CE LESSON

Increase Your Allergy Know-How:
A Review of the Latest Relevant Information on Ocular Allergy

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GOAL STATEMENT:
Seasonal and perennial allergies are a significant global health issue, particularly in industrialized nations such as we see here in the United States. In fact, ocular allergy is often the main reason cited for patient visits to eye care professionals. Over the years, the treatments available have evolved and can be tailored to meet each patient’s individual needs. Treatments have not only improved; they have also uniquely addressed the escalating problem that allergies have become over time. This educational program is designed to provide ophthalmologists with a better understanding of the magnitude of ocular allergy, its consequences, and the treatments that can be used to more effectively and proactively intervene.

FACULTY/EDITORIAL BOARD:
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Michael S. Blaiss, MD: Allergies are a hugely prevalent problem, and unfortunately, much of the ocular part
is not recognized. In fact, studies from around the world show that allergic eye symptoms, which tend to go hand in hand with nasal symptoms, affect between 20% and 25% of the population.1 Other studies show the percentage to be higher in the pediatric population.2 I was an investigator in one particular study that found that roughly 14% of the U.S. population suffered from nasal and eye allergies.3

Mark S. Milner, MD: The economic impact from allergies is huge in this country, with an estimated annual cost of nearly $14.5 billion.4 Allergies are also a major cause of work absenteeism, resulting in nearly four million missed or lost work days each year and a total cost of more than $700 million in total lost productivity.5 This covers both work productivity and the health-related economic impact (e.g., trips to the medical doctor and the cost of Medicaid).

Dr. Blaiss: Of course no one dies from allergic conjunctivitis, but it does have a significant impact on quality of life (affecting sleep and the ability to drive),6,7 which is why it’s so important that patients recognize that the problem be treated properly.

Dr. Milner: You also have to factor in the impact of allergic conjunctivitis on the patient’s ability to wear contact lenses and the associated co-morbidities, such as dry eye. Additionally, certain medications may exacerbate dry eye.

THE MANY FACES OF ALLERGY

Francis S. Mah, MD: As Dr. Milner pointed out, there’s a huge financial burden, and there’s a significant impact from the ripple effect, as far as allergic conjunctivitis affecting the workforce and school (kids missing school, having trouble concentrating). Some of it has to do with either misdiagnosis or the patient not even realizing that they have these issues, which then results in the indirect cost of causing further damage to the eye, visual morbidity, and buying over-the-counter (OTC) medications from the pharmacy before seeking appropriate medical care from a physician.

Not only do they have obvious symptoms such as trouble sleeping or breathing, and the obvious implications of contact lens wear, but there’s also a huge issue of red eyes and how that impacts their lives. Part of the problem is simply getting patients to realize that, not only do they have something that might be serious, but also that there is treatment available that they can manage.

Dr. Milner: Dr. Mah brings up an outstanding point about misdiagnosis and its impact on allergies, because the red eye isn't always easy to diagnose. If an allergy patient is being treated for bacterial conjunctivitis, then that’s an unnecessary use of antibiotics. And, children might miss school because their parents think they are contagious. So, the impact of misdiagnosis in allergies is, in my opinion, huge.

Jodi Luchs, MD, FACS: Furthermore, the impact of misdiagnosis is significantly affected by the presence of OTC remedies for allergies, especially for our contact lens-wearing patients. When these patients have a red eye that’s a bit uncomfortable, sometimes they assume that they have allergies or dry eye, and self-medicate with an OTC allergy medication. Sadly, in so doing, they may be harboring a more serious problem, which at its worst could be a corneal ulcer, before they actually seek medical care.

Needless to say, patients need to be educated on the importance of seeing an eye-care professional when they have a red eye or ocular discomfort, despite their ability to go out and get an OTC remedy that may not be relevant to their particular condition. They need a good diagnosis by a physician before they embark upon self-medication.

Paul M. Karpecki, OD: Unfortunately, many patients with ocular surface disease self-medicate before seeing an eye doctor. Of course, the most common would be medications that ‘get the red out’ or vasoconstrictors. The issue of rebound hyperemia is a significant one and if doctors immediately discontinue these vasoconstrictor drops—even if treating the patient with something better—their red eye returns and they question the doctor’s ability.

It may require tapering the use of vasoconstrictors while using topical antihistamine medications and/or corticosteroids. We must also be aware of when to send a patient to an allergist. This might include severe allergies, nonresponsive allergies or patients with a significant systemic component such as rhinitis or allergic sinusitis.

Dr. Blaiss: I get a lot of patients sent to me by their primary care doctors for general allergies, and the patients don’t even realize that they're experiencing ocular allergies. And a lot of times, it is not recognized unless I ask specific questions (e.g., “are your eyes itchy or watery?”). So there’s the potential for these
patients to be undertreated.

**Dr. Milner:** My experience is the opposite of Dr. Blaiss’s. I like that the primary care physicians are asking about ocular symptoms, and I think it’s imperative that eyecare providers ask about systemic symptoms, for several reasons.

For one, as Dr. Mah said, you can help refer patients to an allergist for immunotherapy and techniques on how to avoid the allergens. Another reason is that I don’t think we ask enough questions about atopic disease (e.g., "do you have asthma or eczema, or a family history of either?"). Atopic information is critical because atopic patients don’t mount a response to herpes as well as patients without atopy and may be more prone to getting simplex virus keratitis.

Additionally, there may be a difference in discharge. A patient with hay fever/rhinoconjunctivitis may have tearing or a serous discharge, as opposed to an atopic patient, who may have ropy discharge. So it’s just as imperative for us to ask systemic questions as it is for primary care physicians to ask ocular questions.

