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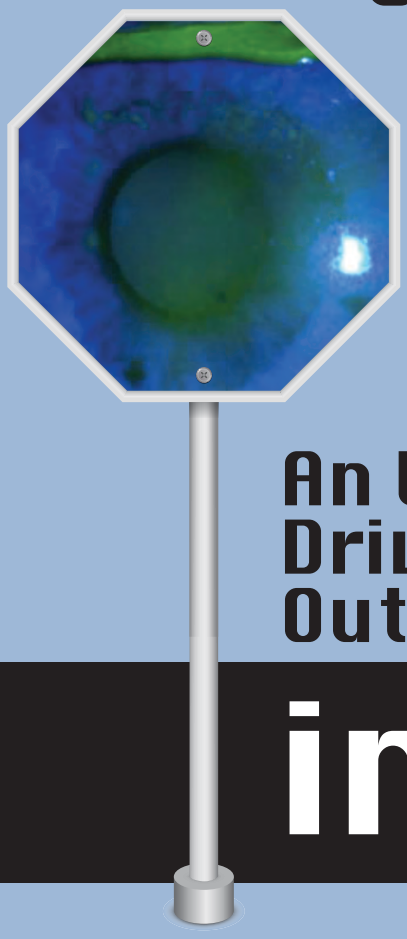
OCULAR SURFACE DISEASE



An Unexpected Driver of Adverse Outcomes in Glaucoma

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ACTIVITY DESCRIPTION AND PURPOSE

Both glaucoma and ocular surface disease (OSD) increase in prevalence with aging and often coexist. Common therapies for glaucoma may increase the risk for OSD and may aggravate existing OSD, mediated primarily by the ubiquitous preservative benzalkonium chloride. Comorbid OSD can have the undesirable effect of reducing adherence with glaucoma therapy to avoid the symptoms of OSD, which in turn can lead to glaucoma progression and potential visual dysfunction. Successful management requires surveillance for OSD among patients with glaucoma, appropriate workup of suspected OSD in these patients, and understanding of the causal relationship between topical glaucoma medical therapy and OSD in order to optimize outcomes of both conditions. In this educational activity, a panel of glaucoma and ocular surface experts will review the relationship between OSD and glaucoma and the role of OSD on adherence to glaucoma therapy and provide strategies for successful assessment of patients with glaucoma. The desired results of this activity are to improve the outcomes of patients with glaucoma.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

LEARNING OBJECTIVES

After completing this activity, participants will be better able to:

- Describe the relationship between preservatives used in topical glaucoma medications and ocular surface disease
- Discuss the role of preservative-mediated ocular surface disease in nonadherence to topical glaucoma treatment
- Assess patients who use preserved topical glaucoma medication for ocular surface disease

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Ocular Surface Disease: An Unexpected Driver of Adverse Outcomes in Glaucoma

INTRODUCTION

Both glaucoma and ocular surface disease (OSD) increase in prevalence with aging and often coexist. Common therapies for glaucoma may increase the risk for OSD and may aggravate existing OSD, mediated primarily by the ubiquitous preservative benzalkonium chloride (BAK). Comorbid OSD can have the undesirable effect of reducing adherence with glaucoma therapy to avoid symptoms of OSD, which in turn can lead to glaucoma progression and potential visual dysfunction. Successful management requires surveillance for OSD among patients with glaucoma, appropriate workup of suspected OSD in these patients, and understanding of the causal relationship between topical glaucoma medical therapy and OSD in order to optimize outcomes of both conditions. In this educational activity, a panel of glaucoma and ocular surface experts will discuss the complex interplay between OSD and glaucoma and highlight strategies for successful comanagement of OSD in patients with glaucoma.

PREVALENCE AND IMPACT OF OCULAR SURFACE DISEASE IN PATIENTS WITH GLAUCOMA

The prevalence of primary open-angle glaucoma in the United States increases with age, from 0.68% among people aged 40 to 49 years to 7.7% among people aged ≥ 80 years.[1] Similarly, among women in the United States, the prevalence of dry eye disease (DED) increases from 5.7% among women aged < 50 years to 9.8% among women aged ≥ 75 years.[2] A similar increase in DED prevalence with age is seen among men in the United States, from 3.9% among men aged 50 to 54 years to 7.7% among men aged ≥ 80 years.[3]

By chance alone, some people will develop both glaucoma and OSD, but the observed rate of comorbidity is far higher than would be expected by chance. Various studies estimate the prevalence of OSD in patients with glaucoma is 30% to 70%.[4-10] This strongly suggests that some aspect of glaucoma or its treatment increases the risk of OSD. In fact, a causal relationship between OSD and the excipient ingredients found in topical formulations of glaucoma medications used to lower intraocular pressure (IOP)—particularly the preservative BAK—has been conclusively established.[11,12]

Preservatives are a critical component of multidose topical formulations that provide antimicrobial activity to ensure

sterility of the product through its shelf life.[13] BAK is by far the most widely used preservative, present in approximately 70% of topical ophthalmic products.[14] BAK is a quaternary ammonium compound that is highly soluble in water and provides bactericidal activity through interactions with bacterial cell membranes, causing cell lysis.[11,14] BAK can also enhance the corneal penetration of active ingredients with which it is coformulated.[11,15,16]

