Supplement to

How Does It Happen—and How Can It Be Stopped? Experts Explain the Science and Practice of Anti-Inflammatories.

Also—Kids Aren’t Short Adults: Tips for Fitting Young Contact Lens Wearers
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By Jeffrey J. Walline, OD

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**Osmolarity Levels in Eye Drops Documented**

Variations in the osmolarity of topical eye drops may influence clinical performance, and this trait warrants greater attention, reports a study published in the May 2015 *Cornea*. Documenting a range of hypo- and hyperosmolarity levels in 87 prescription and OTC drops, the researchers call the effort “a first step in understanding the influence of osmolarity of ophthalmic formulations on the ocular surface.” Hyperosmolar eye drops could have therapeutic efficacy in treating corneal edema, they note.

Researchers in Germany evaluated the impact of hyposmotic and hyperosmotic conditions on ex vivo corneal thickness and integrity (specifically, glucose and lactate levels) in a rabbit model of induced corneal edema by filling the anterior chamber with a hyposmolar solution. After 48 hours, two hyperosmolar solutions—Omnisorb (preserved with BAK) and Ocusaline (preservative-free)—were topically applied every 15 minutes over the course of one hour.

Both “significantly reduced corneal swelling” on OCT, the authors found. Omnisorb reduced corneal thickness by 279µm vs. 258µm for Ocusaline. The authors say that this suggests eye drops containing preservatives may be more beneficial than preservative-free solutions in some cases, at least initially. There was no significant difference in treatment effect at 72 hours.

In the second part of the study, researchers categorized the osmolarity of 87 commercially available eye drops using freezing point osmometry. Forty-three showed an osmolarity value below a physiological tear osmolarity value of 289mOsm/L, while the other 44 demonstrated a higher osmolarity value. Overall, however, the majority of the products fell within a limited range around isosmolarity, suggesting further experiments with application on a corneal model are necessary.

Regardless, “it is important to keep in mind that the osmolarity of eye drops is not an isolated factor; instead, osmolarity is relevant concerning various product ingredients,” the researchers say. “Another factor is the viscosity of eye drops that prolongs their retention time on the ocular surface. This might alter the osmotic effects of eye drops as well.”

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**IN BRIEF**

- Patients with floppy lid syndrome (FES) may have structural changes that could signal risk for glaucoma development, says a study in the May 2015 *Cornea*. Researchers in Spain performed a corneal biomechanical evaluation on 208 eyes—72 with FES and 136 without FES—of 107 patients, measuring corneal hysteresis (CH), corneal resistance factor (CRF), central corneal thickness (CCT), Goldmann-correlated intraocular pressure (IOPg) and corneal-compensated intraocular pressure (IOPct). Noncontact IOP and all corneal biomechanical properties were measured using the Ocular Response Analyzer (Reichert). Mean CH was significantly lower in patients with FES compared with those without FES (i.e., 9.51 ± 1.56 vs. 11.66 ± 9.11), which may “constitute a risk factor due to an association with the response of the corneoscleral shell and the ocular vasculature to IOP-induced stress,” say the researchers.

- Interestingly, mean CH remained statistically significant after adjusting for age and apnea-hypopnea index, but mean CRF and mean IOPct did not. There was no statistically significant difference in Goldmann-correlated IOP and CCT.

- **Hybrid contact lenses with tear vaults of more than 100µm may be detrimental to corneal health because of inadequate surface oxygen supply,** reports a study in the March 2015 *Eye & Contact Lens*! Silt lamp and OCT evaluations and fitting hybrids with the manufacturers’ recommended tear vault of 100µm or less resulted in acceptable corneal surface oxygen values, around 100µm Hg, while vaults greater than 100µm created less ideal corneal surface pO₂, as low as 0mm Hg.

- The researchers had hoped to find an acceptable way to calculate corneal surface pO₂ under a hybrid lens, but inconsistent results between the silt lamp and OCT limited reliability. Despite the study’s limitations, it highlights the need for a better clinical method for measuring corneal surface pO₂, similar to methods used for soft, silicone hydrogel and rigid contact lenses. Such testing would help clinicians better fit hybrids. Until then, the researchers advise fitting hybrid contact lenses with modest vaults to provide adequate oxygen supply.

- **Multifocal Halo Reduction Possible?** A new lens surface modification that smooths out surface discontinuities could reduce the halo effect commonly experienced by patients with multifocal intraocular or contact lenses, reports a study in the December 2014 *Optics Communications*. Coauthor Zeev Zalevsky, PhD, of Israel’s Bar-Ilan University says “the proposed surfacing technique can be very important in significantly improving [vision], especially the night vision performance of any IOL for presbyopia correction,” noting that it could in theory be added to any multifocal lens.
Even Good Compliance May Not Eradicate Fungi

Fungal contamination of contact lens cases can occur despite patient compliance with proper lens handling, cleaning and replacement instructions, reports a study in the March 2015 Eye & Contact Lens.1 Researchers in Greece collected 216 samples of contact lens solution from 117 lens cases of asymptomatic lens wearers; 194 were collected from two-cup storage cases (TCSC) filled with non-hydrogen peroxide-containing solutions, four from TCSCs with a hydrogen peroxide solution and 36 from single-cup storage cases (SCSC) containing hydrogen peroxide solutions. All subjects were using monthly disposable hydrogel, low water content soft lenses on a daily wear basis and were required to comply with lens cleaning, handling and replacement instructions given by the manufacturer or attending optometrist in order to participate in the study.

After culturing the collected lens solution samples, researchers identified the presence of fungi from 15 cultures obtained from 12 storage cases. Seven molds (one *Fusarium solani*, four *Aspergillus niger* and two *Aspergillus fumigatus*), seven yeasts (five *Candida parapsilosis*, one *Candida tropicalis* and one *Rhodotorula rubra*) and one a mold in combination with a yeast (*F. solani with Candida guilliermondii*) were discovered. Interestingly, the peroxide group had a higher rate of fungal isolation compared with the multipurpose solution group, likely due to quick neutralization, selection of naturally resistant microbes adapted to survive repeated peroxide use and biofilm release of catalase that neutralizes peroxide. These results are concerning, say the researchers, because “even when contact lens users report compliance with instructions of contact lens handling cleaning and replacement, it is still possible to have microbial contamination of the stock solutions that may lead to corneal infection.” They say that further improvement of contact lens disinfectant solutions and lens hygiene education is needed.

Another study suggests topical amphotericin B (AMB) and natamycin may be particularly effective against certain fungi—specifically, the *Candida* species.2 Researchers exposed samples of 68 *Candida* isolates (37 *albicans* and 31 *non-albicans*) to AMB 0.2%, natamycin 5%, voriconazole 1% and fluconazole 0.2%, examined for growth after 48 hours and found 100% of the *Candida* isolate samples mixed with AMB 0.2% and natamycin 5% demonstrated growth inhibition, suggesting that both AMB and natamycin 5% demonstrated growth inhibition, suggesting that both AMB and natamycin have been shown in this study to be more effective than the other agents tested.3,4

Is Google Making Us Stupid?

The ubiquity of information online is both a blessing and a curse. How much knowledge is too much?

Not long ago, a colleague of mine mentioned an article she had read in *The Atlantic*, published in 2008 but perhaps even more relevant today. The title—“Is Google Making Us Stupid?”—lured me in; ironically, I used Google to find it. From the long list of comments other readers had posted, I surmised it had made them look at how the online search engine impacts their daily lives. The perceived omniscience of Google absolves us of the need to contemplate, discuss and learn. All answers are just a click away. And it also made me think: how often do our patients question our recommendations or even our diagnosis after consulting Google?

The torrent of online data that flows through our days also affects the ways in which we interact with it, argues Nicholas Carr, author of *The University of Google*, published in 2008 but perhaps even more relevant today. The title—“Is Google Making Us Stupid?”—lured me in; ironically, I used Google to find it. From the long list of comments other readers had posted, I surmised it had made them look at how the online search engine impacts their daily lives. The perceived omniscience of Google absolves us of the need to contemplate, discuss and learn. All answers are just a click away. And it also made me think: how often do our patients question our recommendations or even our diagnosis after consulting Google?

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“Over the past few years, I’ve had an uncomfortable sense that someone or something has been tinkering with my brain, remapping the neural circuitry, reprogramming the memory … I’m not thinking the way I used to think,” he writes. “Now my concentration often starts to drift after two or three pages. I get fidgety, lose the thread, start looking for something else to do. I feel as if I’m dragging my wayward brain back to the text.”

Carr suggests that his inability to focus may be the result of acclimating to the fast pace at which information streams across his computer screen. Reading online blogs, news headlines or email requires less concentration than reading a full-length novel. On the computer, as soon as my interest wanes, I simply click a new link and I’m on to something else.

There have been numerous books, studies and articles written on this phenomenon, including (ironically) by Google—the company claims it would like to turn its search engine into a form of artificial intelligence that would know exactly what the user wants, before the user does (Google Now is already laying the groundwork). It’s little wonder then, as we use the so-called information highway to educate ourselves and communicate, that we become less and less accustomed to pondering, analyzing and connecting pieces of information as we used to do when we read them on pages in a book. Bruce Friedman, a pathologist from University of Michigan Medical School describes his online reading habits as being “staccato,” in that he rapidly glances through small sections of text from multiple sources. “I can’t read *War and Peace* anymore,” he told Carr in a telephone interview. “Even a blog post of three or four paragraphs is too much to absorb.”

