These days, more and more practitioners have turned to fourth-generation agents to help them gain ground against a host of difficult pathogens. In particular, practitioners have concerns about endophthalmitis.

Fourth-generation agents have been very impressive in killing the bacteria that cause this devastating condition, said Eric D. Donnenfeld, M.D., Ophthalmic Consultants of Long Island, N.Y. In the refractive arena, meanwhile, one of the most dreaded pathogens has been atypical mycobacterium.

In recent years, there has been an epidemic of these infections with devastating consequences. “A good number of these patients, probably one-third, end up needing corneal transplants,” Dr. Donnenfeld said. However, with the rise of the fourth-generation fluoroquinolones this has all turned around.

“With the advent of fourth-generation fluoroquinolones, and with information in our 2004 ASCRS (American Society of Cataract & Refractive Surgery) LASIK infection survey, we can now say that the epidemic of atypical mycobacteria has officially ended,” Dr. Donnenfeld said. He points to a 2002 study by R. Mather, et. al. The study, isolates from bacterial endophthalmitis resistant to ciprofloxacin (Ciloxan, Alcon, Fort Worth, Texas) were tested against moxifloxacin (Vigamox, Alcon), gatifloxacin, levofloxacin (Quixin, Santen, Napa, Calif.), oxolin, and ciprofloxacin. Isolates included were coagulase negative Staphylococcus and Staphylococcus aureus.

Investigators found that the isolates responded significantly better to gatifloxacin and moxifloxacin than to levofloxacin, ofoxacin, and ciprofloxacin. The third-generation agents had significantly higher median minimal inhibitory concentrations (MICs), and were significantly less effective than...
their new fourth-generation counterparts.

**Studying fourth generation efficacy**

One of the key factors distinguishing fourth-generation agents from the third-generation is how well they penetrate the ocular surface. Dr. Donnenfeld said that the fourth-generation allows for excellent penetration into the eye.

A study by John Wittppenn, M.D., presented at the 2004 American Academy of Ophthalmology meeting, looked at intraocular concentrations of gatifloxacin after dosing. In the study, 50 patients undergoing penetrating keratoplasty received gatifloxacin Q.I.D. for three days, and one drop every 15 minutes for one hour prior to surgery. When investigators looked at concentrations they found the corneal levels of gatifloxacin were over 15 mcg/ml.

“This is 60 times higher than that needed to kill Staph aureus,” Dr. Donnenfeld said. “So, you’re getting enormous levels into the cornea. That then acts as a reservoir to treat and prophylaxis against infections.”

The fourth-generation agents also get excellent penetration into the anterior chamber. This has been shown in multiple studies, such as those by Y. Ralph Chu, M.D., Frank Price, M.D., and Dr. Wittppenn.

In these studies, gatifloxacin achieved excellent levels in the anterior chamber, according to Dr. Donnenfeld.

In cataract surgery, the goal of antibiotics, of course, is to sterilize the anterior chamber. Dr. Donnenfeld cites a study by Frank Bucci, M.D., as probably the most telling evidence that good levels of the fourth-generation antibiotics are getting into the eye. Dr. Bucci pre-dosed patients with either Zymar or Vigamox, and performed aqueous cultures at the conclusion of cataract surgery.

“In his study of 110 patients that received Zymar and 110 that received Vigamox, there was only one positive culture in both groups, showing that both antibiotics very significantly sterilize aqueous humor at the time of cataract surgery,” Dr. Donnenfeld said.

**Optimizing wound healing**

Optimal wound healing with any antibiotic is also pivotal to good surgical outcome. Interference can result in a myriad of problems.

There can be a whole “Rogues Gallery” of associated problems including SPK (superficial punctate keratopathy), endophthalmitis, DLK (diffuse lamellar keratitis), slipped flaps, and stromal scarring in PRK, according to Dr. Donnenfeld. All these conditions are associated with delays in epithelial wound healing.

One consideration when choosing an antibiotic is that while they are imperative to stave off infection, they also have to potential to interfere with wound healing. Stephen Pflugfelder, M.D., recently conducted a study, where he looked at the issue of epithelial toxicity in a mouse model.

“He dosed these mice with either gatifloxacin or moxifloxacin,” Dr. Donnenfeld said. “Then he looked at epithelial tight junctions — the ability of epithelial cells to adhere to and prevent the degradation of the corneal epithelium, and to prevent the inoculation of organisms through an intact epithelium.”

In the study, Dr. Pflugfelder found that with the use of Zymar the tight junctions remained normal, and the cells remained viable.

On the other hand, with Vigamox there was a significant degradation of the cellular junctions and markedly increased permeability. “At five days this change had become even more significant,” Dr. Donnenfeld said. (Figure 2)

Of course, the main concern is the possible impact that this may have on patients. In a recent study presented at the 2004 American Academy of Ophthalmology meeting, Dr. Donnenfeld considered the effect of Zymar and Vigamox on corneal epithelial wound healing following PRK.

“We took 22 patients and did bilateral PRKs, and then we masked the patients that received either Zymar or Vigamox,” Dr. Donnenfeld said.

One eye received Zymar and the other Vigamox. Every day, the investigators recorded epithelial defect size and determined on which day the epithelial wounds had closed.

Photos were also taken daily until the wounds had healed (Figure 3). In the average case, there was significant closure in both eyes at 24 hours. Wound healing, again, was found to be more rapid with Zymar than with Vigamox.

“At 72 hours, most of the Zymar-treated eyes had completely closed, or had had negligible defects,” Dr. Donnenfeld said, “whereas, with Vigamox there were still significant epithelial defects.”

Investigators found that with the Zymar eyes, nearly all had healed at the four to five day mark, whereas with Vigamox it took seven days for many of these wounds to close.

It is important to note that more rapid wound healing is more than a simple time issue. In fact, delays in re-epithelialization can have serious clinical implications.

