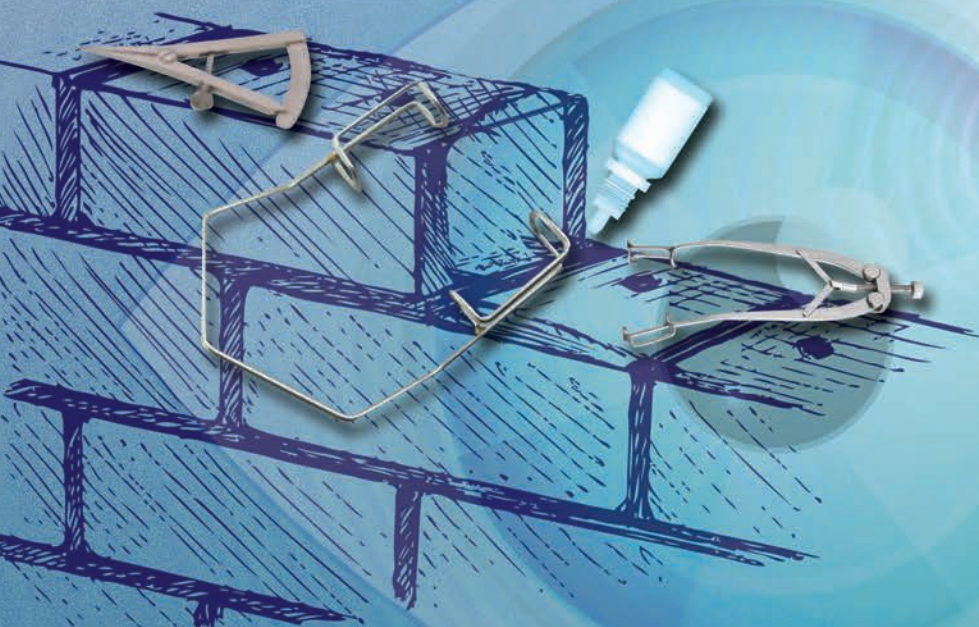


BUILDING FOUNDATIONS

for Successful Ophthalmic Surgery

IMPORTANCE OF INFLAMMATION AND INFECTION CONTROL



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Learning Method and Medium

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Content Source

This continuing medical education (CME) activity captures content from a roundtable discussion held on April 25, 2014, in Boston, Massachusetts.

Activity Description

Recently, much attention in ophthalmic surgery has revolved around technology. Current medical literature suggests that the foundations of inflammation and infection management are key factors in achieving positive outcomes across the spectrum of ophthalmic surgical procedures using new technologies. In this educational activity, a panel of expert anterior segment and glaucoma surgeons discuss the changing landscape of perioperative planning for ocular surgery, using a framework of patient cases to serve as examples of the challenges faced in achieving successful ophthalmic surgery.

Target Audience

This educational activity is intended for ophthalmologists.

Learning Objectives

Upon completion of this activity, ophthalmologists will be better able to:

- Recall data on ocular antibiotic resistance patterns
- Identify effective antibiotics for patients undergoing ophthalmic procedures
- Demonstrate use of evidence-based inflammation-control regimens for patients undergoing cataract surgery, LASIK, and corneal transplant surgery
- Identify optimal preoperative inflammation control practice
- Recall data from clinical trials on the efficacy and safety of new anti-inflammatory agents used in cataract surgery
- Select optimal anti-inflammatory agents while considering efficacy and IOP control for patients undergoing glaucoma surgery

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Photos for Figures 1 through 9 Courtesy of Terrence P. O'Brien, MD

Introduction

Ocular surgery is a major event in many people's lives, and in some cases—particularly cataract or corneal transplant surgery—can be a life-changing event as well. We all hone our technical skills to ensure a safe and effective procedure, and technological advances continue to raise the bar of what is possible to achieve with clinical outcomes. As an example, consider the evolution of intraocular lenses (IOLs). We have seen the progression from early monofocal designs, in which biocompatibility was a principal concern, to multifocal, accommodating, and advanced toric IOLs with improved optical performance, such that we can now provide better postoperative visual function with cataract surgery than ever before. As a result, patients' expectations are changing and ascending. Many patients know someone who has undergone successful cataract surgery and therefore expect the same or better results for themselves. To ensure realization of optimal outcomes to meet these increasing expectations, we must put as much thought into our perioperative interventions as we invest in the surgical procedure itself. Postoperative inflammation can be painful and can jeopardize visual outcomes. The worst-case scenario—a severe infection such as endophthalmitis—is, thankfully, very rare, but for the unlucky patient who does suffer an intraocular infection, the outcome is often devastating. In this educational activity, we have assembled a panel of expert anterior segment and glaucoma surgeons to discuss the changing landscape of perioperative planning for ocular surgery, using a framework of patient cases that we have encountered in our own practices to serve as examples of the challenges we all face in achieving successful ophthalmic surgery.

Our goals are to underscore the need to reconsider older strategies that have stood the test of time and to provide insight into the adoption of newer strategies to secure the best postoperative visual and overall outcomes for our patients.

—Terrence P. O'Brien, MD

Case 1. Infection and Inflammation Prophylaxis in a High-Risk Patient

Dr O'Brien: A 61-year-old woman with a history of inflammatory bowel disease began, in her late 30s, to have anterior uveitis with recurrent episodes of iridocyclitis. She had been controlled with chronic topical corticosteroids and now has developed a painless progressive deterioration in vision with increasing lenticular opacification. She also has significant posterior synechiae with a 3.0-mm pupil that is minimally reactive to light [Figure 1]. She now presents for consideration of cataract surgery. How do we approach this patient case?

