Diagnostic Challenges in Ocular Surface Disease

Derek Cunningham, OD, FAAO

Ocular surface disease includes a group of conditions that not only overlap broadly in symptomatology but also commonly coexist. Awareness of comorbidity can be key to accurate diagnosis and appropriate management of patients with ocular surface complaints. In this premiere edition of *Key Issues in Ocular Surface Disease*, we evaluate symptoms among various forms of ocular surface disease, including dry eye disease, ocular allergy, and infectious conjunctivitis.

Ocular surface disease, the most common condition that primary eye care providers encounter in their daily practice, often represents a diagnostic challenge. One reason for the difficulty in diagnosis is variability in presentation. Ocular surface disease can take several different forms: dry eye disease, meibomian gland dysfunction, ocular allergy, and infectious conjunctivitis. Another reason for diagnostic difficulty is the fact that ocular surface disease in its early stages often lacks distinctive signs and symptoms. A wide range of ocular conditions can start with just redness and a small amount of irritation.

Furthermore, the sheer prevalence of ocular surface disease makes it prone to missed diagnosis—in other words, ocular surface disease is so ubiquitous that it doesn’t stand out. Dry eye, for example, is the most diagnosable disease in all of eye care yet also one of the most undertreated. It is estimated to affect about five million Americans 50 years and older. However, there is a significant disconnect between its prevalence and the frequency with which dry eye patients are actually diagnosed and treated.

**Dry Eye vs Allergy**

Dry eye and ocular allergy overlap significantly in their presenting signs and symptoms. Both conditions can present with eye irritation, tearing, and conjunctival hyperemia. Conventional wisdom holds that dry eye causes burning, while allergy causes itching. However, many patients with ocular allergy also report burning, and itching is not an uncommon symptom of patients with dry eye.

A thorough examination of the ocular surface is important to avoid misdiagnosis. The two key signs of chronic dry eye are abnormal meibomian gland secretion and decreased tear production. It should be noted, however, that a higher tear prism does not exclude the diagnosis of dry eye: a patient could simultaneously have active allergic conjunctivitis, which can increase aqueous production and mask the presence of dry eye.

Point-of-care diagnostic tools can help point the way towards a diagnosis of dry eye or allergy. One is lissamine green staining of the ocular surface. An allergic conjunctivitis patient often shows more stains on the nasal conjunctiva.

**FIGURE 1** Increased lissamine green allergy staining on the nasal conjunctiva. (Image courtesy of Dr. Cunningham.)
tiva or around the punctum, whereas typical dry eye staining is more uniform across the entire intraepithelial conjunctiva or concentrated inferiorly (Figure 1A and B). Another diagnostic tool is a commercial test kit that measures total levels of immunoglobulin E (IgE) in tears (TearScan IgE Diagnostic Test kit, Advanced Tear Diagnostics). IgE is an established immunological marker of ocular allergy.2

One simple trick that may help clear up the clinical picture is to ask patients to rub their eyes. If dry eye is the main culprit, eye rubbing usually alleviates symptoms of discomfort, albeit temporarily, by stimulating the lacrimal gland to produce more tears. If allergy is the primary problem, the opposite happens: the condition will instantly worsen, because eye rubbing is known to trigger mast cell degranulation and histamine release.3

Contrary to what many people assume, history is not always helpful in the diagnosis of ambiguous cases. If a patient comes in and says, “I have my seasonal allergy right now—it’s always exactly this month when it flares up,” there would be little ambiguity in the diagnosis of seasonal allergy. In reality, that scenario is rare. As a matter of fact, roughly 80% of the patients I diagnose with ocular allergy claim that they have never had allergies. From years of experience with cutaneous skin testing for ocular allergens in my practice, I have come to realize that the vast majority of patients do not know what they are allergic to. Many of these patients will never seek out an allergist. Instead, they rely heavily on their primary care physicians. For these reasons, clinicians should not fully rely upon a self-reported history for the diagnosis and treatment of ocular allergy, even though it may be important for differentiating seasonal and perennial allergies.

Presence of Comorbidty

One under-recognized fact about ocular surface diseases is that they commonly present together. In fact, the majority of these patients have comorbidities rather than a single disease form. Given that any one of these conditions is a significant and formidable issue by itself, simultaneous presence of two or even three of them increases the complexity of not just diagnosis but also treatment.