The cytotoxic effects of BAK on ocular surface tissues are diverse and include reduced survival of corneal, conjunctival, trabecular meshwork, and ciliary epithelial cells; conjunctival goblet cell loss; delayed corneal wound healing; lymphocyte infiltration of conjunctival epithelium and stroma; and elevated inflammatory marker concentrations in ocular tissues **(Table)**.[17-29] These adverse effects on ocular surface cells manifest as various symptoms, including pain/discomfort, tearing, increased staining of conjunctival and corneal epithelial surfaces, decreased tear breakup time (TBUT), lower Schirmer scores, higher prevalence of punctate keratitis, and overall worse symptom scores using the Ocular Surface Disease Index (OSDI) **(Table).**[30-41] Furthermore, the chronic ocular surface inflammation and goblet cell loss arising from these cytotoxic effects of BAK exposure can reduce the success of subsequent glaucoma filtering surgery **(Table)**.[42-48] The time to surgical failure is also significantly related to the extent of preservative exposure **(Figure 1)**.[44] In addition, the presence of microcysts in the conjunctival filtering bleb—a significant predictor of postoperative IOP after trabeculectomy—is significantly reduced in eyes with chronic glaucoma medication exposure.[49] Alternative preservatives (such as sofZia, Purite, and Polyquad) are less harsh to the ocular surface, with some studies demonstrating similar but milder effects than those of BAK,[17,19,20,24,50-53] and other studies finding these preservatives had no effects on the ocular surface.[18,27-29] In addition to inactive ingredients, some glaucoma medication formulations contain active ingredients that adversely affect the ocular surface. An example of this is brimonidine, which has a high incidence of allergy—including both contact dermatoconjunctivitis and follicular conjunctivitis—with long-term use.[54]

The severity of OSD in eyes with glaucoma correlates with the extent of BAK exposure. The concentration of BAK in the formulation, number of medications used, number of drops instilled per day, and duration of therapy are all determinants of the presence and severity of OSD.[4-10,55] In 1 study (N = 516) **(Figure 2)**, the prevalence of OSD was nearly twice as high (71%) among patients using 3 medications than among those using only 1 medication (38%).[55]

The evidence strongly supports the relationship between preservative exposure and OSD, making OSD an iatrogenic condition in patients using topical glaucoma therapy. Iatrogenic conditions are often overlooked by clinicians because of lack of awareness, misunderstanding, and,

Table. Ocular Surface Cytotoxic Effects and Clinical Manifestations of Benzalkonium Chloride

Cytotoxic Effects	Clinical Manifestations
Reduced corneal epithelial cell survival[17-23]	Pain and discomfort[30,31]
Reduced conjunctival cell survival[17,18]	Tearing[31]
Reduced trabecular meshwork cell survival[24,25]	Increased ocular surface staining[31-34]
Reduced ciliary epithelial cell survival[24]	Decreased tear breakup time[31,32,35-38]
Goblet cell loss[26,27]	Lower Schirmer scores[31,33]
Delayed corneal wound healing[28]	Increased prevalence of punctate keratitis[35,37,39]
Lymphocyte infiltration of conjunctiva[27,29]	Elevated OSDI scores[32,34-36,40,41]
Increased ocular tissue inflammatory marker concentration[20,21,23]	Reduced success of glaucoma filtering surgery[42-48]

Abbreviation: OSDI, Ocular Surface Disease Index.

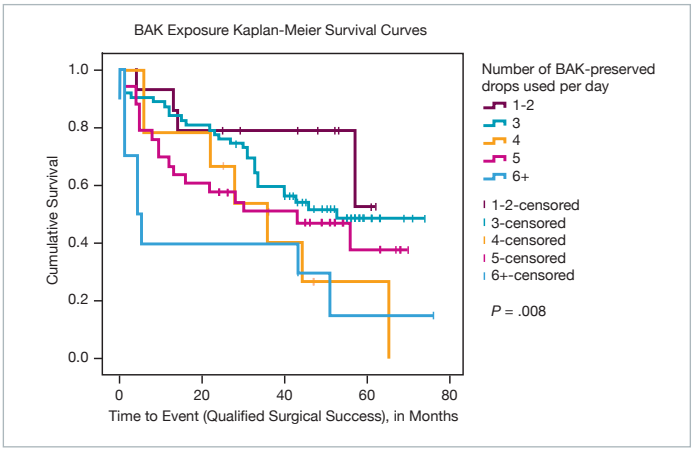

Figure 1. Eyes with higher exposure to preservatives in glaucoma medications experienced glaucoma surgery failure sooner than those with lower exposure in the PESO study[44]

Abbreviation: BAK, benzalkonium chloride.

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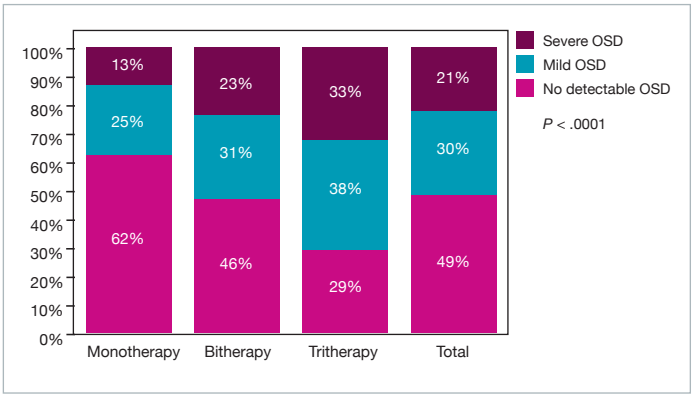

Figure 2. Prevalence and severity of ocular surface disease among patients with glaucoma treated with 1, 2, or 3 medications[55]

Abbreviation: OSD, ocular surface disease.

in some cases, a value assessment, in which the benefits of therapy are considered to outweigh the unintended consequences. Failing to recognize and address iatrogenic OSD has important consequences on both therapeutic adherence and quality of life (QOL).