“A delay in wound healing increases the time for the return of vision, it increases the incidence of post-operative haze in the cornea, it allows the patient to have more pain and more photophobia, and it dramatically increases the risk of infectious keratitis,” Dr. Donnenfeld said.

Overall, the research indicates that there can be a significant delay in epithelial wound healing with Vigamox compared with Zymar.

“This bodes well for Zymar use in the treatment of patients with epithelial defects, LASIK, and PRK,” Dr. Donnenfeld said.
Effects of Zymar® and Vigamox® on Corneal Epithelial Wound Healing Following PRK

**Figure 3:** Wound healing following PRK was faster with Zymar than with Vigamox. At 72 hours most of the Zymar-treated eyes had completely closed, or had had negligible defects, while eyes treated with Vigamox still had significant epithelial defects.

**Effect on the ocular surface**

How the eye tolerates a fourth-generation fluoroquinolone is also of prime importance. Dr. Donnenfeld recently conducted a study in which he looked at the effects of the fourth-generation fluoroquinolones on the ocular surface.1

“We looked at volunteers having either Zymar or Vigamox placed into each of their eyes,” Dr. Donnenfeld said. “We looked at conjunctival erythema before and after injection, and after drops of Vigamox and Zymar.”

Commercially available Vigamox and Zymar solutions were placed in masked bottles. Then investigators randomly placed one drop from each bottle into either the right or left eye. This was repeated two times at one-minute intervals. Patients were then told to close their eyes and rest quietly for five minutes.

Results showed that eyes receiving Vigamox had significantly more irritation and much more vascularity. There was also an unexpected finding.

“The surprise was that we found a decrease in pupil size with Vigamox versus Zymar that showed that the Vigamox eyes had constricted pupils of approximately half a millimeter in many cases,” Dr. Donnenfeld said. “This was most notable in dark rooms with blue-eyed patients, showing that there's something that's being released in these eyes causing pupillary constriction.”

Investigators theorize that this is probably linked to prostaglandin release. Investigators found that patients also experienced significantly more discomfort with Vigamox. “Pain was more significant with Vigamox, and ocular irritation was significantly greater as well,” Dr. Donnenfeld said.

It appears as if there is more cell loss with the Vigamox. A study conducted by Kaufman looked at corneal epithelial cell drop-out in patients receiving Zymar and Vigamox. The study also looked at conjunctival injection and discomfort.

“This showed statistically significant differences between Zymar and Vigamox in ocular biocompatibility,” Dr. Donnenfeld said. Zymar appears to offer more bio-compatibility to patients.

Overall, the fourth-generation fluoroquinolones have had significantly better results against a variety of organisms than their third-generation predecessors. In particular, fourth-generation agents have quelled the mycobacterium epidemic that raged just a couple of years ago.

Infection, however, is only one complication that practitioners must keep in mind.

“Besides the increased risk of infection after cataract and refractive surgery, other risks of abnormal corneal healing include stromal scarring, persistent corneal epithelial defects, recurrent epithelial erosions, epitheliopathies of all types, epithelial in-growth, microbial keratitis, DLK, and flap slippage,” Dr. Donnenfeld said. “The ideal surgical anti-infective is one that interferes with corneal wound healing as little as possible.”

Studies have shown that Zymar is kinder to the ocular surface, producing less clinical signs of inflammation compared with Vigamox. Patients have complained less of ocular irritation and pain with Zymar than with Vigamox.

Study findings from every layer of the cornea -- the epithelium, Bowman’s membrane, and stroma -- have shown Zymar to be a more ideal anti-infective. “Studies demonstrate that gatifloxacin interferes with wound healing less than Vigamox, and with Zymar there is more rapid, complete epithelial and stromal healing, less inhibition of collagen IV expression, and less toxicity,” he said.

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When it comes to fighting infection, clinicians have an ongoing battle with bacteria that they strive to keep at bay using the latest, most potent antibiotic regimens. In many ways, bacteria can have a considerable advantage.

“Unfortunately, the bacteria have the upper hand by virtue of their enormous numbers, their extraordinary virtuosity and capability to adapt to difficult circumstances, and their impressive penchant for reproduction,” said Terrence P. O’Brien, M.D., Tom Clancy Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore.

But now, newer more powerful antibiotics such as the potent 8-methoxy fluoroquinolones are helping to tip the scale back in ophthalmologists’ favor.

The fourth-generation is the latest branch to emerge on the remarkable fluoroquinolone tree. In recent years, the fluoroquinolones have become the drugs of choice in the ophthalmic community.

“The fluoroquinolones revolutionized ophthalmology by providing us with stable commercial formulations of bacteriocidal compounds that exert rapid, broad-spectrum activity against a variety of ocular pathogens,” said Dr. O’Brien.

Nalidixic acid, a fluorine substitution at the 6th position of the basic quinolone nucleus, which offered a limited spectrum of activity mainly against gram-negative bacteria, was the first that spawned quinolone. This was followed by drugs including ciprofloxacin, ofloxacin, and levofloxacin that extended the spectrum against some gram-positive organisms and enhanced activity against gram-negative organisms.

While the early generations of fluoroquinolones such as ciprofloxacin, levofloxacin, and ofloxacin served practitioners well, newer generation 8-methoxy agents such as gatifloxacin and moxifloxacin have more to offer, Dr. O’Brien said.

These show an extended spectrum with enhanced activity against gram-positives including Staphylococci, Streptococci, Enterococci, and even anaerobes. They also have improved pharmacokinetic properties.

The rise of the fourth generation
At the heart of fourth-generation agents such as gatifloxacin and moxifloxacin is a change in the chemical structure.

“There has been a steady evolution in the development of the fluoroquinolone family, moving up the tree with the addition of the 8-methoxy group at the eighth position of the basic quinolone nucleus. This expanded the spectrum of activity of these agents to include gram-positive pathogens and even anaerobes,” Dr. O’Brien said. “By virtue of the side chain substitutions, these designer molecules have become smart bombs in the war to help us effectively battle bacteria.”

