PRESERVING THE OCULAR SURFACE: WHEN AND WHY SHOULD WE GO PRESERVATIVE-FREE?

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In the United States, the FDA requires all aqueous multidose ophthalmic formulations to contain at least one substance to inhibit the growth of microorganisms.[1] These compounds have antimicrobial activity that helps to maintain sterility and cost effectively extend the shelf-life of topical medications. Used in more than 70% of all ophthalmic solutions, benzalkonium chloride (BAK) is a robust microbicidal agent that remains the predominant preservative used today, despite its well-known propensity to cause corneal and conjunctival apoptosis, delay wound healing, decrease goblet cell density, and cause corneal nerve damage.[2-7] Newer preservation systems such as polyquaternium-1, stabilized oxychloro complex (SOC), sodium perborate, potassium sorbate, and ionic-buffered systems (a combination of boric acid, zinc, sorbitol) were developed as less toxic antibacterial and antifungal alternatives to BAK; however, they still retain some cytotoxic effects.[2,8]

Some topical medications are available as preservative-free (PF) solutions, manufactured either as sterile single-use vials, aqueous-free solutions, or multidose bottles with proprietary systems that ensure sterility.[1] Several studies have shown that PF formulations can significantly reduce the ocular symptoms typically associated with preserved formulations and improve quality of life (QoL).[9-17] While PF formulations may be better alternatives, particularly for patients who require chronic polytherapy, eg, glaucoma, or have severe ocular surface disease (OSD), they have some limitations, including cost.

How, then, do we discern between preserved and PF medications for our wider patient base? To create a set of best practices that consider the preservative load on our patients, we convened a panel of esteemed optometrists who understand the importance of a stable ocular surface when managing ophthalmic diseases such as glaucoma or preparing the eye for surgery or contact lenses.

ARE ALL PRESERVATIVES CREATED EQUAL?

Marc R. Bloomenstein, OD, FAAO: We all know and see the effects of preservatives on the ocular surface in

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> —Marc R. Bloomenstein, OD, FAAO

our clinical practice but, apart from imparting sterility, preservatives lower the cost of medications. BAK is stable, adapts to a range of pH without affecting the vehicle, and is an effective preservative even at low concentrations.

Jill C. Autry, OD, RPh: BAK is the most studied preservative for ophthalmic formulations and is probably the least expensive. Even with the alternatives that we now have, BAK remains the most effective across all types of bacteria and fungi, which is likely why companies still use it.

Eric Schmidt, OD, FAAO: Another reason, for glaucoma medications at least, is that BAK has been proposed to enhance drug penetration past the cornea, resulting in higher concentrations of the active ingredient in the anterior chamber.[18] This is likely by breaking down the tight junctions between corneal epithelial cells.[19]

Dr. Autry: This is also why bimatoprost 0.01% was found to be equivalent to bimatoprost 0.03% in lowering IOP.[20] The concentration of BAK was increased four-fold from 0.005% in the original bimatoprost 0.03% formulation to 0.02% in the newer formulation (Table). This allowed the manufacturer to lower the drug concentration as the increase in BAK would increase drug penetrance. Bimatoprost 0.01% also decreased the degree of conjunctival hyperemia and ocular discomfort that was associated with bimatoprost 0.03%.[21]

Leslie O'Dell, OD, FAAO: I was also taught that BAK made glaucoma medications more effective. Having said that, some of these alternate preservatives like SOC or ionic-buffered systems, are so-called vanishing preservatives because they either convert to natural tear components or degrade upon contact with the cations on the ocular surface,[1] meaning they're no longer a factor in determining penetrance.

Dr. Autry: Most of these alternative preservatives are typically found in different brands of artificial tears and less so in glaucoma medications (Table).

Dr. Bloomenstein: We don't necessarily know whether some preservatives are better than others, but studies have shown less cytotoxicity on the ocular surface compared to BAK.

Murray Fingeret, OD, FAAO: When travoprost with BAK was replaced by travoprost with an ionic buffered system, there were many studies published by the Christophe Baudouin, MD, PhD, FARVO, group looking at the toxicity of BAK not just on the ocular surface but also on the trabecular meshwork. There is evidence that BAK could affect glaucoma surgical results.[22-24]

Dr. Bloomenstein: That's correct. One study showed that filtration surgeries in eyes treated without BAK were approximately 90% successful versus those in BAK-treated eyes, which were about 45% successful.[23] Long-term topical combination glaucoma therapy also contributes to failure of glaucoma filtration surgery.[22,24]

Studies have shown that BAK leads to conjunctival inflammation and metaplasia, most likely by affecting the mitochondria,[25-28] which is likely also the source of dysfunction in the trabecular meshwork. Long-term BAK exposure also leads to goblet cell loss.

Dr. Autry: To your point about comparing toxicities between preservatives, I agree that there isn't a lot of evidence to make a definitive statement. I know that animal models have shown that travoprost with an ionic-buffered system reduced conjunctival inflammation and corneal changes compared to latanoprost with BAK,[29] and a few clinical studies have shown that both significantly reduced IOP but the former produced fewer ocular surface symptoms.[21,30,31]

