



# Prevention and Management of Ocular Inflammation Across the Ophthalmic Spectrum

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**Activity Description**

The anti-inflammatory therapeutic landscape has evolved in recent years with the availability of a variety of efficacious agents offering better safety and tolerance than previously available. There is a need for education in the selection of current appropriate therapies for ocular inflammation occurring in a variety of clinical settings, as well as for introductions to future options. An expert faculty panel convened to discuss the current strategies for inflammation management in commonly encountered clinical situations. This activity is a CME/CE monograph of evidence-based practical approaches for optimal prevention and management of ocular inflammation.

**Target Audience**

This educational activity is intended for comprehensive ophthalmologists and optometrists.

**Learning Objectives:**

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

- Demonstrate application of best-practice regimens for reducing inflammation risk for cataract, refractive, and glaucoma procedures
- Demonstrate application of best-practice regimens for inflammation management of primary conditions of dry eye, blepharitis, ocular allergy, and anterior uveitis
- Recognize ophthalmic anti-inflammatory therapies currently in development

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## Introduction

Managing ocular inflammation is an important part of eye care—by ophthalmologists and optometrists alike. Inflammation associated with ocular surgery is of particular interest to eye specialists because this condition can have long-term consequences for both healing and vision. Successfully controlling the underlying inflammation that is instrumental in a number of ocular conditions and diseases is a significant part of an eye clinician's daily practice and can influence the short-term and long-term ocular health of patients.

Recently, a group of leading eye care specialists met to consider management strategies of ocular inflammation in ophthalmic surgery and in primary eye care.

## Surgically Induced Inflammation Prevention and Management

### Cataract Surgery and Cystoid Macular Edema

Traditionally, one of the most feared complications of cataract surgery has been endophthalmitis. Cystoid macular edema (CME), however, is much more common and potentially more damaging to vision than endophthalmitis.<sup>1,2</sup> For this reason, it is important for ophthalmologists and optometrists to develop better strategies to prevent and manage surgically induced ocular inflammation.

### Technology and Inflammation

**Dr O'Brien:** Improvements in ocular surgical techniques and advances in intraocular lens (IOL) technology have heightened clinicians' awareness of the effects of inflammation and CME. What are the current issues or concerns surrounding prophylaxis against CME for our patients undergoing cataract surgery? Dr Lane, we always think of cataract surgery now as very sophisticated, technologically advanced, and minimally invasive. Do cataract surgeons still have to worry about CME?

**Dr Lane:** I think we do. New technologies, such as improved surgical techniques, smaller incisions, and new instrumentation, help us do a better job for our patients by creating less inflammation—the cause of CME,<sup>2</sup> but despite all these advances, we still see CME in our patients, although I believe it is underappreciated. Subclinical CME probably occurs in approximately 10% to 20% of patients.<sup>3</sup> These affected patients do not get the crisp, clear, distinct vision that they expected. What is problematic is that once someone develops CME, he or she often can never recover his or her original level of vision.

**Dr Donnenfeld:** We ophthalmologists, in general, have relied on Snellen Visual Acuity as a parameter for determining visual acuity after cataract surgery. In severe cases of CME, there will be a loss of both contrast sensitivity and quality of vision. Even mild retinal thickening can cause a permanent loss that limits a person's ability to drive at night or on a foggy day. These changes are irreversible, so the key to treating CME is to prevent it.

**Dr O'Brien:** Those are great points. As we implement more advanced-technology IOLs, the impact of any reduction of vision and contrast sensitivity, as well as changes affecting other subtle measures of visual performance, becomes even greater. Dr Pepose, are you worried that CME could reduce visual performance and overall satisfaction in your patients who are interested in having these advanced-technology or other IOLs?

**Dr Pepose:** It is always a concern. Because the moment we make an incision in the eye, we are releasing phospholipids, which then start an inflammatory cascade.<sup>4</sup> We have to dampen that cascade because expectations are so high now—with specialty lenses—and we have to be particularly aggressive in treating patients who have specific risk factors. Examples of patients at higher risk for developing CME include those with diabetes, patients with a history of uveitis or epiretinal membranes, or any patients in whom there is an underlying condition that accelerates the breakdown of the blood-ocular or blood-aqueous barriers. Patients with ocular surface diseases are also at risk. It really

behoves us to quiet things down before the surgery rather than try to play catch-up after the surgery.

Another situation that is becoming more and more prevalent is the number of patients who use alpha-1 inhibitors and develop miosis and so are in need of pupillary-expanding Malyugin Rings. Those patients may be at higher risk for developing CME because of this iris manipulation. Also, when there is a surgical complication, particularly if there is rupture of the capsule, the risk goes even higher.

**Dr Karpecki:** I agree that it is imperative to determine who is most at risk for CME prior to surgery. Optometrists involved in co-management or who work in an integrated eye care delivery system are critical to this process by communicating the risks to the surgeon prior to surgery. Key patient types, as listed previously, include those with diabetes, one of the fastest growing diseases in North America, and those with a history of uveitis. Other patient types to be aware of are those who are more at risk for a capsular tear, including the patient who developed a cataract because of trauma and the patient who has pseudoexfoliation.<sup>5</sup>

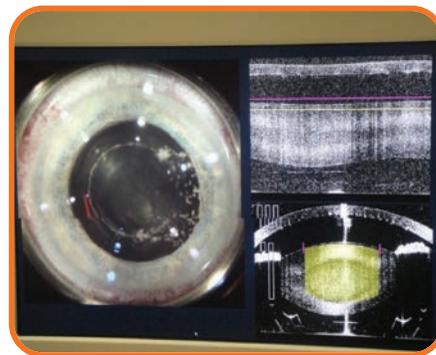
Patients in whom surgery might involve more time inside the eye—patients with intraoperative floppy iris syndrome—also may be at higher risk for CME. And although rare, conditions such as Vogt-Koyanagi-Harada syndrome and other systemic inflammatory diseases, for example, juvenile rheumatoid arthritis, produce increased risk for inflammation and the potential for patients to develop CME. One other risk factor often not mentioned is that of smoking; there is research to support that smokers are more likely to develop uveitis activity leading to potential macular edema.<sup>6</sup>

**Dr O'Brien:** How does CME occur even when the cataract surgery appears uncomplicated?

**Dr Pflugfelder:** There are certain biological factors that affect everyone. For instance, Miyake has proposed that inflammatory mediators are produced by a traumatized lens and iris epithelial cells in many eyes.<sup>7</sup> There is always going to be a low level of inflammation that we must address, and some people (such as those with diabetes and those with chronic uveitis) may be even more susceptible to that inflammation. Another factor that Miyake has mentioned is the presence of benzalkonium chloride (BAK), a preservative found in many of the medications that we use either before or after surgery. These agents can also increase inflammation and perhaps alter the blood-retinal barrier.<sup>8</sup>

**Dr Karpecki:** Other proposed mechanisms for development of CME include a prolapsed or incarcerated vitreous along with the postoperative inflammatory processes mentioned.<sup>9</sup>

**Dr O'Brien:** We are excited about the use of femtosecond lasers in cataract surgery as a newer powerful tool to potentially improve outcomes and reduce complications (Figure 1). But given some of the technical issues at present with femtosecond cataract surgery, could inflammation actually be increased, especially in the early stages of the learning curve, as we saw with diffuse lamellar keratitis and femtosecond laser-assisted LASIK (laser assisted in situ keratomileusis)?



**Figure 1.** Ocular imaging-guided cataract and astigmatic incisions, anterior capsulotomy, and lens nuclear fragmentation with the high precision and control of femtosecond laser.

Photo Courtesy of  
Eric D. Donnenfeld, MD

**Dr. Donnenfeld:** Femtosecond laser cataract surgery has a risk for inflammation because, in my experience, the laser, especially if it is close to the iris border, will cause a transient pupillary miosis, which can induce inflammation. Pretreating these patients before surgery with anti-inflammatories—nonsteroidals and possibly even steroids—is imperative to prevent this miosis.<sup>10</sup> In general, though, because femtosecond laser cataract surgery is associated with less energy input into the eye, this technology will actually induce less inflammation postoperatively. As with all surgery, however, there is still a risk for CME. It is really in everyone's best interest to use appropriate anti-inflammatory therapy to optimize outcomes.

**Dr. Pepose:** Some pro-inflammatory mediators are "prepackaged" in ocular tissues and are already present before surgery begins. It is best to try to deplete them, particularly some of the prostaglandins. Prostaglandin E, in particular, may be very central in terms of resulting miosis.<sup>4</sup> Pretreatment becomes very important in an effort to try to deplete these mediators before surgery.

**Dr. Donnenfeld:** The goal now is to suppress inflammation because once the cascade starts, it is irreversible. The concept behind creating an anti-inflammatory environment in all aspects of medicine is pulse dosing, pretreating and aggressively preventing inflammation, and then tapering anti-inflammatory treatment rapidly postoperatively. We have actually done studies with multifocal IOLs that have shown that even in patients with uneventful surgery, when pretreated with a nonsteroidal, better quality of vision and better contrast sensitivity result compared with outcomes when not using a nonsteroidal.<sup>11,12</sup>

## Guidelines and CME Prophylaxis

**Dr. O'Brien:** Let us shift gears and talk a little bit about guidelines for preventing CME and controlling inflammation around cataract surgery. What is the accepted standard of care and what key studies guide that standard of care?

**Dr. Lane:** Guidelines have been difficult to establish because the inflammation is so difficult to define. We ran into this issue originally with angiography. Today, with optical coherence tomography (OCT), the definition of inflammation becomes much easier. Miyake has done the most work in this area. It is his opinion that nonsteroidal anti-inflammatory agents are really critical in the treatment and prevention of CME.<sup>13</sup> I think Dr. Miyake has clearly shown us the added benefit of adding a nonsteroidal anti-inflammatory drug (NSAID) to the postoperative regimen, thereby influencing 2 different points along the inflammatory cascade.<sup>14</sup> The synergism attained with a nonsteroidal and a steroid becomes a very powerful tool to help decrease inflammation. I think it is the opinion of most eye clinicians that one needs to use steroids and nonsteroidals together.

