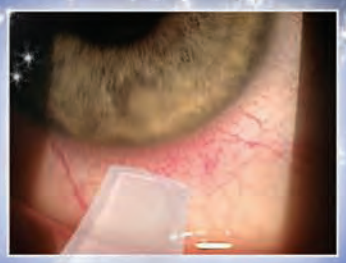
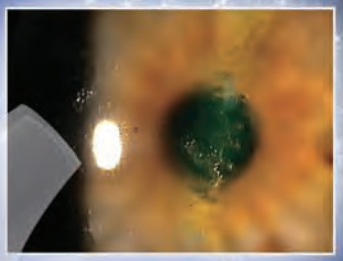
A Supplement to
REVIEW OF OPTOMETRY
June 15, 2010





2010 Clinical Guide to Ophthalmic Drugs

By Ron Melton, O.D.
and Randall Thomas, O.D.

Supported by BAUSCH + LOMB

Current Therapy in Ocular Disease

by Drs. Ron Melton and Randall Thomas

Past recipients of the "Glaucoma Educator of the Year" Award by the American Academy of Optometry

Authors of Review of Optometry*'s annual* Clinical Guide to Ophthalmic Drugs

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- *"They have perfected the tag-team approach with humor, asking each other questions that we would ask."*
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- *If I were to attend only one meeting a year, this would be it.*

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INTRODUCTION

Dear Colleagues:

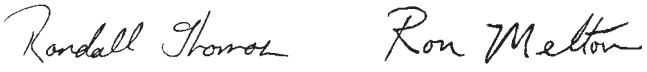
We are grateful to the many colleagues who share with us each year their appreciation of this *Clinical Guide to Ophthalmic Drugs*. It is our honor to be a part of your lifelong learning process.

To all of you consistent, faithful readers, we apologize that every issue is not completely fresh information (only a very few new drugs come to market each year). You all are a solid core of attentive, interested clinicians, and we value your professionalism. However, many of our colleagues, like the authors, have to be exposed to information more than once before it effects a change in their clinical behavior. Furthermore, there are many new O.D.s entering the profession who can benefit from the core principles of medical management. So, please bear with us as we do all we can to bring everyone up to speed.

- In 2010, the big news is that Xalatan is scheduled to lose patent protection in March 2011. This will rock the world of glaucoma patient care, and hopefully will be of huge benefit to our glaucoma patients.
- Valtrex (valacyclovir) and Famvir (famciclovir) have joined acyclovir in the generic camp. This also should be of benefit to many patients.
- A new drug is now available (ganciclovir), marketed as Zirgan by Sirion, and is approved for treatment of epithelial herpes simplex keratitis. Zirgan is likely to displace trifluoridine (Viroptic) from gold-standard status.
- Yet another antihistamine/mast-cell stabilizer, known as Bepreve (bepotastine, Ista Pharmaceuticals), has also come to market.
- Erythromycin, and several other ophthalmic ointments, are readily available again, and this is certainly welcome news.
- For the relatively few glaucoma patients needing an alpha-adrenergic agonist to help control their intraocular pressure, brimonidine 0.2% and 0.15% are now generically available. The 0.2% is the least expensive.
- In the even less frequently prescribed class of drugs, the carbonic anhydrase inhibitors, dorzolamide (Trusopt) is now available in generic form.

As always, we hope the information shared herein will help you better serve the needs of your patients.

Our very best wishes to each of you,



Randall K. Thomas, O.D. Ron Melton, O.D.

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For Perspective: Good Chairside Manner is the Best Policy

"Increasing emphasis on patient-centered care, and other recent developments, should make patient expectations increasingly important ... Honesty was not only the most frequently cited expectation among focus group participants as a whole but also the most frequently expressed expectation area among all subgroups as well."

"The observation that ophthalmology patients place greater emphasis on communication and interpersonal manner than technical interventions is consistent with a previous study, which found that patient satisfaction is more closely linked to patients' perceptions about whether they received nontechnical interventions, such as education, than technical interventions, such as diagnostic tests."

Dawn AG, Santiago-Turla C, Lee PP. Patient expectations regarding eye care: focus group results. Arch Ophthalmol. 2003 Jun;121(6):762-8.

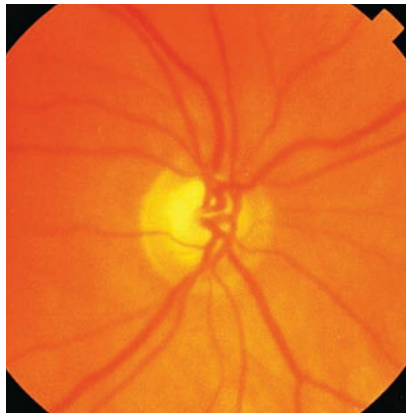
Glaucoma

The challenge in glaucoma is to monitor for progression—especially the rate of progression. Once this is determined, then optimum therapy can be prescribed.

We believe that eye doctors continue to miss glaucoma in wholesale fashion because they either are inattentive to the optic nerve head, or simply fail to act upon their observations—both of which can carry dire consequences.

We have no explanation for the former; however, the "failure to act" scenario can perhaps be explained. If the patient has a normal intraocular pressure, especially in the afternoon (where IOP tends to be at its lowest), then the clinician may simply assume the optic nerve to be physiologically cupped. It is these patients who have suspicious optic nerve cupping that merit another investigative step or two. If the patient was examined in the afternoon, we strongly recommend another intraocular pressure measurement in the early morning within a few days or weeks. Many such "normal tension" glaucomas are simply missed hypertensive glaucomas, because the higher morning time IOP was never detected.

Most importantly, one must not to be lulled into complacency when encountering a suspicious optic nerve head in the presence of a normal intraocular pressure. The most important diagnostic maneuver in such circumstances is to measure the central corneal thickness (CCT)! Many patients with relatively thin physiological corneas (an *independent* risk factor for glaucoma) have measured normal intraocular pressure. These patients can be missed so easily, yet detected with only very minimal effort. Note that a thinned cornea via refractive surgery does NOT confer upon the patient any additional risk of glaucoma, only a reduction in measured IOP.



Glaucoma is all about assessing risk. Does this patient have sufficient risk to justify treatment, or is it in the patient's overall best interest to be followed?

Glaucoma, in large part, is all about assessing risk. Some people have 0.8 cups with IOPs in the 30s and have frank glaucoma. These are the easy ones. It is the 55-year-old patient with a 0.6 to 0.7 cup with a central corneal thickness of 545µm, an IOP of 20mm Hg, an older brother who is being watched for glaucoma, and a normal to borderline retinal nerve fiber layer who is the challenge to "assess risk." Does the patient have sufficient risk to justify treatment, or is it in the patient's overall best interest to be followed every six to twelve months?

At this point in time, everyone has an opinion, but no one knows for sure. In fact, many "glaucoma suspects" remain suspect for many years. If after several years of being followed, there is no evidence of progression, then the patient can finally be declared to have physiologically normal cupping. It must be stressed here that by definition, glaucoma is a "progressive optic neuropathy." Said another way, if there is no progression over five to eight years, then there is most probably no disease. "Progression" is most commonly assessed by documented increase in the C/D ratio, thinning of the retinal nerve fiber layer, and/or visual field compromise.

Regarding visual field progression, it is imperative that any change in perimetry outcome be

documented as repeatable. This typically requires repeating the visual field two to four times in order to confidently declare that true progression is occurring. Such repeat testing is done perhaps every six months. Never believe borderline changes in any visual field unless it can be reproduced on subsequent tests. (More on this critical diagnostic assessment later.)

The measurement of central corneal thickness was shown to be a critical factor in glaucoma assessment via the Ocular Hypertension Treatment Study, as published in June 2002.[1] This incredible revelation allowed for a much enhanced assessment of glaucoma and glaucoma risk. Corneal pachymetry has now become standard of care; yet not all eye doctors have embraced this simple and inexpensive technology.

An example of this disregard of pachymetry is the woman in her 30s who reported that her father was recently diagnosed and treated for glaucoma. She had healthy, pink optic nerves with a 0.2 cup in the central aspect of both optic nerve heads. Her intraocular pressure was 26mm Hg in both eyes, but she had 640µm corneas! It is well established that corneal thickness is the most heritable aspect of the human eye. We have great belief that this woman's father has nothing more than corneal thickness-dictated ocular hypertension and is being treated for a disease he does not have! We strongly urge all optometrists to acquire a corneal pachymeter. We believe that of all the glaucoma assessment technologies currently available, pachymetry offers the best diagnostic power value.

The Ideal Evaluation

Before we get into treatment options, let's describe the ideal glaucoma evaluation:

1. ***Take a really thorough history***, and ask especially about the presence of glaucoma in siblings. Glaucoma does tend to run in families. If your patient is deemed to be at risk for (or to have) glaucoma, be sure to encourage him or her to contact siblings to urge them to have their eyes evaluated for the potential of glaucoma.

2. ***Determine the patient's best corrected vision***.

3. ***Carefully assess pupillary function***, looking especially for a subtle afferent pupillary defect.

4. ***Perform dilated, attentive slit lamp biomicroscopy*** noting any pigment dispersion, iris retroillumination defects, pseudoexfoliation, guttata (which can alter corneal thickness). Also note that topical carbonic anhydrase inhibitors might compromise endothelial function in the presence of endothelial pathology.

5. ***Measure IOP***. Goldmann applanation tonometry is standard of care, so we urge the use of this technology for such measurements. Always note the time the IOP is taken.

6. ***Measure CCT***. Always ask near emmetropes if they have ever had refractive surgery. Note that the CCT reaches stable adult status by age 10.

7. ***Perform gonioscopy***. We prefer the four-mirror gonioscope, as it is quick and efficient.

8. ***Perform binocular indirect ophthalmoscopy***, just to be thorough.

9. ***Do a careful, detailed, high-magnification stereoscopic evaluation of the optic nerve*** head via high-convex (90D, etc.) lens-enhanced slit lamp ophthalmoscopy. This is the single most important aspect of the entire workup.

10. ***Perform standard automated perimetry (SAP)***, preferably with the Humphrey visual field analyzer (HFA-2) using the 24-2 SITA standard or SITA Fast algorithm. (Matrix is in close second place, but is not fully gold-standard.)

11. ***Scan the nerve fiber layer*** (using HRT, GDx-VCC or ECC, or OCT). The premier technology in this category is OCT, because it can provide both retinal/macular tissue assessment, as well as nerve fiber layer analysis. While spectral domain technology is more sophisticated, time domain technol-

Brimonidine

Brimonidine is available in three concentrations: the original 0.2%, which is the least expensive of the three; 0.15%, which is more expensive than the 0.2% formulation; and lastly, 0.1%. Both 0.2% and the 0.15% brimonidine are available generically. The 0.1% concentration is brand-name protected, and is the most expensive. It is known as Alphagan P, from Allergan.

All three strengths are FDA-approved for t.i.d. dosing, which is how they should be dosed as monotherapy. As an additive drug (usually to a prostaglandin analog), however, brimonidine is typically prescribed b.i.d. Interestingly, all three concentrations perform equivalently.

We urge you to have your staff obtain price quotes on brimonidine and other commonly used medicines from a few pharmacies near your office. You'll be amazed at the different prices for this and other medicines.

ogy is amply adequate to provide clinically meaningful measurements of the nerve fiber layer. Remember that none of these wonderful technologies "diagnose" glaucoma; however, they can be a very helpful component within the comprehensive glaucoma evaluation.

12. ***Photograph the optic nerve head.*** Any good retinal camera can provide either two- or three-dimensional documentation of optic nerve head anatomy. Such anatomic comparisons over time (i.e., years) can be useful to document change in the appearance of the optic nerve head. Again, glaucoma is a "progressive" optic neuropathy. So, unless a glaucoma diagnosis is definitive at the initial visit, the challenge is to monitor for "progression," and especially the rate of progression. Once the rate of progression is determined, then optimum therapy can be prescribed.

Finer Points of the Exam

There are a few common diagnostic errors we encounter that need to be addressed. Most of these center around the concept of "micromanagement" of any one of the various diagnostic entities that we have set forth above.

• ***Visual fields.*** These are often highly variable because they generate soft, subjective psychometric data. Therefore, it is vitally important not to believe a defective visual field result unless it correlates with your observation of the optic nerve (or NFL analysis). An isolated, unexplained visual field defect requires re-testing (in days, weeks or months) to either confirm (or deny) the validity of such a visual field defect. There is expert consensus that it may take two to four additional visual field tests to accomplish this. Bottom line: If the visual field correlates to optic nerve anatomy, believe the visual field to be true.

If there is any question at all regarding the validity of the visual

Topical Glaucoma Drugs

BRAND NAME	GENERIC NAME	MANUFACTURER	CONCENTRATION	BOTTLE SIZE
Beta Blockers				
Betagan, and generic	levobunolol hydrochloride	Allergan	0.25% 0.5%	5ml, 10ml 5ml, 10ml, 15ml
Betimol	timolol hemihydrate	Vistakon Pharm.	0.25% 0.5%	5ml 5ml, 10ml, 15ml
Betoptic-S	betaxolol hydrochloride	Alcon	0.25%	5ml, 10ml, 15ml
Istalol	timolol maleate	Ista	0.5%	5ml
Timoptic, and generic	timolol maleate	Aton Pharma, generic	0.25% 0.5%	5ml, 10ml, 15ml 5ml, 10ml, 15ml
Timoptic (preservative-free)	timolol maleate	Aton Pharma	0.25% 0.5%	unit-dose unit-dose
Timoptic-XE, and generic	timolol maleate	Aton Pharma, generic	0.25% 0.5%	2.5ml, 5ml 2.5ml, 5ml
Prostaglandin Analogs				
Lumigan	bimatoprost	Allergan	0.03%	2.5ml, 5ml, 7.5ml
Travatan Z	travoprost	Alcon	0.004%	2.5ml, 5ml
Xalatan	latanoprost	Pfizer	0.005%	2.5ml
Alpha Agonists				
Alphagan P, and generic	brimonidine brimonidine	Allergan, generic	0.1%, 0.15%, 0.2%	5ml, 10ml, 15ml 5ml, 10ml, 15ml
Carbonic Anhydrase Inhibitors				
Azopt	brinzolamide	Alcon	1%	5ml, 10ml, 15ml
Trusopt, and generic	dorzolamide	Merck	2%	5ml, 10ml
Combination Glaucoma Medications				
Combigan	brimonidine/timolol	Allergan	0.2%/0.5%	5ml, 10ml
Cosopt	dorzolamide/timolol	Merck	2%/0.5%	5ml, 10ml

field, always repeat it, and probably more than once (unless the previous questionable defect disappears at the next re-test, which is extremely common). A healthy visual field can generally be believed, but always question the validity of an unexpected or unexplained visual field defect. We generally conduct visual field testing annually, unless there is a medically valid reason to do so sooner.

• ***Pachymetry.*** Forget the conversion tables. Just judge the corneal thickness as thin, normal or thick. Our working ranges are: less than 510µm is thin, and over 590µm is thick. We sometimes use a calculation chart to explain to our patients why they are at greater or lesser risk for developing glaucoma, but this is for patient orientation and education purposes, not for critical clinical management.

• ***Optic nerve head size.*** Large optic nerves tend to have physiologically large cups, and small optic nerves tend to have small cups. Also, glaucomatous cupping tends to evolve more rapidly in a small optic nerve than in a large optic nerve. However, we never use the slit lamp reticule to exactly measure an optic nerve diameter. We simply judge the nerve to be larger than normal or smaller than normal by ophthalmoscopic observation. After a couple of years of clinical experience, this is a relatively easy observation.

Assess Risk

The prime decision in all glaucoma-related cases is: "When do I initiate therapy?" This simple, five-word question is the Holy Grail of clinical decision-making in glaucoma care. This decision is occasionally very clear, yet most of the time it is fraught with anguish. Having acquired considerable clinical experience over the years, we're able to tell patients something like this: "If you were to present to 10 glaucoma experts, probably half of them would treat you and half would simply follow you; I am inclined to just follow you for a while"—or whatever scenario is applicable to the patient at that point in time.

The truth is, knowing the perfect time (if ever) to initiate therapy is based largely on an assessment of risk. Further, if your patient were to seek a second opinion, you have already made it clear to the patient that knowledgeable glaucoma doctors often differ on patient management decisions. Of course, the decision becomes clearer and clearer as you competently and attentively follow the glaucoma suspect patient over the years.

So, how do we appropriately begin therapeutic intervention? While the monocular therapeutic trial is not a foolproof maneuver, we typically do start therapy in one eye and see the patient back about the same time of day (to attempt to factor out any diurnal variation that might be present). If several IOP measurements are made prior to the initiation of therapy, the patient's IOP pattern can be reasonably well established.

For prostaglandins, we generally have the patient return in three weeks, because this time period generally gives these relatively slower-onset drugs time to achieve their full therapeutic effect. For all other drug classes, we have patients back in two weeks.

Beyond the mechanics of a therapeutic trial, it is important that the patient have a meaningful understanding of why they are taking the eyedrops, and what to expect. We always explain that reducing the intraocular pressure will not make their eyes feel better or help them see better.

By the way, we use so-called "glaucoma medicines" for many people who do not have glaucoma. When glaucoma is evident, we use "IOP-lowering medicines" to actively intervene in a disease process. However, a large minority of patients who use these eyedrops are simply modifying a risk factor—elevated IOP.

If a patient has perfectly healthy optic nerves, yet has an IOP of 32mm Hg (and a corneal thickness below 560µm, for example) we could rationally recommend a once-daily eyedrop to reduce this risk factor down to the 25-ish range. If the corneal thickness were 640µm

SAP vs. SWAP in the Detection of Glaucomatous Conversion

"Despite its limitations, standard automated perimetry has become a standard in clinical care across the world. Short-wavelength automated perimetry (SWAP), however, has never gained such widespread acceptance … It is possible that SITA-SWAP will prove to be useful for early detection of glaucomatous conversion. To date, there is insufficient evidence for that. We therefore recommend that clinicians use standard automated perimetry (SAP) rather than SWAP in their daily practices to detect early glaucomatous conversion in patients with ocular hypertension.

"Although early SWAP visual field defects have been suggested typically to precede those in SAP in conversion from ocular hypertension to primary open-angle glaucoma, our prospective, longitudinal follow-up study does not support this suggestion. On the contrary, SAP appears to be at least as sensitive to conversion as SWAP in a large majority of eyes."

van der Schoot J, Reus NJ, Colen TP, Lemij HG. The ability of short-wavelength automated perimetry to predict conversion to glaucoma. Ophthalmology. 2010 Jan;117(1):30-4.

in this same patient, we could perhaps more rationally simply follow the patient every six to 12 months. Therapeutic intervention needs to be based on a comprehensive risk assessment and a thorough discussion with the patient.

Since it would be exceedingly rare to start a patient on therapy at the initial visit, we urge all eye doctors to move slowly, methodically and comprehensively in assessing and treating glaucoma patients. Collect three or four IOP readings at different times of the day. Know the lay of the land before altering the landscape.

Lastly, we try to see our treated patients as infrequently as practical to safeguard their vision. Most patients we see every three to four months, several every six months, and a few patients—who we know to be totally trustworthy and whose disease is well controlled—on an annual basis.

The main reason to see many/most patients is to encourage them to be faithful with their prescribed therapy.

Prostaglandin Pearls

• Although Xalatan and Viroptic are stored long-term under refrigeration, once dispensed to the patient, there is no need to keep these products refrigerated.

Regarding Viroptic, however, since herpes simplex keratitis can be recurrent, we instruct our patients that once the keratitis has resolved and the drops are discontinued, to place any unused medicine back in the refrigerator to store it (until its expiration date) in the event of any recurrence.

Regarding Xalatan, patients whose insurance allows them to get a 90-day supply at one dispensing are generally instructed to keep the two bottles not currently being used in the refrigerator, and to keep the bottle currently in use in a location most conducive to patient compliance. The prostaglandins should never sit in direct sunlight or be exposed to hot temperatures.

• Xalatan loses patent protection (i.e., "goes generic") in March 2011. This will send a shockwave of financial depression throughout the prostaglandin manufacturers' world, and equal joy to millions of patients with glaucoma. While we doubt we will see a major drop in the cost of latanoprost right away, we hope to see considerable financial relief for our patients soon thereafter. This will be a significant defining moment in the natural history of this class of drugs.

• There is little to no reason to switch between the prostaglandins. All three perform clinically identically.

While prostaglandins perform optimally when instilled in the evening, these drops perform excellently regardless of time of instillation. The best time to dose these medicines, then, is when it is most convenient for the individual patient.

• An excellent article in the *Journal of Pharmacology and Therapeutics*, Vol. 20, No. 4, 2004, showed that the ocular hypotensive effect of latanoprost dosed once weekly was "as effective" as when dosed once daily. Based on the evidence gleaned from this study out of Tel Aviv University Medical Center, it would seem rational and prudent to consider q.o.d. or Monday-Wednesday-Friday administration. This would immediately reduce the cost of therapy by approximately 50%. There is no risk in dosing the medicine in this manner; simply recheck the IOP after a month or two to see if target IOP is maintained. If it is, then the goal of effective (and cost-effective) IOP reduction is achieved. It's just that simple!

• Don't forget that, although exceedingly rare, prostaglandins can cause flu-like symptoms and dyspepsia (stomach ache, gastritis). So always listen attentively (or ask proactive questions) when seeing patients for follow-up.

Select Appropriate Therapy

Let's assume we have decided a patient merits IOP reduction, so what drug do we select?

• ***Prostaglandins***. Most of the time, the answer is a prostaglandin, preferably one of the lower-concentration formulations (having less side effect potential) such as latanoprost 0.005% or travoprost 0.004%. All of the prostaglandins perform nearly identically, so prescribing decisions are based on side effect profile for most patients most of the time.

(Note that **Travatan** is no longer available; although **Travatan Z** still is.)

While these drugs may perform optimally when instilled in the evening (or before retiring for those who work second- or third-shift), they perform nearly identically when instilled in the morning time. So, the time of instillation should center around when the patient finds it to be the most convenient. Remember, compliance is the weak link in the treatment chain, so we need to do whatever we can to make adherence most achievable for each patient.

• ***Beta blockers***. Alternatively, if cost is an overriding factor (and cost can compromise compliance), initiate therapy with a non-selective beta blocker such as timolol or

levobunolol; with rare exception, these are the only beta blockers we use. They are available in 0.25% and 0.5% concentrations, and are readily available for about $4 per 5ml at many pharmacies. By comparison, prostaglandins cost about $60 to $80 per 2.5ml.

Since melanin pigments can bind some medicines, we use the 0.5% concentrations for our black patients, and 0.25% for white patients. Furthermore, numerous studies clearly support the use of these two non-selective beta blockers once daily. It is best to have patients instill beta blockers shortly upon awakening for maximum therapeutic effect. Understand that these drugs suppress beta adrenergic tone. Our adrenergic system is active while we are awake, and physiologically asleep while we are asleep. There is little benefit in attempting to pharmacologically suppress a system that is already physiologically suppressed. This is why it is important to dose beta blockers shortly upon awakening.

Beta blockers do little to decrease IOP during the sleep cycle, yet seem to adequately preserve visual

Pearls for Beta Blockers

- Non-selective beta blockers are, by far, the most cost-effective means to lower intraocular pressure. A 5mL bottle sells for about $5.
- The literature consistently states that non-selective beta blockers reduce intraocular pressure about 25%; the prostaglandins, about 30%. Reflect this narrow percentage gap against their cost, and the value difference is staggering.
- The non-selective beta blockers timolol and levobunolol are properly dosed once daily, and shortly upon awakening. Since this class of drug suppresses the adrenergic system (which autonomically "rests" when we sleep), it exerts is most therapeutic effect during waking hours, so instillation upon awakening is maximally therapeutic.
- Timolol and levobunolol are the only two non-selective beta blockers that possess a long enough half-life to enable once-daily administration, and are the only two beta blocker medicines we prescribe.
- We never prescribe more expensive "gel-forming" formulations, since they perform no better than the traditional solution formulations. We never prescribe non-generic beta blocker products because of the expense.
- Whenever we initiate therapy, we ask the patient to dose the medicine every morning for two weeks, but NOT the morning of the follow-up evaluation. This enables us to assess the therapeutic effect over a full 24-hour period.
- Since melanin pigment can absorb some of these medicines, we use 0.5% for our black patients, and 0.25% for our white patients.
- Because of the once-daily simplicity of use, we try a beta blocker as our "add-on" to a prostaglandin when we need additional IOP-lowering.