The fourth-generation agents are true designer molecules. While the 8-methoxy group has expanded the gram-positive activity, the cyclopropyl group has maintained gram-negative activity. Meanwhile, bulkier side chain substitutions have helped to reduce the emergence of resistance by providing hindrance to prevent molecules from being readily ejected from the cells by the bacterial efflux pumps.

“We’ve improved gram-positive activity while maintaining the excellent gram-negative activity of ciprofloxacin, and even getting some anaerobic activity as a bonus on the side,” Dr. O’Brien said.

As a result of the 8-methoxy group addition, the fourth-generation agents possess all of the four requisite “killer bees” -- four ideal features of anti-infective agents, Dr. O’Brien said. “They have Bacteriocidal mechanism of action, Broad spectrum of activity, Biocompatibility in the sense of being non-cytotoxic, and Bioavailability with favorable pharmacodynamics,” he said.

**Anti-infective formulation matters**

By Terrence P. O’Brien, M.D.

Eradication of bugs
When it comes to microbial eradication the addition of the 8-methoxy group has had a profound effect.

“If we look at minimal inhibitory concentration data there is greater activity against the staphylococci that are resistant to earlier generations of fluoroquinolones,” Dr. O’Brien said. “There is also some animal model data that suggests that these fourth-generation fluoroquinolones do have an advantage over the earlier generation -- especially against the methicillin-resistant coagulase-positive, as well as coagulase-negative Staph.”

In a 2002 study by R. Mather, et al., investigators compared the minimum inhibitory concentrations of fourth-generation fluoroquinolones and earlier, third-generation drugs against resistant bacterialocular pathogens causing endophthalmitis in humans. They determined that the fourth-generation agents were much more effective at combating these pathogens than earlier generations of fluoroquinolones.

Likewise, the 8-methoxy agents have also proven to be highly effective against various strains of staphylococcus. In a study conducted by Eser, et al., which was presented at the 2004 ARVO symposium, investigators compared in vitro antimicrobial efficacy of gatifloxacin, containing a low concentration of BAK (benzalkonium chloride), to moxifloxacin, containing no preservative, to a saline concentration.² (Figure 4)

Activity against 12 *Staphylococcus aureus* strains and five strains of coagulase negative *Staphylococcus epidermidis* was examined.

Investigators determined that gatifloxacin had significantly augmented microbicid-
eral effect against staphylococcus strains compared to the moxifloxacin. They also found that the bacteria were eradicated more rapidly with the gatifloxaclin plus BAK than with the otherwise powerful moxifloxacin alone.

“Within 15 minutes after exposure there was a near-complete eradication of large numbers of bacteria,” Dr. O’Brien said. “With the moxifloxacin not containing the preservative, but with an even higher concentration of 0.5%, even out at one hour there were significant survivors.” In short, despite moxifloxacin’s higher concentration, microbial killing was slower with the non-preserved moxifloxacin compared to the gatifloxaclin.

While gram-positive bacteria cause more ocular infection, it is the gram-negative cases that can be particularly virulent. Therefore, it is also important for ocular antibiotics to offer this coverage.

In a study conducted by K. Metzler, et al., which was presented at the 2004 ARVO symposium, the fourth-generation agents were found to be effective in killing *Pseudomonas aeruginosa* and *Haemophilus influenzae*.2

“Gatifloxacin, at least for *Pseudomonas aeruginosa*, did seem to have a statistically significantly greater effect on killing compared to the non-preserved moxifloxacin,” Dr. O’Brien said.

In terms of eliminating bacteria found in and around the eye, Zymar has also proven to be highly effective. A study presented by Dr. Bucci at the 2004 ARVO symposium compared the activity of gatifloxacin and moxifloxacin on postoperative aqueous cultures in patients undergoing routine cataract surgery.1 Group 1 contained 100 patients who received either gatifloxacin or moxifloxacin four times a day for two days prior to the surgery. This included one drop in the morning of the day of the surgery.

Group 2 had 120 patients randomized to receive one of the two quinolones, four times a day for two days pre-op, as well as one drop on the morning before surgery, followed by one additional drop every 10 minutes x 4 in the hour prior to surgery. All conjunctival and eyelid cultures were obtained in a masked fashion.

There were no positive cultures for either fluoroquinolone in Group 1; Group 2 had one positive culture for each drug. The author concluded that there are no significant differences between either gatifloxaclin or moxifloxacin in their ability to sterilize the aqueous humor prior to and during phacoemulsification.

**The preservative question**

In choosing a fluoroquinolone it is important for practitioners to decide whether they want to use one with a preservative or not. While at first blush it may appear that a preservative may increase the risk of cytotoxicity, there can also be certain benefits to choosing a drug containing a preservative.

While some preservatives can provide excessive toxicity if frequently and repeatedly used on the ocular surface, with routine dosing clinically significant problems are rare.

“The fact is that ophthalmic preservatives are present in most of the ophthalmic medications that we use since the early 1950s,” Dr. O’Brien said.

In fact, since 1953, the FDA has required that multidose ophthalmic preparations contain preservative to reduce contamination. Among other things, ophthalmic preservatives decrease the risk of ocular infection and also help to extend a medication’s shelf life.

For example, with multidose preparations there is concern that once the bottle is open, the tip can become contaminated -- something which preservatives can guard against. “The decreased risk of ocular infection with use of preservatives can be an advantage, and it certainly can prolong the shelf life of our medications,” Dr. O’Brien said.

There are actually a variety of different types of ophthalmic preservatives, including detergents, oxidizing agents, and alcohol-based preservatives.