Dr Sheppard: This is clearly a patient who requires meticulous preparation prior to surgery. First and foremost, we want to be sure that her systemic disease is under control. If she has Crohn disease or ulcerative colitis, direct collaboration with her gastroenterologist or rheumatologist is necessary to assure that the systemic disease is under control. Following confirmation that any inflammatory bowel disease is under control—ideally achieved with minimal use of systemic steroids—we likewise need to minimize ocular inflammation. It is imperative that we have zero tolerance for inflammation in the eye: no cell, no flare, no superficial punctate keratopathy, and if possible, no cystoid macular edema [Figure 2], although this may be difficult to assess in a small-pupil cataract patient.

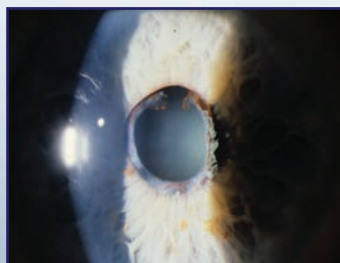


Figure 1.

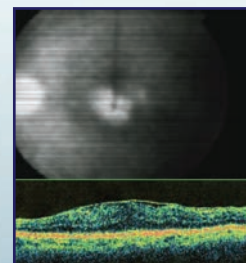


Figure 2.



Once these conditions have been met, we can proceed to the operating room. There we pretreat with higher and more frequent doses of anti-inflammatory agents, and in cases such as this, it is often worth giving a perioperative or preoperative sub-Tenon steroid injection. Factors that support a sub-Tenon steroid injection in this patient are her high risk for reactivating the underlying inflammation, the likelihood of an impaired blood-aqueous barrier promoting greater inflammation, and the certainty of extensive iris manipulation intraoperatively to break the extensive posterior synechiae. She also may benefit from intracameral use of preservative-free steroids; both dexamethasone and triamcinolone are available for this use. The IOL selection is important in this patient. I favor a higher-order hydrophobic IOL material, and clearly, in-the-bag placement is crucial.

Postoperative inflammation control is critically important. We want a potent steroid, such as difluprednate or loteprednol, along with a concomitant nonsteroidal anti-inflammatory drug (NSAID). Patients such as the one we are discussing should be watched very carefully postoperatively. We often see a toxic anterior segment syndrome (TASS)-like picture on day 1 with prolific fibrin in the anterior chamber [Figure 3] and a great deal of cells and flare, which can promote secondary posterior synechiae to the capsule.

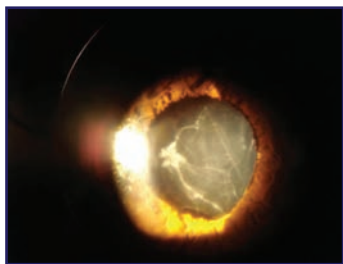


Figure 3.

Dr O'Brien: Preoperatively, this patient also requires frequent pulses of topical corticosteroids for control of her ocular inflammation as well as a topical beta-blocker and carbonic anhydrase inhibitor (CAI) for control of intraocular pressure (IOP). In addition to the posterior synechiae mentioned, gonioscopy disclosed peripheral anterior synechiae with heavy pigment in the trabecular meshwork and a narrowing of the angle. She has been noted more recently to have borderline control of IOP on the current regimen. Dr Varma, do you have any suggestions for the cataract or glaucoma surgeon approaching cataract surgery in this complicated patient?

Dr Varma: With long-term use of IOP-lowering drugs, there is a whole series of inflammatory responses that occur in the conjunctiva secondary to either the preservative in the medication or to the medication itself. This inflammatory component in the conjunctiva reduces the chances of success of glaucoma surgery in the future and will also have bearing on the more imminent cataract surgery. Fortunately, recent studies have shown that cataract surgery alone can result in an effective IOP-lowering for many patients.^{1,2} Postoperatively, this patient's IOP may be easier to control, potentially on fewer medications. Complicating this, however, is her need for aggressive inflammation suppression, which may require high-potency steroids that may raise her IOP. In her case, loteprednol may be preferable to difluprednate because of its relatively lesser effect on IOP than that of other steroids.^{3,4} The trade-off may be an attendant lesser effect on inflammation, so these 2 situations would have to be monitored. On balance, inflammation is likely to cause more damage than transient elevated IOP. I would tend to be more

aggressive with inflammation control, even if the IOP rises, and then taper as quickly as possible to restore IOP control.

Dr O'Brien: In general, when in the perioperative period should we start anti-inflammatory therapy?

Dr Katsev: I pretreat all my patients 2 to 3 days before surgery with both the antibiotic and the anti-inflammatory agents—both the steroidal and the nonsteroidal drugs. I favor pretreatment to get inflammation under control before it starts. I do this in all my patients, but in the case we are discussing now, pretreatment for inflammation is of utmost importance.⁵

Dr O'Brien: I agree that pretreatment with anti-inflammatory agents is rational. Suppression of key enzymes such as cyclooxygenase can deplete the downstream supply of inflammatory mediators such as prostaglandins, leukotrienes, prostacyclins, and thromboxanes. If we wait and allow unchecked conversion of metabolites of arachidonic acid to feed into the cycle, “the horse is already out of the barn” with respect to ocular inflammation. What is the optimal approach to the miotic, mechanically bound pupil in this case?

Dr Katsev: In this case, you first have to get the pupil open. Viscodilation can be effective in many cases and would be the best place to start because it is the least traumatic of the available approaches.

Dr O'Brien: I agree completely with trying the gentler viscodissection/viscodilation approach first. More aggressive pupil strategies such as iris hooks or the Malyugin ring, or similar pupil expander devices, may be necessary, although we initially wish to avoid them. These methods mechanically agitate the uveal tract, thereby releasing many more pro-inflammatory mediators.