Beta Blockers and Asthma Patients

Although everyone knows to avoid use of beta blockers in patients with asthma, we would be remiss not to re-stress this "relative" dogma. Why "relative"? Somewhat surprisingly, beta blockers can be safely and effectively used in some asthma patients. Yes, you read this correctly. Ask any internist—that's how we came to learn this. We had a patient who we felt needed a beta blocker to achieve target IOP, yet noticed he was on a systemic beta blocker and had asthma!

This required an explanation. His internist explained that beta blockers need to be used with caution in patients with asthma, but were only relatively contraindicated. Since that time—and always with internal medicine consultation—we have successfully used topical beta blocker eyedrops in a few select patients with asthma when it was necessary to achieve target IOP.

Furthermore, Paul Lama, M.D., who trained as both an internist and ophthalmologist, published his worldwide review of beta blocker use in the November 2002 *American Journal of Ophthalmology*. Here is an excerpt from his conclusions:

"Ophthalmic beta-adrenergic blockers are effective in lowering IOP and have a long history of success and tolerability, despite the known contraindications. However, many of the beta-adrenergic blocker contraindications have been either disproven or there is no definitive evidence to prove a causal link. In fact, it has been decisively shown that these agents administered systemically improve survival in CHF [congestive heart failure]. This review has identified no scientific studies supporting the development of worsening claudication, depression, hypoglycemic unawareness or prolonged hypoglycemia in NIDDM [noninsulin-dependent diabetes mellitus], sexual dysfunction, or impaired neuromuscular transmission with either systemic or ophthalmic beta-adrenergic blockers. Wide acceptance of such traditionally purported side effects has been largely due to propagation of isolated case reports and short series as well as personal communication felt to reflect expert opinion. Based on the published evidence, many more patients are eligible for ophthalmic beta-adrenergic blockers than previously presumed."

For perspective, note that more than 40 million prescriptions for systemic beta blockers are filled each year in the United States. Beta blockers must therefore be assumed to be a very helpful class of drug, and also quite safe.

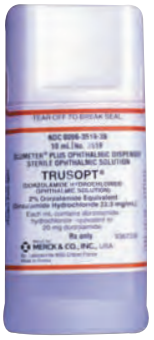
field. Looking at clinical reality, we do not recall an epidemic of uncontrolled glaucoma between the introduction of timolol in 1978 until the introduction of latanoprost in 1996. So, we do not truly know what to make of this finding, but perhaps inexplicably, it does not seem to be a major issue in glaucoma patient care. Just for perspective, all current "combination" glaucoma drugs contain 0.5% timolol. This should be very clear evidence that beta blockers are noble players in the care of patients with glaucoma.

The vast majority of our glaucoma patients are successfully managed with either a prostaglandin, or a beta blocker, or a combination of the two. This is relatively inexpensive, and requires a drop either once daily, or if using both, b.i.d.

If there is non-response (or minimal response) to one or both of these medicines, then the clinical decision-making becomes quite a bit more challenging.

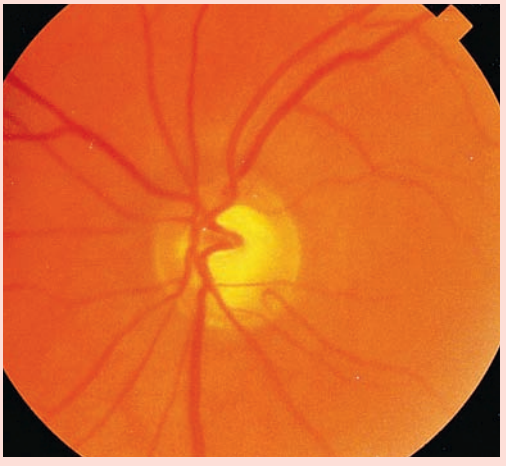
• *Carbonic anhydrase inhibitors and alpha adrenergic agonists*. If there is a need to move beyond a prostaglandin and/or a non-selective beta blocker, then do a therapeutic trial of either brimonidine or a topical CAI—brinzolamide or dorzolamide. Both of these drugs are FDA-approved for t.i.d. therapy, and when used as monotherapy, will best serve the patient as one drop every eight hours. The problem is that there is an inverse relationship between dosing frequency and compliance. In recognition of this reality, these drugs are generally prescribed b.i.d. (approximately every 12 hours). Brimonidine is generically available in its original concentration of 0.2%, in a second rendition of 0.15%, and also (by the brand name, **Alphagan P**) as a 0.1% concentration. We recommend the 0.15% generic product in most patients most of the time, as this nicely balances cost and side effect potential.

The CAIs are known by their brand names: **Trusopt** (dorzolamide, Merck; and generic) and **Azopt** (brinzolamide, Alcon). Since brimonidine seems to be slightly more effective than a topical CAI, we generally try it as our "Plan B" of choice. There is some thought that a CAI is a more effective "add to" drug to a prostaglandin than is a beta blocker. Even if this is true, addition of a CAI (or brimonidine) requires a patient to instill a drop t.i.d., as opposed to just b.i.d. with a beta blocker—we believe "simpler" here trumps perhaps "more effective." Whatever the case, the difference is almost invariably clinically insignificant.



• *Combinations*. What about the "combination" drugs, such as

When to Treat?



Of course, the most challenging decision in glaucoma management is "when" to treat. This requires a keen intellect, a thorough clinical evaluation, and the wisdom to know how to assimilate the clinical picture so as to maximally care for the patient. Once a decision to treat has been made, it now falls to intelligent trial-and-error to find the least amount of medicine to achieve and maintain target IOP for each individual patient. Fortunately, very few people who present in a timely manner ever become symptomatic to their disease.

But, for those people who see the eye doctor every 10 to 20 years (and there are a bunch), undiagnosed glaucoma can be so advanced that the most skilled trabeculectomist cannot save the eye from NLP. There is good reason for all people to see an eye doctor every two or three years.

By the way, when did you last have *your* eyes truly examined? We personally know two colleagues who now have very advanced glaucoma because they did not access eye care in a timely manner. Please take as good care of yourselves as you do your patients.

0.5% timolol with 0.2% dorzolamide (**Cosopt** [Merck], which has been generic since October 2008) or 0.5% timolol with 0.2% brimonidine (**Combigan** [Allergan], an expensive combination of two relatively inexpensive generic products)? Let's become thinking prescribers rather than reflex prescribers. We know that timolol is only needed once daily, and we know that brimonidine and the CAIs are most effective at their FDA-approved labeling of t.i.d. So, does it even make common sense to package these two drugs together? We urge all clinicians to try timolol alone as a therapeutic trial, and to only "add" dorzolamide or brimonidine if truly needed to achieve target IOP. These are rare occasions.

Regarding "maximal medical therapy," we do feel that a prostaglandin and one of these combination drugs would represent such, and would require instilling a drop t.i.d.

In summary, glaucoma can either be easily diagnosed (such as frank glaucoma), or it can be very challenging—sometimes requiring one to follow a glaucoma suspect for many years before circumstances evolve to the point where therapeutic intervention is deemed appropriate. ■

1. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002 Jun;120(6):714-20.

Neuroprotection in Glaucoma Therapy

As there is still some lingering confusion regarding "neuroprotection," we thought it might be helpful to share this information, which was first printed in our *Clinical Guide to Ophthalmic Drugs* in 2002. It is still relevant in 2010.

What About Neuroprotection? Clearly, there are factors beyond IOP that cause glaucomatous optic neuropathy in some patients, particularly where the IOP is never found to be above the upper limits of normal. Apoptosis (genetically programmed cell death) is the centerpiece of neuroprotective research. The causes for apoptotic cell death are the focus of intensive investigation. It may well be that in a few years gene therapy will indeed play a central role in glaucoma management. For now, as sad a state as it may be, all we can do is decrease IOP. Fortunately, this proves to be sufficiently effective in the vast majority of patients with glaucoma.

There is a lot of talk about this concept of neuroprotection and its potential role in glaucoma. We feel it is important to share the perspectives of several authorities in an effort to bring objective enlightenment to this concept.

• "Some drugs have some very interesting properties in experimental and animal models, but I know of no evidence that these results are necessarily relevant to glaucoma. I don't believe we have a drug that has a proven benefit in glaucoma beyond its IOP-lowering effect."

—Robert D. Fechtner, M.D., New Jersey University of Medicine and Dentistry
Eye World, January 2001

• "We do not have neuroprotective drugs that we can prescribe. We do not have devices for retarding ganglion cell loss as of yet, with the exception of pressure-lowering agents."

—Evan Dreyer, M.D., Ph.D., Scheie Eye Institute, University of Pennsylvania
Primary Care Optometry News, February 2001

• "At this time, there is not a drug available to you that has known neuroprotective features."

—Harry Quigley, M.D., Wilmer Ophthalmological Institute
Audio-Digest Ophthalmology, April 1998

• "Although the data on neuroprotection with brimonidine in animal models is compelling, there is not yet any data regarding neuroprotection with Alphagan in glaucoma patients."

—Louis Cantor, M.D., Indiana University School of Medicine
Expert Opinion on Pharmacotherapy, May 2000

• "In the field of glaucoma, this past year [1999] was characterized by a lot of hoopla and some substance. Leading the hoopla camp is the whole area of neuroprotection … one of the most important questions that needs to be answered has to do with why some nerves are sensitive, and other nerves are resistant to the damaging effects of intraocular pressures."

—George Spaeth, M.D., Wills Eye Hospital
Yearbook of Ophthalmology, 2000

• "There is currently no solid evidence that any drug that has a blood-flow change or a neuroprotective aspect has any advantage in the treatment of our glaucoma patients."

—Thom Zimmerman, M.D., Ph.D., University of Louisville
Audio-Digest Ophthalmology, February 2000

Overview of Oral Medicines

There are only a handful of oral medicines germane to eye care. Fortunately, O.D.s in most states can now prescribe most of these oral medicines.

As optometrists, the mastery of a handful of oral medicines can be immensely helpful in effecting a cure for many of the ocular conditions we see. Having this "extended reach" of oral medicines is often necessary to meet the clinical needs of our patients.

The most common use of oral medicines is in the treatment of bacterial infections, most notably of the eyelids. Oral prednisone to quell inflammation, and antivirals for the treatment of zoster conditions, are also oral medicines upon which we heavily rely.

There are few oral medicines germane to ophthalmic patient care. The classes most commonly used are antibiotics, corticosteroids, antivirals, analgesics and carbonic anhydrase inhibitors. Since oral therapy is becoming more widely embraced by doctors of optometry, we want to examine the clinical attributes of these medicines in by providing an overview of select drugs from each of these classes, and some of the specific clinical entities for which these drugs can be used to restore health.

There are numerous drugs in some of these classes; the ones we've selected to discuss are those most commonly used in eye disease management. Since antibiotics are the most frequently prescribed, let's begin with them.

Oral Antibiotics

• ***Penicillins***. The prototypic antibiotics are the penicillins and the synthetic penicillins. By and large, penicillins are rarely used in eye care because most staphylococcal species produce penicillinase, an enzyme that degrades the clinical efficacy of the penicillins.

There are, however, certain penicillins that are "penicillinase-resistant." The classic one is dicloxacillin, which is generic and has been for more than 20 years. The standard dicloxacillin dosage is 250mg q.i.d., and it can be taken without regard to meals. There is some question as to whether this drug can be dosed at 500mg b.i.d.; we have had clinical success with this dosage, but our pharmacological colleagues tell us that because of the drug's relatively short half-life, it is probably best dosed at 250mg q.i.d. for one week.

Amoxicillin is the classic synthetic penicillin. To be clinically effective against bacterial species producing penicillinase, it must be formulated with a chemical known as clavulanic acid, which potentiates the amoxicillin and protects it against the degrading effects of penicillinase. This "combination" drug is commonly known as **Augmentin** (GlaxoSmithKline), and is another excellent choice in combating most common eye and eyelid infections. It is prescribed as 500mg, 875mg, or 1,000mg b.i.d. for one week. The 500mg and 875mg strengths are generically available, while the 1,000mg is still brand-name protected. The dosage is determined by the severity of the clinical condition. For most patients most of the time, we prescribe 875mg b.i.d. for one week. For those patients with less severe disease, choose 500mg b.i.d. For patients with more severe disease, prescribe 1,000mg b.i.d. for one week.

People with an allergy to penicillin have three choices: a cephalosporin, a macrolide, or a fluoroquinolone.

• ***Cephalosporins***. Cephalosporins are closely related to penicillins, so a severe allergy to penicillin precludes the use of these drugs. Internists with whom we have consulted tell us that the selection of a cephalosporin is common for patients who have had a minor adverse reaction to penicillin; however, if the patient does indeed give a history of life-threatening anaphylaxis, then we would not prescribe any cephalosporin. Thus,

in most patients with a history of penicillin anaphylaxis, choose either a macrolide or a fluoroquinolone.

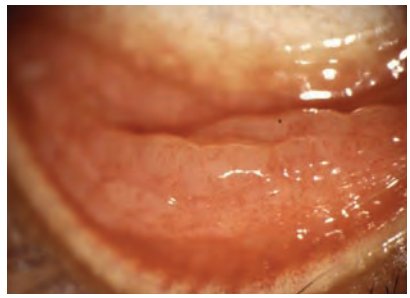
When an antibiotic is indicated, many doctors simply start with a cephalosporin (most commonly cephalexin). Cephalexin is generically available, but is commonly known by its brand name **Keflex** (MiddleBrook Pharmaceuticals). The usual dosage is 500mg b.i.d. for one week.

There are many cephalosporins; however, cephalexin is a real workhorse in clinical practice. Note that there is a 5% to 10% cross-sensitivity with the penicillin, so be attentive with your history prior to prescribing any orally administered medicines.

• ***Macrolides***. The macrolides are represented by erythromycin, clarithromycin and azithromycin. The prototypic representative of this class is erythromycin. It's rarely used for first-line therapy, but is very commonly used as a second choice. Because of its Class B pregnancy rating, erythromycin is the darling of obstetrical medicine when an antibiotic is needed. Erythromycin is commonly prescribed at 500mg t.i.d. for one week.

Clarithromycin is rarely used in eye care, whereas azithromycin is an excellent agent against chlamydial infections. Azithromycin is available in 250mg tablets, 500mg tablets, 1,000mg oral suspension, and **Zmax** (Pfizer), a 2,000mg extended-release oral suspension. One dose of either 1,000mg or 2,000mg azithromycin (in any form) is chlamydiacidal in most cases. Other than in chlamydial infections and/or in pregnancy, we never use a macrolide as a first-line antibiotic.

• ***Fluoroquinolones***. The fluoroquinolones are excellent, broad-spectrum antibiotics. Since less expensive drugs are available (such as cephalosporin), this class is usually reserved for use when there is true penicillin anaphylaxis.



Topical therapy is useless for chlamydial conjunctivitis. The treatment is simple: one 1,000mg dose of oral azithromycin.

While there are several fluoroquinolones available, we generally select **Levaquin** (levofloxacin, Ortho-McNeil). Levofloxacin is a favorite of our local infectious disease specialists, and with regard to nationwide prescribing patterns, is by far the most popular oral drug in this class. (Of course, by virtue of its popularity, and therefore its widespread use, it means this drug will eventually succumb to resistance.)

The usual dosage for levofloxacin is 500mg once daily for one week. In most situations when an antibiotic is indicated, and there is a history of penicillin anaphylaxis, we prescribe levofloxacin.

Oral Corticosteroids

Corticosteroids are often viewed, or approached, with distinct clinical hesitation. Such hesitation is likely borne out of the potential for *long-term* side effects from corticosteroids, and the timidity of teaching on this class of drugs.

However, the clinical wisdom of short-term use of these drugs demonstrates their awesome healing powers and their very few temporary side effects. Of course, for maximum patient care, an accurate diagnosis is essential, regardless of the medicine prescribed.

Corticosteroids can be very helpful for a wide variety of acute inflammatory eye, orbital and eyelid conditions. The universal workhorse of this class is generic prednisone, generally dosed at 40mg once daily, and tapered over a few days to two weeks, depending upon the severity of the presentation and the size of the patient. A modicum of clinical "art" and experience is needed for precise prescribing. Corticosteroids are pregnancy rated as Category C.

Since prednisolone is commonly available in 10mg tablets, prescribing is made mathematically easy. There are also "dosepaks" that can be used. The most common dose pack contains 4mg tablets, taken as six tablets (24mg daily dose) on day one, and then tapered by a reduction of 4mg per day until day six, when only a single 4mg tablet is taken. However, a starting dose of 24mg is often insufficient, so we rarely prescribe dose packs.

There are also now available generically 5mg and 10mg "dosepaks," which provide a starting dose of 30mg and 60mg respectively. These are prepackaged just like the original 4mg pack, and also provide a six-day course of treatment. We rarely use these dose packs because we prefer more control over dosing. For example, in a patient with pronounced facial and orbital allergic dermatitis, we would commonly dose 60mg for one to two days, then 40mg for two days, then 20mg for two days and then stop. Such prescribing is highly variable, depending upon the severity and nature of the clinical condition.

Some conditions, such as orbital pseudotumor, may require higher initial dosing. We generally divide the dose at 60mg and higher, so that 30mg is taken b.i.d., 40mg b.i.d. (if 80mg is prescribed), etc. Steroids are best taken with meals

to minimize the possibility of gastrointestinal upset.

A little perspective: The dosage for acute optic neuritis and giant cell (cranial/temporal) arteritis is 1,000mg of methylprednisolone (500mg q12 hours) IV daily for three days. By comparison, the dosages we use orally are considerably more tame.

Oral Antivirals

The antivirals are routinely employed in the management of ocular and dermatologic herpetic disease.

Acyclovir (ACV), valacyclovir (**Valtrex**, GlaxoSmithKline) **Famvir** (famciclovir, Novartis) are now all available generically. Because ACV has a short half-life, it is dosed five times daily (roughly every 3 1/2 hours), whereas valacyclovir and famciclovir, having longer half-lives, are dosed t.i.d. (roughly every eight hours). They are all relatively clinically equivalent.

The special chemistry of all these medicines confers upon them great clinical safety. Let us explain: All of these medicines are in fact placebo in nature until they are converted by virally expressed thymidine kinase into active medicine through a process known as phosphorylation. The virally-activated drug now rapidly, effectively and non-toxically eradicates viral replication, resulting in clinical cure. The drug is minimally uptaken into non-virally infected cells, which renders such excellent safety. The dosage is fixed, and can therefore be rotely memorized.

One distinction, however, is made between varicella zoster (shingles) and herpes simplex disease. Varicella zoster virus infection is the prime target disease of these antivirals; therefore, their standard prescribing dosages are for the treatment of such varicella infections, almost exclusively shingles. For acyclovir, the dose is 800mg five times a day for one week; for valacyclovir, the dose is 1,000mg three times daily for one week; and for famciclovir, it is 500mg three times daily for one week.

Since the herpes simplex virus (HSV) is less virulent than is the varicella zoster virus, herpes simplex requires less antiviral to achieve virucidal levels; in fact, it is prescribed at exactly half the standard anti-zoster dosage. Thus, to treat any HSV disease, the dosage of acyclovir is 400mg five times daily for one week; for valacyclovir, it is 500mg three times daily for one week; and for famciclovir, it is 250mg three times daily for one week. All dosages are used for seven to 10 days, most often for one week. It's simple, really, but you may want to keep this table handy:

To Treat Shingles (VZV), Give Double the Dose Used for HSV

Antiviral Drug	Dosing for Varicella Zoster	Dosing for Herpes Simplex
Acyclovir	800mg 5x q.d. x 1 week	400mg 5x q.d. x 1 week
Valacyclovir	1,000mg t.i.d. x 1 week	500mg t.i.d. x 1 week
Famciclovir	500mg t.i.d. x 1 week	250mg t.i.d. x 1 week

Acyclovir is available in 200mg capsules, 400mg and 800mg tablets, and in a 200mg-per-teaspoon (5ml) banana-flavored oral suspension. Valacyclovir comes in 500mg and 1,000mg tablets. Famciclovir is available in 125mg, 250mg and 500mg tablets. All the oral antiviral medicines are Pregnancy Category B.

The only precaution for these antivirals centers around kidney function, as all of the antiviral drugs are eliminated via the urine. So always ask patients, especially older patients, about any known renal disease. Patients with clinically significant kidney disease are usually aware of such. Should you encounter an older patient with acute shingles whose renal function is impaired, there are computer-based algorithms and formulas to quickly and easily determine the appropriate dosage. You will need to contact the patient's physician or nephrologist/urologist to obtain the glomerular filtration rate and/or creatinine clearance rate.

Once this information is in hand, your physician partner or pharmacy partner can calculate the dosage of the antiviral for you. This is a very standard and routine maneuver. This situation occurs very rarely; however, in the face of such kidney disease, the dosage is reduced. Since the drug is not readily excreted through the kidneys, it remains at a chemotherapeutic level for a longer period of time.

Other than this one wrinkle, antivirals are safe, highly effective medicines for treating all stripes of herpetic viral disease.

Analgesics

Usually, a topical cycloplegic agent and/or a topical NSAID sufficiently control ocular pain; the cycloplegic is used for uveitic conditions, and the NSAID for ocular surface disorders.

However, there are times when oral therapy is needed to keep the patient tolerably comfortable. For perspective, an opioid analgesic (hydrocodone/acetaminophen) is, by far, the most frequently prescribed oral drug in the United States.[1]

Fortunately, eye-related pain, which can certainly be intense, is invariably short lived. Corneal abrasions, recurrent erosions, inflammatory keratitis, severe iritis and some

eyelid processes are common causes of eye pain that might require supplemental oral analgesia. The most straightforward approach is to ask patients what they generally use for pain. The most common answers are extra-strength acetaminophen and ibuprofen, and these usually carry the patient through.

Acetaminophen (N-acetyl-para-aminophenol, or APAP) is indeed an excellent analgesic, which also has antipyretic (fever-reducing) properties. It is known commonly by its original brand name Extra Strength Tylenol (McNeil), but generics are now ubiquitous. Acetaminophen is synergistic with oral narcotic analgesics and is commonly found as a component to most such drugs.

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are likewise very broadly used and are generically available. Ibuprofen is available over-the-counter as 200mg tablets or capsules. The optimum dosage of ibuprofen is 1,600mg per day. It is most often dosed as two 200mg tablets taken every four hours. This dosage is generally sufficient and approximates that of a Schedule III opioid.

There is an abundance of oral opioid analgesics. (The best we've read on the topic of pain control is, "Drugs for Pain," published in *The Medical Letter*, Vol. 42, issue 1085, August 21, 2000, www.themedicalletter.com. If you want a quick, thorough, and clinically relevant overview on this topic, we highly recommend this article.) Narcotic prescribing requires state statutory authority (the Optometric Practice Act), and formal registration with the Drug Enforcement Administration (DEA).

Narcotics are available at five scheduled levels. We will focus mostly on Schedule III drugs, which include codeine and hydrocodone, by far the most prescribed schedule.

Tylenol #3 has historically been the workhorse in this class of drugs. It is a combination of 30mg of codeine and 300mg of acetaminophen. Because of its propensity to cause nausea, and the realization that hydrocodone is more effective for controlling pain, it has lost considerable ground to hydrocodone as the Schedule III favorite. All narcotics can cause nausea, so it is always best to take them with food.

Abuse Alert for Analgesics

Beware of weird histories, weird presentations, and weird patients who know more about this class of drugs than the doctor. These patients may be "narcotic-seeking." People have been known to harm themselves (Munchausen syndrome) in order to extract a prescription from a doctor.

Hydrocodone with acetaminophen is the most commonly prescribed narcotic analgesic, and one with which we all need to be familiar and comfortable. While generic, these are commonly referred to by their original brand names **Lortab** (UCB Pharma) and **Vicodin** (Abbott), but signed as "generic substitution permitted" on the prescription pad:

- Lortab contains 2.5mg hydrocodone with 500mg APAP.
- Lortab 5 contains 5mg hydrocodone with 500mg APAP.
- Lortab 7.5 contains 7.5mg hydrocodone with 500mg APAP.
- Lortab 10 contains 10mg hydrocodone with 500mg APAP.
- Vicodin contains 5mg hydrocodone with 500mg APAP.
- Vicodin ES contains 7.5mg hydrocodone with 750mg APAP.
- Vicodin HP contains 10mg hydrocodone with 650mg APAP.

For most patients most of the time, we simply write for Vicodin, and sign over the "generic permissible" line on the prescription pad. If you feel your patient needs 7.5mg or 10mg of hydrocodone, then write accordingly. The factors that determine the level of analgesia are the patient's general threshold for pain, the nature of the injury or condition, and the patient's perception of the pain's intensity. Generically speaking, the greater the pain, the more drug is needed to achieve pain control.