TABLE. PRESERVATIVE-CONTAINING AND PRESERVATIVE-FREE GLAUCOMA EYE DROPS

BRAND NAME	ACTIVE INGREDIENT	PRESERVATIVE USED/PRESERVATIVE-FREE
EYE DROPS WITH BENZALKONIUM CHLORIDE (BAK)		
Iopidine	Apraclonidine 0.5%, 1%	BAK 0.01%
Betoptic S	Betaxolol 0.25%	BAK 0.01%
Betoptic	Betaxolol 0.5%	BAK 0.01%
Lumigan	Bimatoprost 0.01%	BAK 0.02%
Lumigan	Bimatoprost 0.03%	BAK 0.005%
Lumify	Brimonidine 0.025%	BAK 0.01%
Alphagan	Brimonidine 0.2%	BAK 0.005%
Combigan	Brimonidine 0.2%/timolol 0.5%	BAK 0.005%
Azopt	Brinzolamide 1%	BAK 0.01%
Simbrinza	Brinzolamide 1%/brimonidine 0.2%	BAK 0.003%
Trusopt	Dorzolamide 2%	BAK 0.0075%
Cosopt	Dorzolamide 2%/timolol 0.5%	BAK 0.0075%
Xalatan	Latanoprost 0.005%	BAK 0.02%
Rocklatan	Latanoprost 0.005%/netarsudil 0.02%	BAK 0.02%
Vyzulta	Latanoprostene 0.024%	BAK 0.02%
Betagan	Levobunolol 0.25%, 0.5%	BAK 0.004%
Rhopressa	Netarsudil 0.02%	BAK 0.015%
Isopto Carpine	Pilocarpine 1%	BAK 0.01%
Timoptic	Timolol 0.25%, 0.5%	BAK 0.01%
EYE DROPS CONTAINING ALTERNATIVE PRESERVATIVES		
Alphagan P	Brimonidine 0.1%, 0.15%	Stabilized oxychloro complex 0.005%
Xelpros	Latanoprost 0.005%	Potassium sorbate
Timoptic-XE	Timolol-XE 0.25%, 0.5%	Benzododecinium bromide 0.012%
Travatan Z	Travoprost 0.004%	Ionic-buffered system (combination of boric acid, zinc, sorbitol)
PRESERVATIVE-FREE EYE DROPS		
Cosopt PF	Dorzolamide 2%/timolol 0.5%	Preservative-free
Iyuzeh	Latanoprost 0.005%	Preservative-free
Zioptan	Tafluprost 0.0015%	Preservative-free
Timoptic in Ocudose	Timolol 0.25%, 0.5%	Preservative-free

Dr. Schmidt: Brimonidine tartrate with SOC has also been evaluated against brimonidine tartrate with BAK, during a use period of up to 12 months.[32-34] The studies showed comparable IOP reductions for both, but better comfort and tolerability with the former.

Dr. Autry: I question how much of these toxicity implications are relevant for patients who only require once-a-day dosing or are on a short course of antibiotics because most of our understanding of BAK toxicity is from clinical trials or long-term studies. Most studies comparing preservatives tend to look at the kill rates. For example, travoprost with an ionic-buffered system was shown to offer less effective microbial protection than latanoprost with BAK.[35]

Dr. Bloomenstein: As a cationic surfactant quaternary ammonium detergent, BAK is highly hydrophilic, so it is retained in the tears for much longer, which may facilitate increased drug penetrance. As a derivative of BAK, polyquaternium-1 is 27 times larger. This may reduce its hydrophilicity and penetrance, thereby mitigating its cytotoxic effect. However, from a cost perspective and, as Dr. Autry noted, from a microbicidal perspective, we should consider whether medications containing alternative preservatives are on par with those containing BAK. Certainly, the absence of preservatives in medications and artificial tears typically increases the cost compared to preserved formulations.

With glaucoma medications, in particular, how might we differentiate between the side effects of the medication itself versus the preservative?

Dr. Autry: It's challenging to make that distinction because you must treat the glaucoma first. Drops are first-line therapy, so you could try medications with alternate preservatives or go PF. On the other hand, if you have a 70-year-old LASIK patient with rheumatoid arthritis and glaucoma, I might argue against using eye drops entirely and opt for selective laser trabeculoplasty, microinvasive glaucoma surgery, or another form of treatment.

Dr. Fingeret: I agree that the distinction can be difficult especially with certain drugs, like netarsudil, that can impart side effects. I've always associated hyperemia, redness, and irritation, to a certain extent, with the drug itself. Symptoms associated with BAK toxicity tend to take longer to manifest. In other words, if the patient develops symptoms early on, that's likely due to the medication. As Dr. Autry and others have pointed out, people who use one drop a day may or may not develop enough of a preservative load to impact the ocular surface. Admittedly, at times, it is a guess and clinical judgment.

However, glaucoma-related OSD is now known to be more common than we once thought. Studies using the Ocular Surface Disease Index (OSDI) found that the prevalence of dry eye disease (DED) is 40% to 59% among patients with glaucoma using topical therapies.[9,36-38] We're typically dealing with elderly populations and the prevalence of both OSD and glaucoma increase with advancing age. These patients are often taking multiple medications, each with preservatives like BAK, over a long period of time. There is strong evidence of BAK-induced toxicity, so you can imagine how BAK can be problematic over time.

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TAKING A CLOSER LOOK AT OUR PATIENTS' PRESERVATIVE LOAD

Dr. Bloomenstein: When we start thinking about patients who are affected by preservative-induced or -exacerbated toxicity, are there any specific groups that we recommend stay away from preservatives?

