Noninfectious Keratitis: An Expert Panel Recommendation

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ABSTRACT

An expert panel of US physicians met via a 2-hour webinar to discuss treatment of specific noninfectious keratitis disorders and to evaluate newer therapies as part of a step-wise treatment regimen. The panel evaluated treatments for ocular surface disease (including dry eye), for ocular manifestations of autoimmune disorders, for peripheral ulcerative keratitis, and for neurotrophic keratitis. Steroid treatment remains first-line therapy, but the commercial introduction of other classes of medicines to treat ocular inflammation has broadened the field.

INTRODUCTION

Keratitis—inflammation of the cornea—can be caused by any number of infectious or noninfectious stimuli,¹ and treatment of infectious keratitis will depend upon the underlying etiology. Noninfectious keratitis, however, can result from contact lens wear, dry eye, allergies, foreign body, corneal injury (trauma, chemical exposure), or ultraviolet exposure,² or as the manifestation of an autoimmune systemic disorder. Treatment for noninfectious keratitis is not as clear-cut because of its highly variable nature.

Noninfectious keratitis does not seem to be limited to a particular age. A Chinese study found noninfectious corneal diseases occur mainly in people aged 10 to 19 years, but in patients 80 years or older, the most common cause was Terrien-marginal degeneration and Mooren ulcer.³

Some autoimmune disorders may lead to noninfectious keratitis,⁴⁻⁶ and the most severe ocular manifestation of autoimmune disorders is peripheral ulcerative keratitis (PUK).⁶ PUK is rare, and Mooren’s ulcer, senile marginal degeneration, sclerokeratitis and peripheral corneal melt of rheumatoid origin are some other potential causes (Figure 1).⁷ There is emerging anecdotal evidence that treatment of the ocular symptoms may affect or improve the systemic disease.

Other common causes of noninfectious keratitis (after PUK) include vernal ulcers, staphylococcal marginal keratitis, contact-lens related sterile infiltrates, and phlyctenular keratitis.⁸ Some disorders have been associated with several subsets of keratitis; for example, Salzmann nodular corneal dystrophy has been associated with phlyctenular keratitis, interstitial
keratitis, vernal keratitis, and Thygeson superficial punctate keratitis. Neurotrophic keratitis may lead to decreased ocular surface sensation and dry eye.

Infectious and noninfectious keratitis may overlap each other (as in the case of contact lens wear as a causal factor). Noninfectious keratitis may become infectious by pathogenic or nonpathogenic microbes, which can lead to sight-threatening complications. While infectious keratitis often has a finite duration and set treatment regimens, the inflammatory components of noninfectious keratitis can be chronic and persistent, often requiring a step-wise approach to disease management. Managing and resolving the inflammatory component remains part of a carefully managed active process.

For refractory disease, patients may be managed surgically. Intense pulsed light (IPL) and conjunctival resection may also be considered (the latter for cases of PUK).

The recent increase in commercially available treatments for ocular inflammation, dry eye, and neurotrophic keratitis means clinicians have numerous treatment options in their armamentarium, which then must be assessed for efficacy in comparison to older treatments and in developing a treatment regimen to include these newer agents. Treating the ocular disorder must be accomplished in the setting of the patient’s overall health, and in the case of autoimmune disorders, often in a comanaged situation. The panel developed this paper, therefore, intended to serve as a potential guideline for the treatment and management of noninfectious keratitis.

PATIENT EVALUATIONS

Keratitis is typically classified by location, severity, and cause. Superficial keratitis affects only the surface layer of the cornea, whereas stromal keratitis or interstitial keratitis affect deeper layers of the cornea. Keratitis can be acute or chronic, may be unilateral or bilateral. Allergies to airborne pollens and autoimmune disorders can lead to noninfectious keratitis. Corneal ulcers and stem cell deficiency can be signs of vernal keratoconjunctivitis (typically considered the most severe form of ocular allergy). Noninfectious keratitis has also been associated with systemic disorders. In some cases of rheumatoid arthritis (RA), patients may develop marginal corneal ulceration with thinning of the cornea.