## Pharmacoeconomics

**Dr. O'Brien:** Another consequence of inflammation and CME with cataract surgery is the additional associated expense, which can be considerable. Managing chronic CME may increase prescription and medical costs for the surgical patient, thus emphasizing the importance of pretreatment with NSAIDs or corticosteroids.

**Dr. Donnenfeld:** The expenses a patient incurs when CME develops include those for extra visits to the physician, possibly a retinal consultation, and the need for more pharmaceuticals postoperatively. Most importantly, there exists the potential for permanent loss of quality of vision, and even Snellen Visual Acuity. Also, when not using a nonsteroidal, it has been shown that time in the operating room can increase because the pupil will constrict more, increasing phacoemulsification time, endothelial cell loss, and the risk for capsular rupture.<sup>10</sup> Postoperatively, there are going to be many more nonreimbursed patient visits because the ophthalmologist is managing unhappy patients. From a socioeconomic and a practice-building perspective, the use of nonsteroidals is extraordinarily important in cataract surgery.

**Dr. Lane:** Where I practice in Minnesota, the pharmacist has the legal ability to change a medication from a branded product to a generic form. I think we as physicians really have an obligation to educate the patients about their medications and to explain that while there are generic "equivalents", certain brand-name medications are more efficacious or

safer and might be specifically recommended over a generic formulation. Patients should be informed that there might be an attempt on the part of a pharmacist to substitute a generic product, and thus they should be advised to insist on getting the medication specifically prescribed by the physician. Patients have to be their own advocates, and we need to teach them how to do this.

**Dr. Donnenfeld:** I have taken it 1 step further than that. My partners and I have prepared a brochure for patients who are having cataract surgery. In the brochure, we enter which medication we want a patient to take. We give him or her the opportunity—if the patient chooses—to use a generic medication, and then list the generic that we recommend. In our experience, 90% of our patients will choose to go with the branded medication. That is a patient-informed consent decision that patients make on their own.

**Dr. Karpecki:** We also incorporate something in our practice similar to that used in Dr. Donnenfeld's practice. Again, it's education of the patient; once a patient understands the importance and potential differences of the various medications, he or she can make the best decision. Most patients believe that generics are indeed equivalent to branded medications, and we have to make recommendations for both branded and generic options. There are some patients who truly can not afford the branded medication and who, without a generic option, would go without the medication; that is likely to be worse than a generic option. Our practice experience is similar in that the vast majority of our patients select the branded medications, and all patients considering a premium IOL procedure select the branded medication list. We should also take time to educate pharmacists, who receive very little training in ophthalmic medications compared with other classes of medications and systemic drugs.

## Steroid/NSAID Combinations: Working Together

**Dr. O'Brien:** Dr. Pflugfelder, please review mechanisms of action and exactly where along the inflammatory pathway corticosteroids and nonsteroidals work, and how this synergism may be beneficial to our patients.

**Dr. Pflugfelder:** Several mediators are involved. Nonsteroidal anti-inflammatories inhibit cyclooxygenase,<sup>15</sup> an enzyme that converts arachidonic acid into lipid mediators of inflammation, such as prostaglandins. Corticosteroids inhibit phospholipase A, which is also involved in the synthesis of arachidonic acid from cell membrane phospholipids.<sup>16</sup> Corticosteroids also have a downstream effect in inhibiting production of inflammatory mediators by blocking intracellular signaling pathways.<sup>17</sup>

**Dr. O'Brien:** Dr. Donnenfeld, when ophthalmic nonsteroidals were first introduced, many of us had hopes that these agents would replace corticosteroids and their associated complications, but you, Dr. Lane, Edward Holland, MD, and others were all part of those early clinical trials in which only the nonsteroidal agent was used, absent the corticosteroid. Please relate the experiences of using only a nonsteroidal.

**Dr. Donnenfeld:** After surgery, patients will usually experience some redness and inflammation, and generally tend to have more discomfort when using only a nonsteroidal. We also have performed some studies on nonsteroidals examining the pharmacokinetic dose-response curve.<sup>11</sup> Nonsteroidals should be started at least 1 to 3 days preoperatively in order to maximize their effectiveness in controlling inflammation. In high-risk patients, ophthalmologists should start nonsteroidals a week before surgery. Postoperatively, CME peaks at approximately 4 weeks. But all the nonsteroidal medications are approved for 2 weeks postoperatively.<sup>18,19</sup> Two weeks is not adequate time to control inflammation, so we continue nonsteroidals in our practice for 4 to 6 weeks postoperatively off-label on a routine basis.

**Dr. Pepose:** The eye has several mechanisms that naturally suppress inflammation and so, many cases of CME resolve spontaneously. All of us would agree that if a case of acute CME becomes chronic CME, the prognosis is much worse. Using both steroids and nonsteroidals is very important to prevent acute CME from becoming chronic CME.

**Dr. Lane:** The other important thing to consider is that steroids are more of an acute mediator, and they traditionally have a certain number of side effects associated with them. A nonsteroidal is more a

chronic mediator, and it allows for the opportunity to show that nonsteroidals alone do work. I agree that using steroids and nonsteroidals together works best because doing so eliminates that immediate discomfort, pain, and redness patients may have after surgery. The steroids can be tapered off very quickly, but the nonsteroidals can be continued over a longer period of time.

**Dr Donnenfeld:** From a patient perspective, a surgical procedure is a success when 2 conditions are met: 1) the patient sees well, and 2) there was no discomfort. Nonsteroidals and corticosteroids each play an extraordinarily important role in meeting both conditions. In the US Food and Drug Administration (FDA) trials that concerned pain following cataract surgery, the use of either corticosteroids or nonsteroidals has been shown, individually, to dramatically and significantly reduce the incidence of pain.<sup>20,21</sup> Pretreating with nonsteroidals definitely reduces the discomfort following cataract surgery.

**Dr Karpecki:** I agree that the 2 medications work synergistically. In fact, NSAIDs have a unique property that allows for more effective relief of corneal pain—a property lacking in topical corticosteroids—almost a low-grade, short-term anesthetic effect<sup>22</sup> that includes the mechanical receptors, chemical receptors, and thermal receptors, followed by longer analgesic effects.<sup>23</sup> Studies have shown an analgesic effect with NSAIDs to last as long as 24 hours.<sup>24</sup> Furthermore, it has been demonstrated that the NSAIDs provide markedly better pain control when inflammation is not present, and thus, corticosteroids, to control inflammation, are critical.<sup>22</sup>

### NSAID Safety in the Cataract Patient

**Dr O'Brien:** There was a time when cataract surgeons were somewhat averse to using ophthalmic nonsteroidals because of safety concerns. Dr Pflugfelder, please review briefly the epidemic of ulcerative keratolysis, the lessons learned, and why now we feel that current ophthalmic nonsteroidals are safe to use routinely.

**Dr Pflugfelder:** Many of us have seen cases of sterile keratolysis that appeared to occur more often with use of a generic diclofenac, perhaps because of the formulation or the preservative in the formulation.<sup>25,26</sup> I have not observed this occurrence with other nonsteroidals, although I know sterile keratolysis has been caused by others such as bromfenac, nepafenac, and ketorolac.<sup>27-29</sup> I think that many current formulations that have lower drug concentrations or that are preservative-free carry a lower risk. Ocular surface conditions, such as dry eye and blepharitis, may increase the risk for keratolysis.

**Dr O'Brien:** With some of the earlier NSAID agents and generic versions, there may be a greater risk for corneal cytotoxicity, especially with patients with ocular surface disease. With the current generation of nonsteroidals, however, we see fewer complications; these agents are quite safe.

**Dr Donnenfeld:** Ten years ago there was an epidemic of sterile ulceration associated with the use of generic nonsteroidals. I am seeing some of that again now. I have not seen frank ulceration, but I do see more superficial punctate keratitis (SPK) with the use of generic nonsteroidals. Generics do play a role in ophthalmology, certainly, but the one place where I would really want to consider the use of a branded medication is in the use of a nonsteroidal.

**Dr Karpecki:** My experience is similar in that we're seeing cases of SPK with some generic NSAIDs, but fortunately, it has been a long time since I've seen a patient present with keratolysis related to topical NSAIDs like generic diclofenac as we saw 10 years ago. Still, I steer patients at higher risk toward branded NSAIDs rather than the generics—patients with a diagnosis of rheumatoid arthritis or other advanced systemic inflammatory diseases, patients with advanced ocular surface disease, and patients with inferior exposure keratopathy.

**Dr O'Brien:** We are seeing the same thing, and I share your concerns that some of the generic formulations are less friendly to the ocular surface, especially when dosed more frequently than the more potent advanced-generation NSAIDs. Dr Pepose, please review briefly the evolution of ophthalmic nonsteroidals, comparing and contrasting the potency of earlier-generation formulations with advanced-generation nonsteroidals.

**Dr Pepose:** The earlier-generation formulations, such as flurbiprofen, had lower potency and required more frequent dosing. That property may lend itself to some of the complications of NSAIDs that were seen in the past in higher-risk patients. But the newer arylacetic acid derivatives, bromfenac, and the prodrug nepafenac, which is converted into active form upon passage through the cornea, have more favorable pharmacokinetics. Their penetration has increased, while their toxicity has decreased compared with older agents. The dosage was 3 times a day, then twice a day, and now once a day, so we have seen an evolution in terms of drug penetration and better pharmacokinetics.

**Dr Lane:** I think the nonsteroidal inflammatory drugs that we have today are all excellent. I do find it difficult to determine any real difference in terms of what I see from a clinical standpoint. I have seen incidences of more irritation to the eye after surgery with generic medications.

### Steroids in CME Prophylaxis

**Dr O'Brien:** What are some of the new developments in ophthalmic corticosteroidal agents and their potential advantages and disadvantages?