“Oxidizing agents and alcohol-based preservatives are used, but the most commonly used ophthalmic preservative actually dating to the 1930s is benzalkonium chloride (BAK), which is present in a number commercial preparations of eye drops,” Dr. O’Brien said. This common preservative falls under the umbrella of detergent preservatives.

Zymar contains 0.005% BAK preservative. While still enough to be effective, this amount is less than in many other ophthalmic medications.

BAK is, in fact, a quaternary ammonium compound that has a long fatty tail like a lipid, with a positively charged nitrogen at one end. “These are very potent anti-infective agents,” Dr. O’Brien said. “They work very well in the lab by themselves to kill bacteria.”

These BAK preservatives are effective not only against bacteria but also against a variety of fungi as well. “They have surfactant effect that can disrupt cell membrane permeability and cause lipid dispersion,” Dr. O’Brien said. This leads to lysis of cytoplasmic contents in microorganisms and, ultimately, leads to death of the bacteria.

As a result, BAK has the potential to be a valuable addition to an ophthalmic preparation.

**Preservatives’ effects on bugs**

In some cases, preservatives can help to augment antimicrobial activity. Some investigators have considered the effect that preservatives can have with yeast, mold, and bacteria. Yeast is something that affects many individuals.

Approximately 80% of the healthy population carries the *Candida* species. This is a common cause of mycotic post-surgical exogenous endophthalmitis. As a matter of fact, *Candida parapsilosis* was determined to be the cause of an epidemic of...
Preservatives can be beneficial to accelerate microbial killing — they can protect and serve.

Terrence P. O’Brien, M.D.

exogenous endophthalmitis stemming from the use of contaminated irrigating solution.2

“There have been some epidemics of Candida and other fungal infections with cataract surgery, and we know that these are virulent, dreaded pathogens,” Dr. O’Brien said.

Other common pathogens include Aspergillus, a species of mold that has been linked to cases of endophthalmitis and fungal keratitis, and Staphylococcus bacteria, which is commonly found in many ocular infections.

In the United States coagulase-negative Staphylococi has been deemed responsible for about 70% of endophthalmitis cases stemming from post-cataract surgery. This is followed by Staphylococcus aureus, viridans group Streptococci, other gram-positive micro-organisms, and by gram-negative organisms — all of which have been known to cause ocular infection.

Yeasts is also important to have on the radar. In a study conducted by D. Rupp, et al, which was presented at the 2003 Ocular and Microbiology and Immunology group (OMIG) meeting, investigators considered how the fourth-generation fluoroquinolones fared against yeast.4 They evaluated how the anti-microbial preservative efficacy of Zymar, preserved with 0.005% BAK, fared against preservative-free Vigamox versus 20 strains of yeast isolates. Dr. O’Brien found the results to be striking.

“At four hours, the other powerful fourth generation agent, Vigamox consistently allowed more fungal recovery than did Zymar for 20 strains of yeast that were tested,” he said. “At seven days, Vigamox still allowed more fungal recovery in 15 of the 20 strains, whereas the Zymar uniformly eradicated the fungi, probably due to the efficacy of benzalkonium chloride.” (Figure 5)

Investigators concluded that Zymar, with BAK, can be a protective agent against yeast.

This also seems to hold true against many bacteria strains tested. In a study that Dr. O’Brien collaborated on at the ocular microbiology lab at Johns Hopkins University, investigators sought to compare the antimicrobial efficacy of Zymar, preserved with 0.005% BAK, to that of preservative-free Vigamox versus four strains of Staphylococcus aureus.6

“While it was a rapidly negative-sloping kill curve for both Staphylococcus aureus isolates against all four strains that we tested for these species of coagulase-negative Staph., compared to the Vigamox that does not contain the preservative,” Dr. O’Brien said. “The same was true for E.coli as well.”

In vivo studies have also supported these same conclusions. A study conducted by Francis S. Mah, M.D., University of Pittsburgh, which was presented at the 2003 OMIG meeting, showed that Zymar could effectively treat gatifloxacin-resistant Staph. aureus.8 In the study two rabbit models of the resistant strain were successfully treated with Zymar.

Investigators determined that Zymar preserved with BAK was more efficacious than either gatifloxacin or moxifloxacin alone.

“Two rabbit models of gati-resistant Staph. aureus showed that Zymar could successfully treat these challenging pathogens in the rabbit tissue, and then we could see that the preserved Zymar is more efficacious,” Dr. O’Brien said. “So, sometimes preservatives can be our friends, especially in eradicating potential pathogens that can be contaminants.”

Overall, opthalmic preservatives can have a positive or a negative effect depending upon how they are used, Dr. O’Brien said. When used properly, preservatives can offer a healing boost.

“Preservatives can be beneficial to accelerate microbial killing — they can protect and serve,” Dr. O’Brien said. “The combination of BAK and gatifloxacin can act as a dual mechanism agent to augment microbial killing and increase the rapidity of bacterial eradication compared to no preservative.”

Also, the addition of BAK equalizes formulation differences in concentration and provides protection against contamination with yeasts and filamentous fungi. However, practitioners must still guard against misuse.

“We still have to be cautious with excessively frequent or prolonged dosing — clearly cytotoxicity is possible,” Dr. O’Brien said.

When used properly, however, Zymar preserved with BAK can effectively kill a variety of problematic yeasts, molds, and bacterial strains of Staphylococcus more effectively than it could hope to, were it not for the preservative.

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The corticosteroids act at the beginning of the pathway to partially block prostaglandin synthesis. “In spite of our best efforts, some pro-inflammatory cytokines make their way through, free arachidonic acid is produced, and much of it goes down the cyclo-oxygenase pathway,” Dr. McDonald said. “That’s where the NSAIDs block COX-1 (constitutive prostaglandins) and COX-2 (inducible prostaglandins).” Cutting off the production of prostaglandins is important because these lead to ocular inflammation, miosis, itching, photophobia, and increased susceptibility to pain.