**Dr. Luchs:** Very often, I will see patients come in to my office complaining of vague ocular surface disease (OSD) symptoms (e.g., dry, gritty, uncomfortable eyes, maybe some tearing), but not necessarily complaining about classic allergy symptoms (e.g., itch, redness, swelling, etc.). Upon further questioning or examination, it turns out that they clearly have ocular allergy as part of their symptom complex.

How often in your practices do you see previously unrecognized ocular allergy per the patient and from their initial chief complaints, yet when you actually go about taking a careful history and examining them, they have allergies?

**Milton Hom, OD:** Not only are we seeing undiagnosed allergy in our offices, but we also are seeing long-time patients coming in with new symptoms of allergy; symptoms they never had before. My feeling is that much of the ocular allergy is undiagnosed. We recently conducted multi-site studies on the prevalence of papillary conjunctivitis. A whopping 75% of the patients had a papillary response. The amounts of allergy symptoms seen were much lower. This leads me to think there is a huge component of sub-clinical ocular allergy waiting to surface.

**Dr. Mah:** We do refractive surgery in my office, so for me, the bulk of the patients whom I identify are either known allergic conjunctivitis sufferers or those who are unknown and are refractive surgery-seeking patients. They come in because they can’t wear their contact lenses anymore and want a solution other than glasses, and no one has ever diagnosed them with allergy or allergic conjunctivitis. They know they have some issues with redness, they take their contact lenses out and there’s been this progressive decline in their use of contact lenses. Or you examine them and they really never sought any medical care and they’re interested in refractive surgery.

We can positively impact our outcomes by identifying and pre-emptively treating ocular allergy prior to any type of keratorefractive surgery, while also decreasing some complications, including ocular surface disturbances. Postop conditions such as haze following photorefractive keratectomy, or diffuse lamellar keratitis following laser-assisted in situ keratomileusis, have been directly associated with allergic conjunctivitis.

**Dr. Milner:** Dr. Luchs, you asked about the prevalence in our offices. We deal with both seasonal and perennial allergies, so the prevalence can easily be bimodal. The key point to teach is that the ocular allergy should be on everyone’s differential diagnosis list when a patient presents with ocular surface complaints or a red eye.
Dr. Luchs: Great summary, Dr. Milner. I would also add contact lens intolerance to that list. A number of reports show that the prevalence of allergy has been increasing over the past several decades,$^{11,12}$ and there are quite a few hypotheses as to why that is be the case. What are your thoughts on that?

Dr. Hom: We see a large segment of contact lens intolerance caused by ocular allergy. It seems as though everyone has contact lens dryness these days. Actually, one of my first-line treatments for most contact lens discomfort problems is prescribing a topical antihistamine. Past studies support this thinking.$^{13,14}$

We know that a contact lens sitting on the ocular surface causes inflammation that is sometimes apparent, sometimes sub-clinical. Antihistamines seems to mitigate some of the inflammatory response, and many times, that is just enough to increase wearing time and comfort.

Dr. Karpecki, OD: It seems that most practitioners deal with patients experiencing contact lens discomfort by changing materials; modalities, such as daily disposable lenses; adding a rewetting agent, or changing solutions, etc. Rarely is the idea of treating the MGD or allergy discussed as an initial treatment. Yet, I believe that if we managed allergic eye disease, dry eye/MGD patients would be able to stay in their contact lenses for a lot longer and we would see a decrease in the annual contact lens attrition rate. In fact, we should be looking for signs of allergy, MGD or dry eye in all contact lens wearers so we can prevent them from getting to a point that they can no longer comfortably wear contact lenses.

**THE ALLERGY EXPLOSION**

Dr. Blaiss: The data have shown—especially over the last 50 years—that the rate of atopic conditions, whether we're talking about food, skin, eye or nasal allergy, has all been dramatically increasing.$^{15}$ There are many theories, such as the hygiene hypothesis, climate change with increasing levels of pollen and longer pollen seasons, changes in diet, and low vitamin D levels, but no one has a definite answer. The bottom line is that we are seeing an increase.

There has also been some debate over why we're seeing a high level of food allergy. From 1997 to 2007, the prevalence of reported food allergy increased 18% among children under age 18 years.$^{16}$ Again, no one has any good theories associated with this trend, but we do know that children who have food allergy and atopic dermatitis are at much higher risk of developing allergic rhinoconjunctivitis as they get older, commonly referred to as the “atopic march.”$^{17}$ So once you have this allergic tendency, it is more prone to continue to progress.
**Dr. Hom:** I have seen this in several patients. It’s almost as if there is a progression similar to dry eye. Mild allergies becomes moderate and subsequently progress to severe. I think environment (pollen) has a lot to do with this progression, and as a result, my treatment strategies have changed. Now, my philosophy is to treat earlier to stop or slow the progression.

**Dr. Karpecki:** I too am a believer in the progression of ocular surface diseases including dry eye and allergic eye disease.

It makes sense that the disease could progress since inflammatory cells are involved as well as mast cell degranulation and knowing the synthesis phase that exists with allergies. We often use the term “inflammatory cascade” and to me, that refers to increasing inflammation over time. Also regarding systemic diseases, we have to educate parents that children with perennial allergies should be examined for asthma, as there appears to be a high correlation. 18

**Dr. Blaiss:** I tell the parents of children with food allergies that their children are at an increased risk as they get older for allergic rhinoconjunctivitis and asthma. Unfortunately, there is nothing currently available that will stop this march of atopic disease, though studies are ongoing with different types of allergen immunotherapy.