Common dosing of any of these narcotic analgesics is one tablet p.o. every four to six hours p.r.n. for pain. The quantity of drug prescribed by the doctor is a clinical judgment. We typically dispense 10 or 12 tablets, and spell out the number (i.e., "ten" rather than "10") to prevent numeric tampering.

Schedule II narcotics include oxycodone with APAP. These drugs do offer a slight increase in analgesia control. The common players are **Tylox** (Ortho-McNeil) and **Percocet** (Endo Pharmaceuticals). Tylox contains 5mg of oxycodone and 500mg of APAP. Percocet is most commonly prescribed as 5mg of oxycodone with 325mg APAP.

Schedule III drugs can be telephoned or faxed to a pharmacy; Schedule II drugs can only be dispensed with a written prescription.

In summary, the opioid analgesics are a safe and effective class of drugs that can help patients with select conditions gain tissue restoration with minimal discomfort. The risk of addiction occurs with long-term use of Schedule II or Schedule III drugs; not for a day or two as in the treatment of painful eye conditions. ■

1. IMS Health web site. 2009 Top Products by U.S. Dispensed Prescriptions. www.imshealth.com (Accessed May 31, 2010.)

The Simplicity of Allergy Management

Allergy management is rather straightforward. Identify the predominant symptoms —and the signs—then treat accordingly.

For the most part, when a patient presents with symptoms of a dry, scratchy, itchy, burning and gritty feeling, this is a patient suffering from "dry eyes." Even though itching is a component of the constellation of presenting symptoms, this subcomponent itching is likely an opportunistic expression resulting from ocular surface tear film dysfunction, i.e., dryness. This dry eye-associated symptomatic itching is best managed by treating the underlying primary dry eye. This is extensively discussed under the dry eye section.

On the other hand, if itching is the predominant symptom, drug selection is dichotomous:

If there are minimal associated signs of allergy, such as chemosis, conjunctival injection, and/or eyelid edema, along with the predominant itching, then an antihistamine/mast cell stabilizer is an excellent clinical approach. Within this class, there are five drugs:

- azelastine (**Optivar,** Meda Pharmaceuticals)
- bepotastine (**Bepreve,** ISTA Pharmaceuticals)
- epinastine (**Elestat,** Allergan)
- ketotifen (**Zaditor,** Novartis; now available generically and OTC)
- olopatadine (**Patanol/Pataday,** Alcon).

Notwithstanding fine differences, all of these antihistamine subtype 1 receptor blockers nicely suppress ocular itching. All are dosed initially b.i.d. (except Pataday, which is dosed once-daily). We recommend after two weeks at b.i.d., try reducing these to once-daily as "maintenance" therapy. In our experience, once symptomatic itching has been brought under control, it takes less pharmacological intervention to maintain control.

Perhaps the best news for the consumer is the loss of patent protection for Zaditor. Ketotifen is now available generically and OTC. There are several brand-name OTC ketotifen preparations, such as **Alaway** (Bausch + Lomb),

Update on Bepreve

Bepreve (bepotastine, ISTA Pharmaceuticals) is the first new topical ophthalmic drug for allergic conjunctivitis approved in several years.

Here is *The Medical Letter*'s summary statement, from February 8, 2010, regarding Bepreve: "Bepotastine besilate 1.5% ophthalmic solution (Bepreve) is likely to be effective for treatment of ocular itching associated with allergic conjunctivitis. There is no evidence that it offers any advantage over other ophthalmic H_1-antihistamines."

(*The Medical Letter*, www.medicalletter.org, is an independent, peer-reviewed, nonprofit publication that offers unbiased critical evaluation of drugs, with special emphasis on new drugs. It is completely independent of the pharmaceutical industry.)

Furthermore, this same article includes a cost comparison on the antihistamine/mast cell stabilizing drugs. All drugs in this class cost about $100 for a standard size bottle, except for generic ketotifen (Alaway, Claritin Eye, and Zaditor), which was less than $15.

Since Bepreve (Rx) and Alaway (OTC) come in 10mL bottles—compared to 5mL for most other topical allergy drugs—these clearly offer the most value per drop. We should be mindful of these facts when we place pen to prescription pad.

Claritin Eye (Schering-Plough) and **Refresh Eye Itch Relief** (Allergan). All come in 5mL bottles (except for Alaway, which comes as a 10mL bottle.) Interestingly, our casual observations in a variety of pharmacies reveal that the cost of 10mL Alaway is very near (and occasionally cheaper) than the price of its 5mL competitors. So, it should be clearly evident that OTC Alaway is the most cost-effective way to suppress ocular itch.

If there are one or more concurrent signs of allergy, such as conjunctival redness, chemosis, and/or eyelid edema, along with the predominant itching, then a topical corticosteroid such as **Alrex**, Lotemax or FML ophthalmic suspension would be more appropriate treatment.

The only other decision tree involves frequency of instillation, which could be q2h for two days, then q.i.d. for one week, followed by b.i.d. for one more week. Once the inflammatory signs are controlled, then consider switching the patient to an antihistamine/mast cell stabilizer for ongoing symptom control. Long-term treatment with Alrex b.i.d. as maintenance therapy can be done, if need be.

According to a conversation we had with Mark Abelson, M.D., a world-renowned ocular allergist at Harvard Medical School, there is little or no clinical use for pure mast cell stabilizing drugs. He says that the antihistamine/mast cell stabilizer drugs more effectively stabilize the mast cell membranes than standalone mast cell stabilizers such as pemirolast (**Alamast**, Vistakon), nedocromil (**Alocril**, Allergan), or cromolyn sodium (generic). Based on this expert opinion, we no longer prescribe these pure mast cell stabilizers.

Remember, allergy is an expression of inflammation. Cold compresses can be helpful in almost all ocular surface inflammatory diseases. (Infectious processes, on the other hand, are commonly helped by the application of warm soaks.)

In summary, if itching is not the primary symptom, be sure to consider dry eyes as the foundational condition and treat accordingly. If itching is primarily expressed, determine if it is an isolated symptom or if it is associated with concurrent inflammatory signs, and then treat accordingly.

Remember:

• *Symptoms only*—use an antihistamine/mast cell stabilizer.

• *Symptoms with signs*—use a steroid such as Lotemax, Alrex or FML.

Actually, allergy management is very straightforward. ■

Ocular Allergy Medicine Profile

BRAND NAME	GENERIC NAME	MANUFACTURER	PEDIATRIC USE	BOTTLE SIZE(S)	DOSING
Acute Care Products					
Acular LS	ketorolac tromethamine 0.4%	Allergan	3 years	5ml, 10ml	q.i.d.
Alaway (OTC)	ketotifen fumarate 0.025%	Bausch + Lomb	3 years	10ml	b.i.d.
Alrex	loteprednol etabonate 0.2%	Bausch + Lomb	12 years	5ml, 10ml	q.i.d.
Bepreve	bepotastine besilate 1.5%	ISTA	2 years	10ml	b.i.d.
Claritin Eye (OTC)	ketotifen fumarate 0.025%	Schering-Plough	3 years	5ml	b.i.d.
Elestat	epinastine HCl 0.05%	Allergan	3 years	5ml	b.i.d.
Emadine	emedastine difumarate 0.05%	Alcon	3 years	5ml	q.i.d.
Optivar	azelastine hydrochloride 0.05%	Meda	3 years	6ml	b.i.d.
Pataday	olopatadine hydrochloride 0.2%	Alcon	3 years	2.5ml	q.d.
Patanol	olopatadine hydrochloride 0.1%	Alcon	3 years	5ml	b.i.d.
Refresh (OTC)	ketotifen fumarate 0.025%	Allergan	3 years	5ml	b.i.d.
Zaditor (OTC)	ketotifen fumarate 0.025%	Novartis	3 years	5ml	b.i.d.
Chronic Care Products					
Alamast	pemirolast potassium 0.1%	Vistakon Pharm.	3 years	10ml	q.i.d./b.i.d.
Alocril	nedocromil sodium 2%	Allergan	3 years	5ml	b.i.d.
Alomide	lodoxamide tromethamine 0.1%	Alcon	2 years	10ml	q.i.d.
Crolom	cromolyn sodium 4%	Bausch + Lomb	4 years	10ml	q.i.d.
Opticrom	cromolyn sodium 4%	Allergan	4 years	10ml	q.i.d.

Insights Into Adenoviral Infections

A keen understanding of the natural history and pathophysiology of adenoviral infection is crucial to precise management. To maximize the therapeutic response, initiate treatment as early as possible.

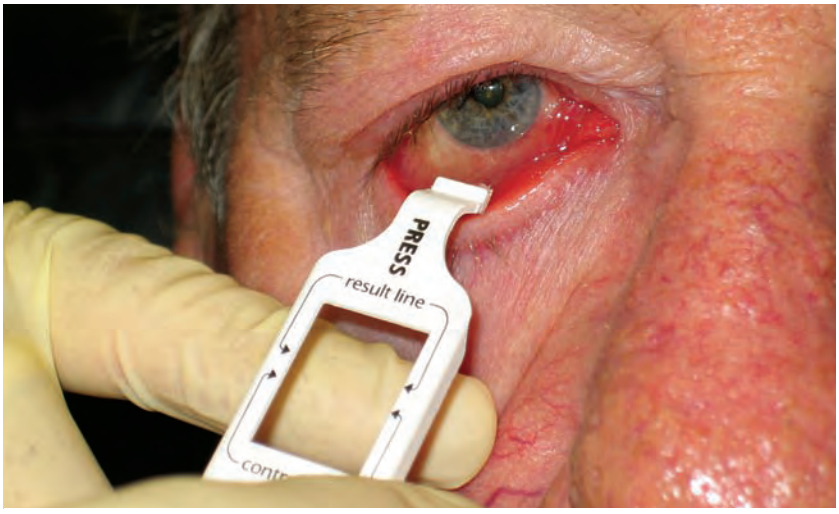
Following are two diametrically opposed statements. You decide which one is true:

"Since viruses incorporate themselves within host cells and use host cell machinery for replication, they are notoriously hard to treat without unwanted toxic effects. Adenoviruses are no exception, as there are currently no available treatments for these diseases, although most infections typically resolve themselves."

Review of Ophthalmology, *March 2010*

"Dear Doctors, you know it never fails—go to a meeting and then see the very thing the lecturer was discussing. Well, I had a patient with the worst EKC I had ever seen—started in one eye, then the other, and now comes in wearing two pairs of sunglasses and miserable. I gave her the bilateral Betadine treatment protocol late Wednesday afternoon, and the staff paid close attention. (You know, 'Does he really know what he is doing? – Watch.') She returned this morning, less than 48 hours later, with only trace injection, no infiltrates, smiling, no sunglasses, and headed to school! Thanks for making me look like a genius!"

–E-mail correspondence, November 20, 2009



If diagnosis of adenoviral disease is elusive, the RPS Adeno Detector may help.

So, how do we reconcile these apparently contradictory statements? We probably have to resort to such observations as "the proof is in the pudding," and just good, old-fashioned common sense. We're privileged to speak to many thousands of our colleagues each year, and in inquiring of these highly diverse audiences, we discover two consistent findings: Very few O.D.s have performed Betadine treatment for patients with epidemic keratoconjunctivitis (EKC). And of those who have, 100% of them have had excellent success. This, too, is difficult to reconcile—this treatment is unbeatable, yet so few eye doctors use it.

To that end, we set forth the following Betadine protocol for acute EKC, which we have successfully used more than 200 times.

In using this Betadine protocol, it is important to understand the natural history of adenoviral infection. There are approximately eight days of *latency* between the

time of viral acquisition and overt disease expression. Then, there are approximately eight days of *active disease*, when the eye is injected and uncomfortable. It's during this acute infectious stage that viral eradication via **Betadine 5% Sterile Ophthalmic Prep Solution** (povidone-iodone, Alcon) is most beneficial to the patient. Just as with the oral antivirals in treating herpes simplex or herpes zoster infections, the earlier in the acute disease phase that you can intervene, the more beneficial the therapeutic effect.

Let's look at the clinical features of acute EKC. Patients typically present with a history of acute redness starting in one eye, then spreading to the fellow eye in two to three days. A watery discharge is a constant feature. A palpable preauricular lymph node is commonly detected (if you feel for it) on the side of the initially infected eye. In more advanced cases, the bulbar conjunctiva can demonstrate multiple petechial hemorrhages, most commonly seen superiorly.

By contrast, bacterial conjunctivitis can have variably expressed microvascular injection of the conjunctiva and evident mucopurulent discharge. Only in "hyperacute" bacterial conjunctivitis is there evident preauricular lymphadenopathy.

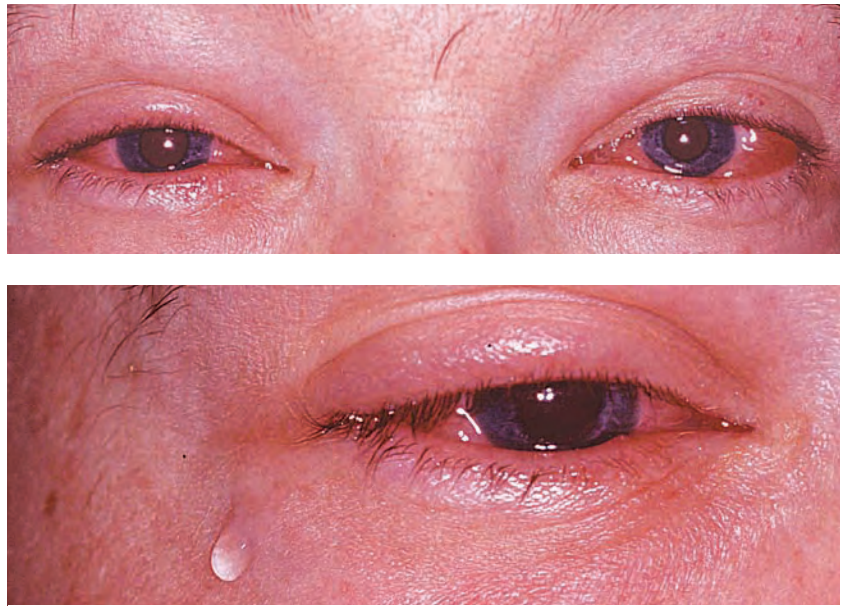
If diagnostic certainly is elusive, the RPS Adeno Detector (www.rps-tests.com) may be helpful.

The EKC-Betadine Protocol

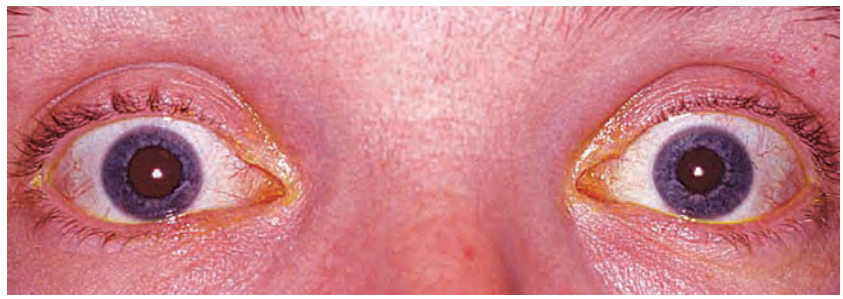
When we encounter a patient with moderate to advanced EKC, we generally use the following **EKC-Betadine Protocol**.

- By history, rule out any allergy or sensitivity to iodine, the molecular backbone of Betadine.
- Instill a drop of 0.5% proparacaine into the eye(s), since Betadine can sting upon instillation.
- Because Betadine can cause mild stippling to the corneal epithelium resulting in marked stinging, instill a drop or two of a topical NSAID prior to instillation of the Betadine.
- Now instill four to six drops of Betadine into the eye(s).
- Ask the patient to gently close the eyes and roll them around to ensure thorough distribution of the Betadine across the ocular surfaces.
- After one minute, lavage out the Betadine (to avoid any unnecessary toxicity and discoloration of the tissues) with any sterile ophthalmic irrigating solution. *Note*: The package insert states to leave the 5% Betadine in contact with the ocular surface for two minutes (when prepping for intraocular surgery); however, our experience in the treatment of EKC has been that one minute of contact is sufficient.
- Just for good measure, instill another drop or two of the NSAID (or even proparacaine if the patient has any discomfort).
- Add a potent corticosteroid q.i.d. for four days.

Since using this protocol, we have not had a patient to go on to develop the legendary subepithelial infiltrates. We reason that by rapid diminution and/or elimination of live virus from the ocular surface,



This patient presented with severe EKC. He had the classic signs of acute red eye (top) and watery discharge (above).



Just two days after treatment with our EKC-Betadine protocol, his eyes were white and quiet.

'Off-label' Use of Ophthalmic Drugs and Devices

"The practice of ophthalmic off-label drug use is neither uncommon nor new," says an editorial in the May 2007 *American Journal of Ophthalmology*. "The prevalence and clinical importance of prescribing drugs for unlabeled uses are substantial … thus the prescribing of drugs for unlabeled use is often necessary for optimum patient care."[1]

The article also quotes an FDA statement on "off-label" usage: "Good medical practice and the best interest of the patient require that physicians use legally available drugs according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the products' use and effects."

In summary, "Treatment with any drug or therapy is based on a consensus between a well informed patient and physician. This is no different in the case of the use of off-label ophthalmic medications. The more scientifically sound the information supporting its use, the more confidently can the physician and patient assess the possible value of the proposed unapproved treatment."[1]

"The Ophthalmic Mutual Insurance Company recognizes that 'off-label' use of approved medications is a legal and necessary part of the practice of medicine."[1]

For additional perspective: "A drug or device becomes 'on-label,' or approved, when a sponsor conducts a prospective multicenter clinical trial to show its safety and efficacy for a particular indication. Often these regulatory trials are of limited value, for several reasons. First, often the approved indication is of little value, whereas off-label indications are the primary use," says a letter to the editor in the January 2010 *American Journal of Ophthalmology*.[2]

This writer goes on to say, "Manufacturers often take the most direct route to an approval rather than demonstrating the best use of the product in a clinical trial. For example, topical ophthalmic antibiotics universally are approved only for the treatment of bacterial conjunctivitis, a self-limiting condition with little morbidity. However, their greatest value is in the treatment of bacterial keratitis and in prophylaxis after ophthalmic surgery. These applications are proven off-label uses. The use of these agents is entirely ethical."[2]

A follow-up letter in the same journal states, "In ophthalmology, off-label drugs and devices play an enormously important role in our ability to care for patients … Ophthalmology has a strong, proud, and vibrant tradition of practicing off-label."[3]

1. Parrish R 2nd, Sternberg P Jr. Does "off-label" mean off limits for patient care? Am J Ophthalmol 2007 May;143(5):853-5.
2. Maloney RK. Off-label use of drugs and devices. [Correspondence]. Am J Ophthalmol. 2010 Jan;149(1):170.
3. Rosenfeld PJ, Goodman KW. Off-label use of drugs and devices. [Correspondence]. Am J Ophthalmol. 2010 Jan;149(1):170-1.

there is insufficient time for enough viral particles to migrate into the anterior stromal tissues to incite an immune response.

Take note of the safety and efficacy of this approach. As an example, Betadine is used in just-born infants to prevent ophthalmia neonatorum: "Topical azithromycin is likely as effective for the important causes of ophthalmia neonatorum as its fellow macrolide erythromycin ... A controlled clinical trial comparing erythromycin 0.5%, povidone-iodine 2.5%, and silver nitrate 1%, for ophthalmia neonatorum prophylaxis demonstrated that povidone-iodine was more effective than the other agents for preventing infectious conjunctivitis, including chlamydial conjunctivitis ... We believe povidone-iodine would be a suitable and perhaps preferable alternative to azithromycin for ophthalmia neonatorum prophylaxis."[1]

Sources for Betadine 5%

We're often asked, "Where or how can I acquire 5% Betadine?"

There are probably many sources. Here are a few:

- OCuSOFT.com
- www.hilco.com
- Eyecareandcure.com
- Sigmapharmaceuticals.com

These companies offer a broad array of ophthalmic products. The 30ml opaque plastic bottle of Betadine 5% sells for approximately $16.

Also, if "sampling" becomes an historic event, one can purchase at minimal cost a wide variety of generic ophthalmic drops from these same sources to keep in the office for altruistic use for indigent patients, or when seeing emergency patients after hours.

Stopping Sequelae

Now, back to the "rule of eights": If left untreated, after eight or so days of active viral expression, a secondary immune response is commonly seen, typically clinically expressed as infiltrative viral keratitis, as evidenced by disciform subepithelial keratitis.

For perspective, Thygeson's SPK is an *intra*epithelial disease process, and therefore some fluorescein dye uptake can be seen. However, the *sub*epithelial infiltrates following adenoviral infection are indeed subepithelial, and therefore do not

stain.

If such sequelae to EKC occur, then a protracted course of corticosteroid therapy is usually required to subdue or clear these inflammatory subepithelial lesions. We would select loteprednol, because of the multi-week to multi-month therapeutic intervention that may be required to clear the cornea. Our treatment for symptomatic (blurred vision) subepithelial infiltrates is typically Lotemax q.i.d. for one month, t.i.d. for one month, b.i.d. for one month, and then daily for one month.

If the steroid is halted prematurely or is tapered too quickly, the immune-mediated lesions can reform. Not until the viral particle antigen load is reduced below a biologic threshold level capable of inciting an immune response can corticosteroid suppression be stopped. This is accomplished through biological antigenic attrition, and may take many weeks to months. Until this natural degradation of viral antigenic load occurs, we attempt to use the least amount of steroid possible to maintain acceptable vision. Individualization of therapy, as always, is certainly indicated here.

Bear in mind that when these subepithelial infiltrates occur, the eye is usually white and quiet. The acute infectious phase has passed, and now the patient presents with the complaint of blurred vision in a relatively quiet, comfortable eye.

A keen understanding of the natural history and pathophysiology of adenoviral infection is crucial to precise management of the spectrum of disease that can be encountered.

Again, if you treat EKC early on, you'll almost always prevent these secondary immune responses. ■

1. Keenan JD, Eckert S, Rutar T. Cost analysis of povidone-iodine for ophthalmia neonatorum prophylaxis. Arch Ophthalmol. 2010 Jan;128(1):136-7.

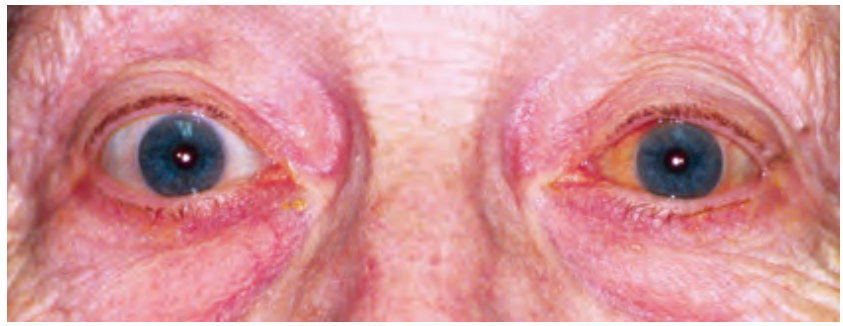
Antiviral Update on Zirgan

The eyecare professions have greatly enjoyed the improvement trifluridine (Viroptic) gave us over idoxuridine (IDU) about 30 years ago. Thankfully, pharmacotherapy continues to improve. While trifluridine performed well, there always loomed the potential for epithelial toxicity because the drug attacked both uninfected as well as infected cells.

As of 2010, Sirion Therapeutics has brought us an ophthalmic formulation of ganciclovir, a systemic antiviral approved by the FDA in 1989. Oral ganciclovir has been extensively used to treat cytomegalovirus infections since it came to market. Like acyclovir, ganciclovir is essentially an inert compound until it is activated into a chemotherapeutic medicine via phosphorylation by viral enzymes. Because ganciclovir targets only virally-infected cells, it has a greatly expanded therapeutic safety profile.

Zirgan (ganciclovir 0.15%) is an ophthalmic gel-drop that comes in a 5g tube, and is specifically FDA indicated for the treatment of acute herpetic keratitis. Typical dosing is five times daily for four to five days, then t.i.d. for three to four more days, depending upon tissue response. We are thrilled with the prospect of having a topical drug that is equally efficacious as trifluridine, yet one with a much enhanced safety profile available for the treatment of epithelial herpes simplex keratitis.

While truly exciting, keep in mind that the least expensive treatment for epithelial infections is oral acyclovir 400mg five times a day for a week. If/when the generic for valacyclovir drops in cost to the level of acyclovir, we will abandon that antiviral with its five-times-daily dosing in favor of generic valacyclovir with its three-times-daily dosing schedule as a result of its longer half-life of therapeutic activity.



