Ophthalmologists are beginning to turn to non-steroidal, anti-inflammatory drugs (NSAID) on many occasions. These can be helpful with a number of different goals in ophthalmic surgery such as inhibiting and treating cystoid macular edema (CME), preventing intra-operative miosis, and managing post-operative inflammation, pain, and discomfort. As a consequence, NSAIDs can provide an important adjunct in our prophylactic regimens.

Part of the reason they are such a powerful addition to our armamentarium is that the mechanism of action for these drugs is different from that of steroids. With NSAIDs, the inflammatory cascade is inhibited at the cyclooxygenase step whereas with the steroids this occurs more superiorly, at the phospholipase A2 level (Figure 1). That's why the two are synergistic in the treatment of post-operative inflammation.

CME prophylaxis

CME concerns us all. Some of the risk factors for CME include pre-existing intraocular inflammation, epi-retinal or vitreoretinal interface membrane problems and diabetic retinopathy. Many practitioners also select NSAIDs for patients who suffer from other ocular cardiovascular diseases or from retinitis pigmentosa.

For high-risk patients, such as these, prophylaxis should be started earlier and maintained for longer periods.

It is believed that CME that occurs following cataract surgery is a result of intraocular inflammation. It has also been hypothesized that the aging process is a contributing factor, as well as systemic vasculopathy and glaucoma.

These risk factors potentially can foster CME at the time of surgery because of breakdown of the blood aqueous barrier and liberation of prostaglandins in the aqueous and vitreous that occurs following an intraocular insult.

The prevention of CME with ophthalmic NSAIDs has been shown to have beneficial visual results making this an important prophylactic measure. To maximize the effects of the NSAID, it's critical to obtain adequate concentrations in the posterior chamber.

It is important to note that in various studies NSAIDs have been shown to be a much more effective treatment and prophylactic agent against CME than are topical steroids. Steroids alone really don’t effectively prevent or treat CME.

To effectively prevent CME pre-operative dosing is typically one to three days for the routine patient, and is used more frequently and started earlier for those patients at higher risk.
risk such as those with diabetic retinopathy. This helps to blunt the onset of that inflammatory cascade.

Administration should also be used immediately pre-operatively to prevent surgically-induced miosis.

Post-operatively, NSAID therapy should be maintained for three to four weeks for routine patients, but may be used for longer periods of time in those who are at high risk. (Figure 2)

Because CME can be a late onset event, especially in high-risk cases therapy may need to be extended beyond the usual two to three week period.

Ultimately, the ideal NSAID is one that penetrates the target intra-ocular tissues at therapeutic levels in both the aqueous humor and in the posterior chamber.

It needs to have excellent anti-inflammatory efficacy and analgesic properties, and it certainly needs to be cornea-friendly and comfortable for the patient to use.

**New horizons in NSAID therapy**

A new NSAID known as Nevanac suspension (nepafenac 0.1%, Alcon, Fort Worth, Texas) may help us attain our prophylactic and treatment goals. Nevanac suspension, formulated in a 0.1% concentration, is seeking an FDA indication for the treatment of inflammation and pain following cataract surgery. If approved, it will be the first and only prodrug non-steroidal anti-inflammatory agent.

It is Nevanac suspension’s unique prodrug formulation that may enable practitioners to maximize the efficacy of NSAIDs.

The prodrug target-specific nature of Nevanac suspension will provide enhanced intraocular penetration, optimal distribution at the various target sites, and a longer duration of action in both the cornea and anterior chamber, and in the retina choroid.

The drug quickly penetrates the ocular tissues due to the prodrug structure.

What happens with Nevanac suspension is that while having efficacy on the surface of the cornea as it penetrates, the drug is intracocularly converted from nepafenac to amfenac (Figure 3). Very high levels of amfenac are then attained in the aqueous, retina, and choroid.

As a result of Nevanac suspension’s ability to rapidly penetrate the eye, surface accumulation is minimized, thus maximizing safety and comfort.

On the other hand, conventional NSAIDs typically penetrate the cornea and intra-ocular tissues at a much slower rate than nepafenac (Figure 4), thus providing reduced intra-ocular levels of the drug in the retina and choroid, the target sites for CME prevention.

There is also minimal systemic absorption with Nevanac suspension — 1,700 times less than the oral medication, which has been proven safe.

Two large, multi-centered, randomized clinical trials indicate that Nevanac suspension dosed three times per day, in the absence of steroid therapy, is effective in controlling pain and post-operative inflammation associated with cataract surgery.6,7

More than 80% of patients treated with Nevanac suspension were pain free on day one, compared to only 40% to 50% in the placebo group.