Ulcerative inflammation of the cornea is associated with autoimmune diseases, and RA is the most frequent underlying cause. Development of PUK associated with systemic autoimmune disease may represent the progression of a potentially life-threatening disease, as the mortality after a diagnosis of PUK can be higher than 50% (although the percentage drops significantly for those on immunosuppressive therapies). Ocular manifestations are a significant comorbidity of autoimmune disorders, including RA, but evidence is emerging that suggests PUK may not be as prevalent as once thought. For instance, Vignesh and Srinivasan found only 1% of patients with RA presented with PUK and sclerosing keratitis. The same group found multiple ocular manifestations of RA, including filamentary keratitis, episcleritis, sclerosing keratitis, and scleritis in addition to PUK. The progression of PUK can be compounded by the presence of dry eye.
Patients with keratitis may be comanaged by rheumatologists, dermatologists, or a primary care physician when the initial presentation is outside the ocular system. For example, systemic diseases such as rosacea are also associated with ocular inflammation (via abnormal blood vessels in the lid margins), although the large majority of patients noting ocular complaints are overlooked. At present, there is no “gold standard” treatment for ocular rosacea, with topical treatment often insufficient and oral treatment providing only moderate benefits. For these patients, IPL can be effective; its use in treating skin rosacea has been well accepted for more than a decade. Numerous review publications support this technology’s use in treating dry eye as well.

Nearly half the patients with RA will have clinical features of dry eye and more than one-third are symptomatic. Patients with RA will not show symptoms or signs of ocular involvement until later in their disease progression. Further, these patients present with both aqueous-deficient and evaporative dry eye. Vascularization of the peripheral cornea (with or without epithelial defect), stem cell deficiency (with either limbal or corneal changes), and corneal thinning also indicate keratitis. If the stromal presentation of blood cells is superficial, stem cell deficiency should be considered whereas if the presentation is deep, allergies may be a more appropriate diagnosis.

**TARGETING TREATMENT**

The members of this panel believe steroids should remain the first-line treatment for most incidents of keratitis, but that in today’s clinical environment physicians should have a low threshold to consider additional or alternative therapies that provide better safety profiles; we further advocate comanagement with other specialties when autoimmune disorders are present. The Table provides a brief overview of our recommendations.

In general, we advocate a 4- to 6-week cycle of steroids at the maximum, with an aggressive schedule for titration and a switch to a steroid-sparing or steroid-eliminating treatment. Pseudophakic patients can titrate at a slower rate because the threat of cataract formation is nonexistent. Anecdotally, two panelists (MT and RT) have patients who, upon presentation to an ophthalmologist, had an history of oral steroid use lasting 10 to 15 years.

**Ocular Surface Disease**

In 2017, the TFOS DEWS II report noted “many of the treatments available for the management of dry eye disease lack the necessary Level 1 evidence to support their recommendation” for a variety of reasons. TFOS DEWS II recommended tear replacement approaches, tear conservation approaches, tear stimulation approaches, and antiinflammatory therapy as overarching categories of therapy.

Topical corticosteroids had been the mainstay in targeting the inflammatory components; in dry eye topical cyclosporine and lifitegrast (Xiidra, Shire) have become most clinicians’ preferred pharmaceutical therapy if topical lubricants are deemed ineffective. Topical nonsteroidal antiinflammatory drugs, however, have not been shown to have a consistent safety profile for patients with dry eye. Biologics have shown promise, specifically recombinant human nerve growth factor (rhNGF), tumor necrosis factor inhibitors, and antiinterleukin-17 (IL-17) therapy. Of interest, neuropeptides have been studied in moderate and severe neurotrophic keratitis in patients with concomitant dry eye. For patients with refractory or more severe ocular surface disease, surgical approaches may be warranted.