Dr. O'Dell: I would advise patients who have severe DED or keratoconjunctivitis sicca and those who have Sjögren

Courtesy of *Modern Optometry*

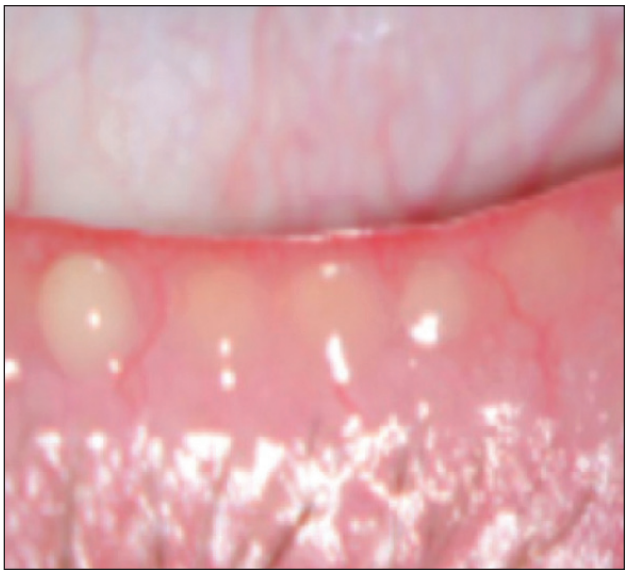

Figure 1. Typical presentation of MGD in patients using certain classes of glaucoma medications.

syndrome against using preservative-containing medications and artificial tears. If they also have glaucoma, I think about the preservative load and frequency of dosing. I try to shift those patients to alternate therapies altogether to gain IOP control because comfort is such a priority for them. I keep an eye on newly diagnosed patients with glaucoma, who are currently only at risk for OSD. If you haven't spent enough time educating and alerting them to the side effects of some of these glaucoma medications, they may become poorly adherent to drops early on. It's been great to see the evolving understanding of the role of the ocular surface in glaucoma because, 20 years ago, we didn't have these conversations. Glaucoma surgeons would look past the cornea and focus on the optic nerve.

Dr. Schmidt: You're right. During our residencies and fellowships, we were always taught that the most important concern in glaucoma is to reduce IOP and everything else is gravy. We certainly have a more enlightened view of it now. However, the reality is that patients with glaucoma who generally have worse QoL scores or corneal staining tend to have lower IOP.[39] The disease is better controlled but that is accompanied by worse side effects, and there's the rub. If you stabilize IOP for these patients without the burden of OSD, that's a big win. Traditionally, however, we haven't been able to do that and the more eye drops that are used, the better the IOP, in most cases.

Dr. Bloomenstein: That's a great point. For all intents and purposes, we prescribe eye drops that cause the tear film to evaporate too quickly, resulting in a higher OSDI score and reduced patient QoL. It would behoove us to try to improve patients' adherence to their regimen by ensuring they didn't experience sequelae that affected QoL in the first place.

Patients with DED and glaucoma are absolutely the ones who are more susceptible to OSD. Do we really want to keep these patients on drops that may result in adverse side effects over the long term simply because they may or may not have better corneal penetrance, be easier to access, cheaper, and a longer shelf life? I'll add patients with neurotrophic keratitis (NK) and neuropathic corneal pain to the list of patients who should not be using preserved eye drops. Preservatives can have a tremendous effect on reducing nerve function.[40-42] Are there any other kinds of patients in whom you would avoid using BAK?

Dr. O'Dell: Before you start prescribing therapies, especially with the prostaglandin class, you must know the status of the meibomian glands. The meibomian glands may be structurally healthy with nonobvious dysfunction or poorly secreting glands. The glands need to be assessed before medications are started, especially medication classes that are known to cause meibomian gland dysfunction (MGD) and atrophy. Long-term use of glaucoma drops can affect meibomian gland morphology and function (Figure 1), and MGD is prevalent in up to 80% of patients with glaucoma.[43-45] You should be on the lookout for this at any stage of therapy, screening all patients, not just those with MGD or symptoms of MGD.

I see many cases of gland atrophy in my clinic and I'm careful when considering prostaglandins for monotherapy because studies have shown that prostaglandins (usually preserved with BAK) have a much higher rate of MGD.[46-49] For example, one study showed that 92% of patients on prostaglandin monotherapy had MGD versus 58.3% of patients on nonprostaglandin therapy.[47] In these patients, I typically prescribe prostaglandins containing alternate preservatives, like travoprost with an ionic-buffered system or brimonidine tartrate with SOC, or PF formulations such as tafluprost.

Dr. Fingeret: How do you evaluate the eyelids?

Dr. O'Dell: Mostly with the slit lamp. I use a transilluminator to look for the absence or presence of glands. I then use the meibomian gland evaluator and apply standard pressure to the glands to determine if they're secreting normally. This takes less than a minute for each patient.

Courtesy of *Modern Optometry*.

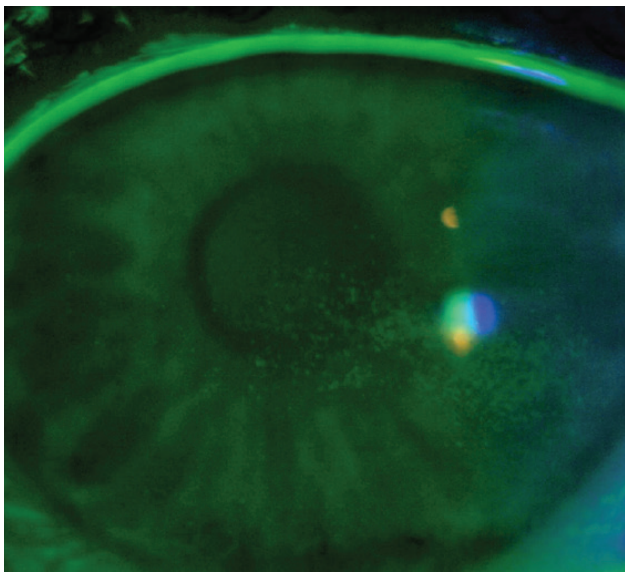

Figure 2. Inflammation of the ocular surface can lead to superficial punctate keratitis.