Take dry eye and ocular allergy. The two disease states often go hand-in-hand. One main function of the tear film is to wash away allergens. Anyone with dry eye will therefore have increased exposure of the conjunctival mucosa, conjunctival blood flow, and the eyelid tissue to airborne allergens. This may trigger an exaggerated allergic response, sometimes far worse than if they did not have dry eye. Hence, all dry eye patients are presumably at increased risk of al-

KEY ISSUES IN OCULAR SURFACE DISEASE – ISSUE 1

STATEMENT OF NEED

Although sometimes used as a synonym for dry eye disease, the term “ocular surface disease” refers to a cluster of anterior eye disorders that includes dry eye (evaporative or due to tear insufficiency), bacterial and viral infections, blepharitis, meibomian gland dysfunction, allergic conjunctivitis, ocular surface problems associated with glaucoma treatment, and the ocular manifestation of systemic inflammatory diseases and endocrine disorders [e.g. Sjögren’s syndrome, arthritis, and thyroid disease]. While prevalence data vary considerably based on the population studied and disease definition, all of these conditions are common.1-3 In addition, they share pathogenic mechanisms, have overlapping clinical signs and symptoms, and are often comorbid.4 For example, allergic conjunctivitis, blepharitis and Sjögren’s syndrome—dry eye disease—are inflammatory conditions that affect the ocular surface and share a number of symptoms, including discomfort, itching, dryness, and irritation.5,6

Diagnosis and treatment of ocular surface disease are clearly important, but they are rendered difficult by a number of factors: the frequency of comorbid conditions with similar signs and symptoms; incomplete understanding of the underlying pathogenesis; frequently poor correlation between signs and symptoms; occasional systemic disease as an underlying factor; and the absence of simple, clear diagnostic tests. Even after diagnosis, adherence to best practice in patient management is complicated by the number of agents available and competing claims for them in the marketplace. Each installment of Key Issues in Ocular Surface Disease will look at two important topics in the management of ocular surface disease in order to support optometrists’ clinical reasoning and decision-making abilities and navigate the growing body of sometimes contradictory evidence on ocular surface disease. The benefits are substantial: accurate diagnosis and effective treatment of ocular surface disease will contribute greatly to patient comfort and satisfaction, help patients enjoy comfortable contact lens wear, and significantly enhance outcomes in cataract and corneal refractive surgery.

References


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This CE activity is sponsored by New England College of Optometry and is supported by an unrestricted educational grant from Shire.

DATE OF ORIGINAL RELEASE


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Course ID #52577-6S  Event ID #812918

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lergic conjunctivitis. Likewise, patients with allergic conjunctivitis are more susceptible to dry eye. Chronic allergic conjunctivitis often results in a disrupted tear film as well as chronic inflammation on the ocular surface, which will in turn lead to decreased tear production.4

Knowing that comorbidity is common, one should remain alert to the presence of multiple disease states until proven otherwise. For any given patient, the presence of dry eye should prompt an increased suspicion for allergic conjunctivitis. By the same token, dry eye should be considered as an underlying exacerbating factor in any case of allergic conjunctivitis. Currently, the most specific and accurate diagnostic tool for ocular allergy is tear IgE testing. Unfortunately, it is not available in all practices. Unless the diagnosis of allergy or dry eye can be excluded, one has to take into consideration both disease states and treat comprehensively.

**The Challenge of a Red Eye**

Because infectious conjunctivitis has the potential to cause severe damage to the ocular structures, clinicians presented with a nondiscriminatory red eye often presume it is an infectious case and quickly resort to topical antibiotic drops. However, eye redness can be a presenting sign of all of the ocular surface diseases. True bacterial conjunctivitis is relatively rare in the adult population. Besides, simple bacterial conjunctivitis is self-limiting in the vast majority of cases, typically lasting only 1 to 2 weeks without antibiotic treatment.5,6

One common yet often overlooked cause of red eye is acute exacerbation of chronic ocular surface inflammation, most often linked to dry eye. The chronic inflammation may periodically flare up to become acute. Because of overlapping signs and symptoms, these episodes of inflammation are often misdiagnosed as infectious conjunctivitis.

Patient history can be helpful in differentiating the two disease states. Both bacterial and viral conjunctivitis tend to be acute, which means that patients do not normally experience it. If a patient comes in and complains of chronic irritation, it is likely a case of exacerbated inflammation. Additional diagnostic clues may be found in the patient’s clinical presentation. Mucopurulent discharge and large papillae are hallmark signs of a bacterial infection, whereas viral conjunctivitis tends to be more acute in its presentation and is usually accompanied by a set of indicative signs and symptoms including excessive tearing, conjunctival follicles, photophobia, and even subepithelial infiltrates.