By day 14, approximately 95% of patients were pain free when treated with the drug, compared to 45% to 60% of patients in the placebo group.

Results for inflammation control were similarly positive, as greater than 85% of patients treated with Nevanac suspension had no clinically significant inflammation at day 14, compared to approximately 47% of patients in the placebo group.

These efficacy measurements of inflammation and pain were statistically significant. Nevanac suspension was safe and well tolerated in both clinical studies.

In addition, in a randomized, 60 patient, multicenter study investigators evaluated the analgesic effect of Nevanac suspension against that of Voltaren (diclofenac sodium, Novartis, Basel, Switzerland) for the reduction of pain and photophobia following PRK.8 Investigators found that Nevanac suspension was able to provide an equivalent effect at all time points as compared to Voltaren in patients who underwent PRK.

Nevanac suspension’s safety has been confirmed in multiple studies, as the prodrug appears to have an extremely low potential for ocular surface toxicity.9,10 Even when dosed for six months at concentrations 15 times its commercial formulation, nepafenac did not show signs of ocular or systemic toxicity.

Additionally, during the clinical trials continued on page 4.
For the past five to 10 years, fluoroquinolones have become the standard when it comes to keeping ocular infections at bay. They surpass other antibiotics due to their broad spectrum of activity, wide safety margin, and excellent pharmacokinetics. Fluoroquinolones also have excellent pharmacodynamics and kill very rapidly.

With older fluoroquinolones, practitioners had to contend with the emerging problem of resistance. Bacterial isolates have shown increasing resistance to these drugs. Our ocular microbiology laboratory, the Charles T. Campbell Eye Microbiology Lab, University of Pittsburgh Medical Center, reported that as of 2002, just 40% of Staph. aureus isolates remained susceptible to older fluoroquinolones in endophthalmitis cases.

It was this emerging resistance that brought about the evolution of the current fourth-generation fluoroquinolones, moxifloxacin and gatifloxacin (Zymar, Allergan, Irvine, Calif.). These now offer an extended spectrum of activity, including anaerobes and atypical mycobacteria. They also offer enhanced activity against gram-positives such as streptococci and the resistant gram-positives, and they offer improved pharmacokinetic properties.

The real advantage of these fourth-generation fluoroquinolones is the addition of the 8-methoxy group into their molecular structures. This has markedly extended the spectrum to include more gram-positive organisms, which are the primary cause of post-operative, post-cataract surgery infections.

In addition, moxifloxacin has a unique bicyclic side-chain at the C-7 position. This addition was specifically engineered to further enhance potency and slow the development of resistance. (Figure 1)

Assessing the fourth-generation agents: Potency and penetration

One way to evaluate these new antibiotics is to consider their potency. To assess this, we look at the minimum inhibitory concentration (MIC), which is the minimum amount of drug necessary to inhibit bacterial growth.

Within a class, we are looking for the antibiotic that has the lowest MIC or, in other words, the least amount of antibiotic that will inhibit the growth of bacteria. Potentially, such a drug will kill more bacteria and, theoretically, is less likely to induce resistance. This is a very important characteristic when we think about selecting a drug for prophylaxis.

Other factors to consider in selecting an antibiotic for prophylaxis are the minimum bactericidal concentration (MBC) and the mutant prevention concentration (MPC). The MBC is typically three to four times the MIC and usually causes 99.9% eradication of bacteria. The MPC is the concentration that prevents mutation. This is typically somewhere between four and 10 times the concentration of the MICs. (Figure 2)

In addition to a drug’s potency, we want to be sure that the antibiotic we choose maintains its efficacy at the key intraocular target sites, the cornea, and the anterior chamber.

“The greater the antibiotic’s concentration above its MIC against the most common infection-causing pathogens, the greater the degree of patient protection against infection. Our study demonstrated a proof of principle that topical antibiotic therapy could prevent bacterial endophthalmitis. This model has been attempted with other antibiotics; only moxifloxacin, however, has been shown to be capable of completely preventing endophthalmitis.”

Francis S. Mah, M.D.
We know that the pathogens which cause endophthalmitis are primarily gram-positive organisms and, therefore, we really have to be concerned about covering these organisms.

A recent study by R. Mather, et. al. published in a 2002 issue of the American Journal of Ophthalmology showed that when it comes to combating endophthalmitis isolates, the fourth generations are superior to levofloxacin, ciprofloxacin, and ofloxacin. 