**INSIDE THE TYPICAL ALLERGIC RESPONSE**

**Dr. Blaiss:** Take a person who is genetically predisposed for the development of allergy on exposure to a particular allergen (e.g., oak pollen). To begin with, that pollen is processed by dendritic cells that present the pollen antigen to T-h2 cells, which then interact with B-cells that become plasma cells that produce immunoglobulin E (IgE) to oak pollen. Then, the IgE for this particular allergen binds to the high-affinity IgE receptors on the mast cells. The conjunctiva of the eyes has large numbers of mast cells. On re-exposure to that allergen, if it binds at least two IgE molecules on the mast cell, one gets a change in the cell membrane of the mast cell, calcium influx into the mast cell occurs, and the mast cell literally explodes and releases hundreds of different chemical mediators, including histamine, leukotrienes, tryptase, chemotactic factors, and many others that lead to what we call the early-phase reaction.

The chemotactic factors bring the eosinophils and other inflammatory cells into the conjunctiva, and set up the late-phase or inflammatory reaction over the next several hours. There is an acute reaction primarily related to histamine and some of the mediators, and then we get into an inflammatory condition. Therefore, it is important to understand that allergic conjunctivitis is an inflammatory condition and not just due to histamine.

**Dr. Luchs:** Typically, of course, that acute inflammatory reaction is manifest clinically as itch, redness and swelling—the classic triad of the allergic response that we see. But as we all know as clinicians, many of our patients don’t necessarily come in complaining of these allergic responses. Usually, by the time they make it into our offices, that acute reaction has largely resolved which, illustrates the importance of taking a careful history.

Dr. Blaiss, that pathophysiology is more or less the same, regardless of the particular site of the allergy (i.e., eye, nose, lungs, etc.), correct?

**Dr. Blaiss:** That is correct. The pathology is the same for allergic rhinitis, food allergy, and allergic asthma, and involves the same type 1 IgE-mediated hypersensitivity reaction at different locations in the body.
**Dr. Hom:** Interestingly enough, there is another pathway that exacerbates ocular allergy. It’s caused by neurogenic inflammation. The neuropeptides released by the nerves actually attenuate the histamine release. These neuropeptides (Substance P, VIP, etc.) are released in both allergic rhinitis and allergic conjunctivitis. There are not only histamine receptors on the mast cells, but also receptors for these neuropeptides. So, you have pollen penetrating the epithelial layers of the conjunctiva, which causes the mast cell to release histamine and start the inflammatory cascade. The nerves in the eye and nose release neuropeptides, bind to the receptors on the mast cells, and cause even more histamine release. Allergic rhinitis can exacerbate ocular allergy. Both should be treated at the same time.  

**Dr. Luchs:** Interestingly, with respect to the eye, the antigens are gaining access to those conjunctival mast cells by virtue of the fact that the antigens can dissolve directly into the tear film. Especially in an individual whose eyes are dry and who doesn’t have the degree of turnover of the tear film that someone without dry eye has, those antigens can actually concentrate on the ocular surface, which can dramatically increase the magnitude of the allergic response. Consequently, patients with dry eyes or who are taking medication that produce dry eyes, may experience worse allergies or allergic symptoms. This explains why oral allergy medications such as antihistamines may sometimes paradoxically worsen their ocular allergic symptoms.

**Dr. Karpecki:** I agree with that, there are studies showing that using systemic antihistamines such as Claritin, which is arguably a less drying antihistamine than many others, can lower the tear volume by 34% after just four days of use. Most patients who have allergic conjunctivitis have concurrent rhinitis, as mentioned previously, so it is common to see patients already on oral antihistamines, which may worsen their allergic response. Many topical antihistamine eye drops appear to help other nonocular symptoms such as rhinitis, itchy palate or nasal congestion, so I tend to insist that my patients discontinue oral antihistamines if possible, so as not to exacerbate the allergic conjunctivitis they present with in our offices. The one exception might be allergic sinusitis. It is relatively common to see patients with sinusitis in optometric offices because the pain is often associated around the eyes (i.e., frontal and maxillary sinuses). In these cases, I would suggest an antihistamine with a decongestant such as fexofenadine HCl/pseudoephedrine HCl (Allegra-D, Chattem) or loratadine/pseudoephedrine sulfate (Claritin-D, MSD Consumer Care Inc.) and simply have the patient increase the use of artificial tears.

**Dr. Milner:** When patients have an ocular surface issues such as dry eye in addition to allergies, the barrier that helps keep the allergens out of the substantia propria becomes damaged, and you end up getting an increased influx of those allergens simply because the integrity of the surface is compromised. We talk so much about allergies being hay fever, and that’s really primarily a type I hypersensitivity response, but we know that vernal and atopic conjunctivitis, and even giant papillary conjunctivitis, are type I and type IV responses, so there is a T cell-mediated response with these atopic individuals. This means that when we decide to treat these patients, we want to treat the type I response with a mast cell stabilizer/antihistamine, but we have to start thinking about treating our atopics with something that suppresses T-cells as well.

**SEASONAL AND PERENNIAL ALLERGIC CONJUNCTIVITIS**

**Dr. Mah:** As Dr. Milner mentioned, patients who have seasonal allergic conjunctivitis typically present in the spring and fall, depending on the region and the pollen rates, whereas those who have perennial allergic
conjunctivitis come in throughout the year. Upwards of 15% of the global population is affected by seasonal and perennial allergic conjunctivitis, with the majority being affected by the seasonal variety. In industrialized countries, an estimated 90% of all allergic eye conditions are seasonal and perennial conjunctivitis.