Surgery can be a trigger causing an inflammatory response throughout the eye. (Figure 7) “Basically, we are operating on the front of the eye, and we trigger inflammation. Prostaglandins are released in the anterior portion of the eye but they diffuse through to the posterior portion of the eye to produce inflammation and CME,” Dr. McDonald said. “So, optimal control of inflammation involves using both an ophthalmic NSAID and a steroid because they work on different portions of the arachidonic acid cascade.”

How NSAIDS work
The key with NSAIDs is that they help to block the inflammatory pathway. (Figure 6) “Blocking the arachidonic acid cascade is key,” Dr. McDonald said. “Prostaglandins are responsible for post-op inflammation, and the arachidonic acid cascade leads to prostaglandin synthesis as well as leukotriene synthesis.”

In particular, the NSAIDs block cyclo-oxygenase (COX), directly limiting the production of prostaglandins. Steroids, meanwhile, work indirectly to accomplish this. “Steroids have many effects, including the inhibition of the arachidonic acid release which inhibits prostaglandin synthesis indirectly,” Dr. McDonald said.

Because they work by different mechanisms, NSAIDs can provide adjunctive relief to that of steroids. “The direct effect of NSAIDs augments the indirect effect of steroids,” Dr. McDonald said. “So, our goal is to block multiple points in the pathway to prostaglandin synthesis.”

The importance of NSAIDS
While practitioners need ophthalmic corticosteroids there are definite disadvantages to them. They do not provide direct pain relief. They have also been known to have adverse effects.

“They increase intraocular pressure in a significant percentage of the population,” Dr. McDonald said. “They also interfere with wound healing in all of the population if used long enough, and they will cause cataract formation in all phakic patients if used long enough.”

Meanwhile, NSAIDs can be extremely helpful additions to a steroid regimen. “NSAIDs can provide numerous additional benefits. They reduce the incidence of CME, pain, and miosis,” Dr. McDonald said. “They increase intraocular pressure in a significant percentage of the population,” Dr. McDonald said. “They also interfere with wound healing in all of the population if used long enough, and they will cause cataract formation in all phakic patients if used long enough.”
McDonald said. Miosis can, of course, make cataract surgery much more difficult. (Figure 8) “We all know small pupils make cataract surgery much more challenging, and greatly increase the risk of posterior capsule rupture,” Dr. McDonald said. As a result, it’s important to prevent prostaglandin synthesis. Application of an NSAID before the first incision can help do that. When it comes to CME, NSAIDs can also be an asset. This condition has an evolving definition. “Classically, we’ve always said that cystoid macular edema is a retinal condition in which there is an abnormal collection of fluid that may be intercellular in the outer plexiform and inner nuclear layers of the retina. Or it may be intracellular, causing Muller cell degeneration with intracellular vacuolation. The macula usually acquires a characteristic petaloid appearance that is easily detected upon physical examination and fluorescein angiography. All the experts agree on these two states.

Ms. B. McDonald, M.D.
Considerations in choosing anti-inflammatory regimens

Prostaglandins are the principal mediators of post-surgical inflammation responsible for multiple sequelae from pain to miosis. Fortunately, NSAIDs such as Acular (Ketorolac 0.5%, Allergan) and Acular LS (Ketorolac 0.4%, Allergan) are valuable surgical tools, helping to block the formation of prostaglandins.

“We know that only our non-steroidals will directly inhibit the formation of prostaglandins,” said Calvin W. Roberts, M.D., clinical professor of ophthalmology at Cornell University Medical College, New York.

Despite their efficacy at reducing inflammation, practitioners traditionally have not begun using NSAIDs until after surgery. Dr. Roberts wondered why this was and decided to launch a study to see if prophylactic use of NSAIDs before surgery could help.1

“We wanted to find out if we could treat our patients prior to surgery, and block cyclo-oxygenase so that when that cascade occurred we would get less production of prostaglandins,” he said.

Patients in the study were randomized into three groups. One group started non-steroidals four times a day, three days prior to surgery. The second group started their non-steroidals pre-operatively, on the day of surgery, when they arrived at the surgery center. Finally, the third group received no pre-operative non-steroidals.

“We found that the initial amount of inflammation that develops post-operatively.”

**NSAID use for miosis, pain relief, and CME**

Keeping pupil size from constricting during cataract surgery can also be an important consideration -- one that can be linked to an increased risk of capsule rupture. Dr. Roberts also looked at the effect that NSAIDs could have.

“We looked at patients who started their non-steroidals three days prior to surgery compared to those who started non-steroidals on the day of surgery,” Dr. Roberts said. This was a departure from how things were traditionally done in the past, when practitioners would start patients on NSAIDs on the day of surgery, and then would look at pupil size during the case.

In this study, investigators videotaped patients and then analyzed the video after the procedure, looking at the effect of the epinephrine in the bottle.

“We found that not only did the patients who had three days of pre-operative non-steroidals start out with larger pupils, but also as the case proceeded the effect of the intra-operative epinephrine actually made the pupils bigger. Meanwhile, in the patients who only started their non-steroidals on the day of surgery, we noticed that the pupils actually started to get smaller.”

This bodes well for use of non-steroidals. “Not only will three days of pre-operative non-steroidals decrease the initial amount of inflammation, but also they’ll allow our pupils to be larger,” Dr. Roberts said. This makes things far easier for the practitioner during the surgical procedure.

Providing patients with pain-free surgery is, of course, a paramount goal for practitioners.

“I think pain-free surgery is probably the most important thing that I do in my surgery in terms of patient satisfaction and internal marketing,” Dr. Roberts said. How patients feel on the first pre-operative day is what they remember. “I think patients remember when the surgery doesn’t hurt,” Dr. Roberts said.