The toxic interplay between glaucoma, its therapy, and OSD leads to a vicious cycle. Glaucoma medical therapy causes cytotoxic damage to ocular tissues that causes or worsens OSD and also worsens glaucoma-mediated trabecular meshwork cytotoxicity, leading to higher IOP, more medications, and a perpetuation of the cycle that leads to surgery, the outcome of which is also adversely affected by the history of medication exposure **(Figure 3)**.[56]

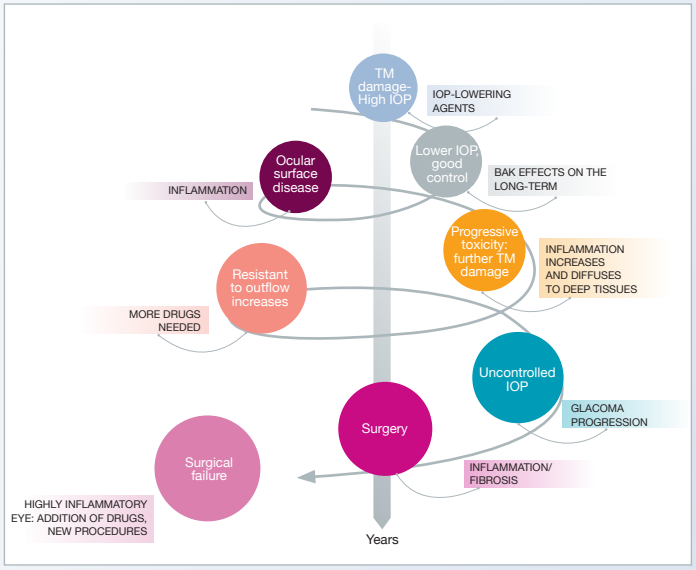

Figure 3. Vicious cycle of interplay between glaucoma, medical therapy, and ocular surface disease[56]

Abbreviations: BAK, benzalkonium chloride; IOP, intraocular pressure; TM, trabecular meshwork.

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PANEL DISCUSSION

Q: How big a problem is preservative toxicity in your patients with glaucoma?

Dr Baudouin: This is an important issue, especially in patients with preexisting OSD or OSD developing over time. With multidrug therapy, the cumulative daily dose of preservative increases, which subsequently increases the risk of OSD. In addition to excipients such as preservatives, the active compounds of glaucoma therapies can also contribute to OSD; for instance, brimonidine has a high rate of late-onset allergy.[57] Comorbid OSD adversely impacts QOL in patients with glaucoma. Using 2 validated instruments, Rossi et al found significantly worse QOL among patients with glaucoma who had OSD, abnormal TBUT, and the presence of punctate keratitis than those who did not.[9] Skalicky et al reported similar findings using a third QOL instrument, confirming this association.[10] This adverse impact of glaucoma therapy on QOL is important, given that preservation of QOL is the primary goal of glaucoma therapy in both US and European treatment guidelines.[58,59]

Dr Ahmed: As health care providers who treat glaucoma daily, I think we have become somewhat desensitized (no pun intended!) to preservative toxicity in our patients. Upon closer consideration, however, it is a burden that is visible and invisible for so many of our patients. Ranging from worsening lid margin issues to tear instability and corneal/surface issues to conjunctival inflammation, this deteriorates our patients' QOL and leads to poor adherence. It also impacts cataract/intraocular lens surgery outcomes. Furthermore, chronic exposure can lead to permanent tissue changes that can cause vision loss and increase the risk of glaucoma surgical failure.

Dr Gupta: In my clinical practice, I often see patients referred for corneal evaluation after they have been on topical medications to treat their glaucoma for many years. Unfortunately, presenting in late disease stages makes treatment difficult. We certainly can blame toxicity from BAK in many of these patients as the root cause of their OSD. Educating clinicians on the detrimental effects of chronic exposure to preservatives is needed in addition to earlier intervention to manage the OSD so that we are not first seeing patients after decades of damage.

Dr Radcliffe: Preservative toxicity is ubiquitous in my practice. Because I am often referred patients with years of exposure to preserved topical agents, it is difficult for me to know when the problems began and which therapies are to blame. Additionally, OSD and dry eye from preservatives can be insidious, with a slow onset, and the effects can linger long after the offending agent has been stopped. It is my experience that OSD caused by multiple preserved topical medications can lower the threshold for other agents to cause signs and symptoms of intolerance. Many patients will require complex medication adjustments along with nonmedical therapies (eg, laser) to get the surface rehabilitated. We know that preserved eye drops can interfere with tear film stability,[60] which likely decreases the quality of vision. In the most severe cases, I will see limbal stem cell deficiency (LSCD), which can lead to blindness and severe pain.

Q: How do preservative toxicity and OSD affect adherence in your patients?

Dr Baudouin: The impact of medication adverse effects on adherence with glaucoma therapy is difficult to quantify, in part because robust techniques for measuring adherence are lacking. In an analysis of > 17,000 patients participating in 36 glaucoma medication studies, the occurrence of adverse events was the most common reason for study drug discontinuation and study withdrawal, representing 46% of all such cases.[61] In studies of risk factors for nonadherence, adverse effects of medications are often identified as contributory.[62,63] Despite the paucity of data linking adverse effects with nonadherence in real-world

settings, it stands to reason that some patients may find the discomfort of eye drops to be worse than their typically asymptomatic glaucoma and may therefore skip some or many doses to avoid the unpleasant adverse effects.