Inflammatory cells (including lymphocytes, monocytes/macrophages, and neutrophils) express melanocortin receptors. The literature finds adrenocorticotropic hormone (ACTH) to be more effective than corticosteroids, and steroid-sparing. Although the mechanism of action is not fully understood, anecdotal evidence suggests ACTH is not only beneficial in treating ocular inflammation, but also in alleviating symptoms when there is an associated systemic disorder.

This panel also recommends topical treatments, including T-cell modifiers. These treatments include cyclosporine, lifitegrast, and tacrolimus. Both tacrolimus and cyclosporine block T-lymphocyte activity. The exact mechanism of action of lifitegrast is
**TABLE. NONINFECTIOUS KERATITIS MANAGEMENT RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Ocular Surface Disease</th>
<th>Level 1: Mild Ocular Disease</th>
<th>Level 2: Moderate Ocular Disease</th>
<th>Level 3/4: Severe Ocular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Features/Presentation</td>
<td>Blurred vision, episodic foreign body sensation, Low tear film, conjunctival staining, +MMP-9, elevated tear film osmolality</td>
<td>Blurred vision with FBS daily: Signs of ocular inflammation, and staining on peripheral cornea</td>
<td>Severe symptoms, diffuse staining on cornea, filaments, ulceration of cornea, stem cell changes</td>
</tr>
<tr>
<td>Treatment</td>
<td>Artificial tears, nutritional supplements</td>
<td>PFATs, prescription anti-inflammatory, plugs</td>
<td>PFATs, topical steroid, prescription anti-inflammatory, systemic immunosuppression</td>
</tr>
<tr>
<td>Management</td>
<td>OTC medications and disease state education</td>
<td>Start with prescription topical antiinflammatory, PFAT, consider plugs if minimal signs of inflammation on tear film testing.</td>
<td>Use of topical steroid and work up for inflammatory disease. Consider use of oral immunomodulator aggressive topical treatment. Consider placement of self-retaining AMT</td>
</tr>
</tbody>
</table>

**Autoimmune Disorders**

<table>
<thead>
<tr>
<th>Clinical Features/Presentation</th>
<th>Level 1: Mild Ocular Disease</th>
<th>Level 2: Moderate Ocular Disease</th>
<th>Level 3/4: Severe Ocular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild ocular injection, ocular ache, mild anterior chamber reaction</td>
<td>Moderate symptoms, significant corneal staining, signs of inflammation in tear film (MMP-9, tear film osmolality)</td>
<td>Severe staining, diffuse corneal staining, signs of ocular inflammation, corneal erosions, filaments</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Prescription topical antiinflammatory agents</td>
<td>Topical anti-inflammatory agents</td>
<td>PFATs, topical steroid, prescription anti-inflammatory, systemic immunosuppression</td>
</tr>
<tr>
<td>Management</td>
<td>PFAT, nutritional therapy, and topical prescription cyclosporine or lifitegrast</td>
<td>Consider topical steroid and NSAID. Must control inflammatory disease with systemic immunomodulator</td>
<td>Institute systemic immunomodulator. Aggressive topical treatment with steroid and NSAID. Consider placement of self-retaining AMT or another ocular surface surgery if warranted</td>
</tr>
</tbody>
</table>