Patients with EKC typically present with acute redness starting in one eye, then spreading to the fellow eye in two to three days. A palpable preauricular lymph node is commonly detected (if you feel for it) on the side of the initially infected eye.

Insights in Antibiotics

Use antibiotics for active bacterial infection or when there's significant risk of opportunistic infection. Otherwise, consider a steroid/antibiotic combo drop.

In addition to the introduction of Besivance last year, there's now a higher concentration of gatifloxacin available as Zymaxid, from Allergan. Thus, we are fortunate to have a wide array of antibiotics from which to choose.

The key decision regarding this class of drugs is not so much which antibiotic to use, but how often, and for how long. We stress the limited indication for this class of drugs: either evidence of an active bacterial infection, or prophylactically when there is significant risk of opportunistic infection, such as when using a bandage soft contact lens to treat a corneal abrasion.

If the red eye diagnosis is not certain, rather than blindly prescribe an antibiotic, consider that an antibiotic/corticosteroid combination drug has a vastly enhanced chance of effecting tissue resolution since ocular surface inflammatory processes are much more common than are bacterial infectious processes.

To give more insight into microbial resistance and antibiotic

Topical Antibiotic Drugs

BRAND NAME	GENERIC NAME	MANUFACTURER	PREPARATION	PEDIATRIC USE	BOTTLE/TUBE
Fluoroquinolones					
Besivance	besifloxacin 0.6%	Bausch + Lomb	suspension	≥ 1 yr.	5ml
Ciloxan, and generic	ciprofloxacin 0.3%	Alcon, and generic	sol./ung.	≥ 1 yr./ ≥ 2 yrs.	5ml, 10ml/3.5g
Iquix	levofloxacin 1.5%	Vistakon Pharm.	solution	≥ 6 yr.	5ml
Ocuflox, and generic	ofloxacin 0.3%	Allergan, and generic	solution	≥ 1 yr.	5ml, 10ml
Quixin	levofloxacin 0.5%	Vistakon Pharm.	solution	≥ 1 yr.	5ml
Vigamox	moxifloxacin 0.5%	Alcon	solution	≥ 1 yr.	3ml
Zymar	gatifloxacin 0.3%	Allergan	solution	≥ 1 yr.	5ml
Zymaxid	gatifloxacin 0.5%	Allergan	solution	≥ 1 yr.	2.5ml
Aminoglycosides					
Tobrex, and generic	tobramycin 0.3%	Alcon, and generic	sol./ung.	≥ 2 mos.	5ml/3.5g
Genoptic, and generic	gentamicin 0.3%	Allergan, and generic	sol./ung.	N/A	5ml/3.5g
Polymyxin B Combinations					
Polytrim	polymyxin B/trimethoprim	Allergan, and generic	solution	≥ 2 mos.	10ml
Polysporin	polymyxin B/bacitracin	Monarch, and generic	unguent	N/A	3.5g
Neosporin	polymyxin B/neomycin/ gramicidin	Monarch, and generic	sol./ung.	N/A	10ml/3.5g
Other Antibiotics					
AzaSite	azithromycin 1%	Inspire Pharm.	solution	≥ 1 yr.	2.5ml
Ilotycin, and generic	erythromycin 0.5%	Dista, and generic	unguent	≥ 2 mos.	3.5g
AK-Tracin, and generic	bacitracin 500u/g	Akorn, and generic	unguent	N/A	3.5g

effectiveness, a nationwide system of study and evaluation of these concerns was established in 1996, the year levofloxacin was brought to market. This system is called "Tracking Resistance in the United States Today," or TRUST. More recently, in 2005 to 2006, Ocular TRUST was established, which looks specifically at ocular bacterial isolates.[2] You'll be rather amazed at what has been discovered. Basically, with regard to MRSA infections, the fluoroquinolones—levofloxacin, moxifloxacin and gatifloxacin—all performed identically and were effective only about 20% of the time. In contrast, trimethoprim was effective against 95% of MRSA isolates. These fluoroquinolones were effective against 80% of methicillin-sensitive *Staphylococcus aureus* (MSSA) isolates, whereas both tobramycin and trimethoprim were about 100% effective.

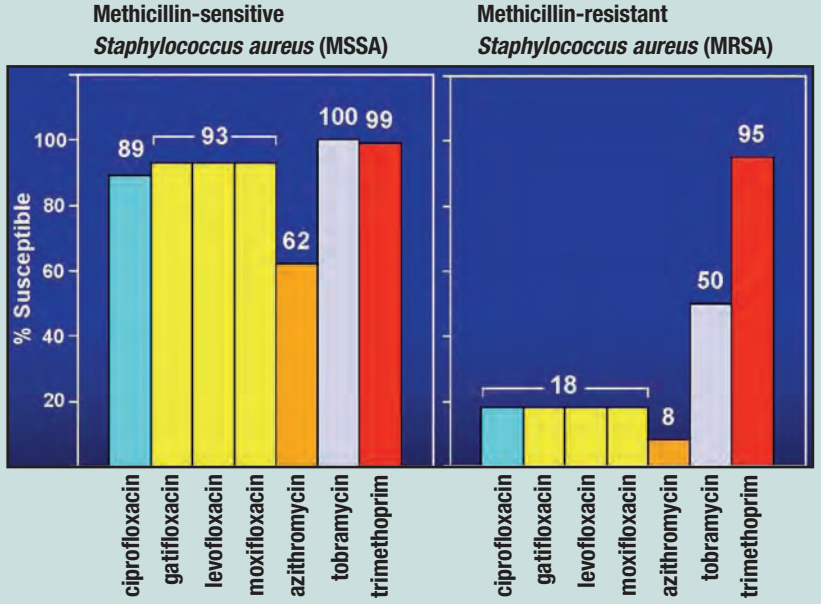
Regarding *Streptococcus pneumoniae*, these three fluoroquinolones were 100% effective. Against *Haemophilus influenzae*, the three fluoroquinolones were 100% effective and trimethoprim was about 85% effective.

Now, from a clinical practical perspective, what does all this mean? To explain, the Ocular TRUST authors state: "Although in vitro activity may be predictive of efficacy, it is not a guarantee because a multitude of factors influence clinical response."[2] Most all of our currently available topical antibiotics, used frequently enough, will eradicate most bacterial infections of the conjunctiva and cornea. If you're not achieving clinical cure with a fluoroquinolone, an aminoglycoside or trimethoprim, then switch or add one of these other classes/drugs. On rare occasions, we add Polysporin or Neosporin ophthalmic ointment at bedtime.

The general principle of treating with antibiotics or a corticosteroid is to have the patient use whichever drug you prescribe frequently (for example, every two hours) for at least a couple of days before dropping down to q.i.d. for four to six more days. It is not particularly the antibiotic chosen, but the frequency of the instillation that determines the clinical efficacy of most drugs.

Now, let's take a clinically practical look at each drug:

MSSA and MRSA in Ocular TRUST



McDonnell PJ, Sahm DF. Longitudinal nationwide surveillance of antimicrobial susceptibility in ocular isolates (Ocular TRUST 2). Presented at the American Academy of Ophthalmology 2007 annual meeting, New Orleans, November 10-13, Poster PO052.

Bacitracin

Developed in 1943, bacitracin is an excellent gram-positive bactericidal drug. Its mechanism of action is the destruction of the bacterial cell wall. It is only available as an ophthalmic ointment, which severely limits its clinical use, because adults do not like to have highly viscous ointments in their eyes. It has two main uses: for infectious blepharitis and for nocturnal supplementation to topical eye drops in the treatment of bacterial corneal ulcer. Bacitracin is generically available.

Bacitracin with Polymyxin B

Polymyxin B is excellently bactericidal against most gram-negative bacterial species. Its mechanism of action is destruction of the bacterial cell membrane. Polymyxin B is not a stand-alone drug, however. It is always found in combination products to provide coverage against gram-negative pathogens. The combination with bacitracin is known as Polysporin ophthalmic ointment, and it is not available in the United States in eye drop form. The ointment formulation is available as a generic product. OTC (non-ophthalmic) Polysporin comes as a 15gm tube, contains the same two drugs, and performs identically.

Besifloxacin—A Novel, New Chloro-Fluoroquinolone

Besifloxacin, marketed as **Besivance** (Bausch + Lomb), has several unique features that make it an excellent choice when a more advanced antibiotic is indicated.

• ***Residency time***. Its vehicle is DuraSite, a mucoadhesive agent that provides enhanced ocular surface residency time, potentially allowing greater concentration of the active drug on the ocular surface. This can be a major advantage when treating school-age patients who have bacterial eye infections. A drop can be placed in the eye in the morning, then again up to eight hours later when school is over, and a third drop can be instilled near bedtime. This meets the FDA recommendation for t.i.d. therapy, yet can bridge over an eight-hour time period—a more patient-convenient dosing schedule.

• ***Reduced resistance***. Besivance is not a new generation fluoroquinolone. Rather, it is a first-in-class chloro-fluoroquinolone. Importantly, Besivance is specifically designed to be an ophthalmic drug—there is no systemic counterpart for this antibiotic as there are for the fluoroquinolones. This, along with its rapid kill rate, should minimize any trending toward bacterial resistance. Indeed, it appears to be especially effective against methicillin-resistant *Staphylococcus aureus* (MRSA).[1] The DuraSite vehicle may even further enhance its therapeutic effect.

• ***High potency***. While there are no large studies in humans (other than the obligatory placebo-controlled phase III studies), in vitro and animal studies demonstrate that Besivance's MIC (minimal inhibitory concentration) potency is at least equal or superior to all other tested drugs.[1,2] For these reasons, there is cause to believe that Besivance is a highly potent, clinically effective, new chemotherapeutic agent.

Besivance 0.6% ophthalmic suspension comes in a 5mL opaque bottle. On a practical note: two or three vigorous shakes are all that are needed for this unique suspension, but the last flick needs to sling the viscous liquid toward the tip of the bottle to facilitate ease of drop instillation.

Like many, many medicines, ophthalmic or systemic, FDA approval is often of a limited indication. For Besivance and the fourth-generation fluoroquinolones, the indication is simply for bacterial conjunctivitis. However, based on all the studies to date, there is every reason to believe that Besivance can be used in a broad array of all types of ocular surface bacterial conditions. Most certainly, in one more year we will have even more extensive experience with this promising medicine, and a much better feel for its therapeutic prowess.

We are pleased to have this new, highly efficacious medicine available to us to treat the range of bacterial eye infections.

1. Haas W. Besifloxacin, a novel fluoroquinolone, has broad-spectrum in vitro activity against aerobic anaerobic bacteria. Antimicrob Agents Chemother. 2009 Aug;53(8):3552-60.
2. Bertino JS, Zhang JZ. Besifloxacin, a new ophthalmic fluoroquinolone for the treatment of bacterial conjunctivitis. Expert Opin Pharmacother. 2009 Oct;10(15):2545-54.

Bacitracin, Polymyxin B and Neomycin

Neomycin is an aminoglycoside, which, like polymyxin, is not found as a stand-alone drug. It is always found in a combination formulation. Neomycin works to inhibit protein synthesis and is inherently broad spectrum, with the notable exception of *Pseudomonas* species (this is why polymyxin B is commonly combined within neomycin). Neomycin is an excellent drug, but it is mostly known for its potential to cause a Type IV delayed hypersensitivity reaction, which is manifested as a low-grade blepharoconjunctivitis, with variable expression of inflammatory blepharodermatitis. This red, weepy skin reaction can easily be reversed by drug cessation. Such so-called "neomycin reactions" occur in 5% to 10% of treated patients, and is nothing more than an inconvenience.

This triple antibiotic is an excellent, broad-spectrum drug that is available generically in both solution and ointment form. Because of solubility issues, gramicidin replaces bacitracin in the solution form. Gramicidin and bacitracin are clinical equivalents in combating gram-positive bacteria.

Trimethoprim with Polymyxin B

Trimethoprim is an excellent, broad-spectrum bacteriostatic antibiotic. Though it inhibits bacterial folic acid synthesis in a manner similar to the sulfonamides, it is not a sulfa-related drug.

Systemically, trimethoprim combined with sulfamethoxazole, historically marketed as Bactrim (AR Scientific) or Septra (Monarch), is a drug of choice when treating systemic soft tissue infections caused by MRSA pathogens. As can be deduced, trimethoprim is not active against some gram-negative bacteria, which is why it is combined with polymyxin B. Because this combination drug is particularly effective against *Streptococcus pneumoniae* and *Haemophilus influenzae*, two common pathogens in the pediatric population, this is the drug of choice in children with bacterial conjunctivitis. Originally known by the brand name **Polytrim** (Allergan), this ophthalmic solution is now available generically.

Erythromycin

The most common use of erythromycin is as a nocturnal lubricant when a lubricant with antibiotic properties is desired. Erythromycin, topically and systemically, has limited use because of its poor resistance profile. It is hardly ever used to actively treat an infection, but is almost always used in a prophylactic role. Just as with bacitracin, ophthalmic erythromycin is available only as an ointment, which limits its practical application.

Erythromycin is essentially bacteriostatic against many gram-positive and gram-negative bacteria. It exerts its antibacterial action through the interruption of protein synthesis. However, because of its systemic use for decades, resistance (particularly against *Staph*. species) has developed and has limited its clinical usefulness.

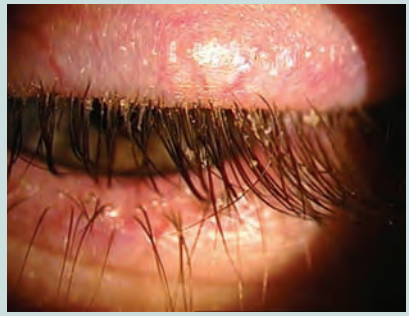
Azithromycin

This more modern rendition of a macrolide antibiotic is well known by its original brand name of Zithromax (Pfizer). It is prescribed systemically as a Z-Pak, and is available in a packet of six 250mg capsules; Tri-Pak, which is available in a packet of three 500mg capsules; or as a 1,000mg oral suspension and 2,000mg oral suspension (Zmax).

Blepharitis

Blepharitis is the most common disease of the eyelids, and appears both anteriorly and posteriorly.

• ***Anterior***. The anterior form of blepharitis is best managed with good eyelid hygiene, but not with baby shampoo. We strongly recommend commercially prepared, unit-dose applicator scrubs. These are easier to use, have an excellent broad spectrum of activity against common eyelid pathogens, and certainly appear more of a medical therapeutic device than hair shampoo.



Manage anterior blepharitis with good eyelid hygiene using applicator scrubs, not baby shampoo.

We often prescribe an effective anti-*staph* antibiotic combined with an effective, safe corticosteroid, such as **Zylet** (loteprednol 0.5%/tobramycin 0.3%, Bausch + Lomb), q.i.d. for a week or two. Patients simply instill the drops as usual, and we ask them to gently close the eyes and rub excess along the eyelid margins. After a week or two, we have them use the drops only once or twice daily for another two to four weeks. This works well and requires only one 5mL bottle.

There is a lot of chatter about the off-label use of azithromycin (**AzaSite**, Inspire Pharmaceuticals) to treat blepharitis. This may help some patients, but let's look at this practice in a thoughtful, scientific way. As clearly demonstrated in the TRUST (Tracking Resistance in the United States Today) data, tobramycin is much more staphylocidal than azithromycin. (It comes as no surprise that the phase II clinical trials of AzaSite for the treatment of blepharitis did not show any improvement compared to vehicle, which mirrors our own clinical observation. The drug's primary goal of improving eyelid margin hyperemia did not reach statistical significance compared to vehicle during either the two-week or the four-week clinical trial.)

Secondly, nothing, absolutely nothing, suppresses inflammation more effectively than a corticosteroid. Therefore, based on logical thought and scientific information, a drug containing tobramycin with any steroid is more prudent than using any antibiotic alone. It should be intuitive that an ester-based corticosteroid would be preferable when treating any chronic condition, such as blepharitis, because of the well-established enhanced safety profile of loteprednol. (However, AzaSite is an excellent choice for treating children with bacterial conjunctivitis. It joins generic trimethoprim/polymyxin B (**Polytrim**) as our two drugs of choice for this condition.)

• ***Posterior***. For posterior blepharitis, it must be emphasized that meibomian gland dysfunction is the centerpiece of this disease. Expressing these glands in the office is both diagnostic and therapeutic. Patients need to be shown how to perform glandular expression so they can do this several times a week initially, then perhaps twice weekly thereafter. Pre-expression warm soaks for three or four minutes enhances the efficacy of these glandular massages.

Beyond this, we commonly prescribe oral doxycycline at 50mg a day for two to three months. Such therapy has been shown to enhance the fatty acid metabolism within these glands. To our knowledge, all authoritative medical textbooks recommend only doxycycline for this purpose. We have consulted several dermatologists as to why they prefer doxycycline over azithromycin. Their consistent answer: doxycycline has much enhanced anti-inflammatory properties as compared to azithromycin. We urge you to query your community's dermatologists in a like manner.

One final point regarding oral doxycycline: it can be, and should be, taken with a meal, and never on an empty stomach near bedtime. Such practice occasionally results in erosive esophagitis, an undesired occurrence when our goal is enhancing quality of life.

Remember, once brought under control, the enduring, consistent application of hygienic maneuvers will maintain eyelid health. For episodic "breakthrough" symptoms, re-pulse with Zylet q.i.d. for a week or two, and re-emphasize meticulous eyelid hygiene. Helping patients with blepharitis involves active therapy on the part of the doctor and the patient. Enduring control rests with a well informed and compliant patient.

The ophthalmic formulation of azithromycin, known as **AzaSite** (Inspire Pharmaceuticals), is produced as a high-viscosity eyedrop solution. Because azithromycin has a particularly prolonged intracellular half-life, both in systemic and topical form, it is dosed less frequently than other ophthalmic drugs. For AzaSite, the standard dosage is one drop every eight to 12 hours for the first two days, then one drop daily for five more days.

Its mechanism of action is the inhibition of protein synthesis. Because of its spectrum of activity, it, like trimethoprim (with polymyxin B), has its greatest value in treating pediatric bacterial eye infections.

Its main advantage is its more patient-friendly dosing frequency. Since it is only available by brand name, it is relatively more expensive than generic Polytrim.

AzaSite comes in a white, opaque bottle containing 2.5mL of drug. It has an easy-to-open safety seal very much like that found on the Xalatan bottle.

The Aminoglycosides

Aminoglycosides are a class represented by gentamicin, tobramycin, and neomycin. The first two are the only members of this class with broad-spectrum antibiotic properties, which allows them to function as standalone drugs. The aminoglycosides are not used systemically (because they can cause ototoxicity) and therefore, they have not had their antibiotic properties compromised by widespread primary care use. They exert their bactericidal action through the inhibition of bacterial protein synthesis.

Both gentamicin and tobramycin perform about the same, except that tobramycin appears to be even less likely than gentamicin to cause any epitheliotoxic response. While all aminoglycosides have the potential to cause ocular surface toxicity, this is not a practical concern when used for a short time, as they would be rationally prescribed in eye care (i.e., seven to 10 days), unless the ocular surface was already compromised prior to the institution of treatment. These drugs are generically available in 5mL bottles.

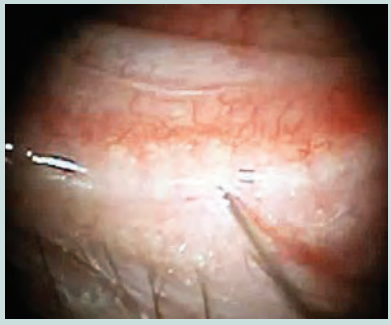
They are excellent, broad-spectrum antibiotics. Like the fluoroquinolones, their forte is in the gram-negative spectrum, and the highest MICs are for streptococcal pathogens. Also like the fluoroquinolones, these two drugs should be dosed frequently (every one to two hours initially until the infection comes under control), then the dosing frequency can be reduced as appropriate for the amount of time deemed necessary to achieve a clinical cure, usually seven to 10 days.

The Fluoroquinolones

Like erythromycin, the oral fluoroquinolones have enjoyed enormous popularity among primary care physicians. This has begun to cause significant resistance to this class of drugs. Most such "resistance" arises from in vitro studies and can usually be overcome clinically because of the huge relative volume of drug-per-surface area achievable on the ocular surface. While there are newer generations of fluoroquinolone (just like newer generations of oral cephalospo-

New Procedure for Blepharitis: Maskin Microprobes

Because so much attention is being given to treating blepharitis, it is especially timely that a new approach has come upon the horizon. Steve Maskin, M.D., has discovered that physically opening clogged inspissated meibomian glands, using tiny wire probe cannulas, can bring rapid relief to most patients with posterior blepharitis. This simple procedure, done at the slit lamp following topical anesthesia, can be performed quickly and efficiently.



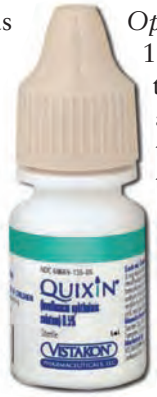
Topical 0.5% proparacaine can be used, but Akten (lidocaine 3.5%, Akorn) may be a better option because of its viscous gel formulation. Just place a couple of drops in each eye, and rub the excess over the eyelid margin.

Rather than detail this new therapeutic procedure here, we prefer to direct you to a couple of websites: www.RheinMedical.com and www.drmaskin.com. Here, you can view a video of the procedure as it is done, and gain further details on how to help patients with posterior blepharitis gain control of this chronic, persistent condition.

We have not yet performed these maneuvers, and do not know of the virtue of doing so, but wanted to make the optometric community aware of this new, potentially promising, in-office procedure for blepharitis.

We have no relationship directly or indirectly with either Dr. Maskin or Rhein Medical.

rins), they are only marginally superior to older ones in clinical performance. Like the aminoglycosides, the fluoroquinolones are concentration-dependent in their bactericidal properties. Ciprofloxacin (**Ciloxan**, Alcon), ofloxacin (**Ocuflox**, Allergan) and gatifloxacin (**Zymar**, Allergan) are all available as a 0.3% concentration; levofloxacin (**Quixin**, Vistakon Pharmaceuticals) and moxifloxacin (**Vigamox**, Alcon) are available as a 0.5% concentration; the newly FDA-approved besifloxacin (**Besivance**, Bausch + Lomb) is available as a 0.6% ophthalmic suspension; and levofloxacin (**Iquix**, Vistakon Pharmaceuticals) is available as a 1.5% concentration. The 1.5% levofloxacin is FDA approved for bacterial keratitis, and other than ofloxacin and ciprofloxacin, is the only fluoroquinolone specifically FDA approved for this purpose.



So what does all this mean clinically? Not very much. When a fluoroquinolone is deemed the class of choice for a particular infectious condition, it is not particularly the specific drug chosen that matters as much as how frequently the drug is dosed. For example, an article in the September 2007 issue of *Ophthalmology*, compared 1% moxifloxacin, fortified tobramycin/cephazolin, and 0.3% ofloxacin in treating bacterial keratitis.[3] The result: they all performed equally. This is one example—of many—of why it is so important for O.D.s to consistently read the literature.

In summary, the topical antibiotics are grossly overutilized—in optometry, ophthalmology, and general medicine. Make every effort to pinpoint an accurate diagnosis (which, in most cases of acute red eye, is not of bacterial etiology), and then select an appropriate drug or drug class to achieve renormalization of tissues.

The frequency of instillation is almost always more important than the drug selected.

As best as we can determine, the four best drugs to combat acute bacterial infection in adults are: bacitracin/polymyxin B/neomycin; tobramycin; 0.6% besifloxacin; and 1.5% levofloxacin.

In children, we use either generic trimethoprim/polymyxin B or topical azithromycin.

The best, general-purpose ophthalmic ointment is a combination of bacitracin with polymyxin B. Only in advanced ocular surface infection would we use eye drops hourly and an ointment at bedtime; otherwise ointments are largely limited to blepharitis care.

We are fortunate to have such an awesome arsenal of medicines available to treat bacterial infections. Use them wisely, judiciously—and aggressively when indicated. ■

1. Abelson MB, Heller W, Shapiro AM, et al; AzaSite Clinical Study Group. Clinical cure of bacterial conjunctivitis with azithromycin 1%: vehicle-controlled, double-masked clinical trial. Am J Ophthalmol. 2008 Jun;145(6):959-65.
2. Asbell PA, Colby KA, Deng S, et al. Ocular TRUST: nationwide antimicrobial susceptibility patterns in ocular isolates. Am J Ophthalmol. 2008 Jun;145(6):951-958. Epub 2008 Mar 28.
3. Constantinou M, Daniell M, Snibson GR, et al. Clinical efficacy of moxifloxacin in the treatment of bacterial keratitis: a randomized clinical trial. Ophthalmology. 2007 Sep;114(9):1622-9.