**Dr Pepose:** Difluprednate is a very potent anti-inflammatory drug. It can be used as a pretreatment and in a pulse format.<sup>11</sup>

**Dr Donnenfeld:** Difluprednate is a stable emulsion, which ensures dose consistency, and, because it is a stable emulsion, lowers the need for the patient to shake the medicine bottle before inserting drops. This medication is more potent than prednisolone and can be used to manage a variety of conditions, including uveitis, in which it was found to be as effective as prednisolone acetate when the difluprednate was dosed 4 times a day and the prednisolone was dosed 8 times a day.<sup>30</sup> Note, there can be an associated intraocular pressure (IOP) increase associated with difluprednate,<sup>31</sup> but the incidence of IOP elevation in the FDA trials in which dosing was 4 times a day and tapered over a full month was only 3%.<sup>32</sup>

**Dr Karpecki:** The fact that difluprednate does not require shaking has turned out to be more important than I had at first thought. I have been surprised at how many patients have admitted to forgetting to shake their previously prescribed steroid suspension drops. Also, the degree of shaking required is often more than most older patients will perform, especially the very elderly or those with arthritis. I also like that there is no BAK in difluprednate; it is instead preserved with sorbic acid.<sup>33</sup> Finally, I think it is important that clinicians understand that because of the potency of difluprednate, it should be dosed at approximately half the dosing of other medications, for example, prednisolone acetate or loteprednol, 0.5%.

**Dr Pepose:** The studies show that approximately 3% of patients may have an IOP increase with difluprednate,<sup>32</sup> so you do have to be careful to monitor IOP. Loteprednol is a drug that seems to have a lower prevalence of increased IOP,<sup>34,35</sup> so that is an advantage with loteprednol, and studies suggest it has similar efficacy in suppressing inflammation to other strong steroids.<sup>34-36</sup>

**Dr Donnenfeld:** I believe the evidence indicates loteprednol is an extremely potent corticosteroid with excellent anti-inflammatory effects and safety profile. It has really become my steroid of choice for induction of anti-inflammatory cyclosporine therapy in dry eye, but it is also very effective in cataract surgery. There is a recent study that was done by Buznego and colleagues that compared loteprednol to prednisolone acetate.<sup>37</sup> There was no difference in anti-inflammatory effect between the 2 medications. Other studies demonstrate similar findings.<sup>38,39</sup>

**Dr Karpecki:** My experience with loteprednol is similar to that of Dr Donnenfeld. In fact, we often substitute loteprednol as the steroid of choice in glaucoma patients undergoing cataract surgery; I have not witnessed any difference in postoperative inflammation or pain compared with using ketone steroids such as prednisolone acetate. The IOP safety data suggesting an approximately 2% chance of a significant rise in IOP provides a great safety-to-high-potency ratio.<sup>35</sup>

**Dr Lane:** We just completed a multicenter study that compared a 1% branded prednisolone with loteprednol and found that there was no statistically significant difference in the amount of inflammation

between the 2 groups of patients.<sup>40</sup> In fact, we did see a higher trend in IOP following surgery in the prednisolone acetate group compared with the loteprednol group. This has really allowed me, as a clinician, to change what I do in terms of dosing so that I now prescribe both medications for use 3 times daily, which improves compliance (S. Lane, MD, unpublished data).

**Dr Donnenfeld:** Chang and colleagues<sup>41</sup> recently showed that in patients who are highly myopic, the incidence and magnitude of pressure spikes was really very significant with prednisolone acetate. He suggests that there is a risk for steroid side effects in these patients and has recommended that loteprednol be the corticosteroid of choice in significantly myopic patients who are having cataract surgery.

### Today's Steroid Formulations

**Dr O'Brien:** We have talked about eye drops like loteprednol and emulsions like difluprednate. We now have a commercially available preservative-free ointment form of loteprednol etabonate, and a loteprednol gel with a minimal amount of BAK. In what clinical situations would a preservative-free corticosteroid offer some advantages and utility?

**Dr Pflugfelder:** I have not used the ointment yet for postoperative inflammation because of the blurring that an ointment causes. Many postoperative patients may find this annoying. But I have been using the ointment for a variety of ocular surface diseases, including blepharitis and dry eye. I find that patients using an ointment probably do not use it more than twice a day, and often just at night. It is expected that the gel formulation of loteprednol is less likely to cause blurred vision.

**Dr O'Brien:** There is a subset of people who, despite a successful technical outcome of surgery, struggle because of ocular surface compromise. For them, I think the preservative-free ointment has played a beneficial role. For those with significant ocular surface disease, the gel preparation also offers considerable advantages.

**Dr Lane:** The other instance in which I find an ointment very useful is in ocular surface procedures. We have been forced in the past to use antibiotic/steroid combinations, simply because a pure steroid may not have been available. The availability of a preservative-free steroid-only medication is an excellent option to have. I use it routinely for post-surgical treatment after lid procedures.

**Dr Karpecki:** In addition to ocular surface disease treatments, I've had success in using a preservative-free corticosteroid ointment at bedtime in uveitic conditions. Consider that uveitis is to inflammation much as a bacterial ulcer is to infection: we would never consider not providing treatment overnight for a corneal ulcer. To go without therapy for possibly 6 to 8 hours does not seem logical. For a uveitis, why would we also not want to have some therapy overnight? I have found that patients seem to resolve their inflammation much more quickly with this overnight ointment. I also would not be opposed to adding loteprednol ointment at bedtime in postcataract patients with significant inflammation or risk for CME.

**Dr O'Brien:** Additionally, a steroid-only ointment or gel makes sense when you need to avoid potentially toxic antibiotics, such as aminoglycosides. Are there issues with acceptability or compliance with an ointment or gel formulation?

**Dr Pepose:** The upside of an ointment is long contact time and good penetration. The downside of an ointment is that if used during the day, it is going to cause blurred vision.

I think many of us have our patients use eye drops during the day and the ointment at night. I find this routine very helpful in postcataract patients in that the ointment plays the dual roles of lubrication and reducing both pain and inflammation.<sup>42</sup> With the loteprednol gel, we get efficacy, very uniform dosing without the patient having to shake the bottle.<sup>43</sup>

**Dr Karpecki:** The gel also avoids the blur we may get with ointments, and with a long contact time, makes daytime use reasonable.

**Dr Donnenfeld:** There are also a large number of surgeons today who do peribulbar lid blocks. Use of loteprednol ointment postoperatively in these patients would be beneficial.

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## Experts' Regimens for Cataract Surgery Patients

Each of the panelists listed his individual treatment regimen for cataract surgery, for both routine cases and for high-risk patients. The agents listed here are the preferences of each surgeon; the timeframe, or duration of the corticosteroid and nonsteroidal medications, may differ from the current FDA approvals for these agents.

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### Terrence P. O'Brien, MD: For routine cataract patients:

- **Preoperatively:** Besifloxacin and bromfenac (or nepafenac) starting 2 days before surgery
- **During surgery:** Off-label intracameral moxifloxacin in higher-risk cases
- **Postoperatively:** Bromfenac and topical steroid for 4 to 6 weeks, with besifloxacin continued for 10 to 14 days

**For high-risk patients:** Start medications a week before surgery and treat postoperatively for at least 2 months. In very high-risk patient, intravitreal triamcinolone acetonide injection preoperatively

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### Stephen S. Lane, MD: For routine cataract patients:

- **Preoperatively:** Loteprednol and an NSAID tid—usually nepafenac—a day before surgery
- **During surgery:** An antibiotic drop—usually moxifloxacin—at the start of surgery
- **Postoperatively:** Loteprednol, NSAID, and antibiotic continued 3 times daily. Moxifloxacin continued for 2 weeks. Loteprednol and NSAID tid until used up, which usually takes a month

**For high-risk patients:** Start NSAIDs at least a week prior to surgery and treat postoperatively for at least 2 months

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### Stephen C. Pflugfelder, MD: For routine cataract patients:

- **Preoperatively:** Bromfenac qd and difluprednate bid starting the day before surgery
- **Postoperatively:** Continue bromfenac and difluprednate for 2 weeks: bromfenac qd, and decrease difluprednate to qd. In patient with a history of glaucoma or steroid-induced ocular hypertension, loteprednol used instead of difluprednate

**For high-risk patients:** NSAID and a steroid the day before surgery and then continue both on a tapering dose for up to 4 weeks

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### Jay S. Pepose, MD, PhD: For routine cataract patients:

- **Preoperatively:** Besifloxacin and bromfenac starting 3 days before surgery, with besifloxacin continued for 14 days. Prednisolone acetate or loteprednol, depending on patient preference, starting 3 days preoperatively
- **During surgery:** Off-label intracameral moxifloxacin
- **Postoperatively:** Bromfenac and topical steroid for 6 to 8 weeks

**For high-risk patients:** Start medications a week before. In very high-risk patient, intravitreal triamcinolone injection preoperatively

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### Eric D. Donnenfeld, MD: For routine cataract patients:

- **Preoperatively:** Bromfenac or nepafenac bid and besifloxacin bid starting 3 days preoperatively. Difluprednate 2 hours preoperatively: 1 drop every 15 minutes for 6 doses
- **Postoperatively:** Difluprednate qid the first day, bid for 2 weeks and qd for the third week. Stop the antibiotic at 10 days postoperative and the NSAID at 1 month postoperative. Switch to loteprednol if a patient needs more anti-inflammatory therapy after several weeks

**For high-risk patients:** Corticosteroid pulse before surgery and immediately after surgery. Then bid after the first day. For extremely high-risk patient, inject intracameral triamcinolone. Perform OCT to manage treatment protocols and IOL selection

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### Paul M. Karpecki, OD: For routine cataract patients:

- **Preoperatively:** Bromfenac and besifloxacin starting 3 days prior to surgery

- **Postoperatively:** Besifloxacin remains for 1 week, bromfenac and difluprednate for 4 weeks. Besifloxacin dosed bid, bromfenac qd, and difluprednate bid. Difluprednate tapered to qd after 2 weeks, provided inflammation appears normal at 1-week follow-up. Continue corticosteroids and NSAIDs for 4 to 6 weeks

**For high-risk patients:** May start the NSAID a week prior to surgery

## Keratorefractive Procedures

For keratorefractive procedures, the bar is raised even higher because the procedure is an elective one. A problem for the keratorefractive surgeon is the fact that subtle subclinical factors may lead to inflammation and a negative outcome.