Dr Ahmed: Poor adherence to glaucoma medications in general has been well established in every study around the world. When patients miss doses, they have a higher risk of progression.[64,65] Although there are many reasons for poor adherence, ocular surface and toxicity issues from drops and preservatives contribute to this. Patients do not like to take drops for an asymptomatic disease that causes numerous adverse effects and symptoms that negatively impact QOL.

Dr Gupta: We know that preservatives such as BAK can cause stinging and irritation in addition to the potential medication adverse effects (such as redness from a prostaglandin analogue). Medication compliance is influenced by so many factors, but in my own clinical practice, I often see that patients who find therapies uncomfortable tend to have greater noncompliance.

Dr Radcliffe: Interestingly, preservative toxicity can often be a sign that the patient is compliant with his or her preserved topical therapy. Once the patient understands the relationship is present, however, it is likely that lower adherence will result. I often change my prescribing schedules according to what I am seeing in the surface of the eye. For example, preserved dorzolamide, brimonidine, and other agents are dosed 3 times daily, but in patients who are dry, I am hesitant to prescribe preserved single-agent therapies that frequently because the preservative load for such a small IOP-lowering benefit is questionable. Many patients with dry glaucoma will require a topical dry eye therapy such as lifitegrast or cyclosporine. These agents are dosed twice daily, and in all likelihood interfere with glaucoma therapy compliance. In patients with glaucoma on 2 agents, compliance with the second agent is lower.[66]

Q: Do you routinely consider the role of OSD in your nonadherent patients?

Dr Baudouin: OSD is easier to detect than is nonadherence in clinical practice, so when I see OSD, I ask patients if the symptoms affect their adherence. Likewise, in patients who admit to nonadherence, I ask if symptoms of OSD are contributory.

Dr Ahmed: Assessing and quantifying nonadherence is difficult and should be evaluated by looking at prescription renewal rates and bottle assessment and having a nonjudgmental chat with patients. Along with this should be at least some assessment of OSD because the disease can lead to poorer adherence. When nonadherence is suspected, it is helpful to dive into the factors, which include OSD. All factors should be discussed and evaluated, with attempts to address them.

Dr Gupta: I think we are just starting to bring OSD into the forefront and are realizing that it complicates so many diseases. I often think if we were more aggressive in treating OSD, patients would feel better and have better visual function. I would hope that this in turn would lead to greater medication adherence and more effective disease treatment.

Dr Radcliffe: For noncompliance, I always try to understand why the patient is not using his or her drops. Low medical literacy (confusion), adverse effects such as dry eye or redness, cost, inconvenience, and perceived inefficacy are at the top of the list. I will educate the patient when it is helpful, but when intolerance is the culprit, it is best to eliminate the offending molecule.

Q: How does the coexistence of OSD affect your glaucoma surgical planning?

Dr Baudouin: Almost all patients scheduled for surgery are using multiple topical therapies at the time, so the preservative load is often high. If the eye has clinical evidence of OSD and inflammation, it is not unreasonable to discontinue some or all topical therapies for a brief period to quiet the eye before surgery. In appropriate cases, IOP can be controlled temporarily with preservative-free medications, selective laser trabeculoplasty (SLT), or even a brief course of oral carbonic anhydrase inhibitors before surgery.

Dr Ahmed: There is no question in my mind that patients who are on chronic medical therapy, especially multiple medical therapies, are at risk for surgical failure because of underlying inflammation and even fibrosis, in some cases, that exists in their conjunctiva. This also makes the tissue more friable and prone to bleeding. Both the molecule and the OSD from toxicity are the culprits. This occurs subclinically, meaning that although we think of the "red eye" as being at risk for failure, it is not just the eye that we need to be concerned with. For these reasons, if OSD and/or conjunctival hyperemia is present, I aggressively manage this by stopping the offending agents and substituting them with nonpreserved glaucoma drops and/or oral carbonic anhydrase inhibitors. Regardless, if the eye is red or OSD is present, I treat lid margin disease and treat the ocular surface with tear supplementation. I routinely use steroids preoperatively, usually for 1 week but sometimes longer. I even tolerate a temporary higher IOP (within reason) for a few weeks before surgery to increase the chances of surgical success.

Dr Gupta: For patients who are suffering from significant OSD-related inflammation, finding therapies that allow for reduction or elimination of BAK are at the forefront. For example, performing SLT or injecting a bimatoprost implant in appropriate candidates can allow patients to have a medication holiday or reduce the overall load of BAK exposure. Furthermore, intermittent rounds of topical steroids can be used, especially preoperatively, to help with

improving conjunctival and corneal inflammation prior to surgery. Lastly, addressing this inflammation prior to surgery may make surgical intervention more successful because we know inflammation can lead to more fibrosis and scar formation.

Dr Radcliffe: I agree with Dr Baudouin that a medication holiday prior to filtration surgery can be very helpful for calming the eye. In some cases, it is "too late", and I will opt to perform a tube shunt, which is less dependent upon a pristine ocular surface for success. We also have to consider that there is an interaction between mitomycin C (MMC), which is often used to prevent fibrosis, and preservative toxicity. In my experience, eyes that have had too much exposure to preservatives are subsequently more sensitive to the toxic effects of MMC, particularly dry eye. In these cases, you have the "double hit", in which a filter with MMC is both more likely to fail and more likely to develop worsening dry eye from MMC exposure.