Most often, patients with red eye have been treated with topical antibiotic drops—either by family or emergency physicians or pediatricians—by the time they see an optometrist. Since the majority of the bacterial strains commonly found in conjunctivitis are susceptible to antibiotic treatment,7,8 persistent redness and symptoms of discomfort despite antibiotics should be deemed an alarming sign of a condition different than bacterial infection.

**Management: A Long-term Process**

All ocular surface diseases—dry eye, ocular allergy, and conjunctivitis—are associated with inflammatory responses on the ocular surface. Ocular surface inflammation is often the pathology that underlies the symptoms of patients with these conditions. When patients present with a significant amount of acute inflammation on the ocular surface, there is no question they need to be treated—most often with topical corticosteroids and, in the case of bacterial conjunctivitis, with antibiotics.

While in the short term these patients can be treated in relatively simple ways, long-term management is more critical in terms of understanding any potential source of their problems. Topical corticosteroids can provide temporary symptom relief but are not a long-term solution because of the risk of serious side effects. For patients with ocular surface disease to be properly managed in the long run, clinicians must identify any predisposing condition and treat that. Very often, that condition turns out to be chronic dry eye.

For patients with dry eye, either as a primary or underlying comorbid condition, long-term management of the disease is necessary to reduce chronic ocular surface inflammation and associated symptoms. Acute exacerbation of the disease may be rapidly controlled using topical corticosteroids, but to prevent further flare-ups, the challenge is what comes after: find the most effective way of controlling chronic inflammation in a safe manner.

**Future Directions**

A nondiscriminatory red eye remains one of the most challenging conditions to diagnose and treat in primary eye care. It never gets easy even after years of practice. Fortunately, several in-office tests are now available to help pinpoint the diagnosis in patients with ocular surface disease. We already have a tear matrix metalloproteinase 9 (MMP-9) test (InflammaDry, Rapid Pathogen Screen-
Key Issues in Ocular Surface Disease

To further improve the diagnosis and treatment of ocular surface disease, we will need clinical knowledge of how patients respond to different therapies and what the best therapy is for any given patient. Ultimately, we have to look at what makes a normal, healthy ocular surface susceptible to these types of inflammatory conditions and how it can be prevented.

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REFERENCES
Allergic Conditions Affecting the Ocular Surface

Mile Brujic, OD, FAAO

Optometrists are regularly called upon to detect and manage allergic conditions affecting the eye. In this review of ocular allergic conditions, we identify distinguishing features and current considerations for diagnosis and management.

The ocular conjunctiva is highly accessible to airborne allergens and a common site of allergic inflammation. An estimated 20% to 50% of the general population experiences some form of systemic allergy, 70% to 80% of whom have ocular involvement. Thus, somewhere between 15% and 40% of the general population experience symptoms related to ocular allergies either intermittently or chronically.1

Factors such as urbanization, air pollution, and even increasing rates of dry eye disease (as patients with reduced tear volume and/or quality have an impaired ability to dilute and wash out ocular surface allergens) may all be contributing to a rise in allergic disease in general in developed countries.2-5

Acute Allergic Conjunctivitis

The most common form of ocular allergy is seasonal allergic conjunctivitis (SAC). As its name implies, SAC occurs in response to seasonal allergens such as tree, grass, and weed pollens. By contrast, perennial allergic conjunctivitis (PAC) describes ocular hypersensitivity to home-based antigens that flourish year round, such as dust mites, mold spores, and animal dander. Within these categories, presentations tend to vary. For example, patients with SAC may have extra-seasonal exposures; conversely, those with PAC may have only intermittent exposures.

Pathophysiology and Symptoms

Although antigen triggers are different for SAC and PAC, the two conditions share a mast cell-mediated pathophysiology. When immunoglobulin E (IgE) on the surface of presensitized mast cells interacts with the corresponding antigen, mast cells degranulate within minutes, releasing histamine and other inflammatory molecules responsible for a cascade of downstream effects. [Figures 1 and 2] These effects include irritation of nerve cells, causing itching and burning; dilation of blood vessels, leading to hyperemia and chemosis of the conjunctiva and the eyelids; and tearing—a protective response against the inciting antigen.

The immediate phase is followed by a delayed inflammatory response over several days, during which time inflammatory cells are recruited to the local tissue; further cellular activation may lead to cellular damage.6

Of note, most patients with allergic ocular conditions—as well as many with other diagnoses—experience ocular itching. Pinpointing the specific location of itching may help identify the cause. In the case of allergic conjunctivitis, the itching sensation tends to localize to the inner canthus. In contrast, itch localized to eyelids is associated more commonly with atopic dermatitis; itch at the eyelash margin is more typical of blepharitis; and itch in the lower fornix region is a common site for irritation in association with mucus fishing syndrome.