**Dr O'Brien:** Dr Donnenfeld, please outline those conditions that you worry may not be detected in a routine screening. What do you do in your practice to aggressively screen patients for risk factors?

**Dr Donnenfeld:** Today, the most common problem facing the LASIK surgeon and patient is the effect of ocular surface disease and dry eye on posturgical results. I think more attention has to be paid to ocular surface dry eye disease. Tear break-up time (TBUT) is important, but new point-of-service tests, such as tear osmolarity and the matrix metalloproteinase (MMP)-9 test, offer great promise in helping diagnose dry eye.<sup>44-46</sup> A standardized preoperative evaluation with specific testing will allow us to screen those patients who are at risk and to treat their underlying conditions to make them better refractive surgery candidates. Inflammation still plays a very important role in management of LASIK patients.

**Dr O'Brien:** Dr Pflugfelder, surveys have consistently shown that dry eye is the single greatest reason for patient dissatisfaction with keratorefractive procedures. What are some of the limitations of the current clinical methods and diagnostic tests for uncovering dry eye in those who are seeking LASIK procedures?

**Dr Pflugfelder:** The current clinical methods for detecting ocular surface problems or tear dysfunction are fairly poor. Dye staining and TBUT may be the best tests that we use, but both are relatively insensitive. Another problem is that many of the people with potential problems do not actually have a classic dry eye, but more of a tear distribution or tear clearance problem. Detecting biomarkers—either in the tears or in ocular surface cells—would go a long way toward improving presurgical testing.

**Dr O'Brien:** We have mentioned the lack of clear guidelines for the practicing keratorefractive surgeon in cataract surgery and I think guidelines are even less clear for the refractive surgeon, but are there some general ones to follow based on organizational recommendations?

**Dr Lane:** There is a dearth of information about this, so we all have developed our own regimens. The 2 things that I am most concerned about are reducing the pain and inflammation associated with the surgery and then using an agent that is very efficacious and very safe to the ocular surface. I do use a drop of a nonsteroidal when the patient is on the operating table to try to limit the pain and discomfort experienced immediately afterward, but I do not send my patients home with a bottle of nonsteroidal medication. I also prescribe loteprednol and very frequent doses of preservative-free artificial tears.

**Dr Karpecki:** I think that preoperative management of ocular surface disease, including blepharitis, dry eye, and meibomian gland dysfunction (MGD), is one of the most critical aspects of successful refractive surgery outcomes. Research has shown not only a potential for worse vision after surgery due to a poor tear film, but also a much higher enhancement rate.<sup>47</sup>

So, if osmolarity is above 308 mOsm/L<sup>48</sup> or if lissamine green or fluorescein staining is present, then treatment of the ocular surface with loteprednol and cyclosporine, for example, is critical (**Figure 2**). And if the signs of dry eye can't be improved, the patient should not be a candidate for surgery. That being said, typically we can improve signs of dry eye in 98% of patients prior to surgery, and we are likely grateful we did not recommend LASIK for the other 2%.



**Figure 2.** Lissamine green staining.

Photo Courtesy of Eric D. Donnenfeld, MD

**Dr O'Brien:** Historically, we discovered the role of ophthalmic non-steroidals for controlling pain after excimer phototherapeutic keratectomy and photorefractive keratectomy (PRK). I have patients use a nonsteroidal once a day or twice a day for a short period of time. I am not sure it changes the outcome, yet patients seem very comfortable, without significant pain.

**Dr Pepose:** I use an NSAID preoperatively and intraoperatively for my LASIK patients, mostly for pain relief. It is also very important to assess and aggressively treat dry eye, ocular surface disease, and MGD in this cohort and to optimize the ocular surface prior to refractive surgery. At least 30% of these patients who come in with dry eyes are completely asymptomatic, so you really cannot rely on their history alone.<sup>49</sup> I do test tear osmolarity and perform vital dye staining on all these refractive surgery patients. I think it is very important to look at the lid because 70% of dry eye is probably from MGD.<sup>50</sup> Without treatment of dry eye prior to and following the LASIK procedure, many of these patients are setups for a less than optimal outcome.<sup>48</sup>

**Dr O'Brien:** One of the things that we must do when we detect ocular surface disease, blepharitis, dry eye, or ocular allergy, is to stop the refractive screening at that point. We should initiate aggressive treatment for 4 to 6 weeks and then reexamine the patient at a later date. Is that a strategy that we can use as a guideline?

**Dr Donnenfeld:** I agree completely. I use my "traffic light" analogy. If I see rose bengal red, lissamine green, or fluorescein yellow—the colors of a traffic light—all those tell me "Stop!"—Stop and Reassess. This cautionary step applies not only to LASIK but to cataract surgery as well.

**Dr O'Brien:** There has been controversy about the use of corticosteroids; our colleagues in Europe, in the early days, did not use corticosteroids in refractive surgery. Yet in the United States, the use of corticosteroids persisted beyond the FDA trials. Dr Lane, do you still use corticosteroids in surface ablations as well as in lamellar refractive procedures?

**Dr Lane:** Absolutely. With surface ablations, we are dealing with the same issues of pain and inflammation as with lamellar refractive procedures, but to an even greater extent, so it is really no different. The best treatment for pain and inflammation that we have available today are the corticosteroids. We have an array of options, depending on the severity of the inflammation and on the comorbidities encountered. It is important to emphasize that this is a younger population of patients that we are operating on, and the effect of some of the ketone steroids for induction of cataracts is not to be dismissed. The corticosteroid should provide a dual combination of potency and safety.

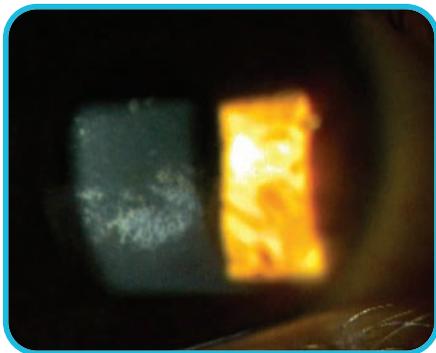
The nice thing, in contrast to cataract surgery, is that the inflammatory process is usually a lot shorter, especially with regard to lamellar refractive surgery. So my regimen for topical steroids in lamellar surgery is usually only about a week. With surface ablation, I will vary the length of treatment depending on the presence of comorbidities or the amount of ablation that takes place. Depending on the ablation, I can prescribe steroids for as long as 3 months (**Figure 3**).

**Dr Pepose:** In a review article, Dr Donnenfeld had pointed out the effect of corticosteroids on cell preservation; regarding surface treatment, we really want to limit the amount of apoptosis.<sup>51</sup> Keratocytes subsequently migrate in and are transformed into myofibroblast cells,<sup>51</sup>



**Figure 3.** Diffuse lamellar keratitis.

Photo Courtesy of Eric D. Donnenfeld, MD



**Figure 4.** Photorefractive keratectomy haze.

Photo Courtesy of Eric D. Donnenfeld, MD

and those seem to be associated with haze formation and, potentially, reticular scarring in some patients (Figure 4). I think there is definitely a role for corticosteroids in minimizing that effect.

**Dr O'Brien:** I think the consensus among our panel of experts here is that nonsteroidals certainly serve a potent analgesic role in preventing pain and are used pre-LASIK and at the time of the LASIK surgery.

For surface ablation procedures, many of us would continue a non-steroidal postoperatively. Corticosteroids have an important role in controlling both pain and inflammation, and their use will vary depending on the clinical circumstance.

### Experts' Regimens for Refractive Surgery Patients

Each of the panelists listed his individual treatment regimen for refractive surgery. The agents listed here are the preferences of each surgeon; the timeframe, or duration of the corticosteroid and nonsteroidal medications, may differ from the current FDA approvals for these agents.

#### For Routine Cases, Except Where Noted

##### Terrence P. O'Brien, MD:

- **Preoperatively:** Besifloxacin, 0.6% and polymyxin B/trimethoprim each 2 doses; bromfenac (or nepafenac) 1 dose for LASIK and PRK
- **During surgery:** Prednisolone acetate, 1%, besifloxacin, 0.6%, polymyxin B/trimethoprim and bromfenac each 1 dose
- **Postoperatively:** Prednisolone acetate, 1% qid and tapering over 1 month; besifloxacin, 0.6% bid for 1 week; bromfenac (or nepafenac) qd for 2 days, then discontinue. For PRK, now use loteprednol gel qid and tapering over 1 month

##### Stephen S. Lane, MD:

- **Preoperatively:** Moxifloxacin or besifloxacin just prior to the procedure
- **During surgery:** NSAID and moxifloxacin or besifloxacin immediately after the procedure
- **Postoperatively:** Loteprednol tid for a week with lamellar procedures; up to 3 months on a tapering schedule for surface ablation

##### Stephen C. Pflugfelder, MD:

- **Preoperatively:** LASIK: None. PRK: Bromfenac
- **During surgery:** LASIK: Prednisolone acetate at the conclusion of surgery
- **Postoperatively:** LASIK: Prednisolone acetate 1% every hour day of surgery, then qid for 1 week; PRK: fluorometholone, 0.1% qid for 2 weeks and bid for 2 weeks; bromfenac daily for 4 days

##### Jay S. Pepose, MD, PhD:

- **Preoperatively:** Moxifloxacin, loteprednol, bromfenac
- **During surgery:** Moxifloxacin, bromfenac, loteprednol
- **Postoperatively:** Moxifloxacin, loteprednol, or prednisolone acetate for LASIK

**For high-risk patients:** Same, with topical steroid given every 2 hours first day

##### Eric D. Donnenfeld, MD:

- **Preoperatively:** Loteprednol and cyclosporine for 2 to 4 weeks in patients with dry eye disease
- **Postoperatively:** Besifloxacin and difluprednate bid for 4 days. For PRK, loteprednol qid for 1 week, tid for 1 week, bid for 1 week, and qd for 1 week. Either bromfenac or nepafenac bid for 3 days

**For high-risk patients:** Patients who are health care providers pretreated with besifloxacin for 1 day prior to LASIK, add trimethoprim/polymyxin at the time of surgery to provide added protection against MRSA and MRSE

##### Paul M. Karpecki, OD

- **Preoperatively:** Treatment of dry eye disease, blepharitis, or MGD, if present and no significant improvement or resolution prior to pursuing surgery
- **Postoperatively:** LASIK: Besifloxacin qid for 4 days; loteprednol qid for 1 week, tid for 1 week, bid for 1 week, and qd for 1 week. PRK: Besifloxacin until reepithelialized; bromfenac qd for pain, and loteprednol qid for 1 week, then taper to tid for 1 week, bid for 1 week, and qd for 1 week

MRSA=Methicillin-Resistant *Staphylococcus Aureus*

MRSE=Methicillin-Resistant *Staphylococcus Epidermidis*

### Glaucoma Surgery and Inflammation

**Dr O'Brien:** What are some of the unique challenges we face with ocular inflammation with the patient having glaucoma surgery?