IMPROVING OCULAR SURFACE DISEASE DETECTION IN GLAUCOMA PRACTICE

Given that comorbid OSD in patients with glaucoma can adversely affect therapeutic adherence, QOL, and the effectiveness of glaucoma surgery, the recognition and treatment of OSD is an important opportunity to improve patients' lives. The diagnosis of OSD often begins with clinical suspicion on the basis of patient-reported symptoms, physician-noted signs, or a combination of both. Although one might expect that symptoms and signs would correlate in most patients, studies have demonstrated a significant mismatch between signs and symptoms[67,68]; some patients with findings of OSD may have few or no symptoms, whereas others with symptoms may have few or no findings on clinical examination. The Tear Film and Ocular Surface Society Dry Eye Workshop II has systematically described the process of diagnosing DED **(Figure 4)**.[69]

Given that many cases of OSD may be clinically asymptomatic despite the presence of clinical signs,[67,68] screening can be undertaken using validated questionnaires, such as OSDI (Ocular Surface Disease Index),[70] the DEQ-5 (5-item Dry Eye Questionnaire),[71] or SPEED (Standardized Patient Evaluation of Eye Dryness).[72] Among those with positive screening results, risk factor analysis should consider contributing factors such as smoking, contact lens wear, and the use of medications (eg, topical glaucoma therapy) that can contribute to OSD.

Numerous tools and techniques are available for the clinical assessment of OSD. Historically, the battery of clinical OSD testing has included the Schirmer test of tear production, TBUT to assess the lipid layer of the tear film, ocular surface staining with vital dyes such as fluorescein or lissamine green to identify regions of corneal or conjunctival cellular disintegrity, and corneal sensation testing to assess the integrity of corneal innervation.

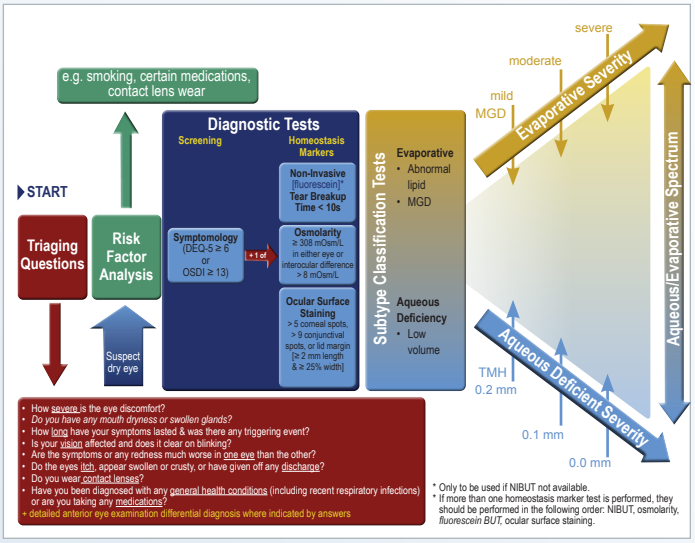

Figure 4. Diagnostic evaluation of ocular surface disease as recommended by the Tear Film and Ocular Surface Society Dry Eye Workshop II[69]

Abbreviations: DEQ-5, 5-item Dry Eye Questionnaire; MGD, meibomian gland dysfunction; NIBUT, noninvasive tear breakup time; TMH, tear meniscus height.

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More recently, tear osmolarity and matrix metalloproteinase-9 (MMP-9) assessment have been added to the diagnostic lineup. Their role in the pathophysiology of OSD is highlighted by the modern definition of dry eye syndrome promulgated by the Tear Film and Ocular Surface Society: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[73] This definition points to hyperosmolarity, inflammation (of which MMP-9 is a marker), and tear film instability as major contributors to OSD and supports evaluation of these factors in the diagnostic process.

Tear film osmolarity is a measure of tear flow rate and of evaporation. Higher osmolarity is associated with worse OSD,[74] mediated in part by adverse effects on goblet cells.[75] Osmolarity can be easily measured using commercially available point-of-care testing and is a reimbursable service to offset the cost of acquiring, operating, and maintaining the equipment. In heathy eyes, tear film osmolarity averages approximately 302 mOsm/L, rising to 315 mOsm/L in eyes with mild to moderate OSD and to 336 mOsm/L in eyes with severe OSD.[74] Commonly, an osmolarity value > 308 mOsm/L or an intereye difference of 8 mOsm/L is taken to be suggestive of OSD[76,77] and can correctly identify up to 81% of normal eyes, 73% of eyes with mild to moderate OSD, and 91% of eyes with severe OSD.[76] Tear osmolarity can also be helpful in identifying conditions that masquerade as DED. In the setting of dry eye symptoms and a normal tear osmolarity level, conditions such as meibomian gland dysfunction (MGD), allergic conjunctivitis, anterior blepharitis, ocular rosacea, and pterygium should be considered.[78]

MMP-9 is a nonspecific inflammatory marker that is elevated in the tear film of eyes with OSD.[79] The normal MMP-9 concentration in tears is < 40 ng/mL.[80] MMP-9 clinical testing is available as a reimbursable and noninvasive point-of-care test similar to that of tear osmolarity. The monoclonal and polyclonal antibody–based test provides a positive test result when tear MMP-9 concentration exceeds 40 ng/mL[80]; this has been shown to provide sensitivity and specificity for OSD of 85% and 94%, respectively.[81]

PANEL DISCUSSION

Q: What triggers you to suspect preservative toxicity/OSD in your patients?