Comorbidities

It is important to uncover relevant ocular and systemic comorbidities in order to arrive at an accurate diagnosis and direct appropriate therapy. Allergic ocular symptoms may occur in isolation or in conjunction with other systemic atopic manifestations, including rhinitis, sinusitis, asthma, and urticaria.4

Dry eye disease often coexists with and exacerbates allergic conjunctivitis.3,5 Compared to patients with normal tear function, those with reduced tear volume and/or quality have an impaired ability to dilute and wash out ocular surface allergens. Further, an unhealthy ocular surface related to dry eye or other underlying disorder is more susceptible to the release of inflammatory cytokines during the allergic response.

Chronic Ocular Allergy

Chronic ocular allergic conditions—including vernal conjunctivitis, giant papillary conjunctivitis (GPC), and atopic conjunctivitis—result from longstanding inflammatory cell recruitment into local tissue. These should be included in the differential diagnosis for patients with severe ocular allergy manifestations.

Vernal keratoconjunctivitis typically presents in young males who ultimately outgrow the condition, although sometimes not before the cornea is affected. Chronic lymphocyte and mast cell infiltration in the conjunctiva cause

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the development of hallmark signs of vernal keratoconjunctivitis: Trantas dots, which are small yellow-white dots on the limbus of the conjunctiva and cornea, respectively; Dennie’s lines, which is lower eyelid creasing; large cobblestone papillae on the tarsal conjunctiva; pseudomembrane formation; and fibrinous discharge.

Atopic keratoconjunctivitis is most commonly seen in individuals between 20 and 50 years of age presenting with severe ocular itching, tearing, and swelling. A family history of atopy is nearly always present and is useful for making the diagnosis. As their names indicate, vernal and atopic keratoconjunctivitis may involve the cornea and cause significant visual impairment.

GPC is a chronic allergic response to an ocular foreign body including contact lenses (particularly when mishandled or overworn). Patients with GPC present with moderate to severe itching, injection, blurred vision, and difficulty tolerating contact lens wear. An examination of a patient with GPC will reveal large papillae on the undersurface of the lid.

Sequelae and Quality of Life
Advanced cases of vernal or atopic keratoconjunctivitis can lead to permanent corneal scarring if undetected or insufficiently treated. GPC, SAC, or PAC are not sight threatening but may reduce quality of life due to symptoms or by causing a reduced ability to perform daily living tasks or wear contact lenses. At its worst, ocular itching associated with ocular allergies has been called “debilitating” by patients, in my experience. Rubbing the eyes has the effect of increasing histamine release, which can create a cycle of worsening symptoms.

Diagnosing Allergic Conjunctivitis
Allergic conjunctivitis is likely under-diagnosed in clinical practice. Patients with minor ocular allergy symptoms often self-treat using over-the-counter medications during an episode. These patients may manifest no symptoms or signs at the time of their routine eye examination. Therefore, it is important to ask during routine eye exams whether or not patients experience allergic symptoms at any time throughout the year—and if so, whether their allergies bother their eyes.

Patients who present with manifestations of acute allergic conjunctivitis complain of itching and sometimes redness, swelling, and tearing; they may have concomitant rhinitis or other systemic symptoms and signs of allergy. [Figure 3] Moreover, most patients with acute allergic conjunctivitis are returning patients with known disease, so the diagnosis is straightforward.

Chronic forms of allergic conjunctivitis are more challenging to identify and diagnose. A thorough history to uncover atopic disease as well as an examination looking for Trantas dots, stringy mucous, or other signs indicative of chronic allergic conjunctivitis are essential. Viral and bacterial conjunctivitis should be considered when a diagnosis of allergic conjunctivitis is in question and appropriate testing performed. In-office adenovirus testing could be considered on patients with an unclear red eye presentation.

Prophylaxis and Treatment
The main goal of allergic conjunctivitis therapy is to provide symptomatic relief. For patients with prolonged exposures or symptoms, an additional goal is to interrupt the cycle of inflammation on the ocular surface. A management approach that includes patient education, lifestyle adjustments, and topical medications may be more effective than an approach based on only one or two of those strategies.

First, reducing or removing exposure to the allergen remains the best prophylactic strategy when feasible. For example, aeroallergens may collect in the hair during the day; patients who experience allergy symptoms upon awakening may benefit from washing the hair before bed. Wearing spectacles or sunglasses can provide a mechanical barrier to aeroallergens.

Other nonpharmaceutical measures include copious lubrication with artificial tears, which helps remove allergens from the ocular surface. Cold compresses against the eyes reduce the heat of inflammation and provide relief.