When we consider just the resistant isolates such as the coagulase negative staphylococci, which cause 70% of endophthalmitis cases, and Staph. aureus, which is the second largest group of pathogens causing endophthalmitis, the difference becomes even more pronounced.

The study also concluded that, concerning the fourth-generations alone, moxifloxacin is more potent than gatifloxacin for gram-positive bacteria, and both are equally potent toward gram-negatives.

**Pharmacodynamics**

We must also consider pharmacodynamics. Not only does the agent have to be able to eradicate in a scientific or experimental setting, but also you actually have to be able to get the antibiotic to the site of the infection or the site where you want to prevent the infection.

It is clear that the fourth-generation fluoroquinolones are potent and have decreasing MICs, which means that they fare better against pathogens. But do they actually get into the anterior chamber and into the cornea to prevent infection?

To help determine this, we used a model that we developed for endophthalmitis, dosing rabbit eyes just as we would using a very modest cataract surgery prophylactic profile.

This entailed dosing the eye with either four drops of moxifloxacin or four drops of saline one hour before the injection of a clinical isolate of *Staph. aureus* which caused a case of endophthalmitis.

We then continued to dose the eye four times a day for a 24-hour period as a prophylactic model.

In the moxifloxacin group, there were zero clinical signs of endophthalmitis versus 100% of saline treated eyes as graded by two ophthalmologists using a masked protocol. (Figure 3)

The cultures also showed that the eyes treated with the moxifloxacin had no sign of endophthalmitis, while 50% of saline-treated eyes had positive cultures in the anterior chamber, and 30% had positive cultures in the posterior chamber.

In order to do so, the antibiotic’s ability to penetrate these tissues is key: The greater the antibiotic’s concentration above its MIC against the most common infection-causing pathogens, the greater the degree of patient protection against infection.

**The pathogens**

In prophylaxis it is crucial that we consider which pathogens are most likely to affect our patients, and use those drugs that provide the best coverage.

The gram-positive bacteria that are the normal flora are a significant pathogen with post-LASIK keratitis — so these cannot be forgotten.

Atypical mycobacteria, a unique pathogen of post-LASIK keratitis, is an opportunistic organism and particularly difficult to eradicate.

In addition, we’re always concerned about endophthalmitis. While post-surgical endophthalmitis rates vary, I think most people would consider the rate to be close to about one in 1,000.

This unique target-specific formulation will increase the efficacy and the tolerability in prophylactic therapy compared to conventional NSAID regimens. Finally, I believe Nevanac suspension will bring about a paradigm shift in the way we think about NSAIDs that will influence our prophylactic treatment regimen following intraocular surgery, and which will help us maximize clinical outcomes for our patients.

The nightmare for all cataract surgeons is the rare, but devastating, introduction of a microorganism at or about the time of ocular surgeries.

Despite technological advances, the feared outcome of endophthalmitis appears to be on the rise with cataract surgery. The role of periocular flora has been documented in a number of eloquent molecular microbiologic studies, and the enemies of the cataract surgeon are the microbial players on the surgical scene.

Even with modern, technologically advanced cataract surgery, if we sample the anterior chamber fluid at the conclusion of the procedure, we will be surprised at the number of positive culture results that may occur. It is likely that the type of surgical approach selected may also play a role. Since I. Howard Fine (M.D., Ph.D.), reintroduced clear corneal incisions in the early 1990s, there has been an evolving preference for this approach.

While there are many benefits to the use of clear cornea incisions, there are also potential concerns that bacteria may gain entry through these incisions.

We now have some evidence based upon the experiments of Peter McDonnell, (M.D.) and colleagues to show that fluid can indeed leak into the eye, especially if there is transient, post-operative hypotony.1 Using India ink as a larger surrogate for microbes, the investigators demonstrated that particles can travel from the cornea surface into the incisions and even into the aqueous humor. (Figure 1)

Strategies to prevent endophthalmitis

There are a few strategies that have emerged that work to prevent post-operative endophthalmitis.

The first is to limit the number of organisms that enter the eye by decreasing contamination with organisms on the ocular surface, thereby preventing intra-operative bacterial contamination.

Moreover, surgeons should carefully construct and ensure that the wounds are watertight so that surface fluid cannot leak into the eye.

One of the prophylactic mainstays is to place topical, dilute povidone iodine 5% directly on the ocular surface. The iodine moiety is rapidly microbicidal, usually working within 30 seconds of application not only on bacteria but also on fungi and viruses, including HIV.