Dr Baudouin: OSD in a patient with no preexisting or underlying OSD, high level of redness, eyelid eczema, MGD, and superficial punctate keratitis, even if the patient has no or few concerns, should make the ophthalmologist aware of a risk of high inflammatory level that will further negatively influence glaucoma outcome.

Dr Ahmed: Unfortunately, unless the eye is obviously red or the patient vocalizes his/her concerns, OSD and drop toxicity are often overlooked. I believe every patient on glaucoma therapy should be screened at baseline and subsequently, especially if medical therapy is added or altered.

Dr Gupta: I think it is important to administer questionnaires to patients (there are many options, such as DEQ-5, SANDE [Symptom Assessment Questionnaire in Dry Eye], SPEED, and OSDI) because they are easy and inexpensive to administer and can help identify a number of patients who may be suffering from OSD. Tear film testing, such as MMP-9 and osmolarity, are like vital signs to me. These tests give us information about the health of the tear film at that given time. Tear film testing, such as MMP-9 and osmolarity, are like vital signs to me. Just as having our height, weight, and blood pressure measured each time we go to the primary care physician, similarly giving patients these tests routinely gives us eye clinicians much information about the tear film, even when patients do not exhibit symptoms. After the screening tests, it is simple enough to perform a focused examination to not miss OSD. I look for corneal and conjunctival staining using a fluorescein strip; I assess the meibomian glands for oil flow and quality; and I assess eyelid mechanics such as complete closure upon blinking.

Dr Radcliffe: At some point, one has to suspect preservative toxicity simply on the basis of the number of medication bottles. In my area of New York, it is common for pharmacies to "split" fixed combination therapies into separate bottles. Of course, this doubles the preservative load, so I always consider preservative toxicity to be likely in any patient with > 1 topical therapy bottle. Corneal staining is a classic sign of BAK toxicity. That said, I ask patients about visual fluctuation and start thinking about preservative toxicity in any patient with fluctuating vision, whether corneal staining is present or not.

Q: Do you screen for preservative toxicity/OSD in your patients? If so, how?

Dr Baudouin: Clinical OSD presents itself, either with signs on examination, symptoms reported by patients, or both. Subclinical OSD is more difficult to detect but is no less important because intervening before the onset of signs and symptoms can interrupt the vicious cycle illustrated in **Figure 3**.[56] Checking for OSD requires little time; simple observation of the eye and eyelid margin and a fluorescein eye drop allows the identification of corneal or conjunctival staining and very unstable tear film in a few seconds. A TBUT of < 5 seconds is highly indicative of dry eye. I see little value in assessing tear film osmolarity or MMP-9.

Dr Gupta: There are many ways to identify OSD. Tear film testing is one such method and can often identify asymptomatic patients. OSD—whether induced by preservative/medication toxicity, MGD, ocular rosacea, or allergy—can lead to destabilization of tear film homeostasis, and both osmolarity and MMP-9 are markers that can be altered early in the OSD disease state. Although not all clinics have access to these tests, they should be considered as additional tools that can aid in screening and diagnosis.

Dr Ahmed: So here is my mantra now. Just as we always assess IOP, the optic nerve, optical coherence tomography (OCT) of the retinal nerve fiber layer/nerve/macula, and visual field testing (with gonioscopy periodically) at regular intervals, I think the time has come to make ocular surface assessment/dry eye part of that routine. A baseline assessment, ideally including a subjective and objective assessment, should be performed. How often are we debating if it is underlying OSD, the glaucoma drop, or both causing the issues? A baseline assessment helps. We also would like to proactively enhance our patients' QOL, assess for risk factors of nonadherence, and reduce surgical failures down the road. Periodically, perhaps yearly or when medications are altered, an assessment should also be made. A patient-reported assessment such as SPEED can be used. An objective look at the tear meniscus, TBUT, and corneal and conjunctival staining can be implemented with minimal cost or resources.

Dr Radcliffe: I think we want to use all the tools at our disposal to find OSD. As I mentioned previously, fluctuating vision or corneal staining are 2 major features. I diagnose a considerable bit of dry eye from reviewing the OCT signal strength. When the eye is dry, the OCT signal strength will drop because the light needs to pass through the cornea to acquire an image. In some cases, the technician will notify me that the patient was dry during the time of acquisition because artificial tear drops were needed for an adequate signal. At other times, I will examine a patient with no media

opacity and a low signal strength. I will reexamine the surface and discover a low TBUT, which was brought to my attention in an asymptomatic patient by the OCT.

Q: In patients with suspected preservative toxicity/OSD, what is your standard workup?

Dr Baudouin: I approach these patients by gradually removing the offending agents until the symptoms improve or abate and then finding alternate therapies to achieve IOP reduction without preservative exposure.

Dr Ahmed: Stop the offending agents and replace them with preservative-free options and/or interventional therapies. This often means SLT or minimally invasive glaucoma surgical procedures.

Dr Gupta: Removing the preservatives is a mainstay of treating these patients. If patients need IOP control after withdrawing the offending medication, interventional therapies such as SLT or bimatoprost implant injection can be of great value. Additionally, switching to preservative-free topical glaucoma therapies can help to achieve IOP control without inducing adverse effects of a heavy preservative load.