We have focused on inflammation control so far, but infection control is also an important foundation for optimal ophthalmic surgical outcomes. What is the best, most rational approach today to try to prevent perioperative infection with cataract surgery?

Dr Sheppard: Ideally, we could provide complete antimicrobial coverage with a single agent. Because of the devastating effects of endophthalmitis, we should use the best fluoroquinolones available when choosing monotherapy. Many of the bacteria that cause endophthalmitis have acquired resistance to our older-generation fluoroquinolones.⁶ I use besifloxacin because it has excellent coverage against gram-positive organisms, and the vast majority of those organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), are still sensitive to it.^{6,7}

Dr O'Brien: Certainly, the use of topically administered agents to reduce ocular surface colonization/contamination and thereby to potentially reduce the likelihood of intraocular contamination has been a longstanding approach. What is the role of intraocular antibiotics?

Dr Sheppard: The European Society of Cataract & Refractive Surgeons (ESCRS) study clearly demonstrated that injecting 1 mg of cefuroxime into the anterior chamber at the end of the operation—coupled with use of postoperative topical levofloxacin—reduced the rate of endophthalmitis 5-fold.⁸ Importantly, this approach has been validated: when the protocol was implemented in various clinical settings, endophthalmitis cases plummeted to near zero.^{9,10} In the Kaiser Permanente system in Northern California, implementation of the ESCRS protocol reduced postoperative endophthalmitis rates 10-fold.¹⁰



Antibiotic Resistance and the Growing Threat of MRSA

Dr Sheppard: The Ocular TRUST (Tracking Resistance in U.S. Today) study published in 2008 demonstrated that 17% of *S aureus* isolates were MRSA, and importantly, most of these MRSA isolates—85%—were also resistant to the fluoroquinolones.¹

Dr O'Brien: In 2010, a prospective study² in patients undergoing cataract surgery showed that 62% of all eyelids are colonized with *Staphylococcus epidermidis* and 15% with *S aureus*. Of these, 47% of the *S epidermidis* and 30% of the *S aureus* isolates cultured from the lids of these healthy people were methicillin resistant.

Dr Sheppard: In a tertiary referral cornea practice, the problem is even worse. We are seeing resistance patterns in our own patients, and our hospital laboratory publishes the resistance patterns biannually. There is a continuous linear increase in the proportion of patients who are culture-positive for *S epidermidis* and *S aureus* species that are multidrug resistant specifically to methicillin and oxacillin. Last year, 65% of the *S epidermidis* and *S aureus* ocular isolates cultured from my own patients were MRSA. If I am using an older fluoroquinolone agent, I am jeopardizing the patient.

Dr O'Brien: More than half our patients are likely to be carriers of methicillin-resistant organisms. If cataract surgeons are not yet concerned, they should be. What has changed in the past 2 decades to make resistance so prevalent in the bacteria about which we are most concerned?

Dr Sheppard: The simple answer to that question is antibiotic overuse. Consider the retina world, in which patients now receive serial intravitreal injections of vascular endothelial growth factor inhibitors, along with antibiotic prophylaxis to prevent endophthalmitis. A recent study demonstrated that the routine use of prophylactic gatifloxacin produced widespread resistance, with 76% of treated patients and only 3% of controls harboring bacteria that are now resistant to gatifloxacin.³ Every time we prescribe antibiotics, we increase the resistance rate. This is why antibiotic overuse results in such a huge problem. We, the doctors, are guilty. We have a very low threshold for prescribing antibiotics. In many countries, antibiotics are not at all well regulated and are essentially available to patients as over-the-counter medications. The effect on resistance can be extremely significant. Because patients self-prescribe and therefore often do not complete a full course of antibiotic therapy, they are clearly creating an ideal environment for resistant microbe proliferation. Our own patients commit the same error when undertreating and not completing a prescribed 7- to 10-day regimen. Not only are antibiotics being overused, they are being *incorrectly* used. It is unlikely that most self-prescribing patients do their homework and select the best antibiotic for their particular infection, according to both the likely organisms involved and the likely resistance patterns of those organisms.

And an even bigger problem is the use of antibiotics in food production. The vast majority of all antibiotics produced are fed to animals to keep them healthy until they can be slaughtered for food. We are breeding resistant organisms in our food supply.⁴ For this very reason, I tend to use older antimicrobials for routine issues like conjunctivitis, and reserve the newer, better agents for perioperative prophylaxis.

Dr O'Brien: We have always believed that topical exposure to antibiotic eye drops cannot contribute to resistance. The data you shared from the intravitreal injections experience proves this to be false. In the total population of bacteria, those that are resistant to antibiotics may be rare, but when we unnecessarily treat with antibiotics and kill off the sensitive bacteria, the resistant strains now become predominant in the overall population. In a practical sense, imagine a patient with conjunctivitis whom we treat with topical antibiotics, but who then stops after a few days. This will kill the majority of organisms that are sensitive, but now the minority that are resistant are all that remain. Once the antibiotic treatment ends, the resistant organisms proliferate and the patient's ocular flora has been changed from sensitive to resistant. Then, when this patient presents for cataract surgery, he or she may have an altered profile and increased endophthalmitis risk brought about by our previous antibiotic treatment.