Dr. Autry: If I'm contemplating preservatives when initiating treatment, it's usually in patients who are at risk of OSD (eg, those with Sjögren syndrome, rheumatoid arthritis, neurotrophic corneas, poor baseline meibomian gland function, a history of refractive surgeries or those who are already on multiple eye drops). In patients without these risk factors, I wouldn't be hesitant about BAK use, except if/when I see issues developing over time. In those cases, I'd pull back on BAK and try a different therapy.

Dr. Schmidt: Let's say you have a patient on a BAK-preserved drop for 3 to 4 years and then they develop superficial punctate keratitis (SPK; Figure 2), which worsens with time. I often wonder whether the SPK will simply resolve if you halt use of the eye drop or if the duration and severity of SPK correlates to the duration of time to resolution.

Dr. Autry: Good question, I'm not sure that we know that to be true. Today, I conducted 10 cataract evaluations, of which nine had SPK and only one of those nine were on glaucoma drops. In these patients, we can't tell if SPK occurs due to age or some other trigger. It's just a byproduct of the lives we now live. In these situations, instead of switching the patient to a PF medication, which has a significant cost consideration, I often prescribe artificial tears.

Dr. Bloomenstein: I assume that every patient I see is an MGD or DED patient waiting in the winds, based on the environmental strains we put on our eyes. Perhaps we should do the same with our glaucoma patients, because the prevalence of SPK in patients receiving topical glaucoma therapy has been reported to be between 18% to 54%.[9,10,50] Furthermore, the Ocular Hypertension Treatment Study (OHTS) found that 39.7% of patients receiving medication were receiving two or more drops after 5 years.[51] The Collaborative Initial Glaucoma Treatment Study (CIGTS) found that about 75% of patients needed two or more medications to reach the predetermined target IOP within 2 years.[52] These studies indicate that most patients with glaucoma will end up needing multiple drops so, to me, it would almost be prudent to consider the preservative load from the beginning of the treatment. To Dr. Schmidt's point, is it better to be proactive about this rather than working backward? That's the million-dollar question.

Dr. Schmidt: In a perfect world, the answer to that is absolutely. With glaucoma, that's not an easy question to answer because the goal of treatment is to lower IOP such that progression and loss of the retinal nerve fiber layer is mitigated. Obviously, above all, do no harm. There's probably more harm done by having the IOP be unacceptably high than the patient developing SPK.

Dr. Autry: An alternative is foregoing drops altogether for surgical intervention.

Dr. Bloomenstein: Yes, or using a PF prostaglandin.

TALKING TO PATIENTS ABOUT OPHTHALMIC PRESERVATIVES

Dr. Bloomenstein: Do any of you have a discussion with your patients about preservatives?

Dr. Autry: I will sometimes tell patients their eyes are really dry and that we should switch them to PF drops. I'll then get a phone call 24 hours later from them because they've decided to stay on their preserved drops because they've seen that the PF drops are not easily obtained or they are more expensive. These patients do understand that the preserved drops are irritating their eyes and making them dry, but it's hard to make that switch.

Dr. Schmidt: Great point. If you could convince me that there's a PF prostaglandin that has equivalent safety and efficacy to the preserved prostaglandins, and its equally accessible and affordable, that's a win. As it stands now, it remains an uphill battle.

Courtesy of Leslie O'Dell, OD, FAAO.

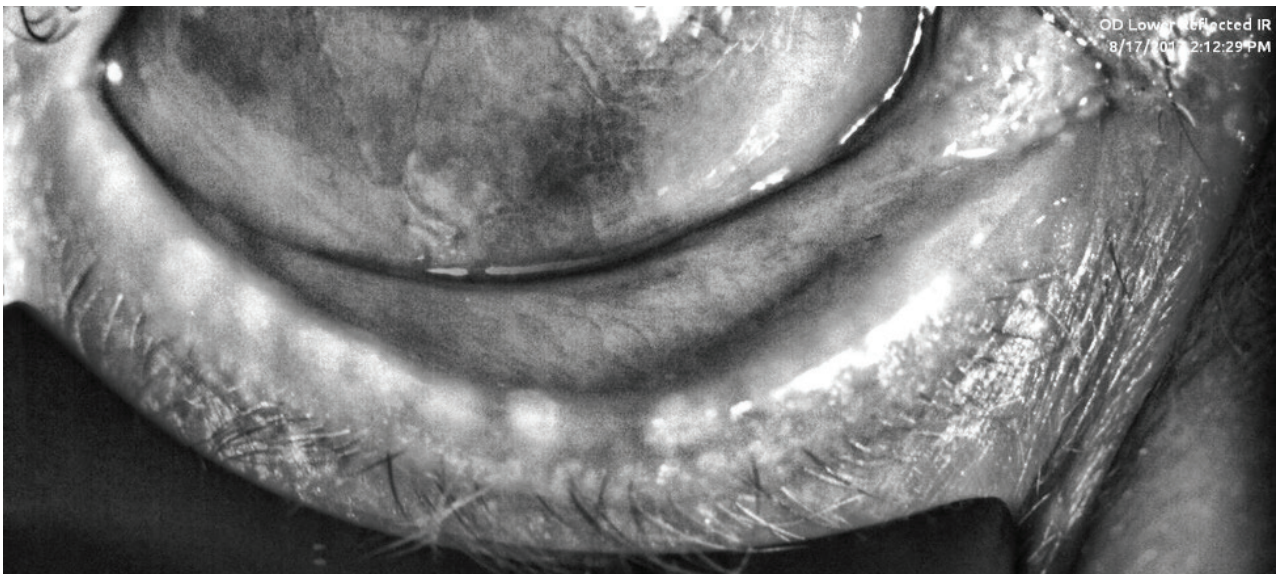

Figure 3. Pretreatment meibography of the lower lid revealing meibomian gland dropout.