Dr Radcliffe: I may be an anomaly in that I rely on clinical assessment for the diagnosis, as described previously. The workup may involve discontinuing therapy and waiting for an improvement. I perform a considerable amount of SLT laser. Since the publication of the LiGHT study,[82] we can now confidently use SLT early in glaucoma therapy, allowing us to stop at least 1 agent.[83] I will make note of patients who feel better after drop cessation with SLT.

Q: How does preservative toxicity/OSD evaluation affect your clinical efficiency and workflow?

Dr Baudouin: I have adopted a limited workup that is efficient and does not greatly impact clinical workflow. It consists of examination of the eyelid margin for redness, fluorescein staining of the cornea and conjunctiva, and TBUT.

Dr Ahmed: As I discussed earlier, a simple baseline and annual assessment for OSD is valuable and can be implemented into all practices. Make it part of the routine and our patients will be happier, IOP will be better controlled, and our surgeries will be more successful.

Dr Gupta: I described my standard workup previously. These tests and examination processes do not take too much additional time and can be used to efficiently make the diagnosis of OSD.

Dr Radcliffe: The main issue I see with dry eye in patients with glaucoma is that it is a significant distraction for patients and physicians who truly need to remain focused on the blinding disease. Yet, dry eye is typically the main issue on the mind of the patient with glaucoma. Ignoring dry eye does not work and erodes confidence. As such, I am a glaucoma specialist who reluctantly focuses his practice on the management of dry eye. That said, I am always trying to spend less time on dry eye and more time on glaucoma, and preventing OSD by wisely choosing glaucoma therapies is a big part of that strategy.

Q: How can we better incorporate OSD evaluation in our busy practices? What is the role of technicians?

Dr Baudouin: Technicians can be helpful in identifying OSD and tear film abnormalities using the newly developed technologies, such as confocal microscopy, meibography, and tear interferometry.

Dr Gupta: Technicians are vital to efficient OSD screening. They can administer questionnaires and, if the results are positive, can direct further tear film testing. Patient education about OSD can also be done by a technician. Patients often value having such detailed information provided to them by their physician's office.

Dr Radcliffe: My technicians have been trained to listen to patients and to document their dry eye complaints, and this can help me streamline my care. My technicians and I do not employ artificial tears routinely because I want to get to the root cause of the dryness, not mask the symptoms. Often, my technicians will discuss topical dry eye prescription therapy or laser with patients prior to my arrival, and I can pick up the conversation from there.

CASE 1: EARLY GLAUCOMA DIAGNOSED AT THE SAME TIME AS DRY EYE

From the Files of Nathan M. Radcliffe, MD

A 45-year-old self-described female presented for routine examination and contact lens adjustment. Recently, her contact lenses had become uncomfortable and her vision had been fluctuating. On examination, she was moderately myopic (-4.25 OU) and had corneal staining and a decreased TBUT. Her IOP was mildly elevated at 23 mm Hg OU. Due to a suspicious appearing optic nerve, an OCT was performed, revealing early glaucoma damage.

Q: How should we initiate a lifetime of therapy in this patient with dry eye and glaucoma? Given that this patient will need many therapies in life, what other approaches should be favored vs avoided? How should the dry eye be addressed?

Dr Baudouin: SLT can be an option as a primary therapy and can spare several years without medical treatments. Otherwise, a preservative-free eye drop is highly recommended for such a condition.

Dr Ahmed: The patient already has OSD, and this should be further investigated and treated prior to commencing glaucoma therapy. The patient may require chronic therapy. I would avoid preserved glaucoma drops, and would offer laser trabeculoplasty first line.

Dr Gupta: This patient has DED, likely exacerbated by contact lens wear. She is young and has many decades of glaucoma therapy ahead of her. A preservative-free topical medication is a good first choice, as is SLT, which would preclude topical therapy. I would want to examine the meibomian glands, and if preexisting MGD exists, I would consider avoiding use of a prostaglandin analogue, which is known to worsen MGD. Regarding the dry eye, given the presence of corneal staining, this patient has at least moderate disease. Corneal staining is not an early finding in DED. As such, she likely needs topical therapy, such as cyclosporine or lifitegrast, to control the ocular surface inflammation.

Dr Radcliffe: In my practice, this patient would be offered primary laser trabeculoplasty, although the recommendation would be slightly less forceful in light of the patient's younger age (45 years) and the lack of long-term data of laser in this age group. Some time would need to be spent discussing the contact lens care and consideration of different lenses, and a different preservative-free cleaning system might be warranted. Additionally, a preservative-free prostaglandin topical therapy would be recommended. Finally, depending on the outcome of contact lens adjustment and the response to initial therapy, topical dry eye prescription therapy, as suggested by Dr Gupta, may be warranted. Fortunately, both of the approved dry eye therapies are preservative free.[84,85]

CASE 2: LIMBAL STEM CELL DEFICIENCY IN CHRONIC GLAUCOMA

From the Files of Nathan M. Radcliffe, MD

A 65-year-old male presented following 5 years of treatment for primary open-angle glaucoma on 3 commercially available BAK-preserved eyedrops (latanoprost, dorzolamide, and timolol) in separate bottles. He had severe signs and symptoms of dry eye, including light sensitivity and foreign body sensation. His eye examination revealed 1+ conjunctiva hyperemia and 3+ diffuse punctate epithelial erosions.

His topical agents were discontinued and laser trabeculoplasty was applied, resulting in several years of acceptable IOP. Over time, however, his IOPs became elevated and his dryness worsened. **Figure 5** shows images of slit lamp photographs of the cornea without (A) and with (B) fluorescein staining and cobalt-blue illumination at follow-up. He was diagnosed with LSCD, likely caused by exposure to ophthalmic preservatives.