1. Asbell PA, Colby KA, Deng S, et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. *Am J Ophthalmol.* 2008;145(6):951-958.
2. Olson R, Donnenfeld E, Bucci FA Jr, et al. Methicillin resistance of *Staphylococcus* species among health care and nonhealth care workers undergoing cataract surgery. *Clin Ophthalmol.* 2010;4:1505-1514.
3. Dorrepaal SJ, Gale J, El-Defrawy S, Sharma S. Resistance of ocular flora to gatifloxacin in patients undergoing intravitreal injections. *Can J Ophthalmol.* 2014;49(1):66-71.
4. Kolman A, Dikici A. Antimicrobial resistance of emerging foodborne pathogens: status quo and global trends. *Crit Rev Microbiol.* 2013;39(1):57-69. ■

Universal adoption of the ESCRS protocol is happening gradually. I use it currently in all high-risk cases—for example, in patients presenting with capsular rupture and vitreous prolapse, in immunocompromised patients such as those who have had organ transplants, in younger patients, in those with a history of prior eye trauma, and in patients with diabetes. In Europe, there is a commercially prepared formulation of cefuroxime available as a single-dose unit specifically meant for intracameral use. In the United States, we are compounding systemic doses, which come with small but real risks. When we have a formulation of cefuroxime in this country that eliminates those risks, I will adopt its use as a universal practice for all my patients.

Dr O'Brien: What are the antimicrobial activity gaps in the spectrum of coverage with cefuroxime and other limitations with this particular antibacterial agent?

Dr Sheppard: The possibility of dilutional errors during preparation are a concern. Also, cefuroxime is an older antibiotic and may have some resistance issues. However, given the high concentration injected directly into the anterior chamber, relative resistance may be overcome. One other issue with the delivery method is that of aqueous turnover time. Is the antibiotic cleared too quickly? This is particularly relevant if there is any wound leak, which could cause faster loss of the drug. For this reason, topical antibiotics are still necessary in the postoperative period.

Dr O'Brien: Will the use of biocompatible adhesive agents at the conclusion of surgery help to seal cataract wounds more effectively and safely?

Dr Sheppard: Absolutely. Antibiotic egress from an incompetent wound is only 1 side of the coin. Surface fluid ingress—potentially carrying bacteria—is the bigger issue. These adhesive agents tend to last several days postoperatively and to provide improved comfort as well as less risk of contamination. With that improved comfort, there is less eye-rubbing, and thereby a dual beneficial effect.

Case 2. Infection Prophylaxis in a MRSA-Colonized Patient

Dr O'Brien: A 59-year-old retired female nurse has hyperopia and is interested in refractive surgery to correct her visual acuity. She has minimal cataract, corrects to 20/20, and is considering LASIK (laser-assisted in situ keratomileusis) surgery. She is a known carrier of MRSA. How would you approach this patient case?

Dr Sheppard: For this patient, whether she is about to undergo cataract extraction, corneal transplantation, or a glaucoma procedure, the surgeon should first obtain a preoperative ocular surface culture with sensitivities. Although nasal carriers do not necessarily also grow MRSA in the ocular flora, vigilance is indicated. If the ocular surface culture comes back positive, we are obliged to sterilize the surface before proceeding, particularly regarding LASIK, in which MRSA is the leading cause of interface infections.¹¹ In addition to a topical antibiotic, this patient may require systemic sulfonamide therapy and nasal mupirocin treatment.



Dr Katsev: I would be less aggressive with this patient, not because it is wrong to be too cautious, but rather because my clinical experience has not led me to fear MRSA carriers. I would not get a preoperative culture. I would use my standard pre-LASIK routine, which includes a combination steroid/antibiotic for convenience. In this case, I would use a separate antibiotic with known activity against MRSA, such as besifloxacin; besifloxacin is formulated for ophthalmic use only.¹² Because it is not being used systemically, the risks for overuse and misuse—which can lead to higher resistance rates—are fewer.

Dr O'Brien: Given how high colonization rates with MRSA are, even in patients presenting for routine outpatient cataract surgery (see *Sidebar: Antibiotic Resistance and the Growing Threat of MRSA*), having the most robust routine approach to effective prophylaxis against these increasingly prevalent subpopulations of resistant bacteria is wise.

Dr Sheppard: I agree that routine preoperative cultures are not productive. In patients with known MRSA infection, however, we must pay serious attention to prophylaxis. Health care workers were considered among the highest risk for resistant staphylococcal carriage, but the rise in community-acquired MRSA incidence has heightened our concern for virtually everyone undergoing elective invasive ocular surgery [Figure 4].

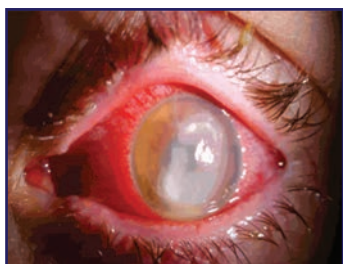


Figure 4.

Dr O'Brien: Following LASIK, this patient may present with a partially hazy cornea in the early postoperative period. How can we clinically differentiate diffuse lamellar keratitis (DLK) from infectious keratitis following LASIK?

Dr Sheppard: Diffuse lamellar keratitis, the infamous Sands of the Sahara syndrome, is a relatively common phenomenon, much more common than infectious interface keratitis [Figure 5]. In DLK, the eyes are hot and inflamed. You can see very fine micropunctate white blood cells that do not look like an infiltrate. They are very discrete, as opposed to a homogenous migratory infiltrate most likely at the edge of the flap with infection. The patient with DLK complains more of blurring and ache than of outright pain and photophobia as do patients with infectious interface keratitis. Diffuse lamellar keratitis tends to occur immediately postoperatively and is very responsive to topical steroids [Figure 6]. There is a nearly 6-fold increased risk of DLK in patients with untreated allergic and atopic disease, and this risk essentially vanishes with treatment.¹³ Evaluating the risk factors and examining the character of the interface phase is very important.