**Dr Pflugfelder:** Studies dating back approximately 2 decades show that inflammation on the ocular surface resulting from chronic use of preserved medications negatively affects the success of filtering surgery. Broadway and colleagues<sup>52</sup> showed that the number of preserved medications used correlated directly with filtering surgery success, and that the more medications the patient took, the greater the inflammation and the less successful the glaucoma surgery.

**Dr O'Brien:** Were the preservatives in those medications having a deleterious effect?

**Dr Pflugfelder:** Absolutely, I think that we are realizing that the majority of the toxicity from glaucoma medications is associated with the presence of BAK. For instance, regarding timolol, the use of a preservative-free preparation is much gentler on the ocular surface and induces less inflammation than use of a BAK-preserved formulation.<sup>55</sup> Therefore, I believe that in any glaucoma patient who may be a candidate for surgery, it is important to minimize drop toxicity and to attempt to treat any inflammation on the eye.

**Dr O'Brien:** What about some mechanical effects of the actual procedures themselves—the elevated filtering bleb or the hardware for filtration devices? Those have an effect on tear film dynamics. Do they promote inflammation postoperatively?

**Dr Pflugfelder:** Absolutely. A large bleb or a scleral or corneal patch over a tube shunt would definitely interfere with tear spread and tear dynamics. Often, a corticosteroid will help, and sometimes I will even judiciously use a nonsteroidal, at least for the pain component. Other times I will use special contact lenses to protect the area temporarily until the bleb decreases in size or can be surgically reduced in size.

**Dr Donnenfeld:** In patients who have been on chronic glaucoma medications, Tenon's capsule is filled with inflammatory cells from the glaucoma medications.<sup>54</sup> If possible, consider stopping the topical glaucoma medications before surgery for a few weeks and add a mild steroid that has potency without toxicity. I might also prescribe an oral glaucoma medication such as acetazolamide to control the pressure for those 2 weeks.

## Concluding Thoughts

**Dr O'Brien:** Dr Karpecki, please share some of the perspectives of optometry in perioperative management strategies.

**Dr Karpecki:** Because many optometrists have been following their patients for years or decades, they have a greater understanding of the patients' demeanor, their risk adversities, and history of disease. Many times patients are not good historians about their ocular diseases and often confuse terms like glaucoma, cataracts, and macular degeneration in family histories or even in themselves. So it is imperative that the optometrist who either co-manages or refers a cataract patient inform the surgeon of the existence of various disease states, ranging from a history of herpes simplex virus (HSV) keratitis to trauma or pseudoexfoliation, as well as making mention of certain medications the patient is taking that may affect the surgery.

## Focus in Primary Inflammatory Conditions

Dry eye, anterior uveitis, and allergy are inflammatory conditions that need to be managed, not only to optimize surgical outcomes, but also for the health of the eye.

## Update on Management of Dry Eye—Inflammation Control Strategies

**Dr O'Brien:** Dr Pflugfelder, as revealed through your and others' excellent seminal work, what is the evidence for inflammation playing a pivotal role in dry eye?

**Dr Pflugfelder:** Inflammation appears to be a component of every type of tear dysfunction. It may result from tear dysfunction or the unstable tear film itself by activation of the epithelial cells on the eye, causing them to produce a variety of inflammatory mediators, including cytokines, chemokines, and metalloproteinases.<sup>55</sup> In some patients, ocular inflammation may also result from systemic inflammation. Inflammation seems to play a key role both by its effects on the ocular surface epithelium as well as its effects on sensitizing nerves on the surface of the eye, which causes a heightened awareness of environmental stimuli and, in some cases, chronic pain.

**Dr Donnenfeld:** Dr Pflugfelder has done extremely important research establishing the inflammatory basis of dry eye disease. What needs to be emphasized is that this inflammation is occurring at a cellular level in the lacrimal gland and ocular surface. Many times these eyes appear white and quiet, while inflammation is creating significant damage.

**Dr O'Brien:** What do we know about blepharitis and its interrelationship with dry eye and inflammation?

**Dr Lane:** That is a complicated story. It is helpful to distinguish between anterior and posterior blepharitis for this discussion because posterior blepharitis, MGD, and meibomian gland disease certainly influence dry eye, but in a fundamentally different way than does an aqueous deficiency. You often see a combination of MGD and dry eye. Many times, the inflammation of the eyelid necessitates treatment followed by support of the eye with some of the more traditional treatments.

Lid treatments include lid scrubs, newer treatments like the LipiFlow®, and other ways of evacuating the gland completely to allow better flow

of normal meibomian gland secretions. The use of nutraceuticals such as omega-3 fatty acids is playing a more important role in the treatment of MGD.

**Dr O'Brien:** Does inflammation cause blepharitis? Or is inflammation a consequence of the blepharitis?

**Dr Pflugfelder:** Anthony J. Bron, Prof, at Oxford has suggested that changes in tear composition affect the lid margin and the meibomian gland orifices.<sup>56</sup> Changes in tear composition may also cause metaplasia of the duct opening, which obstructs the gland in MGD. I definitely subscribe to that theory.

**Dr O'Brien:** What about allergic conjunctivitis and the role it plays in dry eye, sometimes with the overlap syndromes?

**Dr Karpecki:** I am seeing a lot of allergic conjunctivitis patients lately in whom the symptoms may not necessarily be only itching, as we always think with allergy. Itching may be a secondary or tertiary complaint. The reason I think we see so much overlap of dry eye and allergic conjunctivitis is that there is a lot of dry eye in the general population, and patients with dry eye may not do as good a job of washing away allergens in the tear film or on the conjunctiva.

Secondly, treatment-wise, the majority of patients will try over-the-counter antihistamines, and research has shown that oral antihistamines can produce significant ocular drying,<sup>57</sup> which, in turn, exacerbates the dry eye issues. The third factor involved in the overlap of dry eye and allergic conjunctivitis is that inflammation is at the core of both conditions to a great degree and, consequently, many of the signs and symptoms of each condition can actually overlap.

## Managing Inflammation of Dry Eye, Blepharitis, and MGD

**Dr O'Brien:** Dr Pepose, how do you help differentiate, distinguish, and sometimes co-manage the comorbid states in these patients who have inflammation of the ocular surface?

**Dr Pepose:** As Dr Lane pointed out, many of these patients have combined disease. Probably the smallest fraction has a pure aqueous deficiency, and most have evaporative dry eye or some combination of both. There can be many other contributing factors, for example *Demodex* co-infestation, or bacterial overgrowth because the meibomian glands are obstructed. It is a cycle leading to more and more inflammation, ocular surface damage, dry eye disease with hypertonic tears at progressively hyperosmolar set points.

**Dr O'Brien:** In terms of helping establish the treatment regimen, are there point-of-care tests that can reliably assist in making a definitive diagnosis and thus steer us accordingly?

**Dr Lane:** I would not go so far as to say that there are tests that give us the definitive answer, but clearly there are some new tools that can assist us in our diagnoses. These tools provide confirmatory pieces of evidence that will help substantiate what we see clinically. We now have, for example, a tear osmolarity test. Given a constellation of symptoms, tear osmolarity testing is very helpful; I have found it particularly useful to repeat the test after initiating treatment. This can be a very powerful way to make sure that we are being guided in the right direction. We are also just now starting to get a feel for the lipid layer, as measured by the LipiView®, which can give information that will, again, help confirm what we see clinically.

**Dr Donnenfeld:** I agree that the clinical diagnosis of dry eye disease and MGD can be challenging. The new point-of-service tests, such as those for tear osmolarity, the biomarker MMP-9 levels, and the LipiFlow unit that quantizes the lipid layer of the tear film, provide important information that will allow clinicians to improve their diagnostic accuracy and will allow physician extenders to help in the diagnosis of ocular surface disease.

**Dr Pflugfelder:** I am certainly aware of the InflammDry™ test that will give semiquantitative measurement of the amount of MMP-9 in the tears; MMP-9 is known to be elevated in most types of tear dysfunction problems.<sup>46</sup> In the future, there will be other biomarkers for measuring inflammation of the ocular surface, and with that added

information, ophthalmologists and optometrists may be able to more precisely choose the most appropriate therapy.

**Dr Pepose:** We rely on tear osmolarity quite a bit because it is very tightly regulated at around 290 mOsm/L. When tear osmolarity begins to climb (osmolarity above 308 mOsm/L in 1 or both eyes and a difference of 11 mOsm/L between eyes is highly predictive of dry eye),<sup>58</sup> it is indicative of an unstable tear film. Tear osmolarity is often a very helpful metric to have in the office setting because you can show the patient an objective measurement of the treatment effects.