Q: What is LSCD and how is it treated? What special considerations are warranted regarding preservative exposure/toxicity in LSCD? How can this patient's glaucoma be managed with such severe surface disease?

Dr Ahmed: LSCD can be multifactorial, but OSD and chronic glaucoma drop toxicity can be causative. Furthermore, glaucoma surgery can worsen LSCD. This

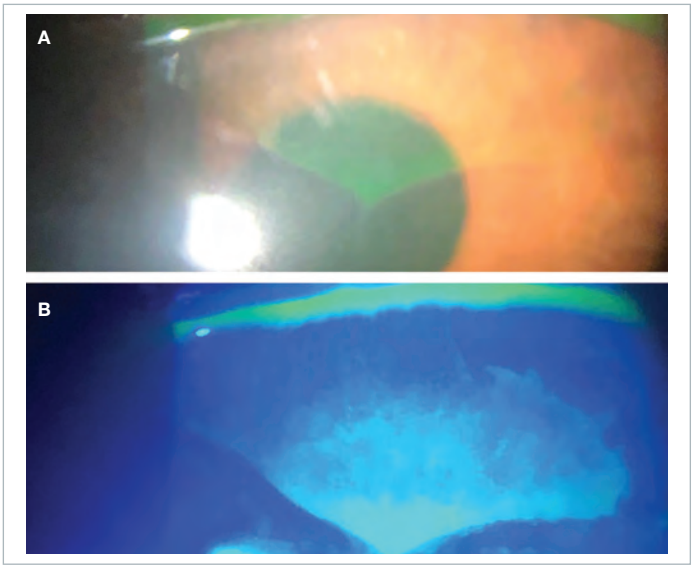

Figure 5. (A) Slitlamp photograph demonstrating superior sectoral limbal stem cell deficiency with irregular corneal epithelium in a characteristic whirl-like pattern. (B) Slitlamp photograph with cobalt-blue illumination and fluorescein staining demonstrating uptake of fluorescein by injured and dysfunctional epithelial cells in the classic whirl-like pattern of limbal stem cell deficiency.

points to the importance of minimizing preservative toxicity and drop load over a patient's lifetime and of treating OSD and inflammation proactively. In this case, all drops may need to be stopped, and the OSD needs to be managed with steroids, immunomodulators, and tear supplements. To control IOP, oral carbonic anhydrase inhibitors can be used temporarily, but this patient likely needs surgery.

Dr Gupta: Chronic BAK exposure can lead to damage of the limbal stem cells, which are essential to repopulate the corneal epithelial cells. Sectoral LSCD is managed by withdrawing offending agents (ie, remove all BAK-containing products) and treating ocular surface inflammation with topical steroids, preservative-free tears, and topical immunomodulators (eg, cyclosporine, lifitegrast). Amniotic membrane can be used to also help repair damaged epithelial cells. This patient's glaucoma should be managed with preservative-free medications and/or surgical interventions to allow the patient to avoid BAK-containing therapies.

Dr Baudouin: My approach to this patient is identical to that of Dr Gupta.

Dr Radcliffe: This is a patient who has in all likelihood been slowly worsening over many years of BAK therapy. He has now reached a severe stage of the disease. Preservative-free therapies are an absolute must from this point forward. A mild steroid can be applied, but IOP must be carefully monitored and thought should be given to a preservative-free steroid when possible. Some consideration to repeating laser trabeculoplasty should be given. This patient is also an excellent candidate for intracameral sustained therapy.

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CME POSTTEST QUESTIONS

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1. Preservatives in topical formulations of glaucoma medications can contribute to:
   A. Refractive changes
   B. Loss of meibomian glands
   C. Cytotoxicity of corneal and conjunctival cells
   D. Prostaglandin-associated periorbitopathy

2. Chronic exposure to preservatives in glaucoma medications can lead to:
   A. Decreased ocular surface staining
   B. Enhanced corneal wound healing
   C. Increased TBUT
   D. Reduced success of glaucoma filtering surgery

3. The preservative exposure burden is related to:
   A. Number of drops per day
   B. Concentration of preservative in the bottle(s)
   C. Duration of therapy
   D. All the above

4. In an analysis of data pooled from > 30 glaucoma medication studies, what was the most common reason for study drug discontinuation?
   A. Lack of efficacy
   B. Study requirements were too burdensome
   C. Adverse effects of therapy
   D. Perception that treatment was not helpful

5. Which of the following describes a vicious cycle regarding preservative toxicity and adherence?
   A. Toxicity is asymptomatic, and patients continue their therapy
   B. Adverse effects of therapy discourage adherence, leading to more medications being prescribed
   C. IOP is lowered, and QOL decreases
   D. Toxicity leads to laser therapy and alleviation of symptoms

6. What proportion of patients using topical glaucoma medications experiences signs and/or symptoms of OSD?
   A. 5% to 10%
   B. 15% to 20%
   C. 30% to 70%
   D. 80% to 90%

7. Which tear film osmolarity value is most consistent with the presence of severe OSD?
   A. 302 mOsm/L
   B. 308 mOsm/L
   C. 315 mOsm/L
   D. 336 mOsm/L

8. A patient presents with a 3-year history of therapy with BAK-preserved topical glaucoma medications. She reports symptoms of OSD. Which assessment would indicate the presence of OSD?
   A. Low tear film osmolarity
   B. TBUT > 10 seconds
   C. Positive MMP-9 test result
   D. OSDI score of 5