Dr. Bloomenstein: Dr. Schmidt, you mentioned this risk-benefit analysis for patients with glaucoma. What happens when the risk, especially in QoL, is worse than the benefit being lower IOP? Would you make the decision to switch to PF drops, especially when the patient's IOP is stable?

Dr. Schmidt: There are three hallmark signs that would prompt that decision, for me: 1) A lot of older patients who are on multiple medications will complain of foreign body sensation or perpetually teary eyes; 2) Worsening or chronic redness is a big one, although as Dr. Fingeret noted, it could also be due to the active ingredient itself; and 3) Sometimes these corneas get so bad, patients with 20/30 VA will drop down to 20/50. It's bad enough the patient has glaucoma but if vision has deteriorated because of the chronic exposure to preserved medications, that should prompt a switch to PF options.

Dr. Bloomenstein: Dr. Autry, how do you treat these patients undergoing cataract evaluations who have OSD? Do you have a conversation about preservatives?

Dr. Autry: Most of those patients aren't on any drops, so that's not relevant. I'm usually trying to get them ready for cataract surgery quickly and making sure the surgeon will get accurate, reproducible keratometric readings. Usually, I prescribe preserved artificial tears and maybe some gel at night. If the ocular surface is in bad shape, I'll prescribe a steroid. I consider PF drops for those who are already on preserved artificial tears because I don't want to add to the preservative load.

Dr. Bloomenstein: Dr. O'Dell, how do you determine whether a patient might benefit from PF solutions?

Dr. O'Dell: In glaucoma patients, I would be evaluating their corneal health at each exam. If I saw clinical signs that I thought were related to OSD at follow-up, I would put them through a dry eye evaluation with point-of-care testing like osmolarity, matrix-metalloproteinase-9 (MMP-9) levels, and a more in-depth meibomian gland evaluation, to determine whether they would benefit from an alternate approach or additional therapy (Figure 3).

Like Dr. Autry, I don't routinely talk about preservatives with all patients, unless I'm explaining my choice to make the switch to PF. Otherwise, they may go to the pharmacy, see the added cost, and wonder why they're paying more for the PF drops, especially if the pharmacist or pharmacy technician suggests the generic is available for a much lower cost.

Dr. Autry: That's a good point. I also explain to certain patients that they specifically need to get the single-use vials instead of the multidose bottles, because they may not understand the significance of the different packaging.

Dr. O'Dell: Your preoperative treatment of these cataract patients is interesting. When we talk about the cost of dry eye, we're talking cost of treatment and the duration of time needed for the treatment to work. As Dr. Schmidt suggested, sometimes if the patient has had SPK for a longer period, it may not be easy to remedy with artificial

tears or gel tears in time for surgery. Once we start to add more therapeutics, that contributes to cost. The age of the patient can also sometimes be a hurdle to quick resolution. Unless I suspect the prolonged SPK to be NK, I start them on therapies that will give me a good response, quickly. Nowadays, we can even do fast fixes with amniotic membranes to heal our patients far more quickly than we would have been able to 10 years ago.

Dr. Schmidt: Yes, great point. In cases where you use the amniotic membrane to jumpstart that process of recovery, you wouldn't then follow that up with preserved artificial tears, which might take away from your progress. That's when you'd use PF artificial tears.

I do talk to my patients about preservatives in artificial tears because, as Dr. O'Dell mentioned, it helps them buy the right drops. In that regard, I think samples are really important because it prevents the patient from picking the least expensive option out of a pharmacy lineup. Having a tangible sample helps them show the pharmacist what was recommended by their optometrist.

Dr. Bloomenstein: I agree with that, and I also talk about preservatives. We have to make a case for why we've made the choice and what's in it for them. I explain to patients that we're trying to minimize the effect of some of their OSD triggers rather than adding to it, whether it be prolonged computer work, glaucoma eye drops, diabetes, or autoimmune disorders. I talk about it with a broad range of patients, so I feel it is important to know which products are PF.

Dr. Fingeret: That's a fair point. My practice is similar to Dr. O'Dell's and Dr. Autry's, in that I don't always talk about preservatives. I bring it up if the patient is developing symptoms or signs of OSD or worsening OSD. But it may be fair to say that we should have this conversation much earlier than that.

Dr. Schmidt: To Dr. Bloomenstein's comment about knowing which products have preservatives and which ones don't, it's rather incumbent upon the optometrist to know which products have preservatives, especially with glaucoma eye drops. Not only whether it is preserved but also the type of preservative.

Dr. Autry: I think that the average optometrist would have trouble with that and the marketing for these drops doesn't help matters. Most optometrists who don't have considerable experience with OSD or preservative-induced OSD assume that travoprost with an ionic-buffered system is PF, when it's really BAK-free. They would say the same of latanoprost ophthalmic emulsion 0.005%, which is BAK-free but contains potassium sorbate as a preservative. We don't really know much about the latter. They might correctly identify tafluprost as being PF because the single-use vials are a clear indicator. It's important to know which medications are truly PF and which contain alternate preservatives. PF-latanoprost was recently approved by the FDA,[53] so when that becomes available, it would be a game changer for some patients.

Dr. Bloomenstein: It sounds like we all agree that the presence of preservatives does impact our decision of which drops to use for different patients.

Dr. Autry: We certainly like to have PF options, but it's a question of whether every patient truly needs it and if it ends up being an affordable switch for them.