**Proliferative Ulcerative Keratitis**

<table>
<thead>
<tr>
<th>Clinical Features/Presentation</th>
<th>Level 1: Mild Ocular Disease</th>
<th>Level 2: Moderate Ocular Disease</th>
<th>Level 3/4: Severe Ocular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular pain and photophobia, foreign body sensation, ocular injection, inflammatory infiltrate at limbus</td>
<td>Moderate to severe pain, limbal injection, and crescent shaped epithelial defect with thinning</td>
<td>Severe pain and injection. Peripheral epithelial defect with thinning/perforation</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Topical prescription antiinflammatory, oral NSAID, topical lubrication</td>
<td>Consider steroid sparing agents, topical steroid drops (difluprednate) MMP-9 inhibitor</td>
<td>Oral steroid Systemic immunosuppression MMP-9 inhibitor Lubrication Self-retaining amniotic membrane</td>
</tr>
<tr>
<td>Management</td>
<td>Work up for inflammatory disease, initiate treatment with topical anti-inflammatory</td>
<td>Aggressive topical lubrication and consider comanagement with rheumatology. Treat with full strength topical steroid and begin systemic steroid sparing agents.</td>
<td>Immediate induction of topical steroid with a steroid sparing agent. Use of MMP-9 inhibitor (doxycycline, vitamin C, etc.). May need to use self-retaining AMT. Consider surgical intervention if no improvement, perforation, or impending perforation with multilayer AMT, or patch graft.</td>
</tr>
</tbody>
</table>

**Neurotrophic Keratitis**

<table>
<thead>
<tr>
<th>Clinical Features/Presentation</th>
<th>Level 1: Mild Ocular Disease</th>
<th>Level 2: Moderate Ocular Disease</th>
<th>Level 3/4: Severe Ocular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain, elevated epithelial ridge with surface staining</td>
<td>Small epithelial defect with rolled edges, diffuse corneal staining</td>
<td>Large epithelial defect with rolled edges and corneal haze, diffuse corneal stain, stem cell changes</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Punctal plugs, NPAT, ointments and gels</td>
<td>Plugs, PF artificial tears, BCL, self-retaining AMT</td>
<td>Plug, PFAT, AMT, tarsorrhaphy</td>
</tr>
<tr>
<td>Management</td>
<td>Aggressive lubrication and placement of punctal plugs</td>
<td>Place plugs and encourage topical drops, consider BCL if epithelium does not close, consider recombinant nerve growth factor (ie, Oxervate)</td>
<td>Plug punctum and use PFATs and ointment. Place self-retaining AMT and consider tarsorrhaphy. Also consider use of recombinant nerve growth factor</td>
</tr>
</tbody>
</table>

MMP-9=matrix metallopeptidase; FBS=foreign body sensation; PFAT=preservative-free artificial tears; OTC=over the counter; AMT=amniotic membrane transplantation; NPAT=nonpreserved artificial tear; NSAID=nonsteroidal anti-inflammatory drug; BCL=bandage contact lens
unknown, but is theorized to involve blocking the interaction between lymphocyte function-associated antigen-1 (LFA-1) and its ligand intracellular adhesion molecule (ICAM-1).

Blood-derived eye drops can supply a mixture of growth factors and cytokines and can promote the healing of natural tears, but more research and randomized clinical trials are necessary before this panel can comment.

**Autoimmune Disorders**

The underlying autoimmune disorder should dictate treatment. Comanagement with a rheumatologist is recommended when treatment involves biologics.

Ocular rosacea typically is treated with a step-wise approach; the disorder can lead to severe and recalcitrant blepharitis. Treatment progresses from lid hygiene and artificial tears to topical and oral antiinflammatory medications. One review suggested oral tetracycline (titrated to clinical response), oral doxycycline, or a combination of the two. However, the specific mechanisms of action in how these medications address ocular rosacea remain unknown. Oral doxycycline, minocycline, and azithromycin have been studied extensively, but results have been varied and side effects remain a common complication. In its review, the American Academy of Ophthalmology noted only a modest level of evidence exists to support using these treatments. The American Acne and Rosacea Society recommends IPL to address specific clinical manifestations that exhibit limited or no response to available medical therapies, and this panel concurs. Topical cyclosporine is also an effective treatment for rosacea-associated ocular complications. Periocular steroids may be considered if the patient is on the verge of a keratitis flare; this panel recommends difluprednate in those instances. IPL is also effective in rosacea-associated meibomian gland dysfunction. Because it is more targeted than oral or topical products, this panel recommends use of IPL for the treatment of ocular rosacea. This panel recommends only short-term use of corticosteroids.