Typically, perennial allergic conjunctivitis is set off by dust mites and animal dander inside the home, and seasonal allergic conjunctivitis antigens are more typically tree pollen, ragweed and grasses.

Dr. Milner: To add to that, cat dander is a huge perennial allergy that's almost ubiquitous even if you don't own a cat.

Dr. Blaiss: That's correct. Fel d I is the major allergen of cat, which is not only found in the dander, but also in the saliva and urine. It is a very sticky protein that binds to clothing, so people actually carry it around with them, making it a significant problem.

It's also important for any physician when making a diagnosis to consider their geographic location and know what allergens are common and at what times of year they are in the air. If you think of seasonal allergic conjunctivitis and you're living in the Midwest or the Northeast, then it is seasonal. But if you live in San Diego, for example, grass pollen is virtually year round, so even though we call it a seasonal allergen, it really is prevalent almost year-round.

Dr. Hom: There is new work on altitude and pollen counts, most of which is affected by wind currents. The pollen environment on the same spot on earth is different depending on how far up you are. Taking this further could explain why toddlers have allergy at such a young age. The pollen counts at one to two feet from the ground may be greater than counts at four to six feet from the ground.

Dr. Milner: That brings up an excellent point about what we call allergy. When patients come in and say they're allergic to medications, again, the pathophysiology is different. It may not be a true allergic response; they may have a toxic response or an idiosyncratic response.

MAKING THE DIAGNOSIS: THE PATIENT HISTORY

Dr. Milner: Clearly, we can't underestimate the value of a patient's history in addition to the physical exam. An excellent history will note what triggers the patient's symptoms, what particular symptoms they experience and when they experience them, which may help in diagnosis. For the most part, itching is an obvious hallmark of ocular allergies. Look for discharge. As mentioned earlier, discharge can often give you an idea about what type of red eye the patient has. Purulent discharge is usually bacterial, watery, or serous discharge may be allergies or viral, and ropy or stringy discharge is classic for atopic or vernal conjunctivitis.

Dr. Karpecki: I also think it is important to investigate the location of the itch. If a person informs us that their itch is in the canthal region or nasal aspect of the conjunctiva, that is typically allergic conjunctivitis, but if they determine it is on the lid margin, then it is more likely blepharitis and may include forms such as demodex blepharitis.

Dr. Blaiss: Family history is a definite factor in the risk of atopic diseases such as allergic conjunctivitis. When both parents have allergies, the risk of their child having allergies is between 45% and 70%. Neither spouse has allergies in the majority of marriages, yet 15% of their children develop allergies. With those facts in mind, I warn physicians that just because there is no family history of allergies doesn't mean that the patient doesn't have allergies.

Dr. Mah: We teach our residents to ask patients who come in for redness and swelling if they have experienced any itching. If there isn't any complaint of any itch ever at all, then you may want to start looking in a different direction than allergy, but, if they do complain about itching, then it brings you back into the realm of ocular allergy. So in my experience, there has to be itching for there to be a diagnosis of allergy.
Dr. Milner: I agree—itching is a hallmark symptom of allergy, but patients may not always divulge that, so it’s important thing to ask.

Dr. Hom: I’ve seen many cases that are clearly allergy, with rhinitis, that do not have itch. I think there may be an overemphasis on itch, and we forget about the other signs and symptoms: redness, swelling and watery. We have done some preliminary work with questionnaires and found other significant symptoms indicated ocular allergy: scratchiness, grittiness, burning and soreness.

**MAKING THE DIAGNOSIS: THE PHYSICAL EXAM**

Dr. Milner: I teach my residents to perform a thorough examination, in a repeatable order, for everything (i.e., checking the lids, lacrimal glands, lashes, conjunctiva and cornea, etc.), because you don’t want to miss anything. Look for blepharitis and dry eye, as well as other co-morbidities that may exacerbate or simulate allergies, such as Mucus Fishing Syndrome. If you see a follicular response, you’re less likely to think it’s allergy, and instead you think viral, especially if the patient has preauricular lymphadenopathy. With atopic conjunctivitis, we are looking for a papillary response with ropy or stringy discharge.

It’s imperative that you look under the upper lid and at the tarsal conjunctiva. An allergic response of a milky or whitish edema is another great sign, especially for atopic conjunctivitis. Also, look for chemosis and limbal signs such as Homer-Trantas dots, cobblestone papillae under the upper lid and shield ulcers in bad vernal cases. These are critical findings, and if you follow a consistent pattern of your examination, you’re less likely to miss them.

Dr. Mah: As far as cinching the diagnosis of allergic conjunctivitis, in the past, your clinical acumen and experience would lead you to that diagnosis. We fortunately now live in an age where diagnostic testing is becoming available that will help take some of the guesswork out of the diagnosis. There’s the C-reactive protein (CRP) test for Sjögren’s syndrome (Sjö, Immco Diagnostics); InflammaDry (Rapid Pathogen Screening Inc.), which detects matrix metalloproteinase-9; LipiView (Tear Science); and the TearLab Osmolarity System (TearLab Corp.).