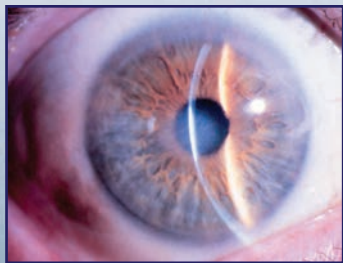


Figure 5.

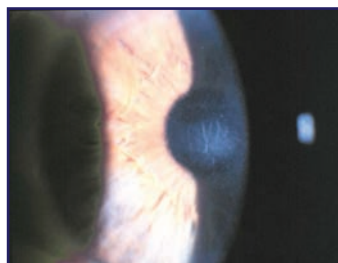


Figure 6.

Dr O'Brien: The presence of anterior chamber cell and flare also can be a helpful clinical sign to suggest infectious keratitis rather than DLK. Additionally, posterior extension of the infiltrate into the stroma can indicate a possible infectious cause for the corneal inflammation. Confocal microscopy can be helpful in real time: in DLK, you see the polymorphonuclear neutrophils in the interface; in *Candida* or fungal infections, you often see hyphal elements in the interface.

Case 3. Prophylaxis for Glaucoma Surgery

Dr O'Brien: An 81-year-old woman has a history of primary open-angle glaucoma and has required multiple agents over an expanse of 20 years to control her IOP. Currently, she requires maximal medical therapy consisting of latanoprost, brimonidine, and a beta-blocker/CAI fixed combination. She also has undergone selective laser trabeculoplasty, with minimal effect on lowering IOP. She is now being considered as a candidate for glaucoma filtering surgery. On preoperative evaluation, she is noted to have moderate meibomian gland inspissation [Figure 7], a rapid tear film break-up time, and punctate staining of the interpalpebral corneal epithelium. How do you approach this patient who is being considered for elective glaucoma surgery?



Figure 7.

Dr Varma: This patient's ocular surface disease (OSD) includes both dry eye and blepharitis, which together increase the risk for postoperative infection. We have to address and control these issues before we proceed to surgery. One likely contributor to her OSD is the chronic use of IOP-lowering medications. It has been well established that chronic exposure to topical glaucoma drugs incites a chronic low-grade inflammation in the conjunctiva,¹⁴ which can diminish the success of subsequent glaucoma surgery.¹⁵ For this reason, I would strongly consider a preoperative course of topical steroid therapy to suppress the inflammation. In addition to OSD, other risk factors for postoperative bleb infection or frank endophthalmitis are the use of antifibrotic agents such as mitomycin-C or 5-fluorouracil, younger patient age, and inferior bleb placement in the setting of superior scarring.^{16,17}

Dr O'Brien: Is it the pressure-lowering agents themselves or the preservatives in their formulations—notably benzalkonium



chloride—that are the culprits in this induced inflammation on the surface of the eye?

Dr Varma: Benzalkonium chloride has significant cytotoxic effects on the human ocular surface and on the cells that make up this layer.¹⁸⁻²¹ Even though subtle conjunctival inflammation may not be clinically apparent, a 4- to 6-week course of topical anti-inflammatory therapy is wise. Loteprednol is a reasonable choice, or fluorometholone if available, because it has potent steroid activity but is less likely to raise IOP compared with prednisolone acetate.^{3,4} Additional benefits of preoperative anti-inflammatory therapy—in this case with ketorolac or fluorometholone—are that it may improve the success of trabeculectomy and reduce the need for postoperative needling of Tenon cysts.²²

Dr O'Brien: Is there a role for noncorticosteroid agents such as topical and/or systemic immunomodulators in controlling the OSD prior to surgery?

Dr Sheppard: Cyclosporine, 0.05%, emulsion is an effective nonsteroidal anti-inflammatory agent. It is formulated for ophthalmic use and labeled for the treatment of dry eye syndrome. There are also systemic drugs—the tetracyclines doxycycline and minocycline, in particular—that are effective in managing OSD. An initial high dose followed by chronic low-dose therapy can provide excellent maintenance well below the typical dosage needed to achieve antimicrobial activity.²³

Dr O'Brien: Usually we try to avoid systemic IOP-lowering medications, especially in those of advancing age, because of the adverse reaction profile associated with CAs. In this type of patient, is there a role for temporarily replacing the topical agents with a systemic agent during the preoperative period while simultaneously initiating the anti-inflammatory pulse to better control ocular surface inflammation?

Dr Varma: This can be a worthwhile consideration. In this patient, however, because of her age (81 years old), the risks associated with systemic CAI therapy may be unacceptable. These risks include numbness and tingling of the extremities, increased urination, depression, development of kidney stones, and in very rare cases, aplastic anemia. If she declines surgery and is willing to accept these risks, a trial of systemic CAI therapy may not be unreasonable. Another option would be a trial of preservative-free IOP-lowering medications to attempt to quiet her eye.

Dr O'Brien: The tear film is the single greatest defense against ocular surface infections. In the postoperative glaucoma patient, the filtering bleb, or the glaucoma drainage device, alters the way the eyelid moves across the ocular surface. This can alter the ocular surface itself, change the tear flow across the surface, and lead to problems with preoperative biometry if cataract surgery follows. Also, the use of antimetabolites can further increase the risk for postoperative infection. Which organisms should we be most concerned about as potential causes of infection in eyes following glaucoma surgery?

Dr Varma: The 2 main forms of postoperative infection in eyes having undergone glaucoma procedures are blebitis and endophthalmitis. Blebitis is limited to infection within the subconjunctival bleb, although some spillover of cells may be seen in the anterior chamber [Figure 8].



Figure 8.