Rituximab (Rituxan, Genentech) has also been used successfully for treating severe scleritis and PUK associated with not only RA, but Sjogren syndrome and in cases resistant to Wegener granulomatosis treated with antitumor necrosis factor.

Repository corticotropin injection (RCI; H.P. Acthar Gel, Mallinckrodt) is biologically derived and includes a 1-39 peptide chain. Among its 19 approved indications is the treatment of severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa (including keratitis). Of note, H.P. Acthar Gel is also approved as an adjunct therapy for short-term administration in select cases of RA.

When choosing a systemic steroid treatment, this panel advocates a maximum prednisone dosage of 1 mg/kg/day, and to consider the side effect profile of endogenous versus synthetic steroids. Systemic steroids should be used as induction agents only. RCI has a preferable side effect profile, but optimal dosing and treatment duration have yet to be established.

Immunosuppressive agents and/or TNF-blockers are often used to treat autoimmune disorders; these may include adalimumab (Humira, AbbVie), etanercept (Enbrel, Amgen), hydroxychloroquine (Plaquinil, Sanofi-Aventis), or infliximab (Remicade, Janssen Immunology). Antimetabolite therapy may include agents such as methotrexate, mycophenolate, or azathioprine. It is common for these agents to be administered by nonophthalmic health care providers.

Because of its safety profile, this panel recommends the use of RCI in lieu of methotrexate.

**PUK**

If there is an infective cause or secondary infection, treating the infection must take precedence over addressing the noninfectious components.

First-line treatment of PUK during acute phases is primarily systemic corticosteroids, but immunosuppressive and cytotoxic agents are required for treatment of PUK associated with multisystem disorders. PUK is often contiguous with adjacent conjunctival, episcleral, and scleral inflammation, but this adjacent tissue can sometimes aggravate the course of PUK and cause serious corneal complications. Necrotizing scleritis is often present in the region adjacent to PUK when autoimmune disorders are present.
Aggressive systemic treatment is often warranted in cases of collagen vascular disease-related PUK to delay the progression of corneal destruction. In cases where disease-modifying antirheumatic drugs, biologic therapy, or high-dose systemic corticosteroids are unsuccessful, rituximab has been used with some success.

A recent study in the United Kingdom evaluated PUK and corneal melt over a 10-year single center review and found all patients had initially been prescribed systemic corticosteroids, and all but two of the 70 were treated with steroid-sparing immunosuppressive agents as well. Among the medications prescribed were prednisolone, methotrexate, mycophenolate, tacrolimus, and azathioprine.

Necrotizing PUK may occur in the absence of raised inflammatory markers of RA.

Rescue therapy and pulsed intravenous glucocorticoid therapy, followed by high-dose oral glucocorticoids in conjunction with steroid-sparing antiproliferative agents (eg, mycophenolate mofetil, methotrexate, and azathioprine) or T-cell inhibitors (eg, cyclosporine, tacrolimus), if the patient is not already on disease-modifying antirheumatic drugs (DMARDs) are necessary to rapidly control inflammation. Severely active necrotizing disease associated with scleritis warrants the use of pulsed oral or pulsed intravenous cyclophosphamide therapy.

The literature also notes treatment with alkylating agents such as chlorambucil and cyclophosphamide may be effective, with cyclophosphamide more commonly used in the treatment of PUK, when PUK is associated with a connective tissue disorder.

Filamentary Keratitis

Patient presentation often includes complaints of foreign body sensation or photophobia, but may also have redness, epiphora, or blepharospasm. Filamentary keratitis is associated with dry eyes, superficial punctate keratopathy, ptosis, and tear film stasis. Pronkin et al found nearly 90% of patients with filamentary keratitis had endocrine pathology, rheumatoid disease, or a combination of both, leading them to suggest this disorder is not a form of severe dry eye but a separate dystrophic corneal disorder with dry eye as its symptom. Indeed, several conditions are associated with filamentary keratitis, including aqueous tear deficiency and exposure syndromes, occlusion syndromes, postsurgical syndromes, manifestations of systemic and autoimmune disorder; certain medications have been associated with this type of keratitis as well.