Dr. Luchs: Other point-of-care diagnostic tools will be available soon to help us with the diagnosis of allergic conjunctivitis. One is a rapid diagnostic test for immunoglobulin E (IgE) levels in the tears with a small tear sample (TearScan IgE Diagnostic Test Kit, Advanced Tear Diagnostics LLC). Another one that will be available soon uses a conjunctival swab to make a very rapid diagnosis similar to the principle behind the AdenoPlus (Nicox) diagnostic test for the presence of IgE in tears.

We also now have the ability to perform in-office skin testing for allergies (Ocular Allergy Diagnostic System, Doctor's Allergy Formula). It’s noninvasive and can be applied quickly and easily to the skin. You can test for up to 60 different antigens, which are tailored to the region in which you live. You get information about the sensitivities that an individual may have to a variety of different indoor and outdoor antigens, which may provide a clue as to whether allergies contribute to the patient’s symptom complex. It has been introduced rather recently and has gained significant traction. It’s certainly been helpful in my practice.

I’m interested to hear from the allergist’s point of view. Dr. Blaiss, what is your perspective on both tear IgE testing and the relevance of skin testing and sensitivity to antigens and the correlation with ocular allergy?

Dr. Blaiss: Whether we’re talking about an in vitro study, blood, skin or tear test, it’s important for the test to be confirmational.
Sensitization does not mean sensitivity. So no matter who is conducting the testing, it has to correlate with what you think from the patient’s physical exam and history.

**Dr. Luchs:** You also mentioned earlier that when you look at the results of your testing and what a patient may be sensitive to, it’s important to know the relevance of the results. Positivity to ragweed pollen, for example, is not necessarily relevant in January when a patient comes in with a symptom complex. So it’s important to understand what the test means so you can properly interpret it.

**Dr. Milner:** Our diagnostic armamentarium is certainly getting better, but other tests (e.g., rapid assays to test for adenovirus and potentially for herpes) are coming down the pike that will rule out allergic conjunctivitis and further help us make a diagnosis.

**Dr. Luchs:** Any diagnostic confusion that we have had will improve with time as better point-of-care diagnostics become available. So once we’ve actually made a diagnosis that allergy is contributing to a patient’s symptom complex, how do we treat these patients?

**TREATMENT: NONPHARMACEUTICAL OPTIONS**

**Dr. Blaiss:** I first discuss what type of avoidance procedures we can follow, depending on what allergen(s)—according to the history, physical and testing—are causing the problem. A great deal of allergy is seasonal or pollen-related. Patients obviously have to go outdoors, so educate them to keep the windows to the house and car closed so that the pollen can’t come in. And when they come in from outdoors, they should get out of their clothes and take a shower to remove the pollen. I also try to convince patients not to use convertibles.

For indoor allergens, such as pets, they need to avoid and/or decrease pet allergen and dust mite exposure as much as possible.

**Dr. Karpecki:** Other environmental considerations might include reducing the speed or shutting off ceiling fans during peak allergy season, looking at websites such as pollen.com to see when allergens are most severe and whether we are in a ‘red zone’ for allergies to minimize outdoor exposure for those few days. Perhaps that is a day they run on a treadmill indoors instead of outside, as an example.

**Dr. Milner:** There are some great nonpharmaceutical treatments out there to help alleviate ocular allergy symptoms. Patients can use artificial tears to dilute the allergen, and I like my patients to store them in the refrigerator, because the cold really helps with symptomatology. Cold compresses are also nice, and many companies are coming out with cold masks that you put on the eyes.

**Dr. Hom:** On that note, we looked at tear meniscus heights and allergy symptoms and found that the lower the heights (more dryness), the greater the symptoms. The take home message is that increasing tear volume will help alleviate symptoms.

**Dr. Mah:** Especially for patients who have perennial allergic conjunctivitis, replacing carpets with hardwood floors, using HEPA filters, not only for furnaces and air conditioners, but also for in-room filters, is very helpful. I also advise patients to use antiallergen pillowcases and bedding covers, if possible.

**Dr. Luchs:** What about the cat? Many patients with pet allergies won’t get rid of the family pet, so is there value to having the patient keep the pet out of their bedroom, if it’s still in the house?

**Dr. Blaiss:** The data show that there may be some mild decrease in symptomatology if the cat is left out of the bedroom at all times. We also suggest that patients remove any carpeting and encase the mattress with an antiallergen cover, as well as run a HEPA filter in the bedroom 24/7.

**Dr. Milner:** I think we tend to underestimate the importance of hand washing, especially with regard to pet allergies. The more you wash your hands, the less chance you have of transferring those allergens to your eyes. Additionally, we should be handing out sheets to our patients and talking with them about tricks to help with avoidance, such as closing windows and using HEPA filters, as Dr. Mah said.

**Dr. Blaiss:** We have a booklet we provide to patients that lists the things they can do in the environment to help decrease their exposure, whether to dust mites, pet dander or pollen allergy. There’s also a lot of information on the web that can help patients as far as avoidance procedures.

**TREATMENT: PHARMACEUTICAL OPTIONS**
Antihistamines

**Dr. Blaiss:** Many physicians believe that oral antihistamines are fairly effective for treating ocular allergies, but the data clearly show that they're not that effective and may in fact dry out the eyes. So in the allergy community at least, these dual-action agents are extremely important, not only for their effect on the early-phase reaction as far as the antihistamine effect, but also for the mast cell stabilizing effect that's important for the latephase inflammatory reaction.

Adherence is also very important. Patients who are suffering immediately will obviously use the medication, but it's hard to get them to stay on it regularly through the whole pollen season.