The most common agents involved are *S aureus* and *Staphylococcus epidermidis*.²⁴ If there is evidence of vitritis, full-blown endophthalmitis is typically present. Early postoperative endophthalmitis after glaucoma surgery—within the first 6 weeks or so—is typically caused by *S epidermidis*. Later onset endophthalmitis, which is usually associated with bleb leaks, can be caused by a more diverse and quite virulent collection of organisms, including streptococcal species, gram-negative organisms such as *Haemophilus influenzae*, *Enterococcus*, *Pseudomonas*, and some other staphylococcal species. Blebitis can progress to endophthalmitis, so it is very important that our glaucoma surgery patients understand that they must have an exceptionally low tolerance for a red eye. Ideally, they will present when the infection is localized to the bleb and, in so doing, the prognosis will be much better. Seidel testing is helpful to identify leaking blebs [Figure 9].

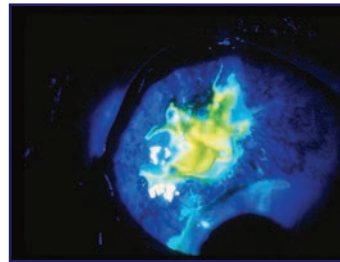


Figure 9.

Dr O'Brien: Prompt attention is essential. What is your current preferred topical approach for blebitis with the goal of preventing endophthalmitis?

Dr Varma: I want to emphasize the importance of culturing the bleb area or the vitreous before beginning anti-infective therapy for blebitis or endophthalmitis, respectively. For blebitis, I prescribe an advanced-generation fluoroquinolone as frequently as every hour initially. I will taper the frequency according to the response.

Dr Sheppard: When I see blebitis accompanied by even a few cells in the anterior chamber, I will use fortified vancomycin. I may also use subconjunctival aminoglycoside therapy, such as gentamicin. I also follow a patient with blebitis very closely, perhaps twice a day for the first day or 2, to be sure the blebitis is not progressing to endophthalmitis.

Dr O'Brien: Consider the patient now 4 years after trabeculectomy with adjunctive mitomycin-C who currently presents with visually significant cataract. The bleb is intact, but very thin-walled and cystic in appearance. What would be your approach to infection prophylaxis in the perioperative period?

Dr Varma: I would examine very carefully, including Seidel testing, to be absolutely sure that the bleb is intact and that there is no low-grade blebitis present. Operating on an eye with a low-grade



Managing Generic Substitutions

Dr Katsev: It is not uncommon for me to prescribe the antibiotic of my choice only to receive a phone call from the pharmacy asking if it can substitute a less expensive agent because my preferred drug is not covered by the patient's insurance. I am often surprised by this as the cost saving for the generic medication can be very minimal in actual dollar amount. Dealing with this is time consuming, and use of the substituted agent can be potentially dangerous. In the perioperative period surrounding intraocular surgery, I want to use the very best agent I can, with the most favorable susceptibility profile. The use of electronic health records can facilitate matters somewhat by showing me what is and is not covered on a patient-by-patient basis when I e-prescribe. Then at least I know which patients may or may not receive optimal prophylaxis.

Dr Varma: In the glaucoma practice, substitution of IOP-lowering medications can be a benign and cost-saving event, or it can become a safety issue. Some of the so-called generic medications are produced overseas and are, in fact, not generic—that is, they are not equivalent in formulation to the branded product. They may contain different concentrations of the drug, be less heat stable, and may have higher levels of contaminants such as particulate matter in the bottles.¹ We strongly discourage the use of generics that have been prepared outside the United States.

Dr Sheppard: Another issue with generics is that their availability changes regularly. Each time a pharmacy renegotiates contracts, it goes with the lowest bidder, and that means the formulation of NSAID you are prescribing, for example, may be produced by a different manufacturer with a different vehicle and preservative every few months. If there is significant variability in the activity and stability of these formulations, we are faced with a new variable in our surgical protocol over which we have little control.

Dr O'Brien: How can ophthalmic surgeons manage this issue so that our surgical patients are provided with differentiated, preferred pharmaceutical agents of our own choosing?

Dr Sheppard: One option is to adopt a business model that includes an in-house pharmacy, to provide complete control of all these variables. In today's regulatory environment, however, to do this can be overly burdensome. In my practice, we make our recommendations for the particular antibiotic, steroid, or NSAID agents that we prefer the patient to use; we have a disclosure document that patients sign as part of their cataract documentation, acknowledging that they understand we are recommending this specific regimen and that we advise against substitution. The substituted drugs may have more side effects, less efficacy, and need to be dosed more frequently. In the event a patient cannot afford our preferred regimen, it is prudent we do our research and have prepared, as a back-up plan, a specified list of generic alternatives, so that we can at least ensure that the patient gets our preferred generic choice rather than one chosen at random by the pharmacy.

I am a firm believer in a high-quality, low dosing-frequency regimen. It improves compliance, it improves efficacy, and it reduces exposure to toxic preservatives. This huge benefit is available only through proprietary topical preparations.

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blebitis can lead to endophthalmitis iatrogenically. Assuming the bleb is intact and functioning, I would then proceed as I do with my more routine cases. I watch the status of the bleb throughout the early postoperative period to make sure its integrity is maintained.

Case 4. Prophylaxis for Corneal Surgery

Dr O'Brien: A 39-year-old man has a history of atopy and ocular allergy. He is known to be an eye-rubber. He was diagnosed with keratoconus, right eye more advanced than left eye 12 years earlier. He has used rigid gas permeable contact lenses in the past, but with significant discomfort, irritation, and inflammation. More recently, he developed acute loss of vision in his right eye and was noted to have a markedly swollen central cornea with what appeared to be a break in Descemet membrane. Now he has thinning and scarring of the cornea, is contact lens intolerant, and is a candidate for corneal transplantation. How do we manage his infectious and inflammatory risks perioperatively?