Acute presentations can resolve spontaneously, but often the disease is chronic, and initial treatment will depend on the underlying etiology. Initial treatment is topical tear film substitutes, but other medical treatments include topical cyclosporine, oral tetracycline derivatives, omega-3 fatty acid supplementation, topical azithromycin, and lid hygiene. Other potential treatments include N-acetylcysteine and bandage contact lenses (BCL). N-acetylcysteine, however, is not available commercially and without a preservative-free formulation, may only be minimally useful. BCLs have shown success when other ocular lubrication treatments have failed. Targeting the inflammation with short bursts of topical methylprednisolone has been successful, as has treatment with topical nonsteroidal antiinflammatory drugs but the latter can be toxic to damaged epithelium.

Neurotrophic Keratitis

Trigeminal nerve damage may cause neurotrophic keratitis (also referred to as neurotrophic keratopathy), and can results from a variety of entities that impair corneal innervation, with treatment based on disease severity. All stages of the disease cause some vision loss and profound vision loss can occur if left untreated (Figure 2).

In Europe, extracellular matrix regenerators (RGTA; Cacicol, Thea) are becoming an efficient and accessible therapy for neurotrophic keratitis. These heparin sulfate analogs have been to protect and stabilize the action of growth factors and case studies in patients with neurotrophic keratitis resistant to conventional therapies reported positive results after treatment with the matrix therapy. Nexagon, a 30-base antisense oligomer (Eyevance Pharmaceuticals), may have potential in the treatment of persistent corneal epithelial defects, but
more data is needed before this panel can endorse the treatment. Nexagon is a first-in-class unmodified antisense oligodeoxynucleotide that inhibits a cell membrane hemichannel forming protein, connexin (Cx43). Nexagon inhibits Cx42 overexpression and the inflammatory cascade to reestablish limbal microvasculature and promote regeneration of the corneal epithelium.

More recently, recombinant human nerve growth factor (cenegermin, Dompe) was recently approved in Europe after several studies found it improved corneal sensitivity and promoted corneal epithelial healing in moderate and severe neurotrophic keratitis. The US Food and Drug Administration approved the drug in August 2018, making it the first commercially available drug with this indication in the United States.

There is some suggestion in the literature that platelet-rich plasma (PRP) may be beneficial in neurotrophic keratitis. Alio et al enrolled 44 eyes (28 patients) with dormant corneal ulcers secondary to corneal surgery and treated them with autologous PRP during the course of 6 weeks. Of the eyes, 28 (65.1%) improved VA by at least 1 Snellen line, while just below 60% had a decrease in ulcer size or even a total closure. Sanchez-Avila et al also found plasma rich in growth factors (PRGF) to be a potentially safe and effective treatment option for patients with stages 2 to 3 of neurotrophic keratitis. Guadilla et al published earlier that PRGF may be more effective than 20% autologous serum in patients with lower grade neurotrophic keratitis, and suggested PRGF may have a greater effect on cell proliferation.

In this panel, experience with using PRGF is limited, but encouraging responses have been seen with PRP for the treatment of neurotrophic keratitis.

Autologous serum for the treatment of persistent epithelial defects has shown promise as well, with a cure rate of 43.8% within 2 weeks and 62.5% within 1 month. A more recent review showed amniotic membrane to be a superior treatment than autologous serum or artificial tears in corneal epithelial wound healing.

CONCLUSION

The treatment of noninfectious keratitis is as varied as its causes. In general, artificial tears and antiinflammatory agents may be sufficient for mild cases. For moderate to severe cases, however, topical steroids, steroid-sparing agents, immunosuppressive agents, and/or amniotic membrane transplantation may be warranted. In cases of autoimmune disorders, comanagement with a rheumatologist is recommended, as treatment may include the use of biologics.

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