**Dr. Mah:** For my patients, I like to try to involve either their primary care doctor or their allergist/immunologist in terms of the management of the systemic agents. If a refractive surgery patient has only an allergic eye condition, but also allergic rhinitis, then I will use fluticasone propionate Nasal Spray, 50 mcg (Flonase, GlaxoSmithKline) to help with the allergic rhinitis component. If they have an asthma component or more of a systemic component, then I will rely on the expertise of our allergy/inflammation/immunology colleagues.

**Dr. Luchs:** Have you witnessed any patients using oral antihistamines who get worse, rather than better?

**Dr. Milner:** Absolutely, especially if they're elderly, because this patient population tends to have more dry eye. And I think it's important for us, like I said, to be thorough and check for other signs and symptoms, such as blepharitis and dryness. If somebody has dry eye and the drying is exacerbated by antihistamines, then we need to treat that component as well. Sometimes patients can't get off their antihistamines. We can try some other treatments, maybe have an allergist help with immunotherapy, but if they can't get off the antihistamine, then it's incumbent upon us to do a better job of treating the ocular surface. Products such as artificial tears, topical cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan) and punctal plugs help us combat the side effects of the ocular drying.

If you do have an atopic patient who has a type I and type IV response, which is a T cell-mediated response, using topical cyclosporine may help with both the drying effects of the allergy medications as well as the T cell-response of the atopic condition.

**Dr. Luchs:** I also see patients who sometimes do get worse rather than better after a while on oral antihistamines exactly as you said—because the drying effect of these medications, reduces their tear production and their ability to flush the antigen from the ocular surface, so the antigen concentrates on the ocular surface and their itch may get worse rather than better. It's important to have a high index of suspicion for this issue and to treat it if it's present, especially because it may not be feasible to get them off the oral antihistamine. Awareness of this issue and treatment of the dryness will then help their ocular allergy symptoms.

What about the role of steroids?

**Steroids**

**Dr. Mah:** Steroids are fantastic drugs that work relatively quickly for ocular allergies. You can get a response within hours, but there is a lot of baggage that goes along with steroids, such as cataractogenesis, IOP spikes, and a decrease in the local immune system, making the eye more at risk for infections—specifically viral conjunctivitis—if the diagnosis has been made incorrectly.

I like to use steroids in a very hot, inflamed eye (e.g., a child with vernal conjunctivitis and a shield ulcer). You really want to try to quiet their eyes, so do a high-dose pulse therapy, and get them on and off the steroid as quickly as possible.

As far as long-term therapy goes, I tend to shy away from steroids. There is one that's specifically being marketed for allergic conjunctivitis—loteprednol etabonate ophthalmic suspension 0.2% (Alrex, Bausch + Lomb).

It is a very low-dose steroid, but you're still not supposed to use it indefinitely, per the FDA-approved product insert. I prefer to try to use combination products over steroids, but I do believe that they have their place in therapy.

**Dr. Milner:** I also try to reserve steroids for significant disease. In some patients, we have found that certain seasons are so bad that we have to use steroids. I like to get patients on and off of them quickly, but I try to avoid them altogether because of the side effects that Dr. Mah mentioned.
I also agree that patients who have atopic and vernal conjunctivitis need steroids much more often than patients who have seasonal hay fever conjunctivitis. We tend to mostly use solution-type steroids rather than suspension-type steroids because the vehicle of the suspension can get trapped—especially within the cobblestone papillae—which can be irritative and propagate the inflammation.

**Dr. Luchs:** I would echo everything you said, Dr. Milner. I use low-dose topical steroids, typically a loteprednol preparation. If the patient comes in with a very hot eye, I will often use that for a short course, usually a week, sometimes two, at a low dosing frequency in addition to an antihistamine/mast cell stabilizer. I don’t prescribe a refill on the steroid, and I have the patient return in that one- or two-week period to make sure they’re better, and I instruct them to stop the steroid and continue on the combination agent to control the remainder of their allergic symptomatology.

I do think that there is a role for steroids in patients who come in with a very acute, inflamed eye to help jump start their therapy and get them feeling better quickly, but it’s important to educate patients about the steroid-related side effects and the need to use it only over the short term.

And of course for those more severe diseases (vernal and atopic conjunctivitis), steroids are used to control the inflammation rapidly because these diseases can have sight-threatening consequences if steroids are not used when patients present with a significant exacerbation.

**Dr. Karpecki:** I take a slightly different approach to the topical treatment of patients with allergic eye disease. I find that the best therapy for a patient experiencing allergy symptoms such as itching, consists of the dual-acting antihistamine/mast cell stabilizer drops such as bepotastine besilate ophthalmic solution 1.5% (Bepreve, Bausch + Lomb), olopatadine HCl ophthalmic solution 0.2% (Pataday Ophthalmic Solution, Alcon) or alcaftadine ophthalmic solution 0.25% (Lastacaft, Allergan). They seem to work faster for symptoms, which begin with histamine release and these are also usually the acute cases. But when signs catch up to symptoms (i.e., the patient’s main complaints match how their eyes look as far as redness, chemosis, lid edema), then I find that nothing treats signs of allergic conjunctivitis better than a topical corticosteroid such as loteprednol. I make my decision based on signs or symptoms.

And if I am not mistaken, none of the antihistamines mentioned previously has an indication that includes signs—just symptoms, such as itching—and Alrex, for example, includes signs and symptoms. I also don’t write refills for corticosteroids so that I can see the patient back in two to four weeks to ensure there are no risks such as IOP elevation. I also agree that the other forms of allergic eye disease such as vernal keratoconjunctivitis, atopic keratoconjunctivitis and giant papillary conjunctivitis will require corticosteroid therapy.