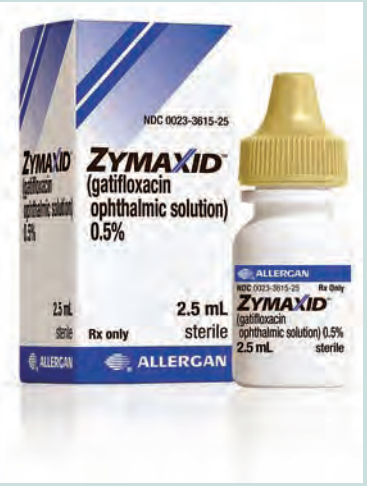
New Gatifloxin Formulation Approved

In keeping with the trend of increasing the concentration of fluoroquinolones, Allergan has reformulated its gatifloxicin from 0.3% (Zymar) to 0.5% (Zymaxid). This new version was just approved by the FDA in late May.

Because fluoroquinolones and aminoglycosides are concentration-dependent antibiotics, this increase in concentration may enhance its clinical efficacy.

Zymaxid is indicated for the treatment of bacterial conjunctivitis. (It is our strong personal opinion that Besivance, Vigamox, Zymar and now Zymaxid are all well-suited to treat bacterial keratitis as well, but the FDA approval process is so bureaucratically onerous that companies generally pursue the shortest, easiest route to approval, having great confidence that learned prescribers will use the drugs for any infectious process where patient care would be enhanced.)

Zymaxid is preserved with BAK, is approved down to age 1, and comes in a 2.5mL opaque multi-use bottle.



Combination Drugs

Perhaps half of all inflamed eyes are best treated with a combination drug, rather than an antibiotic or steroid alone.

This class of ophthalmic drugs is highly useful and rivals the pure topical corticosteroids in the treatment of the acute red eye. As with most drugs, there are clear indications and clear contraindications, with a gray zone in between.

In order to prescribe a combination drug with clinical precision, one has to have a masterful understanding of both antibiotics and corticosteroids. As many as half of all red eyes that we see are treated with a combination drug, rather than either a steroid or antibiotic alone. This observation clearly acknowledges two clinical realities:

- The need for topical antibiotics alone is relatively low.
- Almost all acute red eyes have a significant inflammatory component.

So, how does the astute clinician choose between a pure steroid and a combination drug? The answer is relatively straightforward, but, as always, there are exceptions to generalizations. The pivotal issue is the integrity of the corneal epithelium. If the corneal epithelium is intact, there is little or no reason for prophylaxis against opportunistic bacterial pathogens. This is because an intact epithelium is itself a firewall of defense. If there is significant epithelial compromise, then a combination drug may perfectly match the clinical need.

Remember that the conjunctiva will be inflamed in any patient presenting with an acute red eye. Simply put, the eye is red because it is inflamed. Also, the conjunctiva will be inflamed in almost all cases in which keratitis is present. With either keratitis (with an intact epithelium) or non-infectious conjunctivitis, we almost always use a

Corticosteroid/Antibiotic Combination Drugs

BRAND NAME	MANUFACTURER	STEROID	ANTIBIOTIC	PREPARATION	BOTTLE/TUBE
Blephamide *	Allergan	prednisolone acetate 0.2%	sodium sulfacetamide 10%	susp./ung.	5ml, 10ml/3.5g
Cortisporin *	Monarch	hydrocortisone 1%	neomycin 0.35%, polymyxin B 10,000u/ml	suspension	7.5ml
FML-S	Allergan	fluorometholone 0.1%	sodium sulfacetamide 10%	suspension	5ml, 10ml
Maxitrol *	Alcon	dexamethasone 0.1%	neomycin 0.35%, polymyxin B 10,000u/ml	susp./ung.	5ml/3.5g
NeoDecadron *	Merck	dexamethasone 0.1%	neomycin 0.35%	solution	5ml
Poly-Pred	Allergan	prednisolone acetate 1%	neomycin 0.35%, polymyxin B 10,000u/ml	suspension	5ml, 10ml
Pred-G	Allergan	prednisolone acetate 1%	gentamicin 0.3%	susp./ung.	10ml/3.5g
TobraDex *	Alcon	dexamethasone 0.1%	tobramycin 0.3%	susp./ung.	5ml/3.5g
Vasocidin *	Novartis	prednisolone sodium phosphate 0.25%	sodium sulfacetamide 10%	solution	5ml, 10ml
Zylet	Bausch + Lomb	loteprednol 0.5%	tobramycin 0.3%	suspension	5ml, 10ml

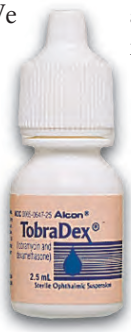
PREGNANCY CATEGORY: All drugs listed above are Category C. * = also available generically.

topical steroid.

If the accurate diagnosis of bacterial conjunctivitis is made, the decision is whether to prescribe an antibiotic or a combination drug. The prime determinants are twofold:

1. The severity of the infection.
2. The degree of conjunctival injection.

If the infection presents with marked mucopurulence, we would likely treat with a pure antibiotic, such as moxifloxacin (and perhaps even culture if the infection was severe). If the infectious expression was only mild to moderate, the degree of conjunctival injection would be the overriding issue in choosing between an antibiotic and a combination drug such as **Zylet** (loteprednol/tobramycin, Bausch + Lomb), **TobraDex** (dexamethasone/tobramycin, Alcon), or **Maxitrol** (dexamethasone/neomycin/polymyxin B, Alcon). We stress again that bacterial infection is uncommon, especially relative to the numerous expressions of non-infectious conjunctivitis.



An exception is the patient who presents with what appears to be a low grade bacterial conjunctivitis (i.e., minimal discharge), yet with moderate to marked conjunctival injection. The patient usually complains that the affected eye was "stuck together when I woke up." Commonly, by the time the patient arrives at your office, any excess debris may have been cleaned from the lids and lashes. Further, blinking has moved considerable mucopurulent debris down the nasolacrimal system so that the objective slit lamp findings reveal only minimal microparticulant debris in the lacrimal lake; a clear, non-staining cornea; and/or a red eye. Here is where a combination product is used mainly to address the conjunctival inflammation, while concurrently eliminating any infectious component, even when the cornea is uninvolved.

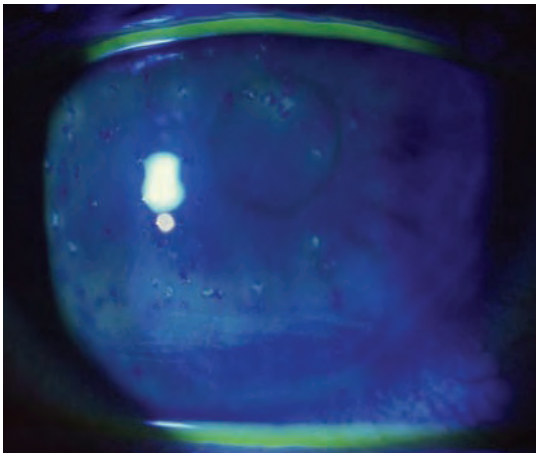
When there is significant corneal epithelial compromise, we almost always use a combination drug. For most cases, the choice of drug class is that simple.

The first blockbuster, highly effective combination antibiotic/corticosteroid was Maxitrol, containing neomycin, polymyxin B and dexamethasone. Maxitrol became a real workhorse in primary eye care. However, the occasional neomycin reaction, while not a major issue, prompted investigation into a "new and improved" combination drug.

Thus was born TobraDex, which replaced the neomycin and polymyxin B with tobramycin. This drug, like Maxitrol, enjoyed market dominance, though from time to time, and again not a major issue, intraocular pressure increases prompted an investigation into a "new and improved" combination drug.

Thus was born Zylet. Keeping the highly efficacious tobramycin, the dexamethasone was replaced with a newer generation, ester-based corticosteroid, loteprednol. Now with Zylet, we have excellent antibiosis along with the safety and potency of loteprednol. It is available in 5ml and 10ml bottles.

Now that we have 90% of this topic covered, we need to spend the bulk of this article discussing other various exceptions and modifications to this rather simple decision tree. The best way to teach the concepts for drug class choice is perhaps by looking at a few specific clinical entities.



A classic presentation of the corneal staining pattern of Thygeson's SPK. (The fellow eye was nearly identical.) This is one of the unusual cases of keratitis in which a modestly potent corticosteroid, such as Alrex (q.i.d. for one week, then b.i.d. for one to two more weeks), quickly brings resolution in most cases.

Thygeson's Superficial Punctate Keratopathy (SPK)

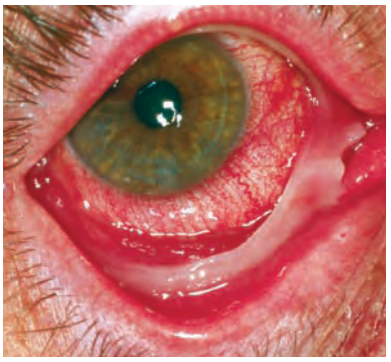
This not-so-uncommon keratitis is seen in young to middle-aged patients. The classic symptoms are foreign body sensation, photophobia and lacrimation. This idiopathic condition has cycles of exacerbation and remissions over the course of 10 to 20 years, until it finally abates. It is during these exacerbations when symptoms prompt the patient to seek medical attention.

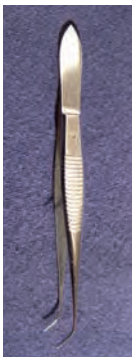
This usually bilateral keratitis shows several tiny, usually central, subtle (but readily seen) staining defects with fluorescein dye. (Note that about 20% of cases are

unilateral, so differentiating Thygeson's from herpes simplex must be done; here is where corneal sensitivity testing can be useful. Also, the Thygeson's eye will generally be white, or minimally injected, whereas the herpetic eye will generally be considerably injected.)

If the patient is significantly symptomatic, a topical corticosteroid readily suppresses the keratitis and its attendant symptoms. If the presenting symptoms are tolerable, then artificial tears and patient education are likely all that is needed. However, the teaching point here is that even though there is some punctate staining in acute Thygeson's SPK, all that is needed is a topical steroid. This is the uniform recommendation in authoritative textbooks.

While 1% concentrations of topical steroids are indicated in most inflammatory eye conditions, Thygeson's is steroid sensitive. Therefore, our drug of choice in these cases is **Alrex** (loteprednol 0.2%, Bausch + Lomb). We generally treat symptomatic patients q.i.d. for one week, then b.i.d. for one to four weeks, until the phase of exacerbation subsides. Artificial tears complement virtually all acute ocular surface conditions, but there is no need for an antibiotic.





Development of thick membranes can be seen in more advanced cases of EKC. After instillation of topical anesthetic, these membranes (note both superior and inferior tarsal) were peeled away with minimal bleeding, using these curved-tip forceps. Zylet was then used q2h for two days, then q.i.d. for four days.

Epidemic Keratoconjunctivitis (EKC)

If the EKC is severe, and especially if tarsal conjunctival membranes have formed, there can be epithelial compromise. The key here is to physically peel away these membranes, as they exert toxic and mechanical trauma to the epithelium. Be sure to wear gloves when performing this procedure, as minor bleeding often results.

These membranes are a marker of intense inflammation, and as such, corticosteroid therapy is of paramount importance. We generally use **Lotemax** (loteprednol 0.5%, Bausch + Lomb) q.i.d. for a week. By the end of this period, natural healing will likely have occurred and the steroid can be stopped, or tapered to b.i.d. for a few more days. While a combination drug, such as Zylet, TobraDex or generic Maxitrol, could be used here, we almost always use a pure topical steroid. Aminoglycoside toxicity on an already toxic ocular surface is probably not a practical concern, but could be in instances in which the patient has concurrent dry eye.

In many advanced cases of EKC, subepithelial infiltrates (which do not stain) can develop. When these cause symptomatic, visual compromise, a steroid will readily clear this unique, immune keratitis. This generally requires two to four months of tapering therapy. Our routine has been to use Lotemax q.i.d. for one month, t.i.d. for one month, b.i.d. for one month, and then once-daily for one month. It usually takes two to four months for sufficient viral antigen to be physiologically leeched from stromal residence. So when the steroid taper is completed, any small infiltrates that might reform should be symptomatically minimal, or silent.

Of note, antibiotics and combination drugs have little or no role in treating patients with adenoviral infections because concurrent bacterial infection is exceedingly rare.

For several years now, we have successfully treated symptomatic patients with acute, grade II or higher EKC with a 60-second treatment of **Betadine 5% Sterile Ophthalmic Prep Solution** (povidone/iodine, Alcon) followed by ocular surface lavage. This accomplishes two objectives. First, eradication of the bulk of the adenoviral load hastens acute symptomatic recov-

Pearls for Using Combination Drugs

- Any time you see any process at or near the limbus, it is inflammatory in nature. Herpetic infection can present at this area, but will typically be linear (as opposed to oval) in morphology.
- In any acute, unilateral red eye with a serous discharge, be sure to rule out herpetic keratitis.
- Never (or rarely) taper combination drugs below q.i.d. because subtherapeutic levels of antibiotic set the stage for antibiotic resistance.
- In the context of a red eye with a mild secondary iritis, instill a short-acting cycloplegic agent, particularly if a pure antibiotic is used. A combination product will generally eliminate such an iritis without the need for a cycloplegic, though this is a fine clinical point.

ery. Second, since the virus particles residence time has been considerably truncated, the potential for viral antigenic (stromal immune) keratitis is largely pre-empted. *(See also "The EKC-Betadine Protocol," page 17A.)*

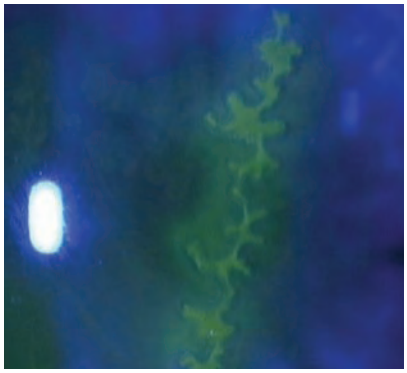
Note: since Betadine stings, always pre-treat the cornea with a drop of proparacaine. Furthermore, to diminish any patient discomfort, we generally instill a drop or two of **Voltaren** (diclofenac sodium, Novartis Ophthalmics) or **Acular LS** (ketorolac tromethamine, Allergan) before, and again after the treatment.

Following the in-office treatment as described above, we always prescribe Lotemax, usually q.i.d. for four to six days, to dampen or eliminate any residual inflammatory keratoconjunctivitis.

Herpes Simplex Keratitis (HSK)

Here is another condition that commonly demonstrates considerable epithelial compromise.

Since corticosteroids cause local immunosuppression, their use is contraindicated—an exceedingly well-known principle. No authoritative textbook recommends the use of a prophylactic antibacterial agent in such cases. As clinicians, we do not know why the herpetic corneal defect does not invite opportunistic bacterial pathogens; we just know that antibacterial therapy is not needed, unless there is clear evidence of concurrent bacterial infection.



Herpes simplex keratitis.

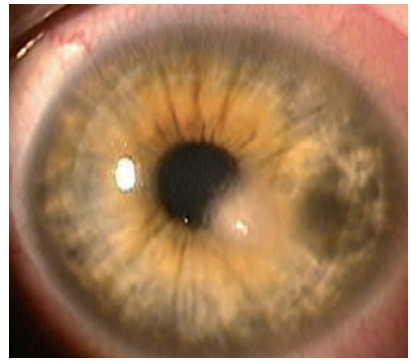
Topical **Viroptic** (trifluridine, Monarch Pharmaceutical), perhaps in conjunction with preservative-free artificial tears, is the only therapeutic intervention warranted for herpes simplex epithelial keratitis. Oral antivirals, such as acyclovir (400mg five times daily for seven days) can be used if there is trifluridine resistance, or if the patient has developed an allergic response to trifluridine.

Corneal Abrasions

Most such defects heal within a day or two, regardless of any therapeutic maneuvers. To our knowledge, no studies have prospectively followed "no treatment" of abrasions, but it would be interesting to know the absolute need for prophylactic antibiotic use, which is standard practice in these situations. We imagine the rate of infectious keratitis would be very small. However, since antibiotics are safe, there is no mandate to take unnecessary risks.

Conservative therapy with antibiotics has evolved into the standard of care for corneal abrasions. There are, however, circumstances—most notably delay in seeking care—in which the abraded eye is considerably inflamed. While fungal infection is always a *rare* possibility if the traumatic agent was vegetative, 99.9% of the time fungus is not a player.

That being said, we have occasionally used a short-acting cycloplegic agent and a combination drug in "hot" eyes with corneal abrasions. The steroid component calms the tissues and thus potentiates corneal re-epithelialization. A further note for the fungal worriers out there: if the delay in seeking care is only two to four days,

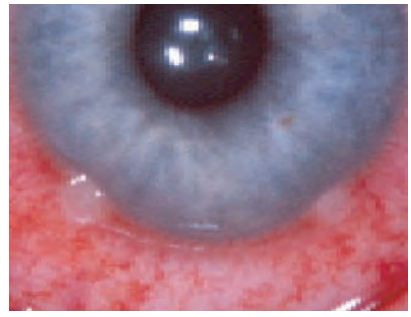


Fungal (*fusarium*) infection with stromal infiltrate.

fungal involvement at this point is unlikely, since fungi are usually slow growing and would take many more days to proliferate to symptomatic proportions.

Now, if the patient gives a history of vegetative trauma, and reports that the abrasion initially healed over a day or two, but is now (perhaps a week later) presenting with a hot eye and stromal infiltrates, consider fungal etiology. However, such symptoms are still most likely associated with a cell-mediated immune response to the initial trauma rather than a fungal infection. The salient features of a fungal keratitis are:

- History of corneal injury (vegetative matter)
- Slowly progressive
- Hypopyon in advanced cases
- Not very painful (relatively)
- Feathery border (hyphate-like)



These classic, limbally expressed phlyctenules were treated with Zylet (q2h for two days, then q.i.d. for five days) with quick resolution.

• Slightly raised, dirty-white infiltration
• Satellite lesions
• Partial or complete ring
• Secondary anterior uveitis

For perspective, in our combined 54 years of intense clinical experience, we have seen a grand total of two cases of fungal infection following corneal abrasion, both of which were treated successfully.

If, however, the traumatic vector of the corneal abrasion was inorganic, and there is marked inflammation, a combination product could be considered. More conservatively, use a pure antibiotic a day or two, then if the traumatic keratoconjunctivitis fails to subside or if symptoms worsen, add a steroid.

Phlyctenular Keratoconjunctivitis (PKC)

Most usually seen in young girls, this staphylococcal hypersensitivity response commonly targets the limbal tissues as one or two raised, whitish lesions, which stain lightly with fluorescein. Nothing else looks like a phlyctenule.

While one would think staphy-

Contact Lens-Associated Keratitis

Confusion abounds in eye care regarding the diagnosis and treatment of contact lens-related keratitis, although in most cases, these clinical presentations are rather straightforward. Of course, our greatest concern is vision loss from a central bacterial corneal ulcer. The good news is that such ulcers are exceedingly rare. The problem, however, is threefold: 1) corneal infiltrates are quite common occurrences; 2) there is a lot of uncertainty among eye doctors as to the differentiation of corneal lesions; and 3) the ever-looming concern, "Is this the beginning of a potentially vision-threatening ulcerative process?" This last point is particularly worrisome when a positive epithelial defect is present.

Corneal hypoxia is the most common cause of corneal infiltrative events, but with the advent of the super oxygen-permeable silicone hydrogel lenses, we hope to see a dramatic decrease in the hypoxic-related keratitis.

Hypoxia can result in a cascade of events that result in leukocytic chemotaxis into the anterior stromal tissues. Once ample leukocytic recruitment occurs, exocytotoxic chemicals can lead to retrograde demise of some of the overlying epithelium as evidenced by a positive fluorescein staining defect. It is these circumstances that lead many doctors to erroneously assume the worst and start the patient on a course of topical antibiotics. While this does no harm, it does no more good than simply discontinuing the use of the contact lenses, which, of course, is the first step of treatment for all contact lens-related eye problems. A steroid, in combination with an antibiotic, is perfectly suited to suppress the immune/inflammatory response, while protecting the cornea against any opportunistic bacterial infections.

There are numerous parameters to evaluating the differential diagnosis of leukocytic infiltration (largely from hypoxia) versus stromal opacification lesions (largely from bacterial infection). (*See "Clinical Perspectives on Corneal Infiltrates," page 17A.*)

Let's look at some risk factors for ulcerative keratitis so that we can better quantify the likelihood of such occurrences:

- Poor tear film function
- Uncontrolled staphylococcal blepharitis
- Smoking
- Swimming while wearing contacts (esp. in fresh water)
- Being under age 22 ±

While this is not an exhaustive list, it gives us some red flags by which we can exercise our clinical judgment, and enhance our patient education.

If you truly feel your patient has an infectious lesion, then start them on a fluoroquinolone such as Vigamox or Zymar every 15 minutes for three to six hours, then hourly until bedtime. We have our patients instill generic Polysporin (or Neosporin) ointment at bedtime. Follow your patient daily and modify therapy based on the clinical response.

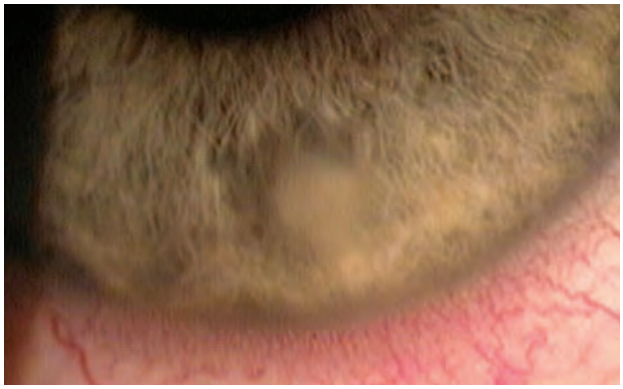
There is a less intensive approach that can be used if you think your patient has a leukocytic infiltrate, but are still concerned about possible infection. Here, use any fluoroquinolone or aminoglycoside hourly until the patient is seen back the next day to assess the clinical course. In either diagnostic circumstance, (bacterial infection or leukocytic infiltration), improvement will most always be evident, mainly because lens wear has been discontinued.

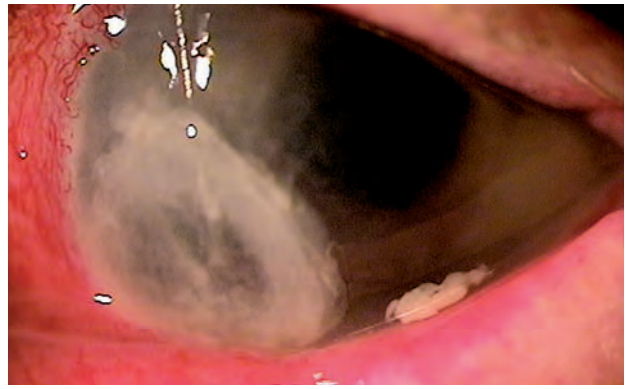
Naïve practitioners who witness such improvement may wrongly deduce that the lesion must have been an infective process, and be glad they used an antibiotic. Once again, infiltrates are very common, and bacterial keratitis is very rare.

The most appropriate therapeutic response to an immune/inflammatory condition (e.g., a leukocytic/sterile infiltrate) is a steroid. Since a small epithelial defect may or may not be present, or clinical judgment may be wrong (if the lesion actually is an early infectious disease process), we always prescribe an antibiotic/steroid combination drug, such as Zylet, TobraDex, or generic Maxitrol to treat these conditions. To this day, tobramycin remains an excellent, broad spectrum bacterial antibiotic.

Prescribe the combination drug to be used q2h for two days, then q.i.d. for four days (mainly to quiet the inflammation and allow the eye to calm down).

Each doctor must evaluate each patient's condition carefully and prescribe with as much precision as possible. As stated at the outset, treatment of contact lens-associated keratitis is rather straightforward in most cases. In ambiguous cases, treat conservatively until the diagnosis becomes clear. For perspective, we have seen less than a handful of cases of microbial keratitis between the two of us.