## Agents for Treatment

**Dr O'Brien:** How did immunomodulatory therapy, as developed in the Tear Film and Ocular Surface Society's International Dry Eye Workshop and in the American Academy of Ophthalmology treatment guidelines, evolve as a standard component for treatment of dry eye?

**Dr Pflugfelder:** Immunomodulatory therapy as a standard of care was based partly on observations of clinicians and partly on evidence from clinical trials. One randomized clinical trial of anti-inflammatory therapies is the cyclosporine A trial,<sup>59</sup> a meta-analysis that showed that cyclosporine A improved Schirmer test scores in a significantly greater number of patients than did vehicle.

Another trial<sup>60</sup> evaluating loteprednol showed improvement in ocular surface inflammatory signs and a significant decrease in central corneal fluorescein staining in the more severe patients. There have also been several recent trials looking at nutritional supplements containing omega-3 and omega-6 polyunsaturated essential fatty acids that have shown significant improvement in irritation symptoms, but regrettably no improvement in ocular surface signs.<sup>61,62</sup> Several trials have actually shown decreases in inflammatory mediators.<sup>63,64</sup> A few other trials are ongoing, including one on SAR 1118.<sup>65</sup>

Because of the amount of high-quality evidence, a number of panels have recommended the institution of anti-inflammatory therapy in the dry eye treatment scheme. Most of the panels, I think, have recommended institution at about a level 2 disease state, which is just when ocular signs begin to manifest.<sup>65</sup>

**Dr O'Brien:** That is a great historical overview establishing the precedent for use of cyclosporine A. Dr Karpecki, from the optometric perspective, where in the realm of severity do you and other optometrists introduce cyclosporine A?

**Dr Karpecki:** Clinicians are realizing that dry eye is a progressive disease, and that the condition will continue to advance in patients so affected. That does not mean that palliative therapies do not help with symptoms between therapeutic medication dosing, but they do not constitute a targeted treatment as do cyclosporine, corticosteroids, nutrition, and even oral doxycycline.

**Dr O'Brien:** Are there any downsides to treatment with cyclosporine? Is there a subset of patients in whom you want to avoid this therapy?

**Dr Pepose:** In my opinion, there are very few downsides to treating with topical cyclosporine. The biggest problem encountered, at least in my practice, has been adherence to long-term therapy because some patients stop using the drug, complaining that it stings. Refrigeration of the vials may help reduce that complaint. Along with cyclosporine, we have also prescribed concurrent topical steroids, another way to reduce the stinging and improve compliance. We have used loteprednol concurrently, or started with loteprednol and then added the cyclosporine.<sup>67</sup> The latter strategy seems particularly useful because the patient is first experiencing the beneficial effects of the corticosteroid, thereby increasing compliance, before getting the long-term positive effects of the cyclosporine in controlling inflammation and increasing tear production.

**Dr O'Brien:** What about patients with herpetic ocular disease? Where does cyclosporine fit for those individuals?

**Dr Pepose:** Generally, the reactivation of herpes simplex is a self-limiting event, particularly in patients without a history of prior HSV stromal disease; however, what causes significant visual loss is the inflammation. I think in the past we were afraid to use anti-inflammatories, but the Herpetic Eye Disease Study<sup>68</sup> has shown that there is a

role for corticosteroids in the treatment of herpetic stromal disease. There may be a role for cyclosporine as well because we have to manage the inflammatory component of stromal herpes simplex, although controlled studies remain lacking. These immunomodulatory drugs should be used concurrently with a topical and/or an oral antiviral.

**Dr O'Brien:** Any concerns with the label warnings or precautions relative to herpetic disease?

**Dr Pepose:** I think you have to explain to patients that using these anti-inflammatories for herpetic disease is an off-label use of the medications, but that the prescribing falls within the realm of the art of medicine.

**Dr O'Brien:** Dr Lane, how do you incorporate corticosteroids into the treatment algorithm for dry eye and in combination with other immunomodulatory agents?

**Dr Lane:** I think when Dr Pflugfelder's paper<sup>55</sup> was published, discussing the role of inflammation in dry eye, everyone's question was, What is the best anti-inflammatory medication we have available? The answer is topical steroids. Certainly you can use some of the immunomodulators, cyclosporine being the most widely available, but the onset of action of cyclosporine is often unacceptable for an acutely inflamed eye. You really can put out the fire quite rapidly with the use of topical steroids, and I do not hesitate to do that. I initiate treatment with topical loteprednol for a few weeks, then add in an immunomodulator like cyclosporine ophthalmic emulsion, 0.05%. I find cyclosporine is much better tolerated under those circumstances. Sometimes I will even use the lower dose (0.2%) of loteprednol because there has been a body of evidence showing that the 0.2% formulation of loteprednol can be used on a long-term basis without many side effects.<sup>69</sup>

**Dr Donnenfeld:** The only medication currently approved for the treatment of dry eye disease is cyclosporine. Many patients have had tremendous improvement in their disease, thanks to this innovation. Regrettably, many patients have not benefited because of premature cessation of their cyclosporine use, which requires 3 months of therapy to achieve an optimal effect. The incidence of burning and stinging, as well as the prolonged therapy, has resulted in many patients stopping therapy. The addition of concomitant immunomodulation with loteprednol increases the speed of onset of dry eye resolution as well as significantly reducing the incidence of burning and stinging.<sup>60</sup>

**Dr O'Brien:** Dr Karpecki, has this realization of the additive effects of a topical corticosteroid and an immunomodulator for helping gain control of inflammation on the ocular surface in dry eye patients been embraced among optometrists, and is the combination of a topical corticosteroid and an immunomodulator being widely used in the treatment algorithms?

**Dr Karpecki:** Yes. I think that research, including Dr Pflugfelder's paper, combined with the safety of loteprednol and the way that it works, really has changed all our practices. The most important thing, I believe, is the use of a corticosteroid as induction therapy. One benefit rarely mentioned is that the corticosteroid helps contribute to patient confidence in the prescriber. The moment patients get that relief, they accept my treatment plans. Then I move to cyclosporine and continue with that longer term because of its excellent safety profile and long-term efficacy.

The good thing about cyclosporine is that once it starts to have its effect, we can be assured of great long-term safety and, according to research, a significant effect on the goblet cell density. The 6-month data is quite compelling.<sup>70</sup> I think this combination, a corticosteroid and cyclosporine, is currently our most successful approach to managing dry eye disease or keratoconjunctivitis sicca (KCS).

**Dr Pepose:** I think there still is a role for antibiotics in some of these patients; those who have very bad MGD, for example, require combination therapy, not just an anti-inflammatory. They still require eyelid hygiene, and many of them do respond to either azithromycin or oral tetracycline derivatives, which may also have independent immunomodulatory effects. There also may be a role for dietary supplementation with omega-3 fatty acids. There is a multifaceted approach that I think needs to be adopted in many of these patients.

## Different Steroid Formulations for Use in Dry Eye

**Dr O'Brien:** Let us discuss the differences between suspensions and emulsions, drops and gels and ointments. How do we incorporate these different formulations in terms of their maximizing advantages and reducing disadvantages?

**Dr Lane:** Obviously the goal is to try to deliver an anti-inflammatory medication in a way that is well tolerated by the patient, yet provides maximum effect. We are beginning to have more powerful tools in our armamentarium now that gels have become a more common vehicle. The gel products allow us to increase contact time with the surface, much as an ointment, but without all the side effects, like messiness, blurring of vision, and difficulty of application. I am very excited about this gel vehicle for use in many of the medications we prescribe, not just steroids, but some of the others as well. I think we will also see the vehicle itself playing a favorable role as a lubricant to the surface. Ointments, however, do play an important role and probably are the best form of treatment for bedtime use. The other advantage that ointments offer is ease of use in children.

**Dr Karpecki:** By using ointment, for example, we can eliminate the preservative, or with gel, decrease the BAK coming into contact with the eye by a significant amount. When dealing with an ocular surface that is already compromised, there is benefit to using lower amounts of preservatives—say, loteprednol ointment at bedtime. The other big advantage with an ointment or a gel is that these formulations allow for dose uniformity. We could expect increased patient compliance and response, and thus better management of the ocular surface disease.

## What is the Role of NSAIDs in Patients With Dry Eye?

**Dr O'Brien:** Is there any role for ophthalmic nonsteroidal anti-inflammatory drugs in patients with dry eye?

**Dr Pepose:** There have been some studies of nonsteroidals as a primary drug for dry eye, but as of now, no agent has been FDA approved, for lack of demonstrating effectiveness in reducing both signs and symptoms of dry eye.

**Dr Pflugfelder:** I am a little reluctant to use nonsteroidals for several reasons. One reason stems from your work, Dr O'Brien, showing that certain nonsteroidals will increase production of proteases, which could lead to tissue destruction and even corneal perforation.<sup>71</sup> I have personally observed this with diclofenac use, but probably not with use of any other NSAIDs on the market. Further, some nonsteroidals may have some anesthetic effects, so they may actually decrease reflex-stimulated tear production in the long term.

## Value of Omega-3 and Omega-6 Fatty Acid/Nutritional Support in Dry Eye

**Dr O'Brien:** Do we have sufficient evidence to give our patients concrete recommendations on dosages or formulations of nutraceuticals and supplementary omega-3 and omega-6 essential fatty acids?

**Dr Pflugfelder:** Yes, there are a few randomized clinical trials showing their efficacy in dry eye.<sup>62,72</sup> The preparations that have shown some effect include a combination of omega-3s from fish oil and 1 omega-6 fatty acid called gamma-linolenic acid (GLA) found in evening primrose oil and black currant seeds. The trials that have actually shown a statistically significant reduction in irritation symptoms have used both omega-3 and omega-6 fatty acids.

A number of preparations on the market contain a combination of omega-3s and anti-inflammatory omega-6 fatty acids. I use them in my patients, especially those with MGD.