**Dr. Milner:** I am very careful when using steroids in allergy patients who wear contact lenses because they have a different bacterial flora.

An effective trick for your severe cases of vernal conjunctivitis, where you’re getting shield ulcers and nothing is touching it, you can double evert the lid and inject triamcinolone acetonide injectable suspension, USP (Kenalog-40 Injection, Bristol-Myers Squibb) in the supratarsal space, which results in is less risk of complications and really helps patients deal with some of the sight-threatening complications.
Dr. Mah: The injection of a steroid is great for vernal conjunctivitis. We’re also using tacrolimus (Protopic, Astellas) off-label right on the eyelids, which will actually get through the thin skin and help with those vernal patients, especially in kids, where they may not be so receptive and you may not be able to inject them in the office.

Dr. Milner: To that point, you can have tacrolimus, which is off-label for the eye, compounded as an ophthalmic preparation and use it topically for your definite vernal and atopic cases.

Dr. Mah: My current therapy preference is to use the dual-acting agents that help stabilize mast cells and block the histamine sites. These agents are more potent, which allows for decreased dosing, and in turn increases not only compliance, but also patient satisfaction. They are also extremely safe.

**Combination Agents**

Dr. Luchs: It makes perfect sense to use an agent with a multi-modal mechanism of action to block the histamine as well as help to impact multiple facets of the later phases of the allergic response (stabilize the mast cells, perhaps reduce chemotaxis and activation of eosinophils and other points within the allergic inflammatory cascade). It’s no wonder the most common class of allergy medication currently available is the combination antihistamine and what I like to call second-generation mast cell stabilizers (Table 1). Drugs currently available in this class include: olopatadine HCl ophthalmic solution 0.1% (Patanol Ophthalmic Solution, Alcon); olopatadine HCl ophthalmic solution 0.2%; multiple ketotifen compounds, available over-the-counter; azelastine HCl ophthalmic solution 0.05% (Optivar, Meda Pharmaceuticals Inc.); bepotastine; alcaftadine; epinastine HCl ophthalmic solution 0.05% (Elestat, Allergan), also available as a generic. I think these are what most of us reach for, not only for their efficacy, but also because they are very safe to use on the ocular surface.

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<th>Table 1. Ocular Allergy Medications</th>
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<td><strong>BRAND NAME</strong></td>
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<td>Dual-Action Agents</td>
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<td>Zaditor (OTC)</td>
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<td>Direct H1-Receptor Antagonists</td>
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<td>Elestat</td>
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<td>Mast Cell Stabilizers</td>
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<td>Cromolyn</td>
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<td>Nonsteroidal Anti-Inflammatory Drugs</td>
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Does anyone want to talk about any differences or nuances between the drugs in this class?

Dr. Mah: One of the key differentiating points is the dosing. It’s much easier for a patient to be compliant with a q.d. or b.i.d. dosing schedule than with a q.i.d. dosing schedule. We now have two q.d. agents available to us, which will enhance compliance even further.

Also, for patients using other agents (e.g., glaucoma drops or artificial tears), this decrease in the dosing of
their allergy medication(s) is going to result in a potential decrease for toxicity from preservatives and so forth.

**Dr. Milner:** Although these newer agents—specifically olopatadine HCl ophthalmic solution 0.2% q.d. and alcaftadine ophthalmic solution 0.25% q.d.—increase compliance simply by being dosed q.d., they're also safe. And incidentally, many of these multi-action agents are approved for children three and older and all of them are pregnancy category C, except for alcaftadine ophthalmic solution 0.25%, which is category B, so the safety, in addition to the once-daily dosing, makes it very attractive as a treatment.

I tell some of my patients who are using one of the q.d. agents that they can go up to b.i.d. if they really have symptoms later on (as an off-label treatment) because I think they're safe enough, but most patients use the drug q.d.

**Dr. Luchs:** I find the same in my practice. What's nice is that both q.d. agents provide significant relief for the majority of our patients and they work very well, as do all of the drugs in this category.

There is currently one comparative study between the two q.d. allergy medications in terms of longevity and efficacy.\(^27\) It enrolled 127 patients and consisted of three treatment arms: alcaftadine ophthalmic solution 0.25%, olopatadine ophthalmic solution 0.2% or placebo. The researchers simply looked at the ability of these drugs to control itch three minutes after the patients were challenged in the typical antigen challenge model, which occurred 16 hours following a single dose of medication or placebo. They found that both agents performed very well and reduced itch significantly better than placebo, but that alcaftadine showed statistically significantly lower itch scores at 16 hours when compared to olopatadine and placebo.\(^27\)

**Dr. Mah:** There was one other statistically significant difference between the two agents in this study, and that was a 16- and 24-hour chemosis, which was statistically significantly better for alcaftadine than olopatadine.\(^27\)

**Dr. Luchs:** This is a big cosmetic issue for our patients, not to mention the fact that it's uncomfortable. Chemosis is of course an off-label parameter, but it's an important finding.

It's exciting that alcaftadine, the latest drug to enter this category of medication, works well and perhaps statistically a bit better than olopatadine at 16 hours and maybe 24 hours. There are some interesting data on the mechanisms of action that may be unique to one of the available combination agents, namely alcaftadine. Dr. Milner, do one of you want to take us through that?