Eycare providers should guide patients away from over-the-counter medications that have potentially harmful effects on the ocular surface. For example, topical antihistamine/decongestants provide a short-term whiting effect but can also cause rebound hyperemia and even trigger allergies in some patients. Oral antihistamines can reduce ocular and monocular allergic symptoms but can also have a drying
effect on the ocular surface due to their anticholinergic property.6

Patients with predictable upcoming exposures to allergens (eg, patients with true SAC) may benefit from prophylaxis with a topical ocular medication given 1 to 2 weeks before anticipated allergen exposure. (Please note that topical ocular anti-allergy medications carry indications for treatment of existing allergy; prophylaxis is an off-label use.)

Topical ocular medications, including dual-acting mast cell stabilizer/antihistamine agents (eg, bepotastine, olopatadine, alcaftedine) are good options for patients whose symptoms are mainly ocular. These dual-acting agents prevent symptoms at two junctures: during early-phase degranulation of mast cells (stabilizing mast cells); and at histamine receptors, preventing their activation by histamine that has already been (or is about to be) released. Dual-acting agents are fast acting and are approved as once- or twice-a-day dosing, which provides convenient options for patients.

Corticosteroids target multiple sites along the inflammatory cascade, including early and late phase allergic response, mast cell proliferation, cell-mediated immune response, and inflammatory cytokine production.7 Patients with moderate to severe allergic conjunctivitis symptoms may benefit from the addition of a topical ocular corticosteroid such as loteprednol 0.2%, which is the only corticosteroid approved by the FDA for the treatment of allergic conjunctivitis. A unique structural modification of loteprednol—an ester group on carbon 20—expedites enzymatic breakdown of the agent on the ocular surface, making it safer than other corticosteroids.9

Chronic forms of allergic conjunctivitis require first-line antiinflammatory treatment with corticosteroids plus concomitant treatment with a mast-cell-stabilizing antihistaminic agent. Once the inflammation is under control, the corticosteroid can be tapered and stopped and the mast-cell-stabilizing agent maintained.

Conclusion

Acute allergic conjunctivitis is typically a mild to moderate self-limited disorder; but some forms, such as chronic allergic keratoconjunctivitis, can be severe. It is important to rule out infectious etiology when the presentation is unclear. Management of underlying ocular surface disease is crucial, as is prescribing appropriate topical anti-inflammatory medication.

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Course ID #52517-AS  Event ID #112918  Expiration: 12/31/2019

1. Which one of the following allergens is NOT a trigger for perennial allergic conjunctivitis in susceptible individuals?
   A. Cat hair
   B. Mold
   C. Flowering plants
   D. Dust mite

2. According to Dr. Cunningham, which of the following tests is most helpful for differential diagnosis of dry eye and ocular allergy?
   A. Lissamine green staining
   B. Measurement of tear prism heights
   C. Tear IgE testing
   D. Both A and C

3. Which of the following is a specific clinical finding of allergic conjunctivitis?
   A. Conjunctival hyperemia
   B. Eye itching
   C. Large conjunctival papillae
   D. None of the above

4. What proportion of the general population experiences some form of ocular allergy?
   A. 5% to 10%
   B. 15% to 40%
   C. 70% to 80%
   D. None of the above

5. Among corticosteroids for ocular use, loteprednol has a unique:
   A. Chemical structure
   B. Pharmacokinetic profile
   C. Indication for treatment of acute allergic conjunctivitis
   D. All of the above

6. Which one of the following is NOT typically associated with vernal keratoconjunctivitis?
   A. Dennie’s lines
   B. Trantas dots
   C. Lymphocytic infiltration of ocular tissue
   D. Contact lens wear

7. Which one of the following statements about dry eye disease is NOT correct?
   A. It is highly prevalent
   B. It can temporarily be exacerbated by eye rubbing
   C. It can occur secondary to ocular allergy
   D. It increases the risk for allergic conjunctivitis

8. The most likely diagnosis for a patient with a watery red eye, photophobia, conjunctival follicles, and subepithelial corneal infiltrates is:
   A. Bacterial conjunctivitis
   B. Viral conjunctivitis
   C. Exacerbation of dry eye
   D. Active allergic conjunctivitis

9. Evaluating patients with allergic conjunctivitis might include which of the following?
   A. Obtaining patient and family history of systemic allergy
   B. Ruling out viral infection
   C. Both A and B
   D. Neither A nor B

10. Which one of the following statements about ocular surface diseases is correct?
    A. They all involve ocular surface inflammation
    B. They rarely exist at the same time
    C. They often present with distinctive signs and symptoms
    D. They require long-term corticosteroid therapy