THE EFFECT OF PRESERVATIVES ON DIAGNOSTIC TESTING

Dr. Bloomenstein: Let's switch gears a little and consider the effect of OSD on diagnostic tests. Dr. Fingeret, are there any data to suggest that OSD affects IOP measurements?

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Dr. Fingeret: That's an interesting question, and as far as I am aware, no.

Dr. Bloomenstein: Dominick Opitz, OD, FAAO, presented an interesting paper about a patient who was on three different glaucoma medications and suffered from severe SPK, inflammation, and elevated IOP. However, once he managed the OSD, the patient's IOP started to lower and he was able to reduce the number of glaucoma medications. There are other reports of this in the literature as well.[54] What do you think was happening there?

Dr. Fingeret: I would've interpreted that case as the patient's eyes being so irritated that he stopped using his drops.

Dr. Bloomenstein: Correct. The preservative load may have been too high, causing OSD, which may have made the patient less apt to use the drops.

Dr. Autry: We certainly know that OSD can distort the mires. My technicians have a harder time getting a decent reading on patients with DED or those with corneal issues. Sometimes, it could be due to a physical scar but other times, it's DED. Usually, I can administer artificial tears or gel tears, let it sit for 5 minutes, and get a much better image.

Dr. Schmidt: Dr. O'Dell mentioned osmolarity testing earlier. Would BAK affect those scores?

Dr. O'Dell: Absolutely. As a detergent, BAK is inducing inflammation, causing tear film evaporation, and reducing tear breakup time (TBUT), so osmolarity scores do increase.[37,55-57] BAK has been shown to affect tear film stability even in healthy subjects.[58,59]

Osmolarity testing can sometimes be frustrating for doctors because of its variability. It's probably why it has had a slower adoption. Doctors will complain that they get a different value every time, but you have to remember that you're measuring a dynamic fluid (Figure 4). It's like IOP. You don't get the same number every time either. However, I notice that the more I do osmolarity testing and the more that I do to improve the ocular surface, the more those numbers fall into the normal range and are symmetric between the eyes. Sometimes it takes months of treating patients to achieve that response. You likely won't see a dramatic response after one drop.

For my practice, point-of-care testing has become standard because it makes evaluation easier and I want to leverage all available tools for my patients with glaucoma, but it certainly doesn't have to be the case for everybody.

Courtesy of Modern Optometry.

Figure 4. Osmolarity testing requires a small volume of tear fluid and can be useful to gauge ocular surface improvements over time.

Dr. Schmidt: On that same note, if a patient with DED is on cyclosporine eye drops and using preserved artificial tears every 2 hours, like a lot of these patients do, could that make the osmolarity reading artificially high?

Dr. O'Dell: I'm sure it could. Regardless of whether they're preserved or not, excessive amounts of artificial tears will influence the osmolarity reading.

Dr. Bloomenstein: You're right. Different brands of artificial tears have been shown to have different osmolarities. To your point, Dr. Schmidt, even artificial tears that have low osmolarity themselves have not been shown to reduce natural tear osmolarity. Patients with severe OSD inherently have higher osmolarity and the osmolarity of the artificial tears alone, independent of their composition, doesn't provide an advantage in lowering natural tear osmolarity.

We know that the signs and symptoms of OSD never match, and the challenge has always been to find a metric that demonstrates whether treatment is working. Osmolarity is one of those metrics. You never get false highs. The reading is either high and the patient has OSD or it's not.

TAILORING YOUR TEAR RECOMMENDATIONS

Dr. Bloomenstein: We know that the tear film is composed of three layers, the outer lipid layer, middle aqueous, and inner mucin layers. We've previously mentioned the known effects of BAK on the tear film and goblet cell density. Dr. Autry, you've stated that you use artificial tears to stabilize the tear film in your patients. Do you differentiate between the types of artificial tears based on the patient's presentation or do you consider their composition at all?

Dr. Autry: I do, but very broadly. I prescribe tears with omega-3 fatty acids or emollients for patients with MGD. With other patients, I tend to use brands that contain demulcents, and there's often no concrete reason behind those decisions. I'll sometimes prescribe gels if they need something thicker.

Dr. Bloomenstein: As you stated, emollients are the lipid-containing artificial tears that are designed to increase the lipid layer thickness, stabilize it, and reduce evaporation. Their use is increasing, as our awareness of MGD increases. Demulcents are the more common type of artificial tear and are easily commercially available. The FDA-approved demulcents include carboxymethylcellulose (CMC), which is the most common demulcent; hypromellose; dextran; propylene glycol; polyethylene glycol; glycerin; povidone; and polyvinyl alcohol. Demulcents form a mucoprotective layer that aid in water retention and decrease friction. Dr. O'Dell, do you differentiate between demulcents and emollients?

Dr. O'Dell: I do, to an extent. The tear film is so complex that it's impossible to capture that in a bottle. What artificial tears can do is provide some of the attributes of the natural tear film. If you have a patient who has floppy eyelids or a lid abnormality that is resulting in poor tear distribution, you may want an artificial tear with high viscosity to help the patient throughout the day. If the patient has evaporative dry eye, the lipid-based tears are more suitable for them. Some of the newer ones have glycerin or hyaluronic acid which hydrate the tissues better.

I sometimes hesitate to overcomplicate these matters because its been such a challenge to shine a spotlight on the ocular surface. What we really want is for practitioners to pay attention to the ocular surface and treat it. The hope is that you'll decrease the osmolarity and inflammation with tears alone, without requiring a therapeutic. However, if you do look at what each brand of artificial tears contains, you can better guide your patients in using over-the-counter relief.