Tara Brabazon, in her book *The University of Google*, describes the challenges of teaching her university students who seem to have lost the ability to think deeply. She claims that online lectures entice students to merely download and read them, rather than attending lectures in person. By doing this, she argues, something is lost when the face-to-face contact ceases.

**COMPETING WITH GOOGLE**

So, how does this affect us as health care professionals? Well, your patients are almost certainly “Googling” information about their disease. Are they self-diagnosing based on descriptions from the Internet? Likely. Are you growing impatient when having to slow down to explain something and undo incorrect assumptions again? Undoubtedly.

These and others are challenges we all face as technology changes. This is not to say that the Internet is evil; our lives are certainly richer because of the instant access to information. But let’s slow down and remember that more often than not humans still prefer face-to-face contact. Your patients will thank you when you look them in the eye, patiently instruct them with hands-on methods and answer questions. Everyone likes to know that they are valued and worthy of your care and concern. So, if you have managed to read to the end of this editorial, let me know your thoughts. But don’t email or text me—pick up the phone and let’s chat.

And the next time one of your patients comes in armed with reams of downloaded information from the “University of Google” that might be contrary to your advice, just carefully listen and smile, as only another person can. Besides, we all know it’s probably just making them stupid! 

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A Different Kind of Colored Lens

Some medications can alter the ocular surface environment—and anything therein.

Roughly three million people over the age of 50 in the United States wear contact lenses. This is also the age when routine medication use becomes a way of life for many patients. So, how do systemic and topical drugs alter the ocular surface environment and the contact lens wearing experience?

CHEMICAL COMPLICATIONS

Silicone hydrogel lenses are known to interact stronger with lipids but weaker with proteins compared to conventional hydrogel lenses. Within this lens class, however, there are differences in the absorption and release rates of biocidal compounds.

Lens characteristics that affect drug absorption of a given molecular compound include water content, pore size, hydrophobicity and ionic charge. For example, hypertonic solutions such as sodium sulfacetamide 10% or pilocarpine 8% can cause loss of lens water content and alteration of the lens curvature. Application of topical medications with an acidic pH can lead to lens dehydration and steepening, while use of alkaline medications can cause hydration and flattening. Topical suspensions may also cause lens intolerance due to a particulate aggregate; this has been observed with drugs containing salicylates, which are secreted into the tear film and can cause ocular irritation. The release of various agents cannot always be predicted.

Next, perform an examination with the lenses in place and look for evidence of steepening or flattening. Consider your findings in the context of the patient’s medication profile and use this data to coordinate treatment regimens with the patient’s other—if any—health care providers.

Use of alkaline medications can cause dehydration and steepening, while use of alkaline medications can cause hydration and flattening. Topical suspensions may also cause lens intolerance due to a particulate aggregate; this has been observed with drugs containing salicylates, which are secreted into the tear film and can cause ocular irritation. The release of various agents cannot always be predicted. The撕

Table 1. Chemicals That Cause Color Changes in Hydrogel and Silicone Lenses

<table>
<thead>
<tr>
<th>Color</th>
<th>Chemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow</td>
<td>• Phenolphthalein (found in some laxatives)</td>
</tr>
<tr>
<td></td>
<td>• Fluorescein</td>
</tr>
<tr>
<td></td>
<td>• Chlorhexidine</td>
</tr>
<tr>
<td>Brown</td>
<td>• Sulfasalazine (for inflammatory bowel disease)</td>
</tr>
<tr>
<td></td>
<td>• Nicotin</td>
</tr>
<tr>
<td>Grayish-Brown</td>
<td>• Topical epinephrine and phenylephrine</td>
</tr>
<tr>
<td></td>
<td>• Oral dopamine</td>
</tr>
<tr>
<td></td>
<td>• Tetracycline</td>
</tr>
<tr>
<td>Orange</td>
<td>• Oral nitrofurantoin</td>
</tr>
<tr>
<td></td>
<td>• Phenazopyridine (for urinary tract infections)</td>
</tr>
<tr>
<td></td>
<td>• Rifampin (for tuberculosis and meningococcal disease)</td>
</tr>
<tr>
<td>Pink</td>
<td>• Hydrogen peroxide (pharmacy-grade)</td>
</tr>
<tr>
<td>Green</td>
<td>• Beta-blockers (systemic; long-term use)</td>
</tr>
</tbody>
</table>

SPECIAL DELIVERY

Interestingly, soft contact lenses are being investigated as a vehicle for topical delivery of certain drugs, including fluoroquinolones, cobrotoxins, ketosteroids, ketocarol, cyclosporine, dexamethasone, epidermal growth factor, timolol and natamycin.

In one study evaluating the use of extended antibiotic-releasing lenses to treat ocular infections, researchers injected a methicillin-resistant strain of Staphylococcus aureus into the anterior chamber of rabbits to model bacterial endophthalmitis. Treatment with a topical fluoroquinolone reduced the bacterial load from 100,000 in the untreated group to 10,000; in comparison, immediate treatment with experimental rifampicin-releasing lenses prevented growth of microorganisms, thus providing an effective potential treatment for perioperative or trauma-related infection. Who wear soft contact lenses, daily disposable lenses may be the best option, rather than trying to purge drugs by soaking lenses overnight in a contact lens solution. Gas permeable lenses typically will not have the same absorptive rate as hydrogel and silicone lenses. Keep in mind, however, that each material is different, so the adsorption of drugs cannot always be predicted.

Cyclosporine—Not Just for Dry Eye?

Literature suggests this immunosuppressant may be suited to treat more conditions than you might think.

Cyclosporine, a non-steroidal immunomodulator that acts primarily by inhibiting T-cell proliferation, is well known to all eye care practitioners. Formulated as an emulsion in a concentration of 0.05%, this drug is FDA-approved to increase tear production in patients for whom it is suppressed, presumably due to ocular inflammation associated with dry eye syndrome.1

As the theme of this month’s edition focuses on anti-inflammatory pharmaceuticals, let’s discuss some nontraditional uses of cyclosporine and the use of medications off-label.

WHAT IS “OFF-LABEL”?

Before discussing the meaning of “off-label,” we must first define the term “on-label.” It describes a specific use for which a drug has satisfied safety and efficacy tests and received FDA approval. It is expensive and time-consuming for pharmaceutical companies to obtain multiple on-label drug indications; trials can take seven to 10 years and cost millions of dollars. Additionally, once a drug becomes generic, motivation to obtain other on-label indications decreases even further.

Once a drug is FDA-approved, physicians often prescribe it for conditions, population segments or doses other than what it was approved for—all of which constitute “off-label” use.2 For example, 75% of prescription drugs have no indications for children, so off-label use is often necessary. Pregnant women and nursing mothers are also often not included in drug studies.

Off-label use is generally legal; the FDA even states, “Once a [pharmaceutical] product has been approved for marketing, a physician may prescribe it for uses in treatment regimes of patient populations that are not included in the approved labeling.”3 However, practitioners should inform themselves about the drug prior to prescribing. The acid test is whether the use meets the “standard of practice” among eye care practitioners.4 In any case, regulations prevent manufacturers from endorsing the off-label use.

KERATOCONUS

Elevated levels of proinflammatory cytokines and matrix metalloproteinases (MMPs) have been shown to be present in the tears of patients with keratoconus. Corneal epithelial cells of keratoconic patients also demonstrate upregulation of some of these cytokines.5,6

In one study, keratoconus patients were separated into a control group and study group treated with cyclosporine 0.05% twice a day for six months. Researchers found MMP-9 levels, which had been significantly elevated at baseline, were reduced to levels comparable to the negative controls at the end of the study. Interestingly, some patients who received cyclosporine showed corneal topographic changes, including focal flattening of corneal curvature, after six months’ use. Others did not manifest these changes, but also didn’t show evidence of disease progression. Researchers concluded that cyclosporine may be an effective treatment strategy for patients with keratoconus.7

CONJUNCTIVOCHALASIS

This condition manifests as loose, redundant, nonedematous bulbar conjunctival tissue; the presentation is typically bilateral and usually inferior. It may also occur nasally and centrally, but is usually noted temporally. The mechanism of onset is thought to be thinning or loss of Tenon’s capsule. Risk factors include dry eye and a history of ocular surgery. Patients with this condition often present with focal pain in the affected area that is exacerbated with eye movement or lid closure. This pain can often be reproduced by applying pressure to the eyelid using a finger. The patient should then be directed to look up and down.

Conjunctivochalasis often needs to be differentiated from dry eye.8 Two recent epidemiological studies in Chinese populations reported prevalence rates of 44% and more than 98%, respectively, in patients older than the age of 60.9,10 Despite the large discrepancy in these findings, conjunctivochalasis is common in the elderly. A separate Chinese study evaluated the impact this condition has on vision-related quality of life using several standardized questionnaires. Patients with conjunctivochalasis had a more significant decrease in tear film stability compared to those with dry eye.11 Tear MMP-9 levels are elevated in patients with conjunctivochalasis, and surgical intervention decreases inflammation.9 Others have proposed that the degeneration of the elastic fibers might be worsened by the presence of pro-inflammatory cytokines such as IL-1β, TNF-α,
Conjunctivochalasis may respond to topical cyclosporine.

IL-1 and IL-6.12,13 Because of the presence of these inflammatory components, conservative treatment of conjunctivochalasis should include pharmacologic intervention. In particular, cyclosporine may be useful because of its inhibitory effect on these proinflammatory cytokines. Topical steroids and NSAIDs have also been advocated. If meds prove ineffective, surgical approaches also exist for managing this condition when moderate to severe.8

ADENOVIRAL CONJUNCTIVITIS

Adenoviral conjunctivitis is a common and highly contagious infection. Following a two-to-day to 14-day incubation period, initial signs include conjunctival hyperemia and edema. Keratitis may develop and, after a period of two weeks in some cases, subepithelial infiltrates (SEIs) may appear. These infiltrates may affect vision clarity, as they often appear centrally. Histologically, SEIs are composed of lymphocytes, histiocytes and fibroblasts, which may also disrupt collagen within Bowman’s layer. These SEIs may persist for months, or even as long as a year.14

Three studies demonstrate that cyclosporine is an effective treatment for SEIs associated with adenoviral conjunctivitis.15,16 Two of the studies evaluated a concentration of 1%, which is stronger than what is commercially available in the United States; however, this concentration could be prepared by a compounding pharmacy. Despite this wrinkle, the findings from these studies do warrant consideration of cyclosporine for treating SEIs.

Note, there have been concerns about the possibility of promoting increased viral shedding due to the use of cyclosporine, but by the time the SEIs appear, viral shedding has often ceased, so benefits ultimately appear to outweigh the risks.18

OTHER POTENTIAL USES

In a small study (n=12), patients with chronic, recalcitrant follicular conjunctivitis were treated with cyclosporine 1%. Researchers observed a reduction in inflammation after one month of use; however, because of the small sample size, further investigation is warranted.19

Another small pilot study (n=20) evaluated cyclosporine 0.05% when administered to patients with ocular prosthetics twice a day for three months. All patients reported marked improvement in their symptoms after one month, and Schirmer tear test objectively improved at the three-month follow-up.20

In conclusion, using the literature to help guide the use of cyclosporine for off-label indications can provide an additional approach to managing inflammation with a safe nonsteroidal alternate.21

1. US FDA. Restasis Highlights of Prescribing Information. Available at: www.accessdata.fda.gov/ community/docs/label/2013/050790s021lbl.pdf.
While a complex, remarkable system with a tough line of defense, the cornea sometimes needs a little help from practitioners.

By Bhawanjot Minhas, OD

The body’s efforts to regulate the immune status of the ocular surface, in particular the cornea, present a unique challenge not found in other tissues. Maintenance of corneal transparency must counterbalance preservation of corneal integrity. Defense against microbial, inflammatory and physical assault, including that which results from contact lens wear, is limited by the deleterious effects inflammatory events may have on the vulnerable structures of the eye. A highly ordered extracellular matrix of collagen and proteoglycans free of vasculature and extraneous cells accomplishes maximal light transmission, and consequently visual function. Changes to this complex structure can irreversibly harm the function of the cornea as a primary refractive surface and structural barrier of the eye.

For clinicians who routinely see cases of corneal inflammation and would like to better understand the complex processes responsible and how to tailor treatment most appropriately, a refresher on the principles of corneal immunology can be enlightening—as well as one more reminder of the elegance of the eye’s robust capabilities to defend and heal itself.

INNATE MECHANISMS

The anatomy of the cornea consists of five well-known layers: the epithelium, Bowman’s layer, stroma, Descemet’s membrane and endothelium. The cornea is essentially a thick layer of transparent connective tissue lined with a single layer of endothelial cells on one side and a four-to-six-layer-thick stratified, nonkeratinized squamous epithelium on its outer border. The corneal epithelium and associated intercellular junctional complexes provide an important first-line innate defense. Gap junctions allow intercellular communication, while tight junctions and adherens junctions maintain a vital epithelial barrier from the external environment, forcing material to go through the cells rather than between them.2

Ocular defensive mechanisms are comprised of both innate and adaptive immune responses, which, while considered separate entities, are not mutually exclusive.3 The innate defenses of the cornea include: tears, epithelial cells, keratocytes, corneal nerves, complement components, neutrophils, eosinophils, macrophages and natural killer cells. Tears are the first part of this nonspecific surveillance system that an antigen may encounter.

In addition to preventing corneal desiccation, the tears flush foreign matter from the ocular surface and contain antimicrobial proteins and immunoglobulins. Three antimicrobial proteins exist in the tears: lactoferrin binds iron, lysozyme destroys bacterial cell walls and tear-specific prealbumin (lipocalin) acts as a bacterial product scavenger.4

Corneal epithelial cells are capable of secreting cytokines to activate immune defense against microbial invasion. One such product is the cytokine interleukin (IL-1α), which is stored and released by epithelial cells in response to cell membrane damage.3 Consequently, keratocytes can also secrete IL-1α; however, only epithelial cells can secrete a natural antagonist of immune activity, IL-1α receptor (IL-1RII).6 This instance outlines perfectly the corneal balance of secreting inflammatory mediators that cause immune invasion and neovascularization (IL-1α) vs. a mechanism to modulate these effects (IL-1RII) by...
suppressing leukocyte infiltration and potential destruction.7

Part of the cornea’s strategy to stay clear and act as an adequate refractive surface is to be void of inessential cells. Keratocytes are flattened fibroblasts found in the stroma that are active in synthesizing stromal collagen and proteoglycans of the ground substance.8 Keratocytes can synthesize IL-6 and defensins under the influence of IL-1α and tumor necrosis factor (TNF)-α, which is secreted by natural killer (NK) cells.9,10 IL-6 is produced by Th2-lymphocytes, monocytes, macrophages and dendritic cells. It enhances proliferation of B- and T-lymphocytes via the route of MIP-1α and MIP-2.11,12 Defensins have broad-spectrum antimicrobial activity against bacteria, fungi and viruses, can accelerate epithelial healing, and are chemotactic for T-lymphocytes and numerous granulocytes.12

Although free of blood vessels, the cornea has a well-developed innervation. Corneal nerves not only relay sensory information from the cornea to cause reflexive and protective movements of the eye, but also cause release of neuropeptides that induce cytokine activity.13,14 Neuropeptides, substance P and calcitonin gene-related peptide are released in response to pain by termini of corneal sensory neurons and induce IL-8 synthesis, leading to neutrophil recruitment.13,14

The complement system consists of the classical, lectin and alternate pathways. All complement components are more concentrated in the peripheral cornea rather than the central cornea. This discrepancy is likely caused by easy diffusion of complement components from the conjunctival limbal vessels to peripheral cornea, as opposed to the avascular central cornea.15

Cells of the innate system consist of neutrophils, eosinophils, macrophages and NK cells. These cells are extremely important in protecting the cornea from invasion by microorganisms and are recruited in response to foreign antigens; however, if left unchecked, they can affect normal function of the corneal epithelial cells, keratocytes and endothelial cells.16 This excessive inflammatory response, which is attributed to neutrophils for the most part but also macrophages to a lesser extent, can lead to loss of corneal integrity and clarity.16 The severity of the inflammation depends on the type and duration of the trauma and microbial products.

Neutrophils are found near limbal vasculature, while macrophages reside in the conjunctiva and in murine corneal stroma.17 Although eosinophils are not normally present in the conjunctiva, they are over-expressed in chronic ocular allergies, paraneoplastic syndromes and parasitic infections.18,19 NK cells are part of the lymphocyte lineage, which include B- and T-lymphocytes, but are a part of the innate immune response.7

**ADAPTIVE MECHANISMS**

Cell-mediated immunity, although critical in bringing pathogenic invaders under control, can be out of proportion to the antigen threat and can lead to irreversible tissue destruction and potential permanent vision loss. Much of the adaptive immune response in the cornea is due to Langerhans cells and cytokines. B- and T-lymphocytes, along with other antigen presenting cells, are present in normal human cornea in small numbers as part of adaptive immunity.12 Like other innate immunity cells, these are concentrated in the vascularized limbal region.13

Many studies focus on the role of corneal epithelial cells in responding to threat; however the existence of Langerhans-like dendritic cells in the cornea is important and should not be overlooked. Langerhans cells are often concentrated in the corneal periphery, but are expressed in higher density in the sub-basal nerve plexus of the epithelium in contact lens wearers as seen in vivo by a confocal microscope.20

This finding suggests that an increase in density of Langerhans’ cells occurs as a heightened immune status of the cornea in potential “high risk” corneas.20 Furthermore, research shows lateral movement of these cells increases from resting state during injury through time-lapse imaging.21 This lateral movement and recruitment of Langerhans cells to an otherwise quiet central cornea is inhibited by IL-1RII, which as described above is secreted by corneal epithelial cells to help maintain corneal clarity.22

Immature Langerhans cells capture antigens, while mature forms are able to activate native T-lymphocytes through major histocompatibility complex (MHC) molecules. Sentinel Langerhans cells are
resident antigen-presenting cells and are responsible for recognizing, processing and presenting antigens.\(^7,12\) Traditionally, Langerhans cells have been thought to have MHC class II antigens. However, recent studies show a class of MHC class II-negative cells in murine models.\(^23\)

Langerhans cells identify an antigen as non-self and migrate to a regional lymph node, process the antigen, transport and express it on their cell surface by MHC molecules.\(^12,24\) T-lymphocytes are activated by the antigen and mature into effector cells: either CD4+, if the MHC molecules presenting the antigen are class II, or CD8+, if the MHC is class I.\(^24\) These activated CD8+ cytotoxic cells directly kill the invading microorganism while the CD4+ helper cells secrete cytokines to recruit effector cells such as microphages.\(^12,24\)

**TOLL-LIKE RECEPTORS**
Toll-like receptors (TLRs) play a critical role in pathogen recognition. As such, they are the initial step in the inflammatory process and innate response. The TLR family is a class of membrane-spanning noncatalytic receptors that recognize a wide variety of exogenous and endogenous molecules, including protozoa, bacteria and viruses.\(^16,21\) More than 10 TLRs that can recognize pathogenic lipids, proteins or nucleic acids have been identified in humans.\(^21,25\) Of note: TLR4, the most complex member of the family, acts as a sensor for gram-negative bacteria by recognizing the lipid A part of lipopolysaccharide.\(^21,27\) TLRs are expressed in both non-immune (epithelial, endothelial cells) and immune cells (monocytes, antigen presenting cells, lymphocytes, mast cells, neutrophils, NK cells and eosinophils).\(^12,16,21,25\) Many of the TLRs have been recognized as responding to a particular ligand via the pathogen-associated molecular patterns (PAMPs). These are conserved structural moieties of the pathogen essential for its survival and are excellent markers for the innate immune system to recognize.\(^25\)

In keratitis, the role of toll-like receptors begins with the exposure of the PAMPs to their respective TLRs; the receptors activate intracellular signals via adaptor molecules, including myeloid differentiation factor 88 (MyD88) and TIR domain-containing adaptor inducing IFN-α (TRIF).\(^25\) The activation of these adaptor molecules initiates downstream signaling events that induce translocation of DNA binding proteins NFκB and IRF-3 and production of proinflammatory and chemotactic cytokines known as CXC chemokines. The CXC chemokines, namely IL-1α, IL-1β, TNF-α and IL-6, cause macrophage and neutrophil infiltration into the central cornea.\(^27\)

As expected, if this inflammatory response is severe, there is a serious loss of corneal clarity due to excessive edema. This potentiates for permanent vision loss as governed by the severity and duration of exposure to the PAMPs.

**LYMPHOID TISSUE**
No lymphoid cells reside in the central cornea. As such, the cornea relies heavily on the conjunctiva as a major support tissue for moisture, nutrition and defense. The conjunctiva is separated into six zones, starting from the lid margin: marginal, tarsal, orbital, fornical, bulbar and limbal.\(^26\)

The ocular surface is thought of as part of the mucosal immune system and consists of lymphoid tissue of the lacrimal gland, conjunctival-associated lymphoid tissue (CALT) and lacrimal drainage-associated lymphoid tissue (LDALT).\(^26\) Together, these are known as eye-associated lymphoid tissue (EALT), which encompasses lymphoid tissue continuous from the lacrimal gland, conjunctival zones and lacrimal drainage system. They are functionally connected by the flow of tears over these surfaces.\(^26\) Inflow and outflow occurs via specialized blood vessels and lymph vessels, respectively. Follicles in CALT and LDALT allow detection of surface antigens, which then recruit effector cells to the ocular surface.\(^26\)
The tarso-orbital topographical zone of EALT has proven to be extremely important in immunity of the cornea and corresponds to the position of the cornea during eye closure. Not only does it act as an “immunological windscreen-wiper” during blinking, but it also plays a role during sleep as an “immunological cushion” of the cornea in a compromised (closed-eye) state.

The immunosurveillance provided by the EALT is thought to correspond to afferent and efferent function. The afferent immunity occurs due to the direct contact of the EALT with the corneal surface. This suggests that EALT can assist in detection of corneal antigens and the appropriate immune response. Efferently, EALT can provide innate and specific antibacterial peptides, proteins and immunoglobulins, namely immunoglobulin A. IgA is not produced by the cornea but rather by the lacrimal gland and conjunctiva. This is particularly important in the closed eye model, where pro-inflammatory factors from neutrophils are upregulated to quell microbial growth during sleep.

MODULATED IMMUNITY
Maintaining corneal clarity is critical to visual function, but must not come at the expense of adequate defense of the ocular surface. As such, the main function of the innate and adaptive immune systems is to balance tolerance against numerous nonpathogenic antigens while still protecting the ocular surface from pathogenic substance. This equilibrium of local immune regulation to maintain corneal integrity is illustrated by the production of different types of effector T-lymphocytes (Th1- or Th2-type helper cells). A difference in corneal inflammation is seen in a contact lens-associated Pseudomonas aeruginosa infection, for example, where a Th1 predominant response causes more extreme damage than a Th2 response. This shows the difference that the severity of inflammation can have on corneal integrity and clarity. If the generation of immune tolerance is impaired in extreme inflammatory cases, uncontrolled antigen access, excessive cytokine release and deregulated lymph cell recruitment can lead to corneal infiltration, edema, severe destruction and permanent vision loss.

CORNEAL FIBROSIS
Transparency of the extracellular matrix (ECM) of the stroma is accomplished via specifically regulated collagen fibril size, growth and spacing. This precise size and spacing of collagen and proteoglycans is maintained by resident keratocytes. When an incidental trauma affects the stroma, keratocytes become hypercellular myofibroblasts that can progress to wound fibroblasts or myofibroblasts. Return to normal stromal structure vs. scar formation is dictated by which fibroblast predominates. Wound fibroblasts along with growth factors IGF-I and IGF-II are responsible for well-organized ECM, which allows the cornea to return to transparency. On the other hand, myofibroblasts and transforming growth factor (TGF-α) cause the formation of a scar. This fibroblast differentiation is mediated by cytokines released during the inflammatory response.

CONTACT LENSES STRESS
Contact lens wear can cause numerous physiological changes in the cornea; however, the biggest hindrance to corneal clarity comes in the form of stromal edema. Oxygen can only diffuse through the material of a lens or dissolve in the tears and pass around the edges to the post-lens space. As a result of this, hypoxic corneal swelling in contact lens wears is mainly governed by oxygen transmission (Dk/t).

An important consequence of hypoxia is the production of lactate due to an increase in anaerobic glycolysis by the cornea in a decreased oxygen state. Accumulating negatively charged lactic acid alters the osmotic gradient; endothelial pumps cannot maintain a water gradient from the cornea to the anterior chamber, which creates stromal swelling. Anything that interferes with pH can also be a confounding factor. Built-up lactate or contact lens wear can cause an increase in carbon dioxide, which can interfere with the carbonic anhydrase function of the endothelial pump. Furthermore, blebs may form on the endothelium...
to 30 minutes after a contact lens is placed on the eye.20,21 These are postulated to occur due to corneal acidosis and hypoxia and affect endothelial pumps.22

Contact lenses can trigger and change the immune response of the ocular surface. Studies show that exposure of epithelial cells to contact lenses in vitro blocks the upregulation of defensins in response to P. aeruginosa, leading to increased susceptibility to the microbe.23 Other studies with confocal microscopes indicate specific changes to the anterior eye in vivo. One such change involves mucin balls, which are seen often in silicone hydrogel cases and have been shown to penetrate the full thickness of the epithelium.24 This can cause activation of keratocytes in the underlying stromal layer and possibly predispose the cornea to infection.25 Keratocyte apoptosis has been noted, which explains contact lens-induced stromal thinning. Mechanical stimulation by the lens itself can cause inflammatory mediators to be released.26 Finally, an increase in leukocyte rolling, a hallmark of inflammation, is seen in limbal vessels in response to low Dk/t lenses, indicating higher susceptibility.27

With constant exposure to both pathogenic and non-pathogenic organisms, the ocular defense system has no other choice but to sustain an elaborate mechanism for protection. Although often overlooked, this delicate balance of modulate immunity while maintaining corneal integrity is key to understanding pathologies that involve this unassumingly transparent yet elegant structure.28

20. Efroin N. Contact lens-induced changes in the anterior eye as observed in vivo with the confocal microscope. Progress in Retinal and Eye Research 26, 2007: 398-436.
1. Corneal properties to keep the visual axis clear include all of the following except:
   a. A lack of blood vasculature.
   b. Highly ordered matrix of collagen and proteoglycans.
   c. A wide variety and supply of extra cells for protection.
   d. Endothelial pumps to minimize corneal edema.

2. Lactoferrin is found in the tears and acts as an antimicrobial protein by:
   a. Binding iron.
   b. Acting as a scavenger for bacterial byproducts.
   c. Destroying bacterial cell walls.
   d. None of the above.

3. The balance between protecting corneal integrity and maintaining clarity is exemplified by the interaction between:
   a. MIP-1α and MIP-2.
   b. IL-1β and IL-8.
   c. TNF and IL-8.
   d. MyD88 and TRIF.

4. Toll-like receptors are expressed in:
   a. Neutrophils.
   b. Epithelial cells.
   c. Eosinophils.
   d. All of the above.

5. Which zone of eye-associated lymphoid tissue (EALT) has been shown to correspond to the position of the cornea during sleep?
   a. Tarsal.
   b. Orbital.
   c. Limbal.
   d. Both (a) and (b).

6. All of the following are involved in restoring corneal transparency following injury except:
   a. Myofibroblasts.
   b. IGF-I.
   c. Wound fibroblasts.
   d. IGF-II.

7. How long after insertion of a contact lens on the eye may blebs form?
   a. 1 hour.
   b. 4 days.
   c. 20 minutes.
   d. 1 week.

8. Substance P and calcitonin are released by corneal nerves in response to pain. They recruit neutrophils with the help of:
   a. IL-2.
   b. TNF-α.
   c. IL-8.
   d. MyD88.

9. In contact lens wearers, leukocyte rolling has been noted in response to:
   a. Large contact lens diameter.
   b. Steep base curve.
   c. Silicone hydrogel material.
   d. Low Dk/t.

10. Corneal stromal swelling and loss of endothelial pump function has been shown to be related to all of the following except:
    a. Contact lens wear.
    b. Presence of lysozyme.
    c. Changes in pH.
    d. Lactic acid build-up.
HOW ANTI-INFLAMMATORY AGENTS WORK

Inflammation—we’ve all seen this quintessential part of the body’s defense network in action, whether due to a serious infection or simply a stubbed toe. The inflammatory process is an immunovascular response involving immune cells, blood vessels and molecular mediators designed to first eliminate the initial cause of cell injury, then remove any necrotic cells or damaged tissues and initiate tissue repair. Its effectiveness requires a delicate balance: insufficient inflammation can lead to progressive tissue destruction by the harmful stimulus (e.g., bacteria) and compromise the survival of the organism, while chronic inflammation can result in loss of tissue function, chronic pain and scarring.

In effect, the concept of inflammation as both a normal, protective physiologic process and as a pathologic damaging process embodies what’s known as the Goldilocks principle: too little and too much are bad; it must be “just right.” So, how can we as eye care practitioners achieve this equilibrium in an environment as complex as the eye?

CORTICOSTEROIDS

Considered the “Swiss army knives” of inflammation control, corticosteroids act as palliative treatment for a host of inflammatory disorders (e.g., uveitis, episcleritis and scleritis) and adjunctive therapy for inflammation associated with injury and infection. Patients suffering from rheumatoid, arteritic, atopic and allergic diseases may also benefit from steroid therapy.

Two primary types of corticosteroids exist: ketones (prednisolone, dexamethasone, fluorometholone, medrysone and rimexolone) and esters (loteprednol). Ketone steroids depend upon liver metabolism to become inactive, while ester steroids do not; instead, they are inactivated locally by a single hydrolytic step. Hydrolysis, from Greek hydro- (“water”) and lysis (“separation”), means the cleavage of chemical bonds by the addition of water. Because the rapid cleavage of ester steroids produces inactive metabolites, these drugs are classified as “soft” steroids. Clinically, this results in a lower incidence of steroid glaucoma (10% less with use of loteprednol 0.5%) and a lower incidence of steroid cataract.

Ultimately, the therapeutic goal of corticosteroid use is resolution of the inflammatory response without any adverse ocular or systemic effects, steroid withdrawal symptoms or effect on normal production of endogenous glucocorticoids. As such, if the diagnosis, dosage or drug is incorrect, the use of these potent drugs can lead to consequences that can be both life- and sight-threatening.

Additionally, while topical steroids are effective to treat superficial or anterior segment inflammation, systemic treatment is necessary to treat diseases of the orbit or posterior segment, as well as arteritic conditions. Thus, as the optometrist’s prescriptive authority expands to include systemic drugs, one must understand both the physiology of the endogenous corticosteroids and pharmacology of their synthetic analogs in order to fully use these.

ABOUT THE AUTHOR

Dr. Onofrey is a clinical professor and executive director of continuing education programs at the University of Houston. He is also an internationally recognized lecturer on pharmaceutical agents and ocular disease management.
agents in a successful anti-inflammatory regimen. This understanding must then be applied when selecting the most effective product and dosing regimen to appropriately treat the patient’s condition. The optometrist should also be able to establish clinical monitoring parameters to identify adverse or toxic reactions and significant drug-to-drug interactions with respect to corticosteroid therapy.

- **Method of Action.** Corticosteroids work at all points of the immune system to inhibit humoral (i.e., antibody production) and cell-mediated (i.e., late-phase cellular response) immune responses, as well as the production of phospholipase A, which leads to a reduction in the body’s major inflammatory cytokines, prostaglandins and leukotrienes (Figure 1). For example, in rheumatoid arthritis, the body’s immune system produces an abnormal form of the IgM antibody via plasma cells that attack normal IgG antibodies. This process eventually results in the inflammatory tissue damage that we see in rheumatoid disease as well as in ocular conditions like uveitis, scleritis and episcleritis. Steroids inhibit plasma cell production of IgM, thus inhibiting inflammation. Additionally, leukotriene production can attract T-lymphocytes that are responsible, in part, for late-phase chronic inflammation, so reducing these cytokines can limit chronic inflammation.

When stress or other neural stimulation is placed on the hypothalamus, corticotropin-releasing factor (CRF) is released, which acts on the anterior pituitary gland to stimulate the release of adrenocorticotropic hormone (ACTH). ACTH then acts as an agonist on cells of the adrenal cortex, causing the production of the glucocorticoid cortisol. As blood cortisol levels rise, they inhibit production of CRF by the hypothalamus, thus inhibiting excessive cortisol production. This is called the negative feedback loop.

Both endogenous systemic cortisol and exogenously administered synthetic glucocorticoids will

---

**Table 1. Adverse Corticosteroid Effects**

<table>
<thead>
<tr>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Baldness</td>
</tr>
<tr>
<td>Truncal obesity</td>
</tr>
<tr>
<td>Impotence</td>
</tr>
<tr>
<td>Hump back</td>
</tr>
<tr>
<td>Amenorrhea</td>
</tr>
<tr>
<td>Moon face</td>
</tr>
<tr>
<td>Psychosis</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Acne</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Hirsutism</td>
</tr>
<tr>
<td>Dry, brittle hair</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Skin discoloration</td>
</tr>
</tbody>
</table>

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**Table 2. Relative Steroid Potency**

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Potency (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20 (equivalent to)</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>2</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
</tr>
</tbody>
</table>

---

**Fig. 1. The arachidonic cascade in inflammation.**

---

**Table 3. Phospholipid Membrane**

<table>
<thead>
<tr>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipase A</td>
</tr>
<tr>
<td>Prostaglandin H</td>
</tr>
<tr>
<td>Lipoxygenase</td>
</tr>
<tr>
<td>Leukotriene A</td>
</tr>
<tr>
<td>Thromboxanes</td>
</tr>
<tr>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Leukotriene B</td>
</tr>
<tr>
<td>Leukotriene C, D, E</td>
</tr>
</tbody>
</table>

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Phospholipid Membrane

NSAIDs

Cyclooxygenase

Arachidonic acid

Prostaglandin H

Thromboxanes

Leukotriene A

Leukotriene B

Leukotriene C, D, E
**HOW ANTI-INFLAMMATORY AGENTS WORK**

produce adrenal glucocorticoid suppression; thus, use of corticosteroids for more than a few weeks can lead to adrenal suppression and adrenal atrophy (i.e., Addison’s disease). Long-term use of systemic corticosteroids can also lead to Cushing’s syndrome (Table 1). Topical ophthalmic steroids, however, do not produce these adverse effects.

- **Glucocorticoid vs. Mineralocorticoid Effect.** Cortisol (hydrocortisone), the primary glucocorticoid produced by the adrenal cortex, is responsible for carbohydrate metabolism. Its overproduction or pharmacologic use may result in hyperglycemia or glucose intolerance. Aldosterone is the major mineralocorticoid, and plays a role in the retention of salt and water to maintain proper fluid/electrolyte balance and blood pressure. Synthetic corticosteroids vary in their relative balance of mineralocorticoid and glucocorticoid effects; however, because all synthetic glucocorticoids can produce some degree of water and salt retention and hyperglycemia, they should be used cautiously in cardiovascular and diabetic patients.

Most of the common oral synthetic corticosteroids have similar glucocorticoid/mineralocorticoid activity, with the main difference being potency. Dosage is calculated based on steroid equivalents, with 20mg of cortisol acting as the baseline dose to which all other glucocorticoid potency is compared (Table 2).

- **Ocular Use.** The ocular properties of corticosteroids are different in some aspect from their systemic counterparts. The ocular version must be in an active form, since it is applied topically and will not undergo hepatic metabolism before reaching site of action. Additionally, it must be capable of penetrating corneal tissues and must possess adequate potency to significantly reduce the local inflammatory response.

  - **Table 3. Ocular Indications For Corticosteroids**

<table>
<thead>
<tr>
<th>Allergic conjunctivitis/blepharitis</th>
<th>Superior punctate keratitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPC/VKC/AKC</td>
<td>Posterior uveitis</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Juvenile xanthogranuloma</td>
</tr>
<tr>
<td>Immune graft rejection</td>
<td>Sympathetic ophthalmia</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Ocular burns</td>
</tr>
<tr>
<td>Cranial arteritis</td>
<td>Episcleritis/scleritis</td>
</tr>
<tr>
<td>Graves disease</td>
<td>Ocular pemphigus</td>
</tr>
<tr>
<td>Rosacea keratitis</td>
<td>Orbital pseudotumor</td>
</tr>
<tr>
<td>Phlebitis keratoconjunctivitis</td>
<td>Marginal corneal ulcers</td>
</tr>
<tr>
<td>Ocular pemphigus</td>
<td>Trabeculitis</td>
</tr>
<tr>
<td>Inflammatory complications</td>
<td>Interstitial keratitis of herpetic disease</td>
</tr>
<tr>
<td>Interstitial keratitis of herpetic disease</td>
<td>Retinal vasculitis</td>
</tr>
<tr>
<td>Epidemic keratoconjunctivitis</td>
<td>Infiltrative keratitis</td>
</tr>
</tbody>
</table>

If the issue is a result of bacterial infection, which can be adequately treated with antibiotic therapy, adjunctive corticosteroid therapy may be used. Note that the concomitant use of corticosteroids within an antiviral agent in the treatment of herpes simplex keratitis is more controversial because their use is limited to disciform keratitis and contraindicated for active dendritic disease in particular. Additionally, corticosteroids should not be used in fungal infections, since the steroid may worsen infection.

When inflammation is due to allergens, the offending stimulus should first be removed if possible. Mast-cell inhibitors or antihistamines can be used to prevent further reaction.

- **Sizing Up the Corticosteroid Options.** When choosing a topical steroid, consider which one has the lowest effective dosage, longest dosing interval and the shortest duration of therapy to prevent adverse effects and allow for discontinuation without withdrawal symptoms or flare-up of the disease. However, overall the specific corticosteroid product and dosage should be chosen based on the severity of inflammation (Table 4).

  - Prednisolone acetate 1% is the most active ocular corticosteroid, and should be the drug of choice when maximal anti-inflammatory effect is required: a dosage of one drop every minute for five minutes each hour has been shown to decrease ocular inflammation by 72%, as compared to a decrease of 51% with hourly dosing and 11% with doses every four hours. This suggests that cumulative dose increases activity of the anti-inflammatory effect of the agent when applied topically.
One of the newer high-potency topical steroids is difluprednate 0.05% (Durezol, Alcon), which has been demonstrated to have an efficacy comparable to that of prednisolone acetate 1% in anterior uveitis. One benefit of Durezol is that it does not need to be shaken, as it is an emulsion; however, prednisolone acetate is available in a much lower-cost generic formulation. Both drugs raise intraocular pressure (IOP) and increase the risk of cataract formation.

Steroid Complications. In general, due to high receptor affinity and rapid inactivation, the likelihood of steroid-linked cataract formation and glaucoma is significantly decreased. Steroid response to loteprednol is less than 3%, according to an FDA comparison of loteprednol 0.2% (Alrex) and 0.5% (Lotemax, B+L) to prednisolone acetate 1%. The study measured the incidence of an increase in IOP >10mm Hg over a 28-day period; prednisolone acetate raised IOP in 7% of tested patients.

The use of corticosteroids has been linked to cataract formation in patients with rheumatoid arthritis. A study in 1961 at the National Institutes of Health (NIH) found 17 of 47 patients with rheumatoid arthritis who received prednisone for more than one year developed cataracts, compared with none in the 19 patients who did not receive the steroids. Specifically, posterior subcapsular cataracts (PSC) were observed in 36% of patients treated with steroids for one to four years and in 69% of patients treated for more than four years. With respect to different dosages of prednisone, 23% of patients treated with a dose 10mg to 15mg per day and 75% of those receiving prednisone equivalent to more than 15mg per day developed cataracts. None of the six patients receiving less than 10mg per day of prednisone and none of the nine patients receiving steroids for less than one year developed cataracts.

PSCs resulting from topical use are similar in presentation to those caused by systemic drugs. Most reports of PSC are secondary to topical ocular corticosteroids that have been administered for more than six months.

Corticosteroids have also been shown to increase IOP. A study evaluating 14 known corticosteroid responders identified IOP increases of 4.4mm Hg to 8.1mm Hg with fluorometholone 0.25% suspension compared to 8.1mm Hg to 11.6mm Hg with dexamethasone sodium phosphate solution 0.1%.

A separate study compared the effects of betamethasone 0.1% combined with sulfacetamide 10% on IOP in three groups of patients treated with a single drop QID for up to two months. Researchers observed a mean IOP increase from 16.9mm Hg to 32.1mm Hg in the 44 patients with primary open angle glaucoma and a mean increase from 17.1mm Hg to 28.3mm Hg in the 32 glaucoma suspects. The 30 normal subjects had a mean pressure increase from 13.6mm Hg to 18.2mm Hg. A second study completed later indicated that IOP increase as a reaction to corticosteroids may be genetically determined; specifically, it is possible that primary open angle glaucoma patients are homozygous carriers of a glaucoma gene, non-glaucoma responders are heterozygous for the glaucoma gene and non-responders are homozygous for the normal (i.e., non-glaucoma) gene.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Decrease in Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone acetate 1%</td>
<td>51%</td>
</tr>
<tr>
<td>Dexamethasone alcohol 0.1%</td>
<td>40%</td>
</tr>
<tr>
<td>Fluorometholone alcohol 0.1%</td>
<td>31%</td>
</tr>
<tr>
<td>Prednisolone sodium phosphate 1%</td>
<td>28%</td>
</tr>
<tr>
<td>Dexamethasone sodium phosphate</td>
<td>19%</td>
</tr>
<tr>
<td>Dexamethasone sodium phosphate 0.05% oint.</td>
<td>13%</td>
</tr>
</tbody>
</table>
HOW ANTI-INFLAMMATORY AGENTS WORK

**NSAIDS**
Nonsteroidal anti-inflammatory drugs (NSAIDs) also play a very important role in the management of ocular disease, despite having an anti-inflammatory efficacy below that of the corticosteroids. Both the topical (Table 5) and systemic NSAIDs are used to manage mild to moderate pain and are frequently combined with opiates like codeine, hydrocodone and oxycodone to enhance their analgesic effect. Topical ocular NSAIDs in particular are used to manage postoperative pain, miosis and cystoid macular edema (CME). It should be noted, however, that all NSAIDs have some degree of potential to inhibit the beneficial antiplatelet activity of aspirin.

Nonselective NSAIDs work by inhibiting all forms of the enzyme cyclooxygenase (COX), which is responsible for the formation of prostanooids (i.e., prostaglandins, thromboxanes and prosta- cyclins) that mediate inflammation, anaphylaxis and vasoconstriction (Figure 1). Prostaglandins in particular play a role in the direct stimulation of pain receptors (nociceptors) and vasodilation (hyperemia), but do not affect the lipoxygenase/leukotriene pathway.

Two forms of cyclooxygenase exist: COX-1 is a constitutive enzyme that is continuously produced and is responsible for the production of prostaglandins necessary for normal physiologic functions, including fabrication of the stomach’s protective coating (i.e., the gastric mucosal barrier), normal renal blood flow and normal blood clotting. Inhibition of COX-1 can lead to gastric irritation, peptic ulcers, gastrointestinal bleeding and blood clotting disorders.

COX-2 is an inducible enzyme that is produced in response to tissue injury. Inhibition of COX-2 can lead to gastrointestinal irritation and ulceration; drugs specifically designed to impede COX-2 can also increase the risk of heart attack and stroke.

**Antipyretic Effect.** NSAIDs are also known to reduce fever. When the body’s healthy state is compromised as a result of malignancy, infection or the introduction of certain chemicals, it raises its internal temperature to increase overall metabolism, enhancing its ability to fight invaders. This elevated temperature may also inhibit bacterial growth, because pathogenic bacteria typically only grow within narrow temperature ranges. This process is triggered by the release of interleukin 1 cytokines, which stimulates the synthesis of prostaglandins E1 and prostaglan- din F2. The prostaglandins then reset the hypothalamic thermostat to a level above the normal 37°C to raise the body’s temperature. The NSAIDs are effective at low doses in reducing this elevated temperature, but have no such effect on normal or subnormal temperature.

**Hemostasis.** Arachidonic acid is a precursor in the synthesis of the prostaglandin analogs prosta- clys and thromboxane A2. Thromboxane initiates platelet aggregation, while prostacyclin antagonizes aggregation. Under normal circumstances, the two analogs are physiological antagonists, and the platelets do not aggregate. The action of NSAIDs on the prostaglandin endoperox- ide synthetase (or cyclooxygenase) causes inhibition of platelet aggre- gation, thus prolonging bleeding time—an effect that can either be therapeutic or cause an adverse reaction.

**Off-Label Use.** Some evidence for the efficacy of topical NSAIDs in the management of retinal edema associated with epiretinal membranes, diabetic macular edema and retinal vein occlusions does exist; however, more information is needed before their use can be recommended.

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**Table 5. Currently Available Topical Ocular NSAIDs**

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acular</td>
<td>ketorolac 0.5%, Allergan</td>
</tr>
<tr>
<td>Acular LS</td>
<td>ketotolac 0.4%, Allergan</td>
</tr>
<tr>
<td>Ocufen</td>
<td>flurbiprofen 0.03%, Allergan</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.1% (generic)</td>
</tr>
<tr>
<td>Voltaren</td>
<td>diclofenac 0.1%, Novartis</td>
</tr>
<tr>
<td>Prolensa</td>
<td>bromfenac 0.07%, B+L</td>
</tr>
<tr>
<td>Nevanac</td>
<td>nepafenac 0.1%, Alcon</td>
</tr>
<tr>
<td>Ilevo</td>
<td>nepafenac 0.3%, Alcon</td>
</tr>
</tbody>
</table>

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Steroids have traditionally carried the stigma of potential serious side effects outweighing their benefits more so than any other class of drugs. Optometric and medical education had previously emphasized the negative consequences of steroid use, making many practitioners hesitant to use them unless the situation is dire.

In reality, the anti-inflammatory effects of steroids far outweigh their possible side effects—in fact, some experts believe withholding steroids has caused more harm to patients overall than their occasional consequences. Research has also supported using them earlier and more often, as we now have a better understanding of potential side effects and more drug options tailored to treat specific conditions.

From the eye care professional’s perspective, prevention of vision loss, earlier return to contact lens wear and a reduction in the amount of work or school days missed are all practical benefits to using topical steroids.

UNDERSTANDING AND MANAGING SIDE EFFECTS

Inflammation is the body’s response to a stimulus (e.g., invasive organism) it perceives as offensive. While an effective defense mechanism, the inflammatory process can cause scarring and damage to healthy tissues that surround the infected area. Steroids work by blocking phospholipase A2, thereby blocking both arms of the chemical inflammatory cascade.1 Thus, they not only decrease vasopermeability and reduce edema and redness, they have the added benefit over nonsteroidal anti-inflammatory agents of keeping polymorphonucleocytes, leukotrienes and other blood cells sequestered from the site of inflammation, thereby reducing collateral damage to surrounding healthy tissue.2 However, while efficacious and unique in quelling the deleterious effects of inflammation, they are not without consequences.

The two common ocular side effects associated with steroid use are increased intraocular pressure (IOP) and cataract formation. Topical steroids are generally more associated with an increase in IOP than causing the classic steroid-induced posterior subcapsular cataract (Figure 1); in fact, risk of cataract formation from short-term topical steroid use is considered small. Cataract formation is instead more commonly associated with prolonged use of oral steroids, though advances in modern cataract surgery techniques have made this less of a concern than it was decades ago.

The prevalence of steroid-associated IOP increase ranges between 5% and 33% of the general population depending on the study cited and the definition used.4 Generally, topical steroids can be used for two weeks with minimal effect on IOP.5 After two weeks, IOP can unpredictably rise with no discernable correlation regarding

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amount or time frame. Thus, the goal of acute topical steroid use is to aggressively eliminate inflammation within the two-week period and then discontinue the drug. If IOP spikes with short-term steroid use, pressure generally returns to baseline two to four weeks after the drug is discontinued. With chronic use, the steroid response can occur months to even years later, so patients on long-term steroid therapy—even just one drop per day—should have their IOP checked every three months until the drug is discontinued.

Should IOP increase to the point that treatment is required, glaucoma drugs can treat the problem. Note, healthy discs can tolerate IOP in the high twenties to low thirties for a few weeks without significant compromise. Steroid-induced glaucoma is attributable to increased resistance to outflow at the trabecular meshwork, possibly due to an accumulation of glycosaminoglycans and other substances in this area. This decrease in aqueous outflow means that drugs that reduce aqueous production make sense for treating steroid-induced glaucoma.

Topical beta-blockers such as timolol, levobunolol and metipranolol have long been used to blunt a steroid-associated increase. Topical carbonic anhydrase inhibitors such as Trusopt (dorzolamide 2%, Merck) and Azopt (brinzolamide 1%, Alcon) have been demonstrated to decrease aqueous production and so work well for treating steroid-induced glaucoma. Alpha agonists such as Alphagan P (brimonidine 1%, Allergan) also decrease aqueous production while simultaneously increasing uveoscleral outflow.

Additionally, combination drugs such as Combigan (brimonidine 0.2% and timolol 0.5%, Allergan) and Simbrinza (brinzolamide 1% and brimonidine 0.2%, Alcon) work well for steroid-induced glaucoma and provide the convenience of less drop instillation. Prostaglandins are also known to lower IOP in steroid-induced glaucoma by increasing uveoscleral outflow; however, they also carry a small possibility of increasing ocular inflammation.

Another concern regarding topical steroids is that their suppression of the ocular immune system may increase risk of infection (Figure 2). Topical antibiotics have improved tremendously as well over the years. Topical fourth-generation fluoroquinolones like Zymaxid (gatifloxacin 0.5%, Allergan) Moxeza (moxifloxacin 0.5%, Allergan) and Besivance (besifloxacin 0.6%, Bausch + Lomb) are well-equipped to provide broad-spectrum coverage against many kinds of bacteria and should be used concurrently with steroids for prophylaxis if potential infection is a concern.

**Picking the Right Drug**

As a result of recent research, we practitioners now have more drug options available to us than ever before. Prednisolone acetate 1% (Pred Forte, Allergan; Econopred, Alcon) remains the gold standard to which all other topical steroid preparations are compared. It is a good a choice for moderate to severe inflammation and it continues to be used postoperatively in many ocular surgical procedures.

So-called soft steroids offer an extra margin of safety for long-term topical steroid use or for patients with a known risk of steroid response. A "soft" drug is a biologically active compound with a predictable inactivation to a nontoxic substance after achieving its therapeutic role. Lotemax (lotepronol 0.5%, Bausch + Lomb) is structurally similar to
prednisolone but rapidly undergoes hydrolysis in the anterior chamber to an inactive derivative. While its efficacy may be a little less than prednisolone acetate 1%, it is less likely to increase IOP.11

A weaker version of loteprednol in a 0.2% formulation (Alrex, Bausch + Lomb) is available for treating seasonal allergic conjunctivitis. Vexol (rimexolone 1%, Alcon) is currently the most potent steroid available.12 Originally developed in Japan as a dermatologic preparation, it has been reformulated as a soft steroid with efficacy approaching prednisolone acetate 1% but with a lower steroid response rate.12 It has a higher steroid receptor binding affinity and is rapidly degraded to inactive metabolites.

If out-of-pocket cost to the patient is a concern, note that many fluorometholone-based steroids are now available generically. These agents also have reduced steroid-induced IOP elevation response. Fluorometholone alcohol 0.1% (FML, Allergan) is effective for mild ocular surface inflammation, while fluorometholone acetate 0.1% (Flarex, Alcon) has better ocular penetration and is appropriate for moderate inflammation.3

Durezol (difluprednate 0.05%, Alcon) is currently the most potent steroid available.13 Originally developed in Japan as a dermatologic preparation, it has been reformulated as an ophthalmic emulsion. The molecule is specially designed to offer both better penetration and higher anti-inflammatory activity, giving it the same anti-inflammatory ability as prednisolone acetate 1% at half the dosing. With its tremendous anti-inflammatory properties, however, have come some reports of significant IOP response.14

STEROIDS AND OCULAR CONDITIONS
Topical steroids aren’t just for uveitis any more. The development of safer drugs with new formulations has led to a reevaluation of the appropriateness of a steroid for many ocular conditions where they were once contraindicated. For example, steroids are now considered appropriate to alleviate symptoms of dry eye on a short-term basis, and are commonly used as immediate discomfort relief while waiting for longer-term treatments like Restasis (cyclosporine ophthalmic emulsion, Allergan), punctal plugs and advanced lubricants to work.15

Topical steroids can also be used in cases when a patient’s symptoms may be temporarily exacerbated. A soft steroid with a lower incidence of steroid response such as Lotemax gel BID to QID (depending on severity) can be used to reduce symptoms during the initial one-month startup of Restasis, or BID to QID for a week or two if symptoms particularly flare up.

Steroids are also considered beneficial when treating conditions that involve lid inflammation, such as posterior blepharitis. This is because while topical antibiotics help reduce associated bacteria, the patient typically does not feel improvement until lid inflammation is controlled.16 Zylet (Bausch + Lomb), which combines the antibiotic tobramycin with loteprednol, is a good choice for this condition. Tobradex ST (Alcon), which combines tobramycin and dexamethasone with xanthum gum, is another good choice because this unique formulation leads to longer surface contact time between the medication and the lids.

Once considered an absolute contraindication, topical steroids have now also been studied in the treatment of corneal ulcers. The Steroids for Corneal Ulcer Trial (SCUT) randomized patients to receive prednisolone sodium phos-
"STEROIDS CAN BE USED FOR TWO WEEKS WITH MINIMAL EFFECT ON IOP."

phosphate 1% or placebo in addition to moxifloxacin.17 The primary endpoint measured was best spectacle-corrected visual acuity at three months after enrollment. Results at this time indicated that while the steroid had no significant effect on overall acuity outcome, there was no apparent increased risk of corneal perforation and no major safety concerns were identified. Further analysis of their subgroups revealed a slight improvement in visual acuity outcome for large central ulcers with steroid treatment, and led to the recommendation that steroids should be avoided for Nocardia, Mycobacterium and fungal infection.

Interestingly, additional data collected at 12 months demonstrated further reduction in scar density in a small number of patients enrolled in SCUT. This continued corneal remodeling was accompanied by an improvement in visual acuity, suggesting steroid use earlier in the course of the bacterial ulcer may in fact contribute to eventual improvement in corneal opacity.18

PEARLS FOR USE

We practitioners are fortunate to have so many topical steroids available now. So, don’t rely on one “go-to” drug for all presenting conditions. Pick your drug based on the amount of inflammation you’re treating: mild, moderate or severe. Mild surface inflammation is easily treated with less penetrating drugs such as Alrex or FML, which typically help avoid the steroid response. Moderate inflammation is handled well with Lotemax or Vexol, while Pred Forte or Durezol should be reserved as treatment for severe inflammation. Many generic topical steroids are also now available for patients with financial concerns.

Next, be sure to consider the potential for steroid response. For a treatment period of two weeks or less, the risk of complications is considered minimal for most available drugs. If treating long term, however, consider using drugs with a reduced steroid response, such as Lotemax, Alrex, Vexol or fluorometholone alcohol or acetate.

If IOP rises during a course of therapy, again bear in mind that otherwise unaffected optic discs can withstand IOP in the high 20s or low 30s for a few weeks without significant damage to structure or function. If IOP does become a concern, however, first consider discontinuing the steroid if possible. In cases where inflammation is still present, substituting a soft steroid can help. If the patient’s IOP level remains unacceptable, add concurrent glaucoma medications as needed until the steroid is discontinued. Remember, IOP usually returns to baseline two to four weeks after the steroid is discontinued for short-term therapy.

With a contemporary knowledge of our topical steroids, there is no reason to hold back on their use. Our newer formulations are safer, and recent studies have made their side effects more predictable and manageable. Research also supports using them earlier and more often in many ocular conditions. Your patients will thank you.

Children who become myopic typically do so around age eight years, requiring some form of vision correction. However, for those children that are active, glasses are considered an impediment during recreational activities. Contact lenses are an alternative vision correction option that can easily be updated as the prescription changes. Research shows children are capable of wearing both gas permeable and soft contact lenses, and thus far there have been no documented long-term consequences of fitting children with contact lenses. Interestingly, children who wear contact lenses exhibit a boost in self-perception of physical appearance, athletic competence and social acceptance, compared with spectacle wearers. Young contact lens wearers who did not like wearing their glasses even report feeling smarter than spectacle wearers.

The purpose of this article is to illustrate differences between fitting children and adults with contact lenses to provide readers confidence when fitting children.

PHYSICAL BENEFITS

In addition to improving self-perception, contact lenses offer other benefits to children that adults may not recognize, such as myopia control. Controlled studies and randomized clinical trials show that corneal reshaping contact lenses can slow the progression of myopia in children. Soft bifocal contact lenses have a similar effect. Maintaining a lower level of myopia ultimately provides myopic patients with more options for vision correction and more predictable refractive surgery results, better quality of life, and possibly a lower risk of sight-threatening issues such as cataract, glaucoma, choroidal atrophy and retinal detachment. Children are also less than college students to experience ocular health problems and corneal infiltrative events associated with contact lens wear.

Despite the benefits of contact lens wear for children and the lower risks of contact lens complications, only approximately 10% of optometrists agree that eight to nine years is an appropriate age to introduce contact lenses, although approximately one-third of doctors said they now fit kids at a younger age than they did one year ago due to the availability of daily disposable lenses and improved lens materials, as well as specific requests from the parent or child.

FIRST TIME CORRECTION

Many optometrists will not fit a child with contact lenses when they first become myopic, instead telling them that it is an option if the child proves capable of responsible spectacle wear for one year. However, there is very little about responsible spectacle care that prepares a child for independent contact lens wear (other than providing additional time to mature), effectively negating the intention to train the child. So, practitioners should provide children with the option of contact lens wear at myopia onset, and monitor their

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progress at follow-up appointments. Of course, contact lens wearers should still have a pair of spectacles to wear in case of issues.

ANXIETY
Compared with adults, children don’t have as much experience seeing a practitioner, and often have an exaggerated response to pain and other negative physical stimuli. Thus, many believe that anything placed in the eye will feel like the standard dilating eye drop. There are two ways—opposite in nature, but equally successful—to confront this issue: either, when inserting contact lenses, explain every detail of what you are doing in a soothing, empathetic tone to help alleviate anxiety; or prepare the contact lens for insertion without allowing the child to notice, distract them and insert the lens before they realize what’s coming. Depending on your personality, the empathetic parent or the crazy uncle routine will help make the fitting process as easy as possible (Figure 1).

MOTIVATION
Doctors often say that a child’s motivation is the most important key for success, but that is not entirely true. Many children believe that anything inserted into the eye will hurt, so they are initially unmotivated to even try contact lenses. In fact, more often than not, it may be the parent’s idea for their child to try contact lenses. Thus, it is important to assess motivation after you insert the lens—children will frequently change their minds once they realize contact lenses improve vision without causing pain, and will thus be more likely to continue wearing them. Conversely, adults simply won’t ask about contact lens wear unless they are motivated, so assess motivation during the initial conversation.

INSERTION AND REMOVAL
Children require, on average, about 11 minutes more than teenagers to learn proper insertion and removal techniques for contact lenses. Most of this difference is due to outliers: twice as many teenagers require less than 20 minutes to learn insertion and removal compared with children, and some children require multiple visits to master contact lens insertion. The median difference between children and teenagers is in fact only five minutes. Children typically remember contact lens care instructions as well as teenagers following initial instruction, but remember less than teenagers at longer intervals. Therefore, each time a child returns for a follow-up, ask them how they care for their lenses, and correct any misconceptions to ensure proper care (Figure 2).

IRRESPONSIBILITY
Optometrists and parents often agree that children who frequently lose or break spectacles are poor candidates for contact lens wear. In fact, children who lose or break their spectacles may be the best candidates. Children rarely remove their glasses because they prefer blurry vision—instead, most cases of lost or broken spectacles happen when the child is not actively wearing them for appearance reasons or during recreational activities and the glasses are forgotten or crushed. Contact lenses provide clear vision without altering appearance, limiting peripheral vision, falling off or fogging up during sports. Children also reported better quality of life scores while handling contact lenses than when handling spectacles. This is presumably because glasses are removed throughout the day for different reasons, but contact lenses are only handled in the morning and prior to bedtime. Less overall manipulation of lenses results in higher handling quality of life than spectacles, even though it is more difficult to insert...
KIDS AREN’T SHORT ADULTS: TIPS FOR FITTING YOUNG CONTACT LENS WEARERS

and remove contact lenses than it is to put on and take off glasses.

COMPLIANCE
Children are often more compliant with contact lens care than older patients, possibly because they are more used to following instructions from teachers and adults. However, children are also more likely to forget these messages if they deviate from their routine—for example, if they spend the night at a friend's house. If a child is sleeping elsewhere for the night, parents should instruct hosts to remind the child to remove their contact lenses before bedtime.

One exception to this might be corneal reshaping contact lenses. Because children typically have lower prescriptions and corneal epithelium that responds more effectively to corneal reshaping lens wear than adults, they often experience uncorrected visual benefits of corneal reshaping lens wear for a longer period than adults. This means they may be able to wear their lenses only every other night, instead of every night. So when they spend the night at a friend's house, they don't necessarily have to remember to insert their lenses.

SWIMMING
Since children swim more frequently than adults, and contact lenses are known to harbor bacteria and other potential pathogens, it is important to educate children and their guardians about contact lens care while swimming. Research shows use of swimming goggles can reduce the bacterial contamination of contact lenses, but no evidence-based recommendations exist regarding what to do with the lenses if goggles are not worn. Potential options include removing lenses during swimming or disposing of or disinfecting lenses immediately after swimming. Regardless of your recommendation, make sure your staff relays the same message to all patients.

CORNEAL RESHAPING CONTACT LENSES
Children are excellent candidates for corneal reshaping contact lenses. These specialty lenses slow the progression of myopia, and are worn at home in a controlled environment. Typically, the corneas of children are easier to correct during the initial adaptation phase because glasses provide appropriate correction later in the day as the cornea begins to return to the baseline curvature.

However, because myopia progresses until