**Dr Sonnenfeld:** I have added omega-3 therapy to the treatment regimen of all my patients with dry eye disease and MGD. The evidence of the benefit of omega-3 on dry eye, macular degeneration, systemic cholesterol levels, heart disease, arthritis, and even Alzheimer disease is overwhelming. I prefer the newer-generation omega-3 therapies that have been purified to remove toxins and then converted back to a natural triglyceride form.<sup>73,74</sup>

**Dr Karpecki:** From my own clinical experience, dosing of omega fatty acid nutrition depends on a number of variables, such as the severity of the patient's ocular surface disease, the level of his or her nutritional intake, and whether the omega supplement is taken in combination, that is, GLA with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as opposed to taking only fish oil. I particularly find that dosing depends on the severity of the patient's MGD or the present state of the disease.

## How Can Ophthalmologists and Optometrists Work Together in Caring for Patients With Dry Eye?

**Dr O'Brien:** Dr Karpecki, is there common ground where ophthalmologists and optometrists can work better together to help provide improved care for our patients suffering from dry eye?

**Dr Karpecki:** More than ever, there is a need to understand how to best manage patients—to know when they require referral to ophthalmologists because of certain progressive diseases or for surgical procedures, or when they can be maintained in a primary optometric practice. Each discipline, ophthalmology and optometry, has certain strengths, and as long as the patient is maintained as the first priority, there always will be common ground. Furthermore, with the number of cataract surgeries expected over the next 17 years or so, it is imperative that the professions work together to provide adequate care for the baby boomer generation, who are at, or approaching, the age at which ocular disease is more prevalent.

**Dr Lane:** Collaboration between optometry and ophthalmology is important. Neither group of clinicians will be able to care for this very large group of patients alone. Working together, we have an opportunity to deliver excellent and widespread care to patients going forward.

**Dr Sonnenfeld:** I agree with Dr Lane. We have a model in our practice that works very well, with optometrists and ophthalmologists *together* providing an optimized care approach to patients with dry eye disease.

## Update on Management of Ocular Allergy

**Dr O'Brien:** Of those people who suffer with allergies, a high percentage of them experience ocular symptoms. An understanding of the allergic cascade of inflammation has helped us develop a more sophisticated multimodal approach to therapy. What is the role of antihistamines and mast cell stabilizers, either alone or in combination, to manage allergic inflammation on the ocular surface?

**Dr Pepose:** Here in St. Louis, we consider ourselves the allergy capital of the world: many of our patients have perennial allergies. There are numerous new medications available now with enhanced dosing for patients. In the past, compliance was a major problem, but now we have topical antihistamines with once-a-day dosing that has helped improve adherence to treatment regimens.

**Dr O'Brien:** Does anyone on the panel prefer the combination products? Or would someone rather break down the elements for those patients who suffer from both seasonal and perennial allergies?

**Dr Pepose:** I prefer the combination products. I think the dual-acting antihistamine and mast cell stabilizer agents can act on both early and late phases of ocular allergy, and their rapid action leads to better compliance. They are more effective than the earlier generations of antihistamine/vasoconstrictor combination products.

**Dr O'Brien:** Dr Lane, is there a place for ophthalmic corticosteroids in treating allergies, and if so, how do you use them?

**Dr Lane:** I think that there is a role for corticosteroids, but as in the treatment of MGD and other forms of dry eye, that role is not necessarily as stand-alone treatment. Corticosteroids are certainly the best treatment during a severe allergic reaction to gain relief for the patient. Afterward, treating with some of the mast cell inhibitors and antihistamines allows a higher safety margin than does treating with corticosteroids long term.

**Dr O'Brien:** That is a good point. Here in Florida, and in other places, I assume, where we have a year-long allergy season, we have to use a corticosteroid acutely to bring the inflammation under control; we then implement a maintenance program to provide relative quiescence of the allergy. Can nonsteroidals play a role in managing allergy?

**Dr Pflugfelder:** One study showed that ketorolac was effective<sup>75</sup> and it does have an indication for treating allergy. I am not sure if ketorolac is at the top of most prescribers' lists of medications to treat allergy, because it does not directly decrease histamine release from mast cells, but may have secondary effects on production of lipid inflammatory mediators and itch symptoms. I also usually use a combination mast cell stabilizer and antihistamine, and then if the patient becomes more symptomatic, move to pulse corticosteroid.

**Dr O'Brien:** Dr Karpecki, you mentioned the exacerbating factor of systemic antihistamines and anti-allergy medicines. How do you manage this in your patients who are using systemic medications?

**Dr Karpecki:** Looking at the overall allergy treatment market, I think there is approximately \$6.2 billion<sup>76</sup> spent on oral allergy medications, including sprays and inhalers, but only \$500 million spent on topical ophthalmic medications. It appears that ocular medications are underutilized and that people naturally will go to the systemics first before even considering topical ophthalmic medications or visiting an eye specialist.

You can expect most patients to self-treat on oral antihistamines. The drying effects are very substantial, and many of these patients have dry eyes. I often recommend that the patient discontinue the oral antihistamine for approximately a week or 10 days and then consider restarting after the ocular surface has improved on therapy. I have found that many times the topical drops, especially the combination-agent drops, will relieve many of the systemic or nonophthalmic symptoms as well.

If there are symptoms such as chemosis or lid edema present, steroids, in my opinion, are the more effective medications. After induction with a steroid, I will prescribe the combination agent later for the longer term.

### Update on Management of Anterior Uveitis

**Dr O'Brien:** Dr Pepose, you are a long-time member of the American Uveitis Society. What are the unique challenges in managing patients with anterior uveitis, and what are some of the differences in how topical corticosteroids are used in anterior uveitis?

**Dr Pepose:** When you are treating patients with anterior uveitis, particularly acute onset autoimmune uveitis, you have to pulse them to treat the inflammation. Frequent dosing with a potent corticosteroid is generally accepted as the first step of therapy in patients with noninfectious uveitis.<sup>50</sup> There is some work being done now to look at other drug delivery modalities for these patients, for example, iontophoresis.<sup>77</sup> I think that pulsing seems to have less of an effect on IOP than treating on a chronic basis with high-dose steroids.

**Dr Lane:** I, too, believe in treating uveitis aggressively. I often begin treatment with a subtenons injection of 1 cc of betamethasone, especially in cases of human leukocyte antigen-B27 uveitis. Hourly difluprednate is also prescribed and used until a decrease in inflammation is noted. If an IOP pressure spike occurs, I do not hesitate to add pressure-lowering agents without a change in the frequency or type of steroid used.

I then taper difluprednate and, as the inflammatory process recedes, I often substitute loteprednol to improve the safety margin. I then taper the loteprednol.

**Dr O'Brien:** It is important to remember that an aggressive pulse to gain control rapidly and efficiently is better than managing the inflammation sporadically, thus allowing it to proceed unchecked. Once unchecked, it is very difficult to bring the inflammation under control and then to maintain it with lesser agents that have fewer side effects.

**Dr Pepose:** We can learn a lot from work in cataract patients. Chang and colleagues<sup>41</sup> conducted a very interesting study in which they looked at cataract patients who were treated with corticosteroids. They found that there were 2 subsets of patients who were more likely to have a rise in IOP—the younger patients, and the patients with axial length greater than 25 mm. We should keep this subset of patients in mind for IOP concerns when we treat other patients with corticosteroids.

**Dr Donnenfeld:** I do not believe we are aggressive enough in our management of uveitis. In systemic medicine, inflammation is managed through pulsed aggressive therapy and then tapered rapidly. We should do the same in ophthalmology. I start my treatment with difluprednate, which has been shown to be more effective than other therapies,<sup>50</sup> and then taper down to loteprednate as quickly as possible.

## Anti-Inflammatory Agents on the Horizon

Agent	Manufacturer	Description	Indication
Bromfenac ophthalmic solution (low-concentration)—concentration not made public at press time	Bausch + Lomb	A lower concentration of bromfenac than the currently available once-daily 0.09% (bromfenac ophthalmic solution) in a new formulation. Phase 3 studies demonstrated statistically greater clearing of subjects' ocular inflammation by day 15 than in the placebo group (49.1% vs 31.8%, respectively), and a greater proportion of patients were pain free 1 day postoperatively than with placebo (76.4% vs 55.5%, respectively). <sup>78</sup>	Treatment of ocular inflammation and pain associated with cataract surgery
Dexamethasone phosphate formulated for ocular iontophoresis (EGP-437)	EyeGate Pharma	Ocular delivery of dexamethasone phosphate utilizing cathodic iontophoresis with an inert electrode to provide adequate therapeutic steroid levels in the anterior segment in patients with chronic KCS. In phase 2 research, ocular iontophoresis of EGP-437 demonstrated statistically and clinically significant improvements in signs and symptoms of dry eye syndrome. <sup>79</sup>	Treatment of chronic dry eye
Dexamethasone delivered via Verisome injection (IBI-10090)	Icon Bioscience	A biodegradable product for injection of dexamethasone into the anterior chamber to treat inflammation associated with cataract surgery. <sup>80</sup>	Eliminates the need for anti-inflammatory eye drops in patients undergoing cataract surgery
Lifitegrast (SAR 1118 ophthalmic solution, 5.0%)	SARcode Bioscience	A small-molecule integrin antagonist that inhibits T-cell inflammation by blocking the binding of 2 key surface proteins (LFA-1, ICAM-1) that mediate the chronic inflammatory cascade associated with dry eye disease. In a phase 2 randomized, placebo-controlled trial of 250 subjects with dry eye disease, SAR 1118 demonstrated significant improvements in both signs and symptoms of dry eye in as early as 2 weeks. It was well tolerated and ocular adverse events were mostly mild, transient, and related to initial instillation of the drug. <sup>81</sup> Phase 3 study currently under way.	Treatment of ocular inflammatory conditions, including dry eye
Mapracorat ophthalmic suspension, 3%	Bausch + Lomb	A selective glucocorticoid receptor agonist (SEGRA), a new class of potent anti-inflammatory agents, structurally and functionally distinct from steroids and NSAIDs. <sup>82</sup> Preclinical studies demonstrated anti-inflammatory efficacy similar to dexamethasone for dry eye and postoperative inflammation, with reduced effects on IOP and muscle wasting. <sup>83</sup>	Treatment of inflammation in dry eye and following cataract surgery
Nepafenac, 0.3%	Alcon	Once-daily dosing of nepafenac, 0.1% dosed 3 times daily. <sup>84</sup>	Prevention and treatment of ocular inflammation and pain after cataract surgery

**Dr Karpecki:** I think nighttime inflammation coverage deserves emphasis. I prefer a stronger corticosteroid (difluprednate) during the daytime. Adding in loteprednol ointment at night gives more than sufficient coverage. It is also my belief that with uveitis, overnight treatment seems to show a significant effect on anterior chamber cell and flare reduction when used with daytime corticosteroid drops and cycloplegic agents.

