreading and becoming epidemic is a key aspect of managing EKC. Preventing transmission is difficult, however, because the signs and symptoms of EKC can show up as much as a week or 10 days after contracting the virus. During this incubation period, asymptomatic patients can unknowingly transmit the disease to others. Careful patient counseling can help limit the spread of EKC. Clinicians should instruct all EKC patients to limit the degree to which they expose others—by staying away from school or work, washing hands frequently, disposing of tissue paper immediately after its use, and not sharing personal items such as towels and pillowcases at home.

Nosocomial infection—from virus left behind in doctors’ offices—is a major cause of epidemic outbreaks of EKC, and protective procedures should be routine in every clinical practice. Examination rooms should be wiped down completely and disinfected; instruments, including tonometer tips, must be sterilized or disposable and strict hand-washing should be practiced.

### Managing Bacterial KC/BKC

Therapeutic goals of treating the bacterial KC and BKC include prompt treatment of infection and restoration of ocular and periocular bacterial balance so that infection does not recur. When bacterial KC is suspected, empiric treatment with a topical ocular broad-spectrum antibiotic (including coverage for *Staphylococcus*) is indicated. For elderly patients and children, my practice is to start with topical ocular erythromycin ointment, a macrolide antibiotic with efficacy at the eyelid, conjunctiva, and cornea. I find that ointment formulation is often easier for patients to apply than drops, adheres well to the ocular surface (even working during sleep), and is well tolerated by patients. Ointment formulations offer an added benefit of soothing pain that often accompanies keratitis.

As ointments are viscous and temporarily blur vision with instillation,
topical antibiotics in drop formulation may be preferable for busy adults. Topical azithromycin ophthalmic solution, also a macrolide, provides excellent broad spectrum coverage against typical bacterial pathogens.\(^7\) The thick drop formulation promotes ocular surface adherence between that of an ointment and drop; further excellent tissue penetration allows for antibacterial activity for about ten days following the final dose. A broad-spectrum fluoroquinolone may also be prescribed.

All patients with KC and BKC should be taught manual eyelid hygiene to reduce bacterial load and prevent reinfection. Not only does eyelid cleaning remove the crust that accumulates overnight, it instructs patients to become more regularly observant about their ocular surface health. I recommend warm compresses and gentle swabs on the eyelid margins to remove excess flaking and crusted discharge upon rising and before retiring at nighttime.

For patients who fail to respond to empiric therapy or when an unusual pathogen such as a fungal pathogen is suspected, performing a conjunctival culture may be advisable. Referral to a corneal specialist or academic center may be necessary for practitioners who are not equipped for in-office culture.

**Conclusion**

Discerning true KC from BKC and considering common and rare etiologic agents lays a foundation for appropriate and timely management and the prevention of vision-compromising consequences.

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**REFERENCES**

1. Transzonular injection in dropless cataract surgery:
   A. Is easier to perform than intracameral injection
   B. Uses drugs prepared by compounding pharmacies
   C. Is widely used in Europe
   D. Has been proven effective in large-scale clinical trials

2. A patient presents with an obvious corneal infection. Which of the following patient characteristics should trigger suspicion of P. aeruginosa?
   A. Blue irides
   B. History of smoking
   C. Contact lens wear
   D. All of the above

3. Which of the following antibiotics was recently approved for prophylactic intraocular use by the US FDA?
   A. Cefuroxime
   B. Moxifloxacin (combined with triamcinolone)
   C. Vancomycin
   D. None of the above

4. Which one of the following prophylactic methods has been proven effective in the ESCRS endophthalmitis study?
   A. Intracameral cefuroxime injection
   B. Postoperative moxifloxacin drops
   C. Preoperative povidone-iodine
   D. Transzonular moxifloxacin injection

5. Which of the following is NOT characteristic or typical of BKC in an elderly patient?
   A. Acute presentation
   B. Redundant eyelid tissue
   C. Ocular surface inflammatory response to bacterial toxins
   D. Lid margin crusts and carrayetes

6. Which of the following bacterial genera is NOT commonly found among normal ocular surface flora?
   A. Staphylococcus
   B. Klebsiella
   C. Streptococcus
   D. Streptomyces

7. Which of the following is important to eliciting the history of a patient presenting with an acute red eye?
   A. Current and recent medications
   B. Exposure to pinkeye
   C. Ocular trauma
   D. All of the above

8. Which of the following is NOT a potential adverse event associated with overdose of intracameral cefuroxime?
   A. Hemorrhagic occlusive retinal vasculitis
   B. Cystoid macular edema
   C. Serous retinal detachment
   D. Hemorrhagic retinal infarction

9. Which one of the following medications is FDA-approved for the treatment for EKC?
   A. Ketorolac tromethamine 0.5%
   B. Cidofovir
   C. Povidone-iodine
   D. None of the above

10. According to Dr. Trattler, intraocular vancomycin should not be used prophylactically because:
    A. It has the potential to cause severe retinal toxicity
    B. It is common for patients to develop allergic reactions to vancomycin
    C. It is the primary agent for use against severe gram-positive bacterial infection
    D. Both A and C

EXAMINATION ANSWER SHEET
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ANSWERS:
1. A B C D 6. A B C D
2. A B C D 7. A B C D
3. A B C D 8. A B C D
5. A B C D 10. A B C D

EVALUATION:
11. Extent to which the activity met the identified:
   Objective 1:  1 2 3 4 5
   Objective 2:  1 2 3 4 5
   Objective 3:  1 2 3 4 5
   Objective 4:  1 2 3 4 5

12. Rate the overall effectiveness of how the activity:
   Related to my practice:  1 2 3 4 5
   Will influence how I practice:  1 2 3 4 5
   Will help me improve patient care:  1 2 3 4 5
   Stimulated my intellectual curiosity:  1 2 3 4 5
   Overall quality of material:  1 2 3 4 5
   Overall met my expectations:  1 2 3 4 5
   Avoided commericial bias/influence:  1 2 3 4 5

13. Will the information presented cause you to make any changes in your practice?  Yes  No

14. If yes, please describe:

15. How committed are you to making these changes?  1 2 3 4 5

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