Is it an ulcer or an infiltrate? At left is a sterile infiltrate. At right is an infectious ulcer. Some rules of thumb: Ulcers are rare; infiltrates are common. Ulcers are usually painful; infiltrates less so. With an infiltrate, the surface area of fluorescein staining is smaller than the underlying stromal lesion.

lococcal blepharitis would always be evident, such is not empirically the case. Certainly, if blepharitis is present, initiate proper care, but first treat the inflammatory keratoconjunctivitis. When there is a staining defect at the corneolimbus, a prophylactic antibiotic is counterproductively conservative.

The key clinical feature is the inflammatory component—the eye is red. Here, a combination product is probably wise. Use a combination drug every two hours for a day or two, then q.i.d. for four to six days, and then stop.

Staph. Marginal "Ulcers"

Much more appropriately called "peripheral inflammatory epithelial defects," these are uncommon events that have a similar pathophysiology to PKC and sterile infiltrates.

In these cases, the staphylococcal exotoxins begin to erode a section of the peripheral corneal epithelial tissues. The eye is red with accentuation of a sector of bulbar conjunctival inflammation adjacent to the affected cornea. The foci of compromised epithelium stains brightly with fluorescein dye. There may be a few cells in the anterior chamber. The epithelium is broken down as a result of the underlying anterior stromal inflammatory process, thus causing retrograde compromise to the overlying epithelium.

Once this subepithelial inflammation is subdued by the corticosteroid component in a combination drug, re-epithelialization is potentiated.

An antibiotic alone in this case is almost worthless. While an antibiotic can serve to protect against opportunistic bacterial potential, it will do nothing to curb the inflammatory process.

As with PKC, a combination corticosteroid/antibiotic product is perfectly suited to address the inflam- matory process while simultaneously guarding the cornea against the possibility of bacterial infection.

Therapeutic management is as described for PKC.

Keratoconjunctivitis Sicca (KCS)

We have all seen dry eye patients with slit lamp-observable, coarse SPK. Also known as punctate epithelial erosions, SPK represents a break in epithelial integrity that theoretically provides a foothold for bacterial adherence and subsequent penetration. Yet, antibiotic intervention is rarely, if ever indicated.

Acknowledging the participation of inflammation in the pathogenesis of many cases of dry eye-related SPK, topical steroid and/or **Restasis** (cyclosporine, Allergan) therapy is often employed (along with artificial tears, etc.) in the successful management of KCS. We have never read of an antibiotic role in the management of KCS.

In summary, select a pure antibiotic when the clinical picture is portrayed by evident mucopurulent discharge, or there is evident (or high risk for) corneal infection.

Select a combination drug in the absence of the above two findings when there is mild to moderate epithelial compromise near the limbus along with considerable conjunctival inflammation.

Select a pure steroid if the eye is red and the corneal epithelium is intact.

We might default to a combination drug if the patient is a contact lens wearer, but it would depend on the individual situation.

We have discussed many exceptions to these general guidelines. The primary purpose of this article is to encourage the reader to limit the prescribing of an antibiotic for the gamut of red eyes and recognize that most red eyes are inflammatory in nature.

Most importantly, prescribe with precision! ■

Corticosteroids

Inflammation is the most common of ocular conditions. Consequently, corticosteroids are the most helpful drugs in eye care.

In acknowledgement of the nature and epidemiologic expression of the acute red eye, topical corticosteroids are heralded as the most helpful class of drugs in eye care. In fact, without these marvelous medicines, we would be virtually disarmed from a chemotherapeutic perspective.

Sadly, the teaching focus of these wonderful drugs is often "side-effect"-centered, rather than "benefit"-centered. The truth is that all drugs have the potential to be two-edged swords, so it is imperative that a clear understanding of their dichotomy be proportionately understood.

So, let's start this discussion appropriately focused on the great virtue of the corticosteroids. Corticosteroids are inextricably linked to clinical success in an extraordinarily wide range of ocular conditions. (*See "The Many Uses of Corticosteroids," p. 33A.*)

Safety in Steroids

While a "rose is a rose," a steroid is not *always* a steroid, exactly. Most steroids are ketone-based in their molecular structure, except for loteprednol, which is the only ester-based formulation. The expanded safety feature of loteprednol takes advantage of the physiological existence of abundant esterases in human tissues, whereas we possess no "ketonases" to dampen the adverse side effect potential of traditional ketone steroids. The virtue of an ester-based corticosteroid is amplified when it comes to chronic care conditions such as dry eye; Thygeson's SPK; chronic uveitis; blepharitis; stromal HSK; chronic, recurrent, inflamed pterygia; etc.

The key to managing most of these inflammatory processes is to select an appropriate steroid medicine and use it frequently until the inflammation comes under control, then conduct an appropriate taper of days to weeks, depending upon the nature, severity, and response of the condition. Selecting a potent

Topical Corticosteroid Drugs

BRAND NAME	GENERIC NAME	MANUFACTURER	PREPARATION	BOTTLE/TUBE
Maximum Strength Steroids				
Durezol	difluprednate 0.05%	Sirion Therapeutics	emulsion	5ml
Lotemax	loteprednol etabonate 0.5%	Bausch & Lomb	suspension	5ml, 10ml, 15ml
Pred Forte, and generic	prednisolone acetate 1%	Allergan, and generic	suspension	5ml, 10ml, 15ml
generic	prednisolone sodium phosphate 1%	generic	solution	5ml, 10ml, 15ml
Vexol	rimexolone 1%	Alcon	suspension	5ml, 10ml
Moderate Strength Steroids				
Flarex, and generic	fluorometholone acetate 0.1%	Alcon	suspension	5ml, 10ml
FML, and generic	fluorometholone alcohol 0.1%	Allergan	suspension	5ml, 10ml, 15ml
FML S.O.P.	fluorometholone alcohol 0.1%	Allergan	ointment	3.5g
Pred Mild, and generic	prednisolone acetate 0.12%	Allergan	suspension	5ml, 10ml

The Many Uses of Corticosteroids

Topical steroids are essential for the restoration of normal tissues for the following diseases, afflictions and conditions:

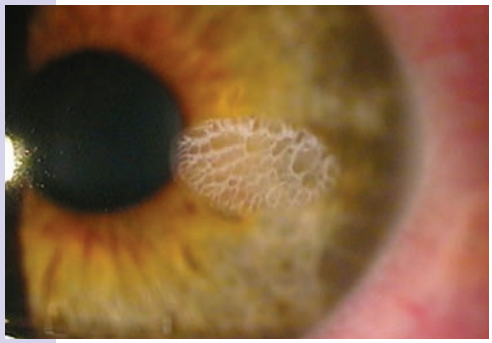
- Iridocyclitis
- Ultraviolet keratitis
- Contact lens overwear
- Inadvertent hydrogen peroxide keratoconjunctivitis
- Thygeson's superficial punctate keratopathy
- Allergic conjunctivitis
- Acute angle closure[1]
- Dry eye syndrome
- Infiltrative keratitis[2]
- Ulcerative keratitis[3]
- Microcystic edema of the cornea
- Vernal conjunctivitis
- Atopic conjunctivitis
- Bacterial conjunctivitis[2]
- Glaucomatocyclitic crisis
- Uveitis-associated ocular hypertension
- Blepharitis[2,4]
- Curling iron/burn injury (thermal keratoconjunctivitis[2])
- Nasolacrimal stenosis[2]
- Traumatic hyphema
- Post foreign body removal[2]
- Acute adenoviral infection[5]
- Acute, symptomatic giant papillary conjunctivitis
- Corneal graft rejection
- Phlyctenulosis ([2], if corneal)
- Inflamed pinguecula/pterygia
- Recurrent corneal erosion[6]
- Post anterior stromal micropuncture[2]
- Herpes simplex viral stromal keratitis[7]
- Episcleritis
- Acute hordeolum (stye)[8]
- Superior limbic keratoconjunctivitis
- Cyanoacrylate-induced chemical keratitis

[1] once IOP is controlled
[2] with antibiotic
[3] once active infection is controlled
[4] with eyelid hygiene
[5] following 5% Betadine treatment
[6] with oral doxycycline
[7] with antiviral cover
[8] with warm compresses

corticosteroid is essential to effecting a clinical cure (or control) in most cases.

There are five drugs in this category: prednisolone, loteprednol, difluprednate, dexamethasone and rimexolone. Moderate-acting steroids are represented by the fluorometholones, and the less potent formulations are represented by the lower concentrations of prednisolone and loteprednol (discussed in detail later).

Using a steroid more than necessary is superior to under-dosing. It is practically impossible to use a topical steroid eye drop too often, but under-treating can allow unchecked inflammation to damage ocular structures. This is probably most applicable to intraocular inflammation such as iridocyclitis. Of course, the ultimate goal is to prescribe with precision, which requires exquisite teaching coupled with clinical seasoning. The more patients one sees, the more precise the clinical care can be.



Curling iron corneal epithelial burn

Most steroids are suspension formulations and need to be shaken well to effect maximum therapeutic benefit. Exceptions to this are two solution formulations: prednisolone sodium phosphate (known as Inflamase Forte by its original brand name; it is now generic), and dexamethasone sodium phosphate (known as Decadron by its original brand name; it is also generic).

The historic dominance of Allergan's **Pred Forte** is being challenged by the user-friendly **Durezol** (difluprednate, Sirion) may work as well with less frequent dosing, thanks to its unique emulsion formulation.

While Pred Forte is typically dosed hourly (while awake) for as long as necessary to quell the inflammation (and this can sometimes be for a few days), Durezol may achieve the same effect with dosing every two hours. Decreasing dosing frequency can be a significant help to many patients. There are yet no head-to-head studies to verify this, so it falls to the clinician to judge the efficacy of this approach. Note that our personal modus operandi is the use of one of these two options for the most severe uveitis and episcleritis cases, and to use **Lotemax** for most other conditions.

There are clinical presentations, most notably high-grade acute uveitis and episcleritis, where topical therapy may be inadequate to control the inflammatory process. There are two options that are commonly employed here: **FML** ointment qhs and/or oral prednisone. We usually opt to add oral prednisone, generally 40mg for three days, 20mg for three to six days, and then 10mg for three to six more days. Every clinical presentation is unique, and individualized dosing is essential in treating every case.

Clinical Perspectives on Corneal Infiltrates

Corneal infiltration is still commonly mistaken for an ulcerative process. There are a number of factors to consider in the differential diagnosis between a leukocytic infiltrate and a bacterial corneal ulcer:

• First, pay attention to the epidemiology of these two conditions: infiltrates are very common; ulcers are very rare.

• An anterior chamber reaction (i.e., cells and flare) is almost always seen with an ulcerative process. While an anterior chamber reaction is usually absent with an infiltrate, trace cells are sometimes seen, especially if the condition has been ongoing for several days.

• The appearance of the conjunctival injection pattern can also be very helpful. With an infiltrate, sector injection is the rule; in an ulcerative process, the entire bulbar conjunctiva is injected.

• While not highly sensitive nor specific, the degree of pain the patient describes can be helpful. An ulcer tends to evoke much more pain than an infiltrate.

• Location can also be helpful, but not absolute. As a rule, ulcers are solitary and tend to be more central, while infiltrates can be single or multiple and strongly tend to express themselves at or near the corneal limbus.

The fluorescein staining pattern of the lesion is probably one of the characteristics we find most helpful in making a definitive diagnosis. With an ulcer, the size of the fluorescein staining pattern closely mirrors the size of the corneal lesion, whereas the staining pattern of an infiltrate is significantly smaller than the underlying lesion. This is because an ulcer begins in the epithelium, and expands laterally and in depth, creating an epithelial defect closely paralleling its stromal invasion. An infiltrate results from the chemotactic attraction of leukocytes from the paralimbal microvasculature. The accumulation of white blood cells in the anterior stromal tissues results in some secondary compromise to the overlying epithelium, which tends to cause a relatively small defect in the center of the underlying stromal lesion.

An attentive clinician should, in most presentations, be able to correctly identify the lesion as either an infiltrate or an infectious ulcer and treat appropriately; however, there are some cases that defy a clear, confident diagnosis. Let's look at diagnostic and therapeutic considerations:

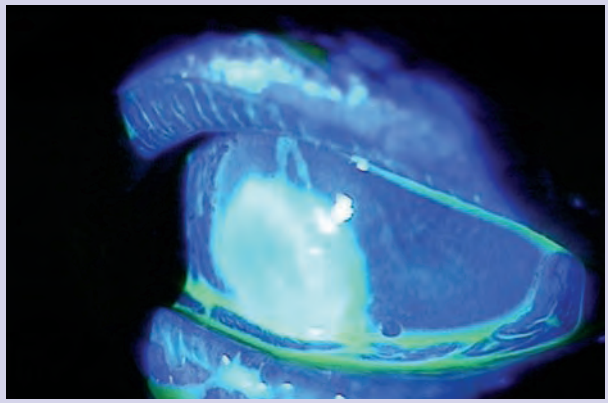
1. If the lesion is clearly infectious, a fluoroquinolone hourly while awake with Polysporin ointment at bedtime may be an excellent initial approach. If there is no response or suboptimal response, add generic Polytrim hourly, because if this ulcer is caused by a MRSA bacterium, the fluoroquinolone may be suboptimal and the trimethoprim should be able to complement eradication of any resistant bacteria.

2. If it is clearly an infiltrate, use Zylet q2h for two or three days, and then just q.i.d. for three to more five days.

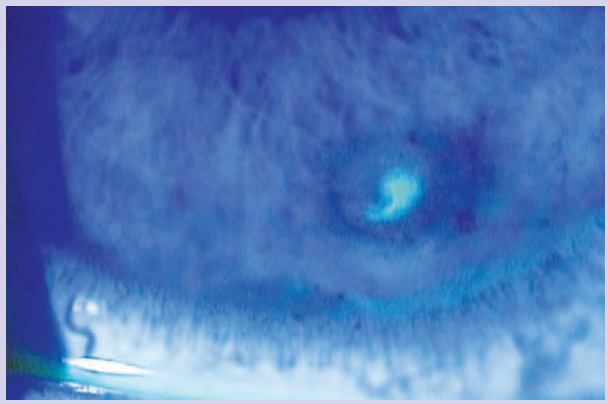
3. If the diagnosis is problematic, then initiate therapy with a fluoroquinolone hourly for a day or two while the patient is awake. If desired, generic Polysporin ointment at bedtime can be added. If there is little or no improvement, the diagnosis is likely a sterile infiltrate, and Lotemax can be added q.i.d. Reassess progress in a day or two. Always remember that hourly around-the-clock eye drop instillation is brutal to the patient. A highly efficacious ophthalmic ointment such as Polysporin should nicely address the infectious process during the sleep cycle, if indicated.

In closing, consider the following quote from prominent Harvard ophthalmologist Mark B. Abelson, M.D., in the January 2005 *Review of Ophthalmology*. His advice perfectly mirrors our approach as set forth above:

"Left untreated, marginal infiltrates generally disappear within a week or two. Ocular steroids have been the best and only recognized drug therapy for sterile marginal infiltrates, and their application will shorten the course of inflammation, regardless of causative origin. For many patients, a quicker recovery from symptoms such as redness, tearing, and discomfort is important for improving their quality of life. Steroids are often prescribed in conjunction with an antibiotic in order to decrease the chance of developing a secondary infection or corneal ulcer and to protect against misdiagnosis."



With an ulcer, the size of the fluorescein staining pattern closely mirrors the size of the corneal lesion.



With an infiltrate, the size of the fluorescein staining pattern is significantly smaller than the underlying lesion.

As a rule, we initiate therapy with eyedrops only. If, in our clinical judgment, the initial presentation is sufficiently pronounced, we may also add FML ointment concurrently with the eyedrops. But if there is not some noticeable improvement in three to four days, we consider adding oral therapy as noted above.

Oral Prednisone

Before initiating oral prednisone, you need to ask the patient three or four simple questions:

1. *Do you have diabetes?*
2. *Do you have (or have you had) peptic ulcer disease?*
3. *Do you have tuberculosis or have you been in areas where tuberculosis is endemic?*
4. *Are you, or could you be, pregnant?*

Let's look at these inquiries one at a time. Regarding diabetes, our endocrinology colleagues give us this perspective: If the patient is non-insulin dependent, just press on with the prescribed short course (three to 14 days) of the prednisone. The patient's blood glucose levels will elevate during the course of therapy, but will renormalize once the oral prednisone is stopped. For the patient who is insulin-dependent, he/she will be best served by using a "sliding dosing scale" of insulin in an attempt to keep blood glucose levels under control. That is, having diabetes is not a contraindication, but is a circumstance that does require more attentive care.

Regarding the patient afflicted with peptic ulcer disease, our gastroenterology colleagues advise having patients take a proton pump inhibitor (such as Nexium or OTC Prilosec or Prevacid) during the course of therapy and for a few days afterward. Again, peptic ulcer disease is not a contraindication, only a complicating factor.

Regarding tuberculosis, our pulmonary colleagues recommend a quick chest X-ray (CXR) and a subcutaneous PPD (purified protein derivative) test. The latter takes a few days to get the results, so start therapy guided by the CXR results alone. As always, we strongly recommend telephone consultation with an appropriate physician with such a unique presentation.

Regarding the establishment of pregnancy, or the possibility of pregnancy, a telephone call needs to be made to the patient's obstetrician to obtain consultation. In like manner, we always have a telephone conversation with the patient's primary care physician (or other appropriate provider/specialist), just to ensure we are all "on the same page" prior to initiating oral prednisone therapy. We should stress at this point that such "encumbering comorbidities" are very rare, and that in most circumstances, our use of oral prednisone is extremely straightforward and completely uneventful. When in doubt, grab the phone, call the

Treating Contact Blepharodermatitis

Patients with contact blepharodermatitis are typically female. Most of these presentations result from exposure to fingernail polish or other (usually undetermined) products such as makeup, shampoos, lotions, etc. Neomycin can also trigger such an epidermal response. The treatment: cold compresses and a topical corticosteroid ointment, lotion or cream.

There are two drugs to effect a cure: FML ophthalmic ointment, or generic 0.1% triamcinolone (non-ophthalmic) ointment, cream or lotion. By far, the most effective and least expensive is the 0.1% triamcinolone. (We discovered triamcinolone years ago when all manufacturers stopped making dexamethasone ophthalmic ointment.) We almost always prescribe triamcinolone because FML comes in a 1/8-ounce (tiny) tube for around $30 to $40, whereas the triamcinolone comes in a 15g (large) tube for under $10.

Do note that on the side of the triamcinolone tube is a statement: "not for ophthalmic use." Be sure and explain to the patient that this is default language (since "ophthalmic" ointments come in a 1/8 ounce nozzle-tipped tube) and that it is to be used on the *skin* and not directly in the eye. (Even if some of it gets into the eye, it will not cause harm.) If a patient is new to us or is just plain persnickety ("I want only an FDA-approved ophthalmic medicine"), we might also explain that triamcinolone (Kenalog) is commonly injected into the eye (to treat macular edema). Once patients hear the cost difference, almost all prefer being prescribed the triamcinolone.

How often we prescribe the treatment, and for how long, is mostly a matter of clinical judgment. A typical treatment is t.i.d. for two days, b.i.d. for two days, then qhs for two to four days. Alternatively, it could be used b.i.d. for three to four days and then stopped. We advise the patient to apply a light application during waking hours and a more generous application at bedtime.

Note that triamcinolone comes in three concentrations of 0.025%, 0.1%, and 0.5%, and in three different forms: lotion, cream and ointment. We always write for the 0.1 % cream.

patient's doctor(s), and put your heads together.

There are two simple approaches to prescribing oral prednisone, both of which are generic and cheap: 10mg tablets prescribed as desired, i.e., "take 4 tabs x 3 days, 2 tabs x 1 week, and then 1 tab x 1 week;" or, "take 4 tabs x 3 days and stop." For the first scenario, order "dispense #33"; for the second scenario, order "dispense #12". These numbers represent the actual number of tablets to be dispensed to the patient . The other option is the "Dosepak," which is prepackaged in 4mg, 5mg or 10mg tablets for a six-day supply. The "original issue" was the 4mg strength tablets, in which the patient takes six tablets the first day (i.e., 24mg), five tablets the second day, etc., until the package is depleted. While not a critical decision, we prefer the 5mg Dosepaks for eye conditions, as this dosage seems to be a bit more clinically effective.

Oral prednisone is usually taken as a single daily dose. Some doctors divide the dose beginning at 60mg, so that the patient takes, for instance, 30mg with breakfast and 30mg with the evening meal. It is best to take prednisone with a meal.

For perspective, patients with acute optic neuritis or giant cell arteritis are treated with 1,000mg of methylprednisolone IV for three days, followed with a high dose oral steroid taper. With this perspective in mind, one can quickly see that the dosages commonly used to treat more "everyday" ocular conditions are relatively low.

In summary, oral prednisone therapy is uncommonly needed in eye care, but when it is needed, it almost invariably can be used safely and effectively. Ask any primary care physician; most prescribe prednisone every day for one simple reason: it helps restore health to inflamed human tissues.

Topical Steroids

Now let's look at various topical therapies. As stated earlier, there are roughly three categories: potent, moderate strength, and weak.

• ***Potent.*** Prednisolone, loteprednol, difluprednate, dexamethasone and rimexolone represent the potent steroid category. All of these drops perform about the same; however, there are some caveats that separate them.

All are ketone-based with the exception of loteprednol, which is ester-based.

All have to be shaken well, except that the emulsion Durezol (difluprednate) and the more suspendable Vexol (rimexolone) only require minimal shaking.

We try to avoid using dexamethasone because it has the greatest propensity to raise the intraocular pressure.

• ***Moderate.*** The moderate strength corticosteroids are represented by the fluorometholones. There are two subtypes, the alcohol (FML) and the acetate (Flarex). The acetate moiety gives the fluorometholone molecule some additional anti-inflammatory effectiveness over the alcohol moiety. The fluorometholone molecule is a fluorinated analog of progesterone.

Fluorometholone ophthalmic comes in four varieties: 0.1% FML suspension, 0.25% FML Forte suspension, 0.1% Flarex, and FML ointment. The 0.25% concentration is beyond the top of the dose-response curve (which is 0.1%) and because there is no additional anti-inflammatory effect, it has no role in clinical patient care. FML is generic and thus reasonably inexpensive. While it possesses less tendency to increase intraocular pressure than the other ketone steroids, we are not nearly as comfortable using it long-term as we are with the ester-based loteprednol.

• ***Weak.*** Lastly are the weaker corticosteroids of 0.2% or 0.25% prednisolone, and 0.2% loteprednol (Alrex). These are pretty much limited to the treatment of allergic conjunctivitis (where there are signs of inflammation accompanying symptomatic itch). Another excellent use of such low-dose steroids is in the care of patients with Thygeson's SPK. In both cases, we prefer loteprednol because of its safety profile. ■

Clinical Pearls for Corticosteroids

• Always consider that a unilateral red eye, especially one with a serous discharge, could be herpetic.

• Hit most cases of inflammation hard and heavy initially. Begin to taper only once the inflammation is well controlled.

• The more protracted the use of steroids, the more protracted should be the taper.

• Tapering is optional for many conditions for which therapy is used for only a few days. Generally, intrinsic conditions such as iridocyclitis require tapering, whereas with some extrinsic conditions, such as traumatic iridocyclitis, tapering is not always required.

• Patients with stromal herpetic disease, chronic uveitis, chronic dry eye inflammation, Thygeson's SPK and corneal grafts may need to use a drop or two or loteprednol daily for many years; perhaps a lifetime.

Clinical Update on the NSAIDs

There are four star players in the field of 'nonsteroidal anti-inflammatory drugs.' Older drugs have been reformulated and new drugs have come to market.

While oral NSAIDs are heavily used in systemic medicine, topical ophthalmic NSAIDs use is relatively limited. The foundational perspective on this class of drugs is the acknowledgement that steroids reign supreme in inflammation control. Topical NSAIDs are never an appropriate substitute when the clinical condition merits a topical corticosteroid.

NSAID use has much more applicability in perioperative care than in primary eye care; however, there are several clinical circumstances in which patient care can be enhanced through the use of such a drug.

Pharmacology of NSAIDs

Let's first understand the pharmacology of NSAIDs. First of all, they have no direct anti-inflammatory properties. They simply inhibit an enzyme along the synthetic pathway to the production of prostaglandins, which are powerful mediators of inflammation. As doctors, it is vital that we have knowledge of this particular pathway. It is known as the *arachidonic acid cascade*.

As you can see in the diagram, The Arachidonic Acid Pathway (*right*), the origin substrate is phospholipids released from cell membranes as a generic response to multiple causes of cellular microtrauma. Corticosteroids inhibit the conversion of these phospholipids to arachidonic acid by inhibiting the catalytic enzyme phospholipase A early in this synthetic cascade.