**Dr. Milner:** There was a head-to-head study that looked at the pathophysiology and the anatomy of patients with allergies and studied the conjunctival cell membranes and their junctional proteins.\(^28\) Epithelial tight junction proteins, such as E-cadherin and zonula occludens (ZO-1) help to strengthen the epithelium as a barrier. In the allergic response, there is a breakdown in the integrity of the cell membrane and a decrease in these tight junction proteins. This study compared alcaftadine to olopatadine HCl ophthalmic solution 0.1% and showed that in the alcaftadine group, the levels of E-cadherin and zonula occludens (ZO-1) was statistically significantly higher than the sensitized, allergen challenged controls.\(^28\) In contrast, the olopatadine group failed to prevent the breakdown of ZO-1 and was not statistically different from the allergen challenged controls for E-cadherin.

Alcaftadine appeared better at stabilizing these two proteins, implying that there was less degradation of the cell membrane, maintaining its integrity and possibly preventing allergens from getting into the substantia propria.\(^28\)

**Dr. Mah:** That was done in a mouse model, and I think it defines why there might be a difference clinically between alcaftadine and olopatadine. The other finding was less eosinophil infiltration.

**Dr. Luchs:** So this model showed a strengthening of the epithelial barrier to the entry of antigen, blocking the access of the antigen to the mass cells in the conjunctiva. The implications here are significant. If you're improving the barrier function of the ocular surface, then you're also improving the integrity of the ocular surface and its susceptibility to other types of damage or infection. And a more intact epithelium means the eye is protected from all of those insults. These are interesting properties of this medication, and it clearly deserves further study.

Dr. Blaiss, what can you tell us about immunotherapy?

**TREATMENT: THE ROLE OF IMMUNOTHERAPY**
Dr. Blaiss: Medications don't cure the condition; they control it. Let's say you have a patient whose quality of life has greatly been affected by allergies and you have seen him the last couple of springs, or he has concomitant other allergy problems (e.g., nasal also associated with it or even asthma). Immunotherapy is the only thing at this point in time that is disease-modifying. And the only approved immunotherapy that has been shown to be efficacious is subcutaneous immunotherapy, where injections are given over a three- to five-year period to build up an immunity to the particular allergen(s).

Sublingual therapy is currently being investigated in the United States, but is not approved, although a daily sublingual tablet to desensitize patients to northern grasses (primarily Timothy grass and rye grass) did receive an FDA Advisory Board Panel approval. A tablet for ragweed is also pending FDA approval, so we may see approval of sublingual immunotherapy in the United States, which may be easier for patients because they won't have to go to a physician's office for weekly administration.

Many other types of immunotherapies are in the pipeline, so I think the future for patients with severe ocular allergy may be very bright, and we'll continue to see better treatments over the next decade.

Dr. Hom: I have seen immunotherapy make contact lens wear more comfortable. Most of the strategies in the optometric world used for contact lens discomfort are lens or solution centric. We usually don't look beyond that. Treating the systemic cause can be more effective than treating just the contact lens or ocular surface.

Dr. Luchs: I’m identifying a lot more allergy lately, thanks to a higher index of suspicion and better point-of-care diagnostics. And I have been sending a lot more of my patients with allergies to allergists and have found that immunotherapy can be quite helpful for those patients. It’s nice that we’re in an era with advancing technology in both the therapeutic and the diagnostic side of allergy.

Let’s talk a bit about the patient whom you believe clearly has ocular allergy, but is not getting better on one of the treatment regimens we’ve mentioned earlier. How do you approach that patient?

MANAGING NONRESPONDERS

Dr. Mah: First, I would make sure my diagnosis is indeed ocular allergy. Obviously, if you've made the incorrect diagnosis, the itching has improved but they're not getting significantly better, then it doesn't matter what you use in terms of combination products; they're still not going to improve. That’s the first thing, just making sure that we’ve made the correct diagnosis.

Second, I would make sure the patient is avoiding whatever is causing their allergy. If they’re not following your instructions for avoidance, try to reinforce their compliance.

Third, it doesn’t matter what prescription you write if the patient is not using the medications, even if they are following avoidance instructions. In order to confirm that an agent is not working, you have to know that the patient has been compliant with its use.

Dr. Milner: To add to that, once you confirm the diagnosis as well as the patient’s compliance and whether they’ve practiced avoidance, then you can seek those other esoteric compounded therapies that we reserve for these patients when nothing else helps.

Also question whether the patient is mucus fishing. That exacerbation of their symptoms will never get better until they stop trying to remove the mucus with their fingernail or cotton swab.

Lastly, don’t be afraid to seek the help of an allergist or corneal specialist.

Dr. Luchs: I have seen missed concomitant ocular surface disease such as dry eyes and blepharitis—especially in patients who are referred to me. Remember that these diseases don't exist in a vacuum; they often are present together in the same patient. So you may have correctly diagnosed ocular allergy, but if the patient also has dry eyes and/or blepharitis, their symptom complex may not be resolved unless you identify and treat those diseases as well, and then the patient ends up much improved.

Dr. Hom: Ocular allergy and dry eye does occur at the same time in patients. In fact, we have found a 40% to 60% overlap in symptoms.29
Dr. Luchs: This is an exciting time for ocular allergy. Allergy in general is a profoundly prevalent condition, affecting more than 50 million people, and we see it every day in our offices. It affects our patient’s lives, sometimes profoundly, and it carries a huge economic impact. That said, ocular allergy certainly deserves our attention as eye-care professionals. Fortunately, we now have better methods to help us identify and diagnose the condition, and we also now have an excellent range of therapeutic options for treating patients. What’s more, we can look forward to even newer developments as they come down the pipeline in the near future.

REFERENCES