> "It's important to know not only which tears have preservatives, but also understand the difference between demulcents and emollients and when you might choose one over the other."
>
> –Eric Schmidt, OD, FAAO

Dr. Schmidt: A lot of ophthalmologists and optometrists think all artificial tears are the same, when they're not. It's important to not only know which tears have preservatives, but also understand the difference between demulcents and emollients and when you might choose one over the other. Otherwise, patients may end up using artificial tears that offer no relief and, in fact, make things worse through overuse. A few years ago, I was part of a panel that classified artificial tears based on their composition and it was a great exercise because it made me think about artificial tears more critically. I appreciate that there are several brands out there and it can be hard to make out any differentiators, but it would be nice if this information were available in an easily digestible form.

Dr. Autry: That's a fair point because patients do take recommendations from their pharmacist or eye care provider. They trust our professional opinion and expertise. I often recommend a specific brand of artificial tears for patients that use digital devices for prolonged periods of time. It's unclear how these tears are specifically designed for digital device users over other brands, but it is a point of difference that makes me confident in making the recommendation. Now, at least, I know that patients will choose this brand over the generics. If there are compelling reasons to similarly recommend PF medications over their preserved counterparts, we would do that.

However, for me, it goes back to the ease of getting the medication and its cost-effectiveness.

Dr. Bloomenstein: We're all in agreement on this then – it's important for optometrists to understand the components of artificial tears. A good example of why this is important, is a molecule called trehalose, which is an osmoprotectant that protects against hyperosmolar stress-mediated injury, and a component of some artificial tears. I like to give patients a compelling reason to fill a prescription or spend a little bit more money and trehalose is a good one. Brine shrimp or "sea monkeys" are essentially desiccated tissue coated in trehalose, which protects them from extreme temperatures and lack of water. As we know, once they encounter water, they become activated. I find that this story helps patients understand that we don't just want to lubricate their eyes, we want them to use artificial tears that will make a real difference to the epithelium, possibly improve inflammation, and change the osmolarity. Trehalose can help with that.

I typically recommend artificial tears only as rescue drops, ie, when a patient's eyes are watering or irritated. When and how do you talk to patients about using artificial tears?

Dr. O'Dell: I do things a little differently. I advise patients use tears once or twice a day instead of waiting until they feel terrible. Otherwise, it's like applying sunscreen after you've been sunburnt. You may get less of an effect. It also depends on the patient. If they're on a foundational therapy and aren't willing to do a gland opening treatment, I'll put them on some kind of lipid-based tear to help stabilize the lipid layer. Those are the patients with whom I usually advise regular tear use.

There are, of course, a lot of patients who only experience dry eye flares in the early stages of the disease and once they're past it, they forget about it and don't mention it to us. In those cases, I guide them to use artificial tears as rescue treatment.

Dr. Bloomenstein: As an aside, we know that artificial tears don't last very long. Often, if we tell patients to administer them twice a day, they may just administer them 2 hours apart, which won't be helpful. I like to instruct patients to use the tears when they know they will be doing activities that will change the quality of their tear film, eg, prolonged computer use or on an airplane. That way, they can derive more benefit from the recommended tears.

Dr. Autry: I do a combined approach. I recommend using it as maintenance, especially if that is their only treatment. If they're already on an immunomodulator, the artificial tears become rescue drops. Otherwise, I suggest they use it after brushing their teeth in the morning and at night. They may need it more when they're on the computer, under a ceiling fan, or playing golf, and that's okay, too. If they're using artificial tears more than five or six times a day, we have a problem and should be exploring other options.

Dr. Bloomenstein: Would you put them on a different drop?

Dr. Autry: I would change tactics. If they're not already using these options, I'd suggest immunomodulators, low-dose steroids, punctal plugs, thermal pulsation systems, or autologous serum tears. My analogy for patients is that if they have acid reflux, they can certainly use antacids, but if they're using antacids every hour, there's definitely a better solution out there. That level of dosing can become frustrating.

> "I advise patients use tears once or twice a day instead of waiting until they feel terrible. Otherwise, it's like applying sunscreen after you've been sunburnt."
>
> –Leslie O'Dell, OD, FAAO

> "The bottom line is if PF options for glaucoma, OSD, or any other disease were accessible, we would get a lot of mileage out of them and would prefer them over the preserved versions."
> —Murray Fingeret, OD, FAAO

Dr. Bloomenstein: Do you have patients on long-term glaucoma medications who complain about having to use a lot of tears? In other words, can artificial tear usage act as a guide to determine whether they're bothered by their medications?

Dr. Fingeret: Sure. Artificial tears can be a temporary relief or rescue for patients whose eyes become bothersome, whether they're stinging, irritated, and/or burning. One of my tricks is to suggest they administer the artificial tears a couple minutes before they administer the glaucoma eye drop. But, as we've discussed, if they're using a lot of artificial tears, you have to wonder what else is going on.

Dr. Bloomenstein: I have a love-hate relationship with artificial tears. They're an important part of what we do, but I also feel they're overrepresented. It's worth taking the time to understand how they work and finding one that is going to ameliorate the ocular surface. With some artificial tears or gels, there can be a temporary blurring of vision. Dr. O'Dell, does that play into your recommendations for artificial tears?

Dr. O'Dell: Yes, I've had patients come into my office after having used gel tears because they've experienced no relief. Usually, they've chosen gel tears over the other brands, based on the perception that they needed stronger relief. But, as we work through their OSD and get them on the right therapies, they realize that a thick gel used six times a day was not helping them visually perform at their best. I reserve these thicker agents for bedtime, not during the day. A lot of patients also have inadequate lid seal or some kind of nocturnal issues. If they are having morning symptoms, ie, their eyes are the driest when they wake up or when they go to use the bathroom overnight, that's less to do with evaporative dry eye, per se, and is more reminiscent of tear evaporation due to exposure.