Once arachidonic acid (AA) is formed, two different enzymes convert it ultimately to either prostaglandin formation or leukotriene formation. Cyclooxygenase converts AA to prostaglandins, and lipoxygenase converts AA to leukotrienes.

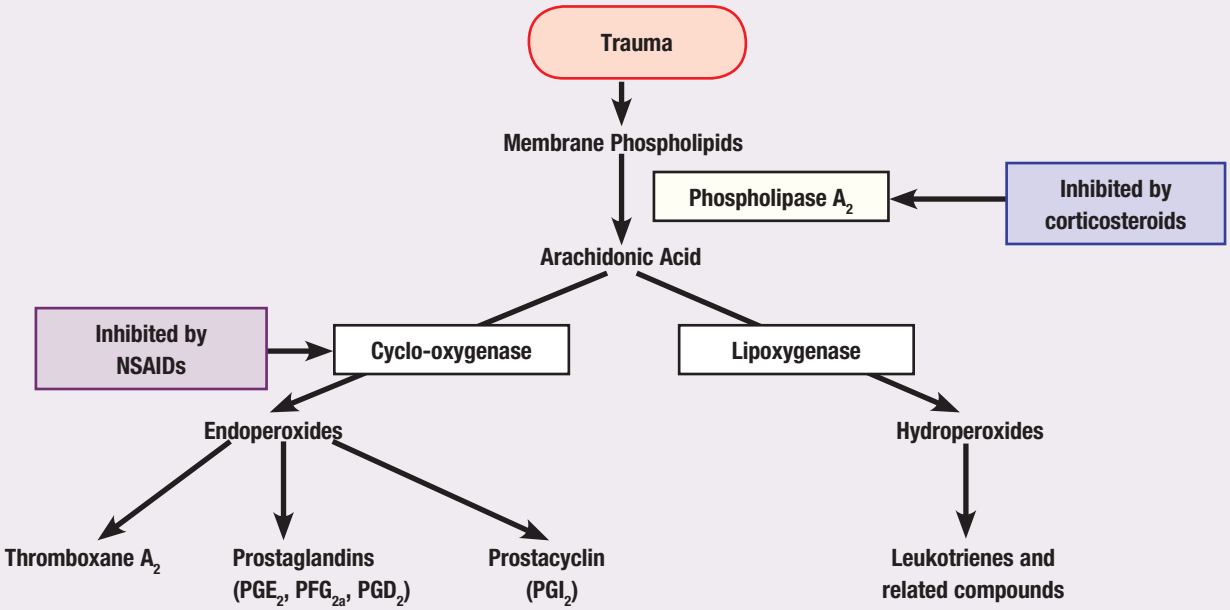
The key point here is that while NSAIDs inhibit the enzymatic activity of cyclooxygenase, they have no effect on lipoxygenase; thereby allowing the production of leukotrienes to go unchecked.

For clinical perspective, remember the early days of photorefractive keratectomy when NSAIDs were initially used postoperatively? Patients experienced problems with white blood cell corneal infiltrates, until it was realized that steroids prevented their formation. Why? Leukotrienes are chemotactic for leukocytes for which NSAIDs do nothing, since they only inhibit the

Non-Steroidal Anti-Inflammatories

BRAND NAME	GENERIC NAME	MANUFACTURER	DOSAGE	PEDIATRIC USE	BOTTLE SIZE(S)
Acular LS	ketorolac tromethamine 0.4%	Allergan	q.i.d.	3 years	5ml
Acuvail	ketorolac tromethamine 0.45%	Allergan	b.i.d.	N/A	unit-dose
Nevanac	nepafenac 0.1%	Alcon	t.i.d.	10 years	3ml
Voltaren	diclofenac sodium 0.1%	Novartis	q.i.d.	N/A	2.5ml, 5ml
Xibrom	bromfenac 0.09%	ISTA Pharmaceuticals	b.i.d.	N/A	5ml

The Arachidonic Acid Pathway



synthesis of prostaglandins and have no activity against lipoxygenase-catalyzed production of leukotrienes.

Since steroids work higher up in the AA synthetic pathway, they inhibit both cyclooxygenase and lipoxygenase, thus inhibiting production of both prostaglandins and leukotrienes.

All this may sound like gibberish to some. The AA pathway is more easily grasped by studying the diagram, which illustrates the processes we have just described. Once you have a clear understanding of the AA pathway, then you can begin to prescribe with enhanced clinical authority and precision.

It is generally thought that steroids and NSAIDs may demonstrate some synergy, and therefore might be beneficial used concurrently. For example, standard-of-care treatment of postoperative cystoid macular edema is usually treated with Pred Forte (1%

Note on Oral NSAIDs

Cyclooxygenase (COX) is the enzyme by which arachidonic acid is metabolized into prostaglandins. There are two subspecies of cyclooxygenase; COX-1 and COX-2.

COX-1 is a constitutive enzyme that synthesizes prostaglandins, which regulate physiological functions such as in the GI tract, kidneys, platelets and vascular endothelium.

COX-2, on the other hand, is an inducible enzyme, which is primarily activated during inflammatory tissue assaults. This is why there was great excitement years ago when COX-2 inhibitors came to market. These purportedly would address inflammation while sparing the physiological prostaglandins, specifically sparing the GI tract from NSAID toxicity.

Unfortunately, a couple of these products, Vioxx (rofecoxib, Merck) and Bextra (valdecoxib, Pfizer) were thought to significantly increase the risk for heart attack and stroke, and were removed from the market. Celebrex (celecoxib, Pfizer) is now used more conservatively, but appears to be less likely to cause such untoward events. All three of these drugs were FDA-approved around the year 2000.

We rarely prescribe oral NSAIDs, but do occasionally use Celebrex (100mg or 200mg b.i.d.) to help our patients in whom we have difficulty tapering off oral prednisone when treating orbital pseudotumor, stubborn uveitis or when treating scleritis. For example, if the anterior uveitis tends to rebound when the oral prednisone is tapered below 20mg per day, we have been successful using Celebrex along with prednisolone 20mg for a week, then 10mg for a week or two, while concurrently using Celebrex for four to six weeks to facilitate the discontinuation of the oral prednisone. Aggressive use of Pred Forte and therapeutic cycloplegia is foundational to these oral supplementary therapies.

There is increased risk of peptic ulcer disease when using both oral prednisone and an oral NSAID (including Celebrex), so we would likely use a proton pump inhibitor such as OTC Prilosec or Prevacid 20mg once daily when we are using such dual therapy.

Uses for Topical NSAIDs

The most common conditions for which topical NSAIDs can play an adjunctive beneficial role are:

- Corneal abrasions
- Just before, and just after, in-office Betadine 5% Sterile Ophthalmic Prep Solution treatment for highly symptomatic EKC
- Post foreign body removal
- Adapting to GP contact lenses
- Post anterior stromal puncture procedure
- Post PKP, or any surface disruptive laser procedure
- Treating and/or preventing cystoid macular edema
- Adapting to punctal plugs
- Allergic conjunctivitis
- Supplemental to steroids in treating recalcitrant uveitis
- Some cases of photophobia
- Post cataract surgery care
- Supplemental to oral NSAIDs in treating scleritis
- Treating and/or preventing inflamed pterygia and pinguecula

prednisolone acetate, Allergan) and a topical NSAID (dosed at its FDA-approved dosing frequency). This synergy is difficult to reconcile based on the dynamics of the AA previously discussed. Perhaps the rapidity of onset and/or the degree of enzymatic inhibition may be considerations for explanation. Contrarily, we find no literature supporting the use of both drug groups in the standard initial treatment of anterior uveitis. There is still a lot to be learned in how these drug classes modify tissue responses.

The Role of Topical NSAIDs

Compared to topical corticosteroids, NSAIDs have a limited role in primary eye care. Nonetheless, there are several situations where NSAIDs can be beneficial. There is a partial disconnect between topical and systemic administration. Systemic NSAIDs are true to their name and do indeed render a marked anti-inflammatory effect, whereas topical NSAIDs have their forte in ocular surface pain amelioration while providing some limited activity against inflammation. (*See "Uses for Topical NSAIDs," right.*)

Voltaren (diclofenac 0.1%, Novartis) and **Acular LS** (ketorolac 0.4%, Allergan) have been the standard bearers of topical NSAID care over the past decade. Both are used q.i.d. and are largely clinical equivalents. One study compared ketorolac and diclofenac head-to-head. Its conclusion: "The decrease in corneal sensitivity in normal human corneas is more pronounced and longer lasting with diclofenac than with ketorolac."[1]

The most recent modification in ketorolac is the introduction of a 0.45% concentration of ketorolac. Acuvail (Allergan) comes as a preservative-free unit-dose indicated for perioperative use b.i.d. one day prior to cataract surgery, and is continued for two weeks immediately postop. However, Acuvail is very expensive, and patients would likely be adequately served with generic diclofenac, or other less expensive NSAIDs.

The original formulation of ophthalmic ketorolac (Acular) was a 0.5% solution, but marked stinging upon instillation was its Achilles heel. The drug was reformulated a few years ago to a 0.4% solution (Acular LS) and is now quite tolerable—a very nice upgrade.

In the recent past, two more NSAIDs have come to market. They are **Xibrom** (bromfenac 0.09%, Ista) and **Nevanac** (nepafenac 0.1%, Alcon).

Xibrom's uniqueness is that it is dosed twice daily, and is well tolerated.

Nevanac is unique in that it is the first available prodrug. Nevanac is enzymatically converted to amfenac sodium, which, like all NSAIDs, inhibits cyclooxygenase. It is dosed three times a day.

All these drugs are generally approved by the FDA for treating postoperative inflammation, and as such, will be used much more in a surgical context. Ketorolac is also approved to treat ocular allergy, and there are a number of other applicable uses for NSAIDs relevant to primary eye care, as enumerated above.

Because of the rare, but real, potential for corneal toxicity and melting, these drugs should be used cautiously when there is preexisting corneal epithelial compromise. As a general rule, we never prescribe any topical NSAID for use beyond

Latest Literature on NSAIDs

If you want the ultimate review of NSAIDs, we urge you to read: "Nonsteroidal Anti-inflammatory Drugs in Ophthalmology," by Stephen J. Kim, M.D., Allan J. Flach, M.D., and Lee M. Jampol, M.D., in *Survey of Ophthalmology,* March-April, 2010. It is excellent.

Some quotes (or in-context paraphrases) from this article, and our commentary (indicated in blue), follow:

• "NSAIDs do not inhibit lipooxygenase (LPO) and thus do not typically prevent generation of leukotrienes. This may explain, in part, their decreased anti-inflammatory effects compared to corticosteroids, which inhibit both LPO and COX (cyclooxygenase). However, celecoxib and diclofenac are notable exceptions and inhibit LPO by direct and indirect means, respectively. In addition, NSAIDs appear to have anti-inflammatory and anti-angiogenic effects independent of their inhibition of COX. Several reports suggest that ketorolac is the most potent inhibitor of COX-1, while both bromfenac and amfenac have staked the claim as being the most potent inhibitors of COX-2.

"The clinical importance of selective COX-1 and COX-2 inhibition for ocular disease remains to be established."

The prostaglandins produced via COX1 are physiologic in their action, whereas the prostaglandins produced from the upregulation of COX2 result in pathologic expression, i.e., pain + inflammation.

• "There is good evidence that topical NSAIDs may be used in place of, or in addition to, topical corticosteroids after cataract surgery to avoid excessive inflammation and to improve visual acuity. Although none of the studies reviewed by the FDA used topical NSAIDs more than 24 hours before cataract surgery, well-designed studies suggest potential benefit from preoperative dosing regimens of up to three days. Furthermore, several clinical studies have reported that concurrent administration of NSAIDs and corticosteroids results in additive effects.

"Therefore at present, there is no evidence to suggest one topical NSAID treatment is better than another in controlling postoperative inflammation."

• "CME remains the most common cause of vision loss after cataract surgery. Despite its significance, the pathogenesis of this syndrome, and its relationship to and its associations with CME in other diseases, is not completely understood.

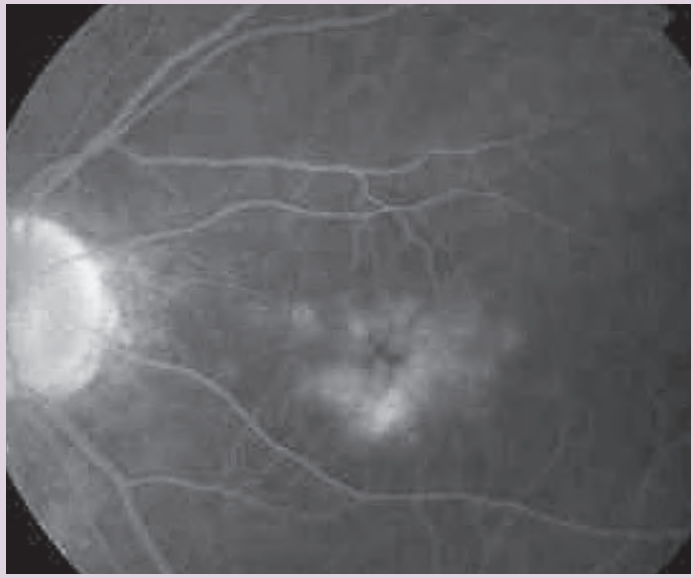
"Systemic NSAIDs provide insufficient drug levels to inhibit prostaglandin production in the anterior segment, especially when compared to topical administration.

"The true incidence of CME following cataract surgery is not precisely known. Despite this continued uncertainty, recent studies have reported incidences following small-incision cataract surgery as high as 9-19% using fluorescein angiography, and 41% as measured by OCT.

"It has long been recognized that the natural history of CME usually includes spontaneous resolution.

"Although there is no FDA-approved treatment for the prevention or treatment of CME following cataract surgery, an extensive review of the world literature… concluded that prevention and treatment of CME with NSAIDs is beneficial."

This is just another example of where the scientific literature trumps FDA guidelines. "Off-label" use of medicines is becoming more and more commonplace; so don't let a governmental



An extensive review of the world literature concludes that prevention and treatment of cystoid macular edema with NSAIDs is beneficial.

one week—with the exception of CME, which we treat with a topical NSAID for a month, concurrent with Pred Forte.

While steroids are often initially dosed as frequently as hourly for a few days, we strongly urge that NSAID use not exceed the FDA-approved dosing frequency.

Our favorite brand-name NSAID is Xibrom, purely because of its simple b.i.d. dosing. Because of its cost, however, on the rare occasions when we do write for a topical NSAID, we generally prescribe generic diclofenac.

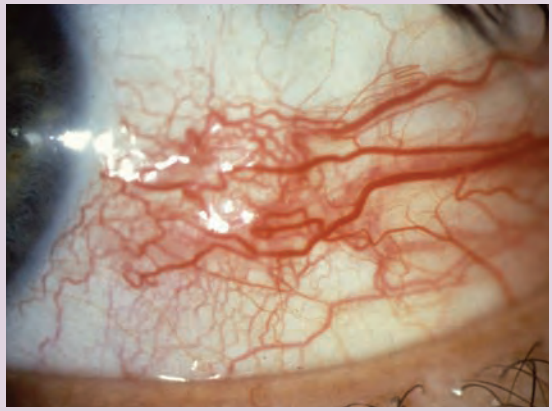
In summary, there are several off-label uses for NSAIDs within the context of primary eye care. Their main use is in the prevention or treatment of cataract surgery-related cystoid macular edema concurrent with a potent corticosteroid. ■

1. Seitz B, Sorken K, LaBree LD, et al. Corneal sensitivity and burning sensation. Comparing topical ketorolac and diclofenac. Arch Ophthalmol. 1996 Aug;114(8):921-4.

bureaucracy override sound, rational and prudent use of a helpful drug.

• "Although there is no FDA-approved therapy for the prevention and treatment of CME following cataract surgery, available evidence suggests that topical NSAIDs may prevent and treat CME when used alone or concurrently with corticosteroids.

"Given the relatively low incidence of clinically significant CME, the cost/benefit of routine prophylactic use of NSAIDs in cataract surgery is a matter of ongoing debate."



Although we would use a topical corticosteroid first, evidence shows that NSAIDs are useful for treating inflamed pingueculae and pterygia.

• "Although no other topical NSAID has been approved for allergic conjunctivitis besides ketorolac, there are studies suggesting that 0.1% diclofenac and 0.09% bromfenac may also be effective.

"Studies have reported that ketorolac 0.5%, diclofenac 0.1%, and bromfenac 0.09% are all effective in treating vernal conjunctivitis."

We would use a potent topical corticosteroid to gain full control of the vernal conjunctivitis first, and then perhaps try a topical NSAID to maintain that control. One could also consider antihistamine/mast cell stabilizer, or continue with loteprednol once to twice daily—whatever it takes to keep the condition under control.

• "Whereas topical corticosteroids are frequently helpful in relieving episcleritis, topical NSAIDs appear to be less effective. Systemic NSAIDs are of value in those unusual cases where topical treatments are ineffective."

This is an excellent example that, when significant inflammation is present, it is a steroid that is needed—not an inferior quasi-anti-inflammatory agent.

• "Regarding scleritis, although topical NSAIDs are not effective, systemic NSAIDs are used as first-line agents. Although many NSAIDs may be effective, indomethacin at 25-50mg three times daily is most commonly used. Side effects include gastric upset that may require concurrent use of an H2-blocker or proton pump inhibitor. A recent report indicated that the COX-2 selective NSAID, celecoxib, at a daily dosage ranging from 200 to 800mg q day was effective in controlling diffuse anterior scleritis in 92% of patients without producing any gastrointestinal effects."

• "There is also evidence that NSAIDs are useful in the treatment of inflamed pingueculae and pterygia."

We would always use a topical corticosteroid to first get inflammation controlled, then consider an NSAID to help keep the condition under control. We typically just maintain Lotemax once- or twice-daily for most of these patients.

• "Corneal perforations and melts have been reported with the use of topical NSAIDs. Therefore, the routine use of topical NSAIDs in dry eye patients may increase the risk of these adverse events."

• "One in seven Americans receives a prescription for orally administered NSAIDs each year."

• "The most well known side effects accompanying systemic NSAID use relate to the GI and central nervous system.

"Often the GI toxicity can be partially ameliorated by adding an H2-receptor antagonist, proton pump inhibitor, or prostaglandin analog; however, many patients will require discontinuation of the medicine."

• "A recent prospective, randomized placebo-controlled trial observed no adverse events or changes in liver chemistries in a large number of patients treated twice daily for fourteen days with topical bromfenac. The off-label use of topical NSAIDs for durations longer than this is common, and clinicians should be vigilant for potential systemic toxicity. In addition, because eyelid closure and nasolacrimal occlusion can decrease systemic absorption of topically applied medications by almost 70%, explaining these techniques to all patients seems prudent."

• "At present there is no evidence that one NSAID is less toxic than another."

• "The over two dozen cases of corneal perforations reported with the introduction of topical corticosteroids over 30 years ago were likely related to improper clinical use and patient follow-up. Thus, many topical medications have the potential for toxicity if unmonitored or used inappropriately."

Note that "over 30 years ago," it was not doctors of optometry who performed "improper clinical use and patient follow up."

• "A definite link between NSAID use and corneal melt remains tenuous. Application of topical NSAIDs for reasonable lengths of time in appropriate patients with proper monitoring appears safe. There is, however, evidence of the continued misuse of these medications."

As can be seen, there are occasions when a topical NSAID can be useful; however, these uses are dramatically overshadowed by the use of corticosteroids. Always keep in mind that the rational, scientifically sound use of a drug "off-label" may be in the very best interests of a patient.

The Mastery of Dry Eye

Most dry eyes can be ameliorated with the use of a multifaceted approach to reduce inflammation and renormalize the tear film.

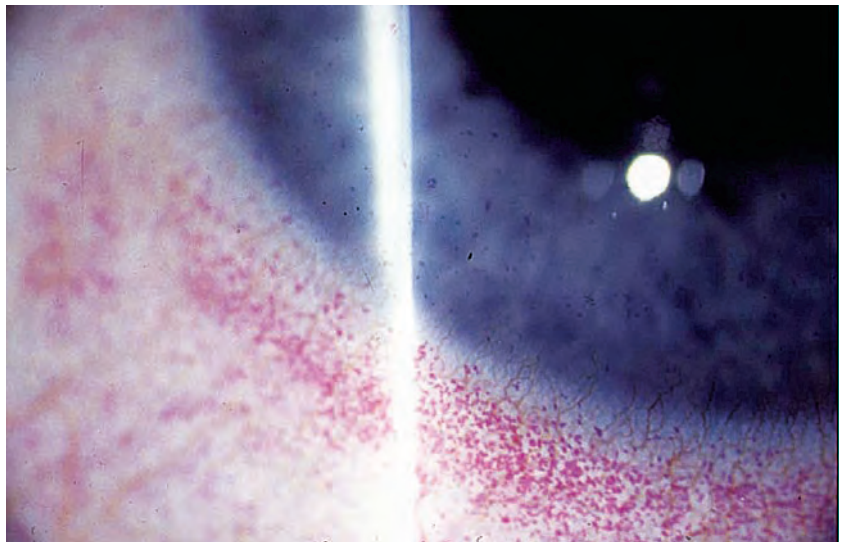
Gaining control of ocular surface dryness can significantly improve quality of life for our patients. There are basically four interventional maneuvers we can employ:

- Artificial tears
- Anti-inflammatory therapy
- Oral doxycycline—or fish oil
- Punctal plugs

Judicious, thoughtful use of these interventions, either singly or additively, can be of enormous benefit to patients with dry eye disease.

There is a lot of marketing spin regarding the medical treatment of dry eye. We propose to set forth a rational, scientifically sound and clinically successful, literature-based protocol for truly helping patients who suffer from ocular surface dryness.

Bear with us as we set the foundation for our clinical approach. Two of the most respected clinicians in this field of study are Michael A. Lemp, M.D., and Gary N. Foulks, M.D. Dr. Lemp is widely regarded as one of the pioneers in dry eye research and has been with the Georgetown University School of Medicine for many years. Dr. Foulks has chaired the cornea service at Duke University and the University of Pittsburgh, and is currently at the University of Louisville, in Kentucky. He is editor-in-chief of the authoritative journal, *The Ocular Surface* (www.theocularsurface.org), a journal we highly recommend to all practicing eye doctors.



Moderate rose bengal staining of the conjunctiva and minimal rose bengal staining of the cornea in a patient with moderate dry eye.

Here are some pertinent quotes from these clinicians/scientists from the peer-reviewed literature. In the July-August 2007 issue of *Survey of Ophthalmology*, Dr. Foulks states:[1]

- "Increasing the thickness of the tear lipid layer improves the stability of the tear film, suggesting that in selecting a dry eye therapy, an important feature would be the ability of the treatment to mimic the lipid layer of the tears."
- "One drop containing Restoryl, the active ingredient of Soothe XP [Bausch + Lomb], more than doubled lipid layer thickness."
- "Restoryl has been shown to replenish the aqueous layer of the tear film. When applied to the eye, Restoryl differentiates into neutral oils (helping to rebuild the lipid layer), interfacial molecules (stabilizing the interface between the lipid and aqueous layers, and supporting the mucin layer), and water (helping to restore the aqueous layer)."

Time to Face the Mucin

Soothe Xtra Hydration (Bausch + Lomb) is new as of May 2010. We have not used this new product and can, at this time, only share the following information from the company: "New Soothe Xtra Hydration, for aqueous-deficient dry eye therapy, moisturizes and restores the deficient aqueous and mucin layers of the tear film to provide lasting hydration and comfort."

Until we can gain clinical experience with this newer product, we will continue to use Soothe XP as our workhorse in the care of our patients with ocular surface dryness.

• "Overall, decades of research have shown a strong correlation between dry eye symptoms and the state of the tear film lipid layer, as well as a clear connection between the status of the lipid layer and the osmolarity of the tear film."

In the September 2008 *American Journal of Ophthalmology*, Dr. Lemp states: "Tear osmolarity is considered 'the central mechanism causing ocular surface inflammation, damage and symptoms, and the initiation of compensatory events in dry eye'."[2]

So, Soothe XP stabilizes the lipid layer, protecting the tear layer from becoming hyperosmotic, as Dr. Foulks explains. Dr. Lemp explains that the (hyper) osmotic tear film as the prime cause of ocular surface inflammation. We believe these two foundational cornerstones establish Soothe XP as a key element in helping patients with dry eye.

Dr. Lemp continues: "Although the exact place of inflammation in the stream of events leading to ocular surface distress is not clear, its role is unmistakable." He goes on to say, "In the use of cyclosporine (Restasis) to modulate immune activity and to suppress inflammation in dry eye, there is increasing evidence that the use of topical corticosteroids as temporary or pulsed therapy can be useful in reducing the damaging effect of inflammation."