Mechanical factors are also important in preventing endophthalmitis. Sequestering the cilia from the operative field with the use of adhesive draping and other measures are important adjunctive methods to discourage discontamination.

The second major strategy is to try to eradicate those organisms that may have gained entry into the eye. Evidence suggests that topical fluoroquinolones may play an important role in eradicating organisms at the intraocular target sites.

continued on page 7
Surgical prophylaxis in corneal and refractive surgery

by Edward J. Holland, M.D.

With elective procedures, such as refractive surgery, the bar for avoiding infection must be set higher than ever. In these refractive cases microbial keratitis is one of the most devastating complications that patients may face.

With severe infections there can be flap necrosis, stromal scarring, and visual loss — this occurring in a group of patients who probably have the highest expectations of any that we treat.

There are basically two types of clinical infections that develop in refractive surgery. There’s the early infection that occurs within the first week. This typically is the result of the gram-positive organisms.

Then, there’s that late opportunistic infection with which to be concerned — which develops as a result of mycobacteria and fungus. In 2001 there was a mini-epidemic of mycobacterium as well as some cases of fungus.

The corneal clinical committee of the American Society of Cataract and Refractive Surgery conducted a LASIK infection survey in 2001, and then repeated it in 2004. The findings were extremely interesting.

The 2001 survey results indicated that approximately 50% of all the serious infections in LASIK were due to atypical mycobacterium. These data reflected what was reported in the literature. The next largest group of causative pathogens was the gram-positive bacteria.

But in 2004, survey respondents reported something very different. Almost all the mycobacterium infections had been eliminated. Currently, the infections that we see are the gram-positive organisms, with only a very few cases of atypical mycobacterium.

The differences between the two surveys (2004 vs 2001) may be attributed to the introduction of the fourth-generation fluoroquinolones.

Indeed, the few cases of mycobacterium in the 2004 survey involved those patients who were not prescribed a fourth-generation fluoroquinolone.

Strategies to prevent infection

An important strategy to circumvent infection in refractive surgery is to identify those patients who might be at risk.

Patients at risk would include those who have ocular surface inflammation and an unstable ocular surface from blepharitis and dry eye. Also, patients with epithelial disease are at risk.

We’re very careful to try to identify patients with epithelial basement membrane dystrophy (EBMD).

Of course, it’s easy to see the patients with large macrocysts or large geographic areas, but you also want to be careful to find those patients with subtle microcysts or history of recurrent erosions.

Cases of occult EBMD may also be troublesome. In these cases, the ocular surface looks normal pre-operatively, but with the pass of the microkeratome, a large epithelial defect occurs.

We would consider not proceeding with the second eye in these cases until we know that that first eye has done well.

Dry eye patients are also at risk for microbial keratitis, and pre-op diagnosis and treatment are key. In evaluating the dry eye patient, it is important to look not only at

Figure 1 - Susceptibilities of Fluoroquinolones Endophthalmitis Isolates (% Susceptible)

Figure 2 - In regards to gram-positive pathogens, the peer-reviewed literature has documented that moxifloxacin has the lowest MICs of any of the currently available fluoroquinolones.
corneal staining but also the new conjunctival stains such as lissamine green. We also look at tear meniscus.

We’re also careful to listen to the patient about symptoms and signs of dry eye to help rule out individuals at risk before they move on to surgery.

In cases where you have a patient with an unstable ocular surface, think about postponing surgery.

Lid hygiene can help in these patients, as well as use of oral doxycycline (various manufacturers) and antibiotic ointments which should be given until the meibomian gland function is normalized, the tear function is improved, and surface inflammation is reduced.

In addition, pre-operative use of non-pre-served artificial tears, topical cyclosporine (Restasis, Allergan, Irvine, Calif.), and punctal occlusion are also important.

Once we decide to proceed with refractive surgery, intra-operatively it is key to treat these patients as much as we can as though they were in an operating room. I recommend a betadine prep around the eye, and careful lid draping to isolate not only the lashes but also the meibomian gland orifices.

If we put a drape on and it isn’t exactly covering the lid margin, we’ll take it off and reapply. We’re careful to protect the epithelium both pre-operatively and intra-operatively.

In those patients with epithelial defects we recommend anterior stromal puncture to those areas of abnormal epithelium at the end of the LASIK procedure.

The epithelium will adhere and reduce the risk of infection, as well as DLK that can occur with abnormal epithelium.