Dr. Roberts had been using 2% xylocaine jelly to provide pain relief for his surgical patients. To see if NSAIDs could also be of benefit for his cataract patients he launched a prospective, masked, randomized trial including two groups of patients.2

The study included 296 patients. One group of patients was given the NSAID, Acular LS, on the day of surgery. The second group started taking the Acular LS three days prior to surgery, dosing four times a day.

Anesthesia used in the study included topical 2% xylocaine jelly, applied first one half hour before the procedure and then again five minutes prior to surgery. Patients were also given intravenous 0.5 cc midazolam (various manufacturers) and 0.5 cc alfentanil (various manufacturers).

“We gave them just a whiff of intravenous sedation,” Dr. Roberts said. “Actually much less than we usually give.”

Patients were then asked to fill out a post-operative questionnaire pertaining to how they felt during surgery. “We found that among the patients who had three days of preoperative non-steroidals a statistically significant fewer number of patients experienced any pain compared to those who did not get the three days of pre-operative non-steroidals,” Dr. Roberts said.

Preventing cystoid macular edema (CME), which can result from intraocular inflammation, is another leading concern for practitioners. NSAIDs have been shown to have an impact here.

In a study by McColgin and Raizman, investigators looked to see how retinal thickness was affected by use of non-steroidals three days prior to surgery had a statistically significant decrease in the amount of post-op inflammation compared to those in the other two groups.
not receive the non-steroidals compared with those that did.” (Figure 10)

This means that patients who use NSAIDs pre-operatively not only show less of an increase in macular thickness, but also show an improvement in terms of their contrast sensitivity. Dr. Roberts said that overall visual acuity is likely not affected because small changes in macular thickness are not large enough to affect Snellen acuity — which is a gross measurement of vision.

“We concluded that macular edema decreases the quality, as opposed to the quantity of post-operative vision,” Dr. Roberts said. “By increasing contrast sensitivity, pre-operative use of ophthalmic non-steroidals can improve the quality of vision for all our patients after cataract surgery.”

Overall, for cataract surgery non-steroidals can be a real boon. They can help to keep the pupil dilated, prevent and control post-operative inflammation, alleviate pain associated with clear corneal cataract surgery, and improve the quality of vision for patients, Dr. Roberts said.

Keeping steroids in the mix
While NSAIDs are very important to patient care, they should not be used to the exclusion of steroids that are also very valuable to ophthalmologists.

When using steroids, however, it is important to keep in mind that some of them can provide more relief than others. Dr. Roberts has found that there is a definite difference between the branded Pred Forte and its counterparts.

Dr. Roberts recently conducted a study to see how Pred Forte fared against EconoPred (prednisolone acetate, Alcon) and generic prednisolone acetate 1% (Falcon Pharmaceuticals, Ltd., Fort Worth, Texas).5 The

![Figure 10: When it comes to contrast sensitivity, those who were not given NSAIDs had a statistically significant decrease in contrast sensitivity in the higher spatial frequencies compared to those who were given NSAIDs.](image-url)
Dr. Roberts said. “The bigger particles, the more they’re going to fall.” Investigators took samples over a six-day period, beginning at what was dubbed “time zero,” and found that at every time point particles of Pred Forte were smaller than those of the other two products. “We found that the particle size — meaning the amount of drug sitting in the drop — was the same for Pred Forte at time zero as it was at every other point along the way for six days,” Dr. Roberts said. “However, with the EconoPred Plus or with the generic, the amount of particles decreased over time.”

Even with the newly engineered version of the generic drug the same settling effect was seen as with the earlier version. “When we looked at samples from the bottom of the bottle after six days the concentration in Pred Forte was the same at the top of the bottle,” Dr. Roberts said. “But the concentration in EconoPred was still much greater down at the bottom of the bottle.”

As a result, Dr. Roberts strongly favors using the Pred Forte for his patients. “I think that the efficacy of Pred Forte compared to EconoPred Plus is still slanting toward Pred Forte in terms of greater efficacy because we’re getting more drug out of a drop than we are with the EconoPred Plus.”

**Three-pronged approach**

Dr. Roberts uses a three-pronged, prophylactic approach for his patients. This includes use of an NSAID, a fourth-generation fluoroquinolone, and a steroid prior to surgery.

“We start our patients three days prior to surgery with Zymar and Acular LS,” Dr. Roberts said. He favors Zymar because it kills many strains more rapidly than the other fourth-generation fluoroquinolone, Vigamox. As a result, it offers greater efficacy.

“We use Zymar along with Acular LS, and find the three days pre-op for the two drugs dove-tails very nicely,” he said.

Dr. Roberts gives patients a pre-printed prescription with directions to put one drop from each bottle into the eye set for surgery. Patients are instructed to do this four times a day for three days prior to surgery.

“If the surgery is scheduled for Monday, the patients start their drops Friday and put them in four times a day on Friday, Saturday, and Sunday,” Dr. Roberts said. “When they arrive at the surgery center they again get Zymar and Acular LS, and then immediately after surgery we add the Pred Forte.”

For the first week post-op, patients are placed on Acular LS, Zymar, and Pred Forte.

“When I see the patients at the one-week visit, assuming that there is minimal inflammation, we stop the Zymar and the Pred Forte,” Dr. Roberts said.

However, he continues patients on the Acular LS, which he sees as offering visual benefits in terms of contrast sensitivity. He does cut back the dose of Acular LS to twice a day for the rest of the month.

At the one-month post-op visit, assuming that the patient is getting the hoped-for visual results, Dr. Roberts usually stops the NSAIDs. However, there are some exceptions. “If there is any concern that the vision is not as good as it should be, or if for any reason the macular thickness has increased, then we’ll continue the non-steroidal for another month, and sometimes for two,” he said.

Overall, Dr. Roberts said that this three-pronged approach combining use of NSAIDs, steroids, and antibiotics serves patients well and offers them optimal outcomes. By bringing an NSAID into the mix pre-operatively he finds that this can help to prevent inflammation, miosis, pain, and CME, and it also helps to guard against loss of contrast acuity.