Furthermore, the Report of the International Dry Eye WorkShop (DEWS), published in 2007, clearly established that "corticosteroids are an effective anti-inflammatory therapy in dry eye disease."[3]

Now, let's talk about the use of the steroids in ocular surface inflammatory disease. Steroids continue to suffer from the myth that they are dangerous. Steroids have the potential to cause harm, but many thousands of people are helped by steroids every day. It is so important to keep the enormous beneficial attributes of steroids in focus. As intensely busy clinicians, we have been able to help thousands of patients over the decades, and we cannot recall a single therapeutic misadventure with corticosteroids.

There are two types of steroid molecules: ketone-based, such as prednisolone and dexamethasone; and one that is ester-based, loteprednol. Human systems do not possess "ketonases," but have an abundance of esterases. It is this reality that sets loteprednol apart as a very safe and very effective molecule. In fact, the loteprednol molecule is nearly identical to the prednisolone molecule except that a ketone moiety is replaced with an ester moiety. So, for a dozen years, the world has had extensive experience with loteprednol and it is authoritatively established as a highly effective, yet very safe, anti-inflammatory medicine. Obviously this makes loteprednol an excellent choice in the management of ocular surface inflammation. We would never be comfortable using a protracted regimen of traditional ketone steroids, but the unique ester-based chemistry of loteprednol makes such a therapeutic approach safe, clinically effective, and cost-effective.

Now, the stage is set so we can care for our dry eye patients in an enlightened manner. We have had the most success with the following protocol, and urge you to consider it as you care for your patients with ocular surface dryness: First, we do a therapeutic trial

Steroids and IOP Increase

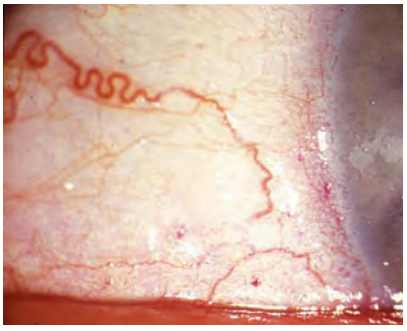
What about the *rare* IOP increases that can accompany loteprednol use? In our experience, a steroid responder is almost always revealed at the time of the one-month follow-up evaluation. If the patient shows no increase in IOP after a month of q.i.d. steroid therapy, it is highly unlikely that there will be a subsequent IOP increase. Plus, by this point along the therapeutic pathway, we are stepping down the Lotemax to b.i.d., thus reducing further the highly remote possibility of untoward side effects. The more you utilize corticosteroid therapy, you will see how true this is.

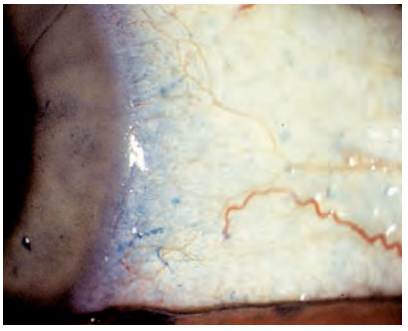
with Soothe XP for a month. We encourage our patients to use the drops as often as they would like, but at least four times a day. Depending on patient symptoms and clinical signs, we commonly prescribe Lotemax (loteprednol 0.5%, Bausch + Lomb) to be used concurrently q.i.d., instructing the patient to wait 20 to 30 minutes between the use of these two eyedrops.

At the one-month follow-up visit, we assess the therapeutic success, and then modify our therapy as needed. We stress here that Soothe XP, being a mineral oil emulsion, is radically different from other artificial tears and cannot be described as "just another artificial tear" due to its completely different molecular chemistry.

Assuming clinical success, we now decrease the Lotemax to b.i.d. for two more months and allow the patient to try to reduce the frequency of instillation of Soothe XP.

At the two-month follow-up (assuming we have a satisfied patient, which is typically the case), we are at another decision tree. By this time, most patients are using Soothe XP two to three times a day, and we can try to stop the Lotemax. Remember that Drs. Lemp and Foulks describe tear osmolarity as "the central mechanism causing ocular surface inflammation." So, via Soothe XP, we have bolstered the lipid layer, thus reducing tear osmolarity and, with Lotemax, we have addressed whatever hyperosmolarity-induced inflammation preexisted. At this juncture, there should be little or no clinically significant ocular surface inflammation.





Rose bengal and lissamine green staining of the conjunctiva and cornea in a patient with Sjögren's syndrome.

Melton and Thomas Soothe XP/Lotemax Dry Eye Management Protocol

One Month	Two Months	Indefinitely
Soothe XP Four to six times a day as needed	**Soothe XP** Three to four times a day as needed	**Soothe XP** Two to four times a day as needed
Lotemax Four times a day	**Lotemax** Two times a day (Consider punctual plugs if needed)	Discontinue **Lotemax** If symptoms breakthrough or continue, then either pulse dose **Lotemax** or **Alrex** four times a day for two weeks, or consider **Lotemax** or **Alrex** once daily as needed.

The risk of increased IOP with Loteprednol is uncommon at high dosage and rare at low dosage.
Our experience has been that if an increase in IOP is going to occur, it will do so at the initial one month follow-up, and not later

Omega-3 essential fatty acids (derived from fish and/or flaxseed oil) **can be initiated at any stage, based on clinical judgment.**

Perspective on Cyclosporine

We are often asked about Restasis (cyclosporine 0.05%, Allergan) and its role in managing dry eye disease. The main reason we are infrequent prescribers of Restasis is because we have experienced firsthand less-than-optimum clinical responses from many of our patients. It was these "necessity being the mother of invention" patient encounters that motivated us to try to find a more effective, and less costly, approach to dry eye management than Restasis provided. Thus was born our discovery of the beneficial effects of loteprednol to control ocular surface dryness.

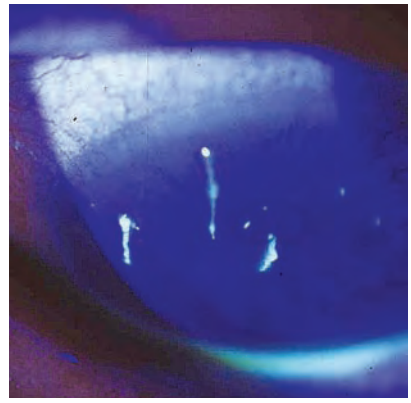
An excellent article (supported by 85 references), "Advancements in Anti-Inflammatory Therapy for Dry Eye Syndrome," by Erin McCabe, O.D., and Srihari Narayanan, O.D., which appeared in the October 2009 issue of *Optometry*, supports our clinical experience in the management of patients with dry eyes.

In their peer-reviewed article, Drs. McCabe and Narayanan state:

- "Within the last decade, advancements in the understanding of the pathophysiology of dry eye syndrome have underscored inflammation as a common thread linking most presenting cases of dry eye. Inflammation often plays a key role in propagating and sustaining the disorder regardless of the cause of the ocular surface disease. These discoveries have triggered the development of a new line of successful anti-inflammatory treatments."
- "Several studies have found that topical corticosteroids effectively treat dry eye. These drugs inhibit cytokine and chemokine production, decrease the synthesis of matrix metalloproteinases and arachidonic acid derivatives, suppress the expression of cell adhesion molecules, and induce lymphocyte apoptosis. Corticosteroid treatment has provided significant evidence of the involvement of inflammation in the pathogenesis of dry eye syndrome."
- In a study utilizing 1% nonpreserved methylprednisone t.i.d. to q.i.d. for two weeks, "All patients reported symptomatic improvement after the initial two weeks of therapy. Corneal fluorescein staining scores decreased in all patients. Many patients noted diminished ocular irritation weeks to months after cessation of treatment, which suggests that corticosteroids may treat causative factors of dry eye, instead of merely alleviating symptoms."
- "One study found that only 3.9% of patients who instilled 0.05% CsA [cyclosporine] twice daily for a course of at least six weeks enjoyed a disease-free state for a year or more afterward."
- "Topical corticosteroids have been mainstays in the eye care field, more so than the newer agent, Restasis, and less potent corticosteroid formulations with few side effects are now available. Pulse therapy of corticosteroids has been shown to stave off dry eye symptoms for several months, and patients were more likely to notice the beneficial effects of corticosteroids earlier than with Restasis."

We urge every optometrist to read this non-industry-supported, comprehensive article. With these observations in mind, we urge you to carefully consider your therapeutic options in caring for your patients with dry eye disease.

McCabe E, Narayanan S. Advancements in anti-inflammatory therapy for dry eye syndrome. Optometry. 2009 Oct;80(10):555-66.



Filaments on the cornea in a patient with moderate to severe dry eye.

Now, back to the decision tree: Following the two to three-month "inflammation suppression" phase, we stress the importance of consistent ocular surface lubrication to help prevent any reestablishment of inflammation, and we generally stop the Lotemax. Keep in mind that we prescribed it q.i.d. for a month and b.i.d. for two months, which is ample time to suppress any ocular surface inflammation. Now, we are in a "maintenance phase," using only artificial tears. Some doctors continue the Lotemax once daily for a few more months, and while we have no issue with this, we do not feel it is necessary in most cases.

One question that is commonly asked is: "What about using Alrex (loteprednol 0.2%, Bausch + Lomb) instead of Lotemax, since a lower concentration would be even safer?" There are no studies regarding this; however, our advice is to use Lotemax q.i.d. for at least two weeks to rapidly suppress the ocular surface inflammation, then b.i.d. until the 5ml bottle is empty. At that point, it would be reasonable to try the use of Alrex b.i.d. for a month or two, and then once-a-day for another month or two.

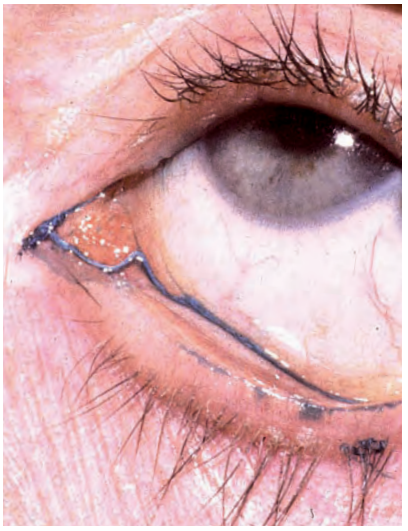
After this course of therapy, use your clinical judgment as to whether to stop the Alrex, continue

Fluramene: The 'No Strip' Stain

From the research laboratories of Donald Korb, O.D., and associates, comes the first combination diagnostic drug containing fluorescein sodium 1% and lissamine green 0.5%. This pharmacologic duo is preserved with ascorbic acid.

Fluramene easily enables the enhanced qualification and quantification of tissue compromise in the setting of any ocular surface disease, particularly ocular surface dryness. Fluramene ophthalmic solution comes in an opaque 5mL multi-use bottle.

For further information, visit http://noblevisiongroup.com/noble-team-blog.html.



Ropy discharge seen in a patient with moderate dry eye that stains with lissamine green.

it once or twice a day, or whether to prescribe Lotemax to be used as pulsed therapy. (*See "When Patients Slack Off, Put Pulse-Dosing Into Play," below.*) In our clinical experience, patients can use loteprednol safely and effectively once or twice a day indefinitely when circumstances indicate.

Remember, every patient is different, and you will need to exercise your clinical wisdom to find the least therapeutic intervention required to keep your patient comfortable. To that end, we offer the following perspectives: it is well established that omega-3 supplementation can be helpful in cardiovascular disease, rheumatologic disease, and meibomian gland dysfunction. Indeed, most adults might be well served to take such supplementation.

Regardless, neither the optimum amount nor the ratio of DHA to EPA has been established in prospective clinical trials. And, even if such data existed, one would still have to treat each patient on an individualized basis. Our approach is generally to suggest supplementation early on in the treatment with the goal of using the least amount of topical eyedrops to maintain comfort. (*For more information, see "The Slippery Facts About Fish Oil," by Larry Alexander, O.D.,* Review of Optometry *May 2010, p. 35.*)

It's been our clinical experience that oral doxycycline more potently and more quickly enhances meibomian gland function than the omega-3s, so we often prescribe 40mg to 50mg per day for three to four months and then replace the doxycycline with one of the omega-3 products for enduring use. (It may be that 20mg of doxycycline each day of would be effective, but we can find no authoritative basis support for this.)

Any antibiotic can cause gastrointestinal upset and, in women, vaginal candidiasis can be problematic, so discuss these issues proactively. Doxycycline can be taken with food, and doing so generally solves any GI issue.

(Unless there is moderate to advanced posterior blepharitis, we would bypass the doxycycline and

When Patients Slack Off, Put Pulse-Dosing Into Play

To continue anti-inflammatory therapy for months or years with either loteprednol or cyclosporine seems counterintuitive. Plus, the clinical reality is that human beings are generally poor patients. They don't come in for follow-up as consistently as they should; they don't use their eyedrops optimally; they stop taking their omega-3 supplements; plugs become extruded; etc.

So, how do we keep these less-than-compliant patients with dry eye disease relatively comfortable? One thing we can do is have straightforward conversations with these patients regarding the natural history and proper care of their chronic disease. Sharing knowledge and concern for their wellbeing can help promote compliance.

Even so, often these patients slack off their therapy and experience "breakthrough" symptoms. In these situations, we often use pulse-dosed Lotemax or Alrex (pulse dosing = q.i.d. for one to two weeks) to regain control of the inflammatory symptoms, and we always encourage them again to consistently use their artificial tears. Our clinical experience is that a single 5ml bottle of Lotemax lasts most patients an entire year! This excellently demonstrates the cost-effectiveness of Lotemax as compared to other ongoing anti-inflammatory therapies. The explanation for this is that pulse-dosing of loteprednol commonly keeps symptoms at bay for several weeks to a few months at a time.

simply urge the taking of 2,000mg of fish oil each morning right before breakfast. The triglyceride formulations are advocated by some as being more desirable than the ester formulations, but there is no firm consensus on which form is overall more beneficial to human health. As more truly scientific research evolves, there may well be more objective clarity regarding the benefits of one type of fish oil over another.)

There is some discussion about using azithromycin (either topically or orally) in place of oral doxycycline. Remember, doxycycline is being used at sub-antimicrobial dosages to reduce meibomian gland inflammation and to enhance the fatty acid metabolism within the meibomian glands. We have consulted several dermatologists and all of them have unequivocally stated that doxycycline has a vastly more beneficial clinical effect than azithromycin in this setting. We encourage you to have a similar conversation with dermatologists in your community.

Punctal plugs can be very beneficial once any ocular surface inflammation has been controlled. To "plug first and steroid later" can actually exacerbate ocular surface inflammation initially. In our opinion, it is senseless to monkey around with dissolvable collagen plugs "to see if the patient is helped temporarily."

We believe the need, or lack thereof, of punctal occlusion should be profoundly evident to a seasoned clinician. "Just do it", if in your judgment the patient can benefit. Whether you chose to plug the more symptomatic eye as a trial (to see how much relief is obtained), or plug both lower puncta simultaneously is a judgment call.

We always employ "punctal" plugs, and never use intracanalicular devices. This is mainly so we—and our patients—can monitor whether the plug is still there or not. (*See "New Insights Into Punctal Plugs," left, on why replugging is often unnecessary should the initial plug become extruded and lost.*)

Dry eye disease can be subdued in almost all patients with use of a multifaceted approach. Soothe XP, loteprednol, and omega-3 supplementation, with or without punctal plugs, can be immensely helpful in providing symptomatic control of dry eye disease. ■

1. Foulks GN. The correlation between the tear film lipid layer and dry eye disease. Surv Ophthalmol. 2007 Jul-Aug;52(4):369-74. Review.
2. Lemp MA. Advances in understanding and managing dry eye disease. Am J Ophthalmol. 2008 Sep;146(3):350-356. Epub 2008 Jul 2. Review.
3. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007 Apr;5(2):171.

New Insights Into Punctal Plugs

Have you noticed that many patients who benefitted from punctal occlusion can return after several months and still be doing well, yet the plug(s) has vanished? If punctal occlusion initially helped patient symptoms, then why would the patient not return to baseline symptomatology when the plug(s) was absent?

The answer to this puzzle is found in the December 2008 *American Journal of Ophthalmology*: "Stenosis of the punctum and proximal canaliculus are reported to be a frequent observation after spontaneous loss of punctal plugs … While stenosis is commonly found at the punctum, it is more commonly found within the vertical portion of the canaliculus … The abrasion of the canalicular inner wall caused by the plug is theorized to be the main cause of stenosis."

Another theory is that "Mechanical stress on the mucosa might lead to a mild chronic inflammation, causing a stenosis."

The authors add, "It appears that plug size is not a major determinant of stenosis, but larger plugs are thought to be more likely to do so than smaller plugs." One might wonder: how long must the plug reside within the punctocanalicular tissues to evoke such an unplanned iatrogenic stenotic response? Interestingly, such stenosis "seemed to develop independently from the time of insertion. In summary, it seems that the stenosis acts like an occlusion with a punctal plug."

We found this to be a particularly enlightening article that provides a rational anatomic explanation for the enduring relief from dry eye symptoms, even when the plug is long gone.

Boldin I, Klein A, Haller-Schober EM, Horwath-Winter J. Long-term follow-up of punctal and proximal canalicular stenoses after silicone punctal plug treatment in dry eye patients. Am J Ophthalmol. 2008 Dec;146(6):968-72.e1. Epub 2008 Aug 23.

Punctal plugs are an underutilized modality in the care of patients with insufficient tear volume. Patients may benefit even after the plug is long gone.

Medical Therapy for Superior Limbic Keratoconjunctivitis (SLK)

SLK is an uncommon, chronic, remitting and exacerbating disorder affecting the superior limbus and corneolimbus. It is bilateral, asymmetric and can be associated with dry eyes and dysthyroidism. Like chlamydial conjunctivitis, SLK is often missed—or misdiagnosed—initially. It is usually the second, third or fourth physician who finally makes the diagnosis in both conditions. This does not compliment either optometrists or ophthalmologists.

Most SLK patients present with the chief complaint of "irritated" eyes. The condition can cause considerable misery, sometimes to the point of even causing the sufferer to miss days from work. The typical patient is a middle-aged otherwise healthy woman, as women are more commonly afflicted than men. Because these patients often have concurrent dry eye syndrome, they are commonly diagnosed and treated for such, with minimal resolution of symptoms. Since SLK runs a 10 to 20-year course of spontaneous exacerbations and remissions (like Thygeson's SPK), the periods of remission can lure the naïve clinician into thinking the artificial tear therapy is responsible.

Diagnosis

The diagnosis is extremely straightforward, however, when one simply thinks to look for the classic injection pattern at the superior juxtalimbal bulbar conjunctiva. If any doubt remains, simply stain the eyes—the involved tissues will stain substantially.

Treatment

There is no FDA-approved medicine for SLK. However, the off-label use of 0.5% silver nitrate ophthalmic solution is a time-honored therapeutic approach that can be very helpful in most cases. Any hospital-grade compounding pharmacy can readily formulate a sterile ophthalmic solution. We usually write a prescription for exactly what we want, then have the patient take it to a pharmacy known to do specialty compounding. We see the patient back in the office in a few days with the 0.5% $AgNO_3$ in hand. Here's how the procedure goes:

- Instill a topical anesthetic O.U.
- Dip a sterile cotton swab into the solution, or drop several drops onto the cotton swab, to saturate it.
- Use a brisk wrist action to sling off any excess (drippy) solution (away from the patient, of course).
- Evert the lid of one eye and, with the patient looking down, roll (as with a paint roller) the cotton swab back and forth over the tarsal conjunctiva for about 20 seconds. Then do the same to the affected superior bulbar conjunctival tissues for about 20 seconds.
- Rinse these tissues with a stream of sterile eye irrigating solution sufficient to dilute and wash away any excess $AgNO_3$, then return the upper eyelid to its normal position.
- Repeat for the fellow eye.

We generally instill a drop or two of NSAID to ameliorate any discomfort following this procedure. Have the patient instill Soothe XP q2h for two days, and p.r.n. thereafter.

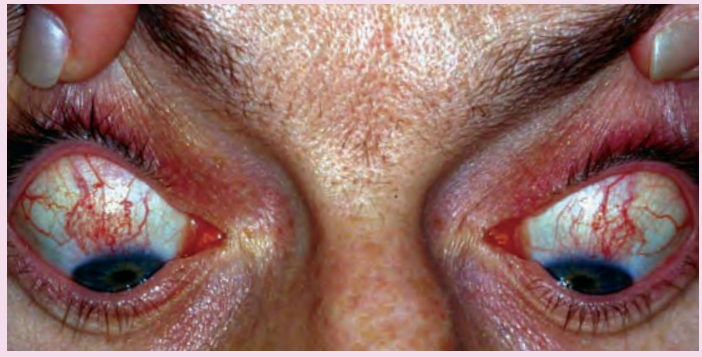
This pharmacy-formulated ophthalmic solution needs to be refrigerated for the duration of its 30-day shelf-life. To be sensitive to cost-efficient therapy, we have the patient return in one month to repeat the therapeutic process a second time prior to discarding the solution.

This therapeutic approach often gives several weeks (occasionally months) of symptomatic relief. The duration of relief can be influenced by the remission/exacerbation cycle, and by the overall stage of the disease process—i.e., whether the symptoms are of recent onset, or the patient has carried this diagnosis for a decade or so.

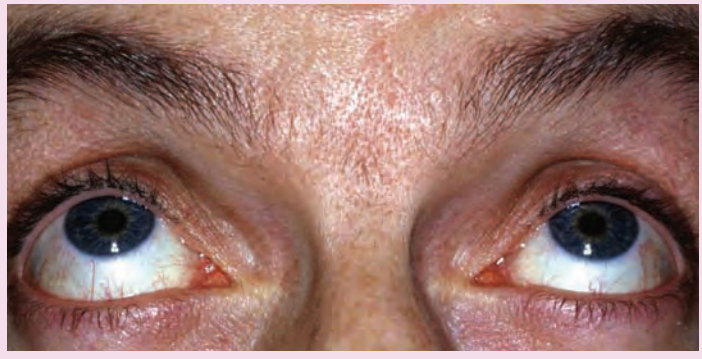
These $AgNO_3$ treatments can safely be repeated numerous times; however, if the relief from treatment is minimal or if the temporal period of relief is short, then it may be in the patient's best interest to have a corneal/external disease consultation.

Conjunctival resection is the time-honored definitive procedure. However, liquid nitrogen cryotherapy is a simple, in-office topical procedure that might be helpful.[1]

1. Fraunfelder FW. Liquid nitrogen cryotherapy of superior limbic keratoconjunctivitis. Am J Ophthalmol. 2009 Feb;147(2):234-238



Classic presentation of superior limbal keratoconjunctivitis.



Note the perfectly normal inferior limbal tissues in the same patient in up-gaze.

Dear Doctor of Optometry: please feel free to remove this sheet, copy it to your letterhead and distribute it to your dry eye & contact lens-wearing patients to whom you recommend Soothe XP.

Soothe XP

(available over-the-counter)

Your doctor has recommended a product known as **Soothe XP** to help you with your dry, burning, sandy, gritty-feeling eyes.

Soothe XP is a premium quality, state-of-the-art "artificial tear" that comes in a 15mL bottle. It is a special "oily emulsion" type of eyedrop and not just another watery, re-wetting tear product. Because of its special mineral oil formulation, it will cause foggy, cloudy vision for 20 to 30 seconds each time you place the drops in your eyes. After a few seconds, your vision will completely clear and you should have 1 to 4 hours of relief from your symptoms.

Soothe XP is completely safe and therefore you can put these drops in your eyes as often as you would like to help keep them comfortable. Most patients get good relief using **Soothe XP** 2 to 4 times a day. Be sure to shake the bottle once or twice before each use. *Note that there is a similar sounding product known simply as Soothe. It is NOT the same as **Soothe XP**, so do not be confused*.

For contact lens wearers: Soothe XP is an excellent lubricating and re-wetting eye drop for both soft and rigid contacts. A statement on the side of the box reads, "remove contact lenses before use;" however, this statement is not accurate. It is not necessary to remove your contacts before using **Soothe XP**. In fact, this product was specifically formulated for use with contact lenses and patients are routinely using **Soothe XP** successfully with their contacts to enhance comfort and prolong wearing time.

Soothe XP is equally effective for patients who wear contact lenses and for those who do not. Because it can be safely used by almost anyone, it was not tested as a "for contact lens use only" product, and therefore is not FDA-approved as such.