Dr Sheppard: Unfortunately, acute corneal hydrops is a fairly typical presentation in these eyes with keratoconus [Figure 10]. Atopy is associated with keratoconus, and controlling the itching will minimize the eye-rubbing and slow or prevent progression. It is too late to prevent this outcome in the right eye, but corneal crosslinking may help reduce a similar risk in the fellow eye. In terms of perioperative prophylaxis, the first step is to control the atopy and the itching. Systemic steroids may be needed to accomplish this. This patient may also require an allergy consult with allergy testing, desensitization, and even immunotherapy. In terms of ocular anti-inflammatory agents, I would start with a high-potency steroid such as topical difluprednate or subconjunctival triamcinolone and then transition to a safer steroid such as loteprednol, which is less likely to raise IOP, for lifelong maintenance. Atopy also poses an infection risk, especially if there is associated blepharitis and, often, a history of chalazia as well. If this is the case, a preoperative lid culture is valuable to identify the resistance patterns of the patient's flora.



Figure 10.

*Photo Courtesy of
John Sheppard, MD, MMSc*

Dr O'Brien: Should we be concerned about the potential added infectious risk associated with the corneal donor tissue being harvested, processed, and maintained in corneal preservation/storage media?

Dr Katsev: A cultured storage media often comes back positive. Having said that, I have not seen a case of endophthalmitis in a corneal transplant patient, so I do not treat these patients any differently than I do my cataract patients.

Dr O'Brien: It is sometimes difficult to interpret the significance of culture-positive storage media, but nevertheless, this is information to which we should pay attention and make certain there are no clinical signs of infection in the individual patient. Contacting the eye bank to obtain information about the fellow-eye donor tissue and clinical status of the recipient also can provide useful information.



Dr Sheppard: Culturing the media from a donor does not make as much sense to me as culturing the actual donor rim. The media contains, among other things, streptomycin and gentamicin at low concentrations, which preclude a highly positive culture rate; therefore we get a great deal of false-negatives when culturing the media. I just culture the rim now. Many times it grows *S epidermidis*. But, the patients do well. I am generally only greatly concerned when the rim culture grows a fungus. I will bring those patients back to the office for a careful examination. I have had a case of Descemet stripping endothelial keratoplasty in which the rim culture grew fungus and the patient—who had chronic lymphocytic leukemia and thus was immunocompromised—developed a fungal endophthalmitis and lost the eye.

Dr O'Brien: Assuming the transplant is successful and the graft is clear, how do you prevent rejection over time in this 39-year-old phakic patient?

Dr Sheppard: All my transplant patients, without fail, receive lifelong loteprednol. It is my maintenance antirejection agent of choice. This is the best anti-inflammatory agent for long-term use because of its safety and efficacy profile.²⁵ I titrate the dose according to the risk profile of the patient, considering factors such as age, previous rejections, and concomitant inflammatory ocular surface or intraocular disease. These are high-risk factors for graft failure. In some cases we can reduce the steroid dose with a steroid-sparing agent such as cyclosporine if the patient has dry eye and if the agent's use is justified, given the added expense.

Summary and Conclusion

Dr O'Brien: As we strive to strengthen the foundation for successful anterior segment surgery through careful perioperative planning and prophylaxis (Table), let us each share 1 pearl that guides our clinical and/or surgical decision-making.

Dr Varma: Surgeons should look carefully at the ocular surface and the lid prior to embarking on any filtration surgery and address any issues preoperatively. Doing so will have a huge effect on the outcome, in terms of reducing both inflammation and the postoperative risk for infection.

Dr Katsev: Start your preoperative medications early—not just a day before, but consider a couple of days before. Quelling inflammation will control OSD, reduce aberration, and optimize IOL calculations. We also should choose the most effective antibiotic we can in terms of minimal resistance among the bacteria about which we are most concerned.

Dr Sheppard: Each patient is different. Each patient needs a specific customized approach to his or her diagnosis and therapy. We are fortunate that so many options continue to be developed to help us individualize patient care.

Dr O'Brien: Infection matters. Resistance is important in ophthalmology. Epidemiologic surveillance of ocular pathogens continues to demonstrate the importance of steering our attention to bacterial resistance, prompting us to alter our strategies to prevent infection from occurring during ophthalmic surgeries. Inflammation also matters: inflammation can lower the success rate of our otherwise technologically advanced ophthalmic procedures. Delaying surgery to address OSD preoperatively may seem inconvenient, but often is prudent to gain the most accurate input data and to avoid potentially devastating complications postoperatively.

Table. New Agents for Perioperative Prophylaxis

Several agents have been developed recently in the ocular anti-infective and anti-inflammatory categories and their salient features are summarized below.

Anti-Infective Agents

- **Besifloxacin**
 - Fluoroquinolone formulated specifically for ocular use
 - Active against ocular pathologic isolates, including MRSA, that are resistant to other antibiotics^{1,2}
- **Gatifloxacin, 0.5%**
 - Reformulation at higher dose (was 0.3%)

Anti-Inflammatory Agents

- **Bromfenac, 0.07%**
 - Reformulation at lower dose (was 0.1%) with once-daily dosing
 - Effective in suppressing postoperative inflammation and pain following cataract surgery dosed once daily in 2 RCTs³
- **Nepafenac, 0.3%**
 - Reformulation at higher dose to achieve qd dosing (was 0.1% tid)
 - Effective in suppressing postoperative inflammation and pain following cataract surgery in RCT⁴
 - Also indicated in Europe for diabetic macular edema prevention in those with diabetes undergoing cataract surgery⁵
- **Loteprednol gel, 0.5%**
 - Reformulation (was a suspension)
 - Corticosteroid designed to be less apt than prednisolone acetate to raise IOP
 - Effective in suppressing postoperative inflammation and pain following cataract surgery dosed once daily in 2 RCTs⁶
- **Difluprednate, 0.05%, emulsion**
 - Potent corticosteroid
 - Emulsion, so no shaking required
 - Prodrug activated after ocular penetration
 - Higher risk for elevated IOP than occurs with other steroids⁷

RCTs=randomized clinical trials.