**Citations**

4. Presented at ASCRS Meeting, April, 2005
Refractive practitioners are in the midst of an exciting era of burgeoning technology and changes occurring on many fronts.

Today’s patients undergoing corneal ablations are seeing better than ever, with improved accuracy and better quality-of-vision, said Roger F. Steinert, M.D., University of California at Irvine.

Practitioners now have a heightened awareness on quality-of-vision issues, and understand that there’s a lot more to the picture than just Snellen acuity. New frontiers are now in reach, said Dr. Steinert.

“We’re detecting and treating high-order aberrations, we’re reducing the creation of high-order aberrations, and we’re getting better laser profiles and better flaps or, maybe getting away from the flap altogether,” he said.

One new idea that has come to fore is the “LASIK Anatomy Hypothesis.”

This is the concept that there is a difference in flaps, and that this can translate into differences in acuities. A recent study conducted by Steven Schallhorn, M.D., and David Tanzer, M.D., San Diego, put this concept to the test.

“They took patients in the Navy who were undergoing LASIK with the VISX CustomVue (AMO) and randomized them between the IntraLase FS Laser (IntraLase Corp., Irvine, Calif.), the Amadeus (AMO), and the Hansatome (Bausch & Lomb, Rochester, N.Y.),” Dr. Steinert said.

“They found a startling difference with IntraLase, out-performing either of the mechanical microkeratomes.”

Investigators found that there is an actual gain in contrast acuity with the IntraLase compared with some loss with the mechanical microkeratomes. (Figure 12)

“This is just one study, but there are other studies that are very similar,” Dr. Steinert said. “So if we do stick with LASIK instead of Epi-LASIK, then it looks as if it may, in fact, be that we do a better job anatomically and create less difficulty with the femtosecond Laser.” As a result, Dr. Steinert sees the femtosecond laser as one that will be around for quite a long time.

Of course LASIK is not the only area ripe for advancement.

“Now, there’s another contingent that says, ‘Stop vandalizing the cornea — this is all wrong and we know about implants — ‘Implants ‘R’ Us.’ We are ophthalmologists, and we do implants,” Dr. Steinert said. The argument is that refractive lensectomy with phakic IOLs is a very predictable, stable procedure, and has a wider range than LASIK.

Dr. Steinert sees a lot of truth in this idea.

“These are technologies and techniques that pretty much have been mastered by cataract surgeons,” he said. “It’s just a small difference to go with a phakic IOL.” There has already been FDA pre-market approval for the Verisyse lens (Ophthea USA, Boca Raton, Fla.), and other lenses are expected to follow shortly.

However, complications, while rare, are more severe with phakic IOLs, and there are also some unknowns to consider.

Long-term tolerance of phakic IOLs is extremely controversial.

“More studies keep coming out raising questions that we don’t have good answers to, and we don’t really know if patient acceptance of elective intra-ocular surgery is going to grow,” Dr. Steinert said. “It’s almost impossible to call at this point because we don’t have the track record to give patients confidence, and there’s some question as to whether that will ever happen.”

The presbyopic frontier

One area that has been a particular boon for advancement is presbyopia. This is perhaps the last true frontier for refractive surgery, said Dr. Steinert.

“We started with the laser thermo-keratoplasty and that segued to conductive keratoplasty which certainly had more promising results in terms of predictability and stability” Dr. Steinert said. Unfortunately, the message does not seem to be getting out to ophthalmologists.

“I do not have a parade of glasses-free 50-year-olds banging down my door.” he said. “They don’t know that this exists — they’d be interested if they found out, but it isn’t catching on the way LASIK has become part of our culture now for myopia.”

There are also alternate technologies to consider for correcting presbyopia, such as use of scleral implants. It’s uncertain whether this is going to pan out or not, or whether practitioners will be able to restore accommodation by change in the zonular stretch despite the thickening and the stiffening of the lens.

Innovative new lens implants may provide practitioners with another option for correcting presbyopia. The latest technology includes the ReSTOR lens (Alcon), the ReZoom (AMO), and the Tecnis-based multifocal IOL (AMO).

“Some data suggests that this really isn’t the same old thing — that these multifocals are going to be better tolerated and will give adequate performance to make most presbyopes happy,” Dr. Steinert said.
A different tact showing promise is the use of accommodating IOLs. The pioneering lens is the Crystalens (eyeonics, Aliso Viejo, Calif.). A potential competing technology IOL is the dual optic Synchrony lens (Visiogen, Irvine, Calif.).

“There’s no question that if you can get two optics moving you can really get accommodation,” Dr. Steinert said. “But we don’t know what the capsular bag is going to do to that, and whether it can be maintained.”

The ultimate goal here would be to have true microincision cataract surgery followed by an injectable polymer, Dr. Steinert said.

Unfortunately, however, this is still out of reach. Presently, the incisions being made are not kept small enough, and there is not yet an injectable polymer in clinical trials.

There are also several remaining questions to be answered. “How do we control the power even if we have a good polymer, and how do we control the capsule with the anterior capsule likely to opacify and become fibrotic?” Dr. Steinert said.

Others are now working on altering the cornea to treat presbyopia. “There’s a whole other contingent that’s working hard on multifocal ablation zones, trying to make that work. They’re saying, ‘We can do this on the cornea,’” Dr. Steinert said.

In addition, there are exciting, seemingly counterintuitive approaches that are also gaining ground. These include intra-corneal inlays. Currently, there’s a small, positive power inlay to be placed in one eye that’s under consideration (IntraLens, Lake Forest, Calif.).

There’s even a pinhole type of inlay for the eye that is being looked at.

“As peculiar as that may sound, the clinical trials outside of the U.S. are actually quite positive, so we may get some surprises there,” Dr. Steinert said.