## 5 Anterior Uveitis Rules for Collaboration Between Ophthalmologists and Optometrists

1. Rule out keratouveitis, such as an infectious ulcer causing the iritis.
2. Check the IOP; higher pressures are more common in iritis secondary to viral conditions such as herpes zoster or herpes simplex.
3. Rule out previous ocular surgery as an increased anterior chamber reaction after a previous surgery (cataract or trabeculectomy, for example) could signify endophthalmitis and require a referral to the surgeon or a retina specialist.
4. Gauge the systemic workup. If there is anything to suggest that the cause of uveitis may be systemic (such as keratic precipitates, recurrence, bilateral presentation, or a hypopyon), it is necessary to involve the appropriate physician for co-management.
5. Treat aggressively or treat boldly.

**Dr O'Brien:** I think we all agree that it is extremely important to identify these patients preoperatively, consult with specialists in ocular immunology/uveitis, and co-manage with rheumatologists and immunologists as needed. The aggressive approach to prevention and control of inflammation in these patients with uveitis is essential to achieving satisfactory outcomes and avoiding complications. Hopefully, newer formulations of existing anti-inflammatory agents and development of anti-inflammatory agents with novel mechanisms of action will further assist in achieving these objectives on behalf of our patients.

## Patient Education

*Dear Readers: This template can be used to create your own Patient Education brochure. It can be customized to suit your practice's needs.*

### Eye Inflammation

Ocular inflammation is nature's response to some kind of injury or irritation to a part of your eye. Some eye procedures naturally cause inflammation, which goes away with care after the procedure. Or, you may have eye inflammation from problems such as "dry eye" or "eye allergy".

Your doctor has recommended that you take certain medications to treat eye inflammation. It is important to follow your doctor's advice so the inflammation can get better. If inflammation continues, you may develop problems with your vision.

### Guidelines

- Tell your eye doctor about all medications—prescription, non-prescription, vitamins, and herbs—that you are taking
- Keep all appointments
- Write down your questions in between visits so you can remember to ask them at your next visit
- Bring your prescribed medications to each postsurgical visit
- If your pharmacist dispenses a generic nonsteroidal medication, you can ask for the branded medication
- **Take your medications as prescribed by your eye doctor.** If you tend to forget or cannot take your medications as your doctor told you to, please tell him or her. It is better that your doctor and the staff know you are having problems taking your medication. They will help you to find a way to take the medications you need.

You have been prescribed (name of agent here)

Picture of agent

Why agent is prescribed: \_\_\_\_\_

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## Prevention and Management of Ocular Inflammation Across the Ophthalmic Spectrum

**Ophthalmologists:** To obtain AMA PRA Category 1 Credit™ for this activity, you must 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 [www.MedEdicus.com](http://www.MedEdicus.com), Educational Activities tab, and click the Post Test button.

**Optometrists:** To obtain COPE credit for this activity, you must complete the CE Post Test online at [www.MedEdicus.com](http://www.MedEdicus.com). Listed below are the questions you will be asked on the online post test.

- How does the occurrence of postcataract cystoid macular edema (CME) compare with the occurrence of postcataract endophthalmitis?
  - CME occurs less often than endophthalmitis
  - CME occurs more often than endophthalmitis
  - CME occurs equally as often as endophthalmitis
  - CME always occurs to some degree whereas endophthalmitis occurs only occasionally
- A 60-year-old man undergoes uneventful cataract extraction. One month after the surgery, the patient can read only 20/30 with coaxing and notes that his vision is "different" from that before the surgery. His examination in the office is within normal parameters. What should you consider as a likely cause of the visual changes?
  - Posterior capsular opacity
  - Retinal detachment
  - Subclinical CME
  - Dislocated intraocular lens
- Conditions that may increase the risk for ocular inflammation and the development of CME after cataract surgery include:
  - Diabetes
  - Uveitis
  - Miosis secondary to use of alpha-1 inhibitors
  - All the above
- Nonsteroidal medications interact in the inflammatory pathway by:
  - Inhibiting phospholipase A
  - Blocking production of lipid mediators such as prostaglandins
  - Blocking intracellular signaling pathways
  - All the above
- Difluprednate has been shown to be as efficacious as prednisolone acetate:
  - With fewer doses per day
  - When used in a pulsed-dose regimen
  - For treatment of uveitis
  - All the above
- According to multiple studies, loteprednol has shown efficacy \_\_\_\_\_ prednisolone with \_\_\_\_\_ rates of intraocular pressure (IOP) elevation in treating inflammation.
  - Greater than, lower
  - Similar to, lower
  - Similar to, similar
  - Lower than, lower
- A study by Chang and colleagues found that specific patients were more likely to develop IOP elevations when treated with corticosteroids after cataract surgery. Those patients are:
  - Those with axial length longer than 23 mm
  - Younger patients and those with axial length greater than 25 mm
  - Those with no history of IOP elevation
  - Those with glaucoma
- Tests that are regularly used to help identify patients with ocular surface disease before refractive surgery include:
  - Schirmer tear test
  - Fluorescein dye staining
  - Tear break-up time
  - All the above
- A 30-year-old woman comes into your office interested in having LASIK surgery. She has no history of dry eye. She would also like the procedure completed as soon as possible; she is in an upcoming wedding party. During the initial evaluation, you notice cuffs and flakes on her eyelashes, with reddened eyelid margins. The best course of action is:
  - Prescribe artificial tears and perform the procedure in a week's time when you can schedule it
  - Schedule the procedure for the next available appointment
  - Treat the blepharitis for 1 month, reevaluate, and then schedule the surgery
  - Refuse to perform the surgery
- Corticosteroids may play a role in preventing \_\_\_\_\_ after refractive surgery.
  - Pain
  - Corneal haze
  - Reticular scarring
  - All the above
- Epithelial cells may create a variety of substances that can cause inflammation, such as:
  - Cytokines
  - Chemokines
  - Metalloproteinases
  - All the above
- The management of meibomian gland dysfunction (MGD) includes a number of tactics, including:
  - Thermal pulsation (ie, Lipiflow®)
  - Lid scrubs
  - Omega-3 fatty acids
  - All the above
- Some reasons that patients with allergic conjunctivitis may also present with dry eye symptoms are:
  - The lack of tears may decrease the ability to wash away allergens
  - Over-the-counter antihistamines have a drying effect
  - Inflammation plays a role in both conditions, leading to some overlap
  - All the above
- When the tear osmolarity increases above \_\_\_\_\_ mOsm/L, a diagnosis of dry eye is highly likely.
  - 256
  - 290
  - 300
  - 308
- You diagnose a patient with severe dry eye. Several studies have noted that patients may be more compliant with the proposed cyclosporine A therapy if you start \_\_\_\_\_ first.
  - Artificial tears
  - Corticosteroids
  - Half-dose of cyclosporine A
  - An antihistamine
- Supplements that have been shown to be effective in the treatment of dry eye disease include:
  - Omega-3 fatty acids
  - Ginkgo biloba
  - Grape seed extract
  - No nutraceuticals have shown any beneficial effect in the treatment of dry eye
- Which statement best reflects the utility of anti-inflammatory agents for ocular allergy treatment?
  - Use of 2% loteprednol has a documented acceptable safety profile for long-term use
  - Mast cell inhibitors and antihistamines allow a high safety margin for long-term inflammation control
  - The NSAID ketorolac affects lipid inflammatory mediators and relieves itch symptoms
  - All the above
- A woman with a history of allergies presents to your clinic with complaints of burning, tearing, and ocular redness. She has a history of dry eye, but had been comfortable with the use of artificial tears. What could be causing her additional complaints?
  - Oral antihistamine use
  - Mast cell stabilizers
  - Oral decongestants
  - None of the above
- A patient has anterior segment inflammation; after a workup, you diagnose anterior uveitis. Which method of treatment will have less effect on IOP?
  - Subtenon depot of corticosteroid
  - Pulse dosing of corticosteroid
  - Corticosteroid dosed every hour
  - None of the above; all will increase IOP equally
- Which of the following agents in development have promising results for the treatment of chronic dry eye?
  - Integren agonist (lifitegrast)
  - Dexamethasone for iontophoresis
  - Selective glucocorticoid receptor agonists (SEGRA)
  - All the above

# Prevention and Management of Ocular Inflammation Across the Ophthalmic Spectrum

Original Release: November 1, 2012  
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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 **The New York Eye and Ear Infirmary–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.

**PARTICIPANT INFORMATION** (Please Print)  Home  Office

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- Yes  No I and/or my family member have a financial relationship with **The New York Eye and Ear Infirmary** and/or refer Medicare/Medicaid patients to it.  
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Signature Required \_\_\_\_\_ Date Completed \_\_\_\_\_

**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:

• Demonstrate application of best-practice regimens for reducing inflammation risk for cataract, refractive, and glaucoma procedures	5	4	3	2	1
• Demonstrate application of best-practice regimens for inflammation management of primary conditions of dry eye, blepharitis, ocular allergy, and anterior uveitis	5	4	3	2	1
• Recognize ophthalmic anti-inflammatory therapies currently in development	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
11	12	13	14	15	16	17	18	19	20