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Post Test

To obtain *AMA PRA Category 1 Credit™* for this activity, complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/Credit Request form on the following page. Alternatively, you can complete the CME Post Test online at <http://tinyurl.com/FoundationsCME>.

See detailed instructions at **To Obtain AMA PRA Category 1 Credit™** on page 3.

- In patients with preexisting OSD, which of the following would be the least desirable method of controlling inflammation in the perioperative period for cataract surgery?
 - Intracameral steroids
 - Topical steroids
 - Systemic steroids
 - Sub-Tenon steroids
- Which of the following is/are an advantage(s) of preoperative anti-inflammatory therapy before cataract surgery?
 - Reduction of postoperative inflammation by reducing precursors to inflammation
 - Less intraoperative miosis
 - Less aberrant biometry for lens power calculation
 - All the above
- As shown in the ESCRS study, to what extent did the use of intracameral cefuroxime at the end of each cataract surgery procedure reduce the risk for endophthalmitis?
 - 2-fold
 - 5-fold
 - 8-fold
 - 12-fold
- Which of the following is false regarding MRSA?
 - The prevalence of MRSA is increasing over time
 - Early-generation fluoroquinolones are highly effective against MRSA
 - Approximately 15% of cataract patients are colonized with *S aureus*, of which approximately one-third are MRSA
 - MRSA is the leading cause of post-LASIK infections
- Diffuse lamellar keratitis and infectious interface keratitis can appear similar. Which of the following is true regarding methods to distinguish between these 2 entities?
 - In inflammatory keratitis, there is typically anterior chamber cell and flare
 - In infectious keratitis, very fine and discrete micropunctate white blood cells can be seen
 - Pain, photophobia, and anterior chamber cell suggest infection rather than noninfectious inflammatory DLK
 - None of the above is true
- Which of the following is false regarding glaucoma and perioperative infection?
 - Topical IOP-lowering medications can cause conjunctival inflammation
 - Preservatives such as benzalkonium chloride promote inflammation
 - Preoperative topical steroids should be avoided because of the risk for IOP elevation
 - Conjunctival inflammation can reduce glaucoma surgery success
- The most common organisms responsible for acute infections following glaucoma surgery are:
 - S aureus* and *H influenzae*
 - S pneumoniae* and *S aureus*
 - S aureus* and *S epidermidis*
 - H influenzae* and *Enterococcus* species
- In a patient with allergic or atopic disease facing intraocular surgery, which of the following is true?
 - Reducing inflammation is necessary to prevent itching and eye-rubbing postoperatively
 - Systemic steroid therapy may be needed, and an allergy consultation may be of value
 - Atopy increases the risk for postoperative infection 6-fold
 - All the above are true
- Which of the following is false regarding the use of prophylactic antibiotics and resistance?
 - The primary cause of resistance is antibiotic overuse
 - The majority of antibiotic use in the United States is within the food production industry
 - Topical prophylactic antibiotic use during intravitreal injections does not lead to antibiotic resistance
 - None of the above is false
- Which of the following best characterizes similarities between branded products and their generic formulations?
 - Same active ingredients
 - Same inactive ingredients
 - Same active and inactive ingredients
 - Same stability to heat



Activity Evaluation/Credit Request

Original Release: December 1, 2014

Last Review: November 1, 2014

Expiration: December 31, 2015

Building Foundations for Successful Ophthalmic Surgery

To receive *AMA PRA Category 1 Credit™*, you must complete this **Evaluation** form and the **Post Test**. Record your answers to the **Post Test** in the **Answer Box** located below. Mail or Fax this completed page to **New York Eye and Ear Infirmary of Mount Sinai–ICME**, 310 East 14th Street, New York, NY 10003 (Fax: 212-353-5703). Your comments help us to determine the extent to which this educational activity has met its stated objectives, assess future educational needs, and create timely and pertinent future activities. Please provide all the requested information below. This ensures that your certificate is filled out correctly and is mailed to the proper address. It also enables us to contact you about future CME activities. Please print clearly or type. Illegible submissions cannot be processed.

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OUTCOMES MEASUREMENT

Yes No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:

5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

• Recall data on ocular antibiotic resistance patterns	5	4	3	2	1
• Identify effective antibiotics for patients undergoing ophthalmic procedures	5	4	3	2	1
• Demonstrate use of evidence-based inflammation-control regimens for patients undergoing cataract surgery, LASIK, and corneal transplant surgery	5	4	3	2	1
• Identify optimal preoperative inflammation control practice	5	4	3	2	1
• Recall data from clinical trials on the efficacy and safety of new anti-inflammatory agents used in cataract surgery	5	4	3	2	1
• Select optimal anti-inflammatory agents while considering efficacy and IOP control for patients undergoing glaucoma surgery	5	4	3	2	1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know. _____

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?

4=definitely will implement changes 3=likely will implement changes 2=likely will not implement any changes 1=definitely will not make any changes

4 3 2 1

Please describe the change(s) you plan to make: _____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face? _____

4. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity. Patient Care Practice-Based Learning and Improvement Professionalism
 Medical Knowledge Interpersonal and Communication Skills Systems-Based Practice

5. What other topics would you like to see covered in future CME programs? _____

ADDITIONAL COMMENTS _____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9	10