The future of LASIK
With so many advances in the offing, LASIK’s future is an area of concern to many practitioners.

“If you are doing refractive surgery, the real question that needs some kind of an answer from a business plan point-of-view is: ‘Will LASIK remain king?’” Dr. Steinert said. “Is this going to remain the patient procedure of popular choice that pulls in the patients and then creates the niche for other procedures that will stay small and continue to be relatively small volume?”

There are two different potential scenarios to consider.

Market scenario “A” is one in which over the next decade LASIK would experience a rapid growth spurt, driven by the improved outcomes of modern LASIK as well as an increase in the number of eligible surgical candidates. It is uncertain as to whether LASIK still has that sort of growth potential, Dr. Steinert said.

With market scenario “B,” interest in LASIK dies off, and with time the procedure becomes little more than a historical artifact.

“Doyle Stulting, M.D., Ph.D., [Atlanta] for one was quoted as saying that he wouldn’t be surprised if in 10 years surgeons don’t use corneal ablation for refractive correction at all,’” Dr. Steinert said. “This is where the crystal ball gets pretty murky.”

Part of the difficulty in foretelling this lies in determining LASIK’s current position on the technology cycle. There are three phases to this well-known cycle.

In the “infancy” phase key developments are made, progress is slow, and few practitioners are involved. In the “explosion” phase rapid progress takes place as key knowledge is disseminated. Then, finally, in the “maturation” phase the status quo is perfected and there is opportunity for new technology to displace the old system.

“Have we matured? Are we just perfecting the status quo? If so, then new technology can displace the old one,” Dr. Steinert said. “Or, are we in the explosion phase where we’re still rapidly gaining knowledge about corneal biomechanics and pharmaceuticals that will lead to ongoing growth.”

While only time will tell, Dr. Steinert said that LASIK has still got a lot of life left in it.

“I think we’re going to see expanded LASIK and LASIK technologies,” he said. “I’m not so sure about presbyopic LASIK, but the inlays certainly do look very interesting, are functioning, and are being tolerated surprisingly well.”

There are new therapeutic applications as well, with full and partial thickness corneal transplants aided by femtosecond lasers, and with intra-corneal ring segments being used with the help of the IntraLase in cases of ectasia and keratoconus.

There is also the issue of the bioptics technique to consider — an approach which combines use of LASIK or PRK with that of phakic IOLs. Even if phakic
IOLs and refractive lens exchange become a bigger part of refractive practices, using bioptics to refine astigmatism refine outcomes is quite a viable issue, Dr. Steinert said.

There are also considerations as to how much of the LASIK market has actually been penetrated. Dr. Steinert cites a 2003 Zyman-IntraLase consumer study that showed that 90% of potential consumers were aware of LASIK.\(^1\) (Figure 13)

The survey showed that while a lot of people have heard the of LASIK, only 14% seemed to have good familiarity with it. And although 13% express interest in undergoing LASIK correction, only 1% actually undergo the procedure.

“There is what the marketing people call a consumption gap,” he said. However, there are some promising marketing opportunities.

“"The things that will bring in people deciding to do refractive surgery of any kind, LASIK or otherwise, are assurances that the vision is going to be sharper, that this is the best treatment, that it’s going to be permanent,” Dr. Steinert said. “Patients also want assurances that the problems are minimized, a feeling that recovery is fast, and to feel better.”

Practitioners can take comfort that marketing strategies such as pricey endorsements from celebrities were found not to be important.

“The good news is you don’t need to have Tiger Woods doing commercials for you in order to get refractive surgery patients,” Dr. Steinert said.

For the future, there’s no telling what the market is going to do. However, if practitioners address the key motivating factors, they are more likely to see ongoing growth in refractive surgery, he said. These factors include the opportunity for better vision, a better treatment experience, more confidence in the outcome, and increased safety.

“That’s where LASIK is directed,” Dr. Steinert said. “If you think about what’s been going on with wavefront technology, and better flaps — that’s why I think the king of LASIK is not dead yet.”

Favorable demographics are another factor to consider. While the average age of the LASIK patient is about 40, there are increasing numbers of younger individuals who are opting for the procedure.

“Those of us who have been doing this for awhile are actually starting to see a really nice phenomenon — that the children of some of the early patients are now coming in,” he said. “These children who have reached their twenties and thirties have seen it with their parents; and are not going to put up with their glasses and wait until they’re 40 or 50.”

There’s also this issue of the boomer generation. While the aging of the baby boomers means fewer patients in the most favorable age demographics for refractive surgery, a new marketing opportunity is also emerging. A new group, dubbed the “Echo Boomers,” is now coming into refractive offices. (Figure 14)

These are the children of the Baby Boomers. That segment of the market is continuing to grow and will likely be almost as big as the boomer market itself, Dr. Steinert said.

Overall, LASIK clinical outcomes are improving and are going to continue to improve. A better scientific understanding of the procedure drives this. And a better understanding of the biomechanics of the procedure, in conjunction with innovative technology and pharmaceuticals, will continue to drive LASIK forward, Dr. Steinert said.

“I think the clinical improvements will motivate consumers and we will see increased adoption from the current low levels, as well as expansion with new indications and range of treatments,” Dr. Steinert said. “We’re also going to get something of a demographic windfall — a definite ‘echo boom,’ as those people enter the refractive age group.”

Dr. Steinert foresees that indications for LASIK and LASIK-related technologies will continue to expand. However, even with exciting new procedures becoming available, LASIK is still likely to remain at the forefront for some time.

“Although we’re having wonderful new technology develop, and I think that we’re going to have a lot of new tricks and good things to offer patients, LASIK will remain our dominant procedure for the foreseeable future,” he said.

**Citations**

1. Presented at the Annual Symposium of the American Society of Cataract and Refractive Surgery, Washington DC, April 2005

2. Data on file, IntraLase Corporation, Irvine CA
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