Dr. Schmidt: This is another reason why doctors should understand the difference between artificial tears. We're all a fan of using analogies—mine is that artificial tears are like hand lotion, they make your hands feel moisturized but only for a few hours. I would encourage patients not only to use their artificial tears, but to use the right ones, especially after intense pulsed light or localized heat therapy procedures. Once we've cleared out the glands, part of the burden or aftercare becomes keeping them that way. It's important to maintain the tear film and an easy way to do that is with a tailored recommendation. Some drops can also increase meibomian gland activity.

Dr. Bloomenstein: You bring up another good point because I also see postoperative patients. I always want to know what's in the artificial tears that I recommend to them, but I also prefer PF solutions. We know that OSD is the chief complaint of poor vision for patients who have undergone cataract or refractive surgery.[60-61] So, I want patients to understand what's in the bottle or single-use vial that I'm giving them, and why it's important that they use that. I'm a big fan of the multidose bottles that filter out one drop of PF solutions because they're more economical and patient-friendly, especially after surgeries.

KEEPING AN EYE OUT FOR PRESERVATIVE-FREE FORMULATIONS

Dr. Fingeret: The bottom line is if PF options for glaucoma, OSD, or any other disease were accessible, we would get a lot of mileage out of them and would prefer them over the preserved versions. The PF-tafluprost may not have caught on because of the cost issue and the lack of familiarity compared to latanoprost. It'll be interesting to see how the PF-latanoprost fares.[53] We also noted that BAK was thought to enhance corneal penetration and aid drug efficacy, but with PF solutions, they have to show comparable efficacy to the preserved version, so it

becomes a moot point.[53] The only remaining concern is that of accessibility.

Dr. Bloomenstein: I always phrase the question of PF as "if it were free or easily accessible, would you prescribe this to your patient?" You're saying that all things equal, you would.

Dr. Fingeret: It's not likely to be as cheap as a generic by any means, but there's a way forward if it were at least comparable in cost to brand-name glaucoma medications. As Dr. Autry has pointed out, some patients just cannot afford PF solutions whether they be prostaglandins or not, so they're not motivated to make the switch no matter how much more benefit they can reap.

Dr. Bloomenstein: Do we think that the packaging has any bearing whatsoever? If a PF medication were packaged in a multidose bottle versus the single-use vials, would patients like them any better or is it the other way around?

Dr. Autry: At first, the single-use vials may be off-putting because patients are unfamiliar with them. They're used to bottles and they know how to use them. With time, patients see advantages to the single-use vials over the bottles, including being able to carry it around and store a few vials in every bag or location so that it's always handy. We've seen this pattern with cyclosporine; once patients get used to them, they prefer the vials over the bottles.

> "With time, patients see advantages to the single-use vials over the bottles, including being able to carry it around and store a few vials in every bag or location so that it's always handy."
> —Jill C. Autry, OD, RPh

Dr. O'Dell: I agree. When cyclosporine became available as a multidose bottle, only a handful of patients were thrilled to have it, and they were the ones who traveled a lot. Most patients appreciated the single-use vials.

Dr. Schmidt: My patients tell me that one of the advantages of single-use vials, especially for a chronic medication, is that they know when they're going to run out. They can see that they're down to a few vials and call in for a refill ahead of time. With bottles, they don't get this heads-up until they squeeze the bottle and see nothing but a bubble.

Dr. Autry: The single-use vials have always been more expensive than the bottle. I imagine that cost plays heavily on the patients' minds, especially for artificial tears, when they see rows and rows of them at the pharmacy and note that the bottles are cheaper.

Dr. Bloomenstein: We've talked around the question of whether all patients should be using PF artificial tears, but we would all agree that if there was an easy, affordable way to access them, the answer would be "yes." In particular, if patients are using them multiple times a day or using them as rescue drops, there's a good reason to go PF. I wouldn't want to expose them to more preservatives than they really need.

Dr. Schmidt: There's now a heightened awareness of OSD in patients with glaucoma, which is great. My closing thoughts are that patients are placed on a particular drop primarily to lower their IOP. However, if we can minimize OSD without sacrificing the IOP-lowering ability, that's a win for everybody.

Dr. O'Dell: If you're trying to preserve the ocular surface, I'm also a big proponent of PF solutions, especially with artificial tears.

Dr. Autry: For the eye care community in general, it's good to know that these options exist. They may not be right for everybody, but some patients may certainly benefit. That's where the education comes in, because when optometrists sit down with patients and think about starting them on a therapy, they will look at the ocular surface and let it influence their decision-making. They might reconsider what they would have prescribed or provide an adjunct treatment to help combat any side effects

> "We need to balance quality of life and treating the disease by understanding the key differences between preserved and PF formulations."
>
> —Marc R. Bloomenstein, OD, FAAO

from their chosen medication. That's true across all practitioners. An oncologist thinks about the side effects of a chemotherapeutic, but they still need to administer the drug to keep the patient alive. Some cholesterol-lowering medications cause muscle issues in some patients but if a patient has high cholesterol, they're given the drug regardless. You have to make tough calls.

As optometrists, we should begin thinking about this approach when we start a medication. Maybe we haven't always done that to the degree we should if we had more PF therapeutic options.

Dr. Bloomenstein: Absolutely. We need to balance QoL and treating the disease by understanding the key differences between preserved and PF formulations. ■

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