**Prophylaxis with the ‘fourth generation’**

Antibiotics also play a crucial role in refractive prophylaxis.

The rationale for using antibiotics pre-operatively is that the organisms are on the surface of the eye, and it’s the local bugs that get in at the time of surgery. Immediately post-operatively when the epithelium isn’t normal can also be a time for concern.

In considering prophylactic medications we need to think about penetration, and potency, defined as the drug’s minimum inhibitory concentration (MIC). We also need to look for nontoxic antibiotics.

When we compare the fourth-generation fluoroquinolones we find that the penetration of Vigamox solution is certainly superior to all the other antibiotic choices we have.

The moxifloxacin provided in the Vigamox solution also is more active against resistant organisms than is gatifloxacin. (Figure 1)

The organisms that refractive surgeons worry about are the gram-positive organisms, which account for approximately 76.6% of cases here. Atypical mycobacteria are still of concern as well.

In regards to gram-positive pathogens, the peer-reviewed literature has documented that moxifloxacin has the lowest MICs of any of the currently available fluoroquinolones. (Figure 2)
A study presented at the Nov. 15, 2003, Ocular Microbiology and Immunology Group meeting offered a comparison between moxifloxacin and gatifloxacin in eradicating mycobacterium, and both showed activity significantly better than older fluoroquinolones for prophylaxis.3

However, moxifloxacin exhibited greater potency, with lower MICs than gatifloxacin.

Vigamox solution has a penetration in the cornea of 21.3 μg/g compared with 4.9 μg/g for Zymar.

When overlaying achievable cornea concentrations of Vigamox solution and Zymar solutions with their respective MICs for atypical mycobacteria, Vigamox solution exceeds the MICs of the tested pathogens, whereas Zymar does not. This may reflect an important difference in terms of the degree of patient protection offered by these agents. (Figure 3)

In terms of side effects, it has been my experience as a corneal surgeon as well as someone who deals with ocular surface disease that the fluoroquinolones in general are nontoxic. This low toxicity is a big difference from what we saw with previous generations of antibiotics, especially the aminoglycosides. Most of the recent studies from ARVO and ASCRS, whether in vivo, in vitro, or in humans now indicate that overall biocompatibility of the fourth-generation fluoroquinolones is very good, with no difference between moxifloxacin and gatifloxacin.4,5 (Figure 4)

However, some of the studies such as the one presented by Burkà, et al. at ARVO earlier this year have actually shown that Vigamox solution, with its self-preserved formulation, is superior to Zymar.6

This independent study in humans which compared epithelial healing following PRK with the fourth-generation fluoroquinolones, showed that on each post-operative day defect sizes were greater for Zymar-treated eyes. (Figure 5)

**Post-operative management**

Post-operatively, even with excellent prophylactic measures, we need to continue to be alert for infection. The 2004 ASCRS survey referenced earlier showed that there is still a significant delay in diagnosis of infectious keratitis after LASIK.

The vast majority of these patients are treated as if they had diffuse lamellar keratitis (DLK) for a day or two. If you see a patient with a consolidated infiltrate, you’re suspecting infectious keratitis should be high. The surgeon should be aggressive about lifting the flap, obtaining cultures, and irrigating with antibiotics. It’s better to overtreat these patients than to wait a day or two because that may make the difference.

Our treatment approach would depend upon the onset of the infection. With early presentation we’re more worried about gram-positive bacteria.

Here, we recommend Vigamox solution alternating with cephalazin 50 mg/mL or vancomycin 50 mg/mL every 30 minutes. The vancomycin story is interesting because we are seeing more methicillin resistant Staph. aureus (MRSA) infections — especially in health care workers. As a result, if we have a health care worker who presents with a possible infection, we think that vancomycin should be used in addition to Vigamox solution. In cases of late, slow progressing infections, these are more likely to be the result of atypical mycobacterium. In this group of patients we recommend using Vigamox solution, alternating with amikacin.

Overall, I think our strategy to prevent infection in our LASIK patients should be to look pre-operatively at those patients who are at risk and then treat any factor that may increase the problems before proceeding to surgery.

Intra-operatively, treat your refractive surgery patients like your other surgery patients - with sterile technique as much as you can. The data show that fourth-generation fluoroquinolones are the pre-operative drug of choice. In opting between these fourth-generation agents I believe that Vigamox solution makes the most sense due to its superior penetration and its potency.

Finally, very aggressive diagnosis and treatment of that patient is imperative if you suspect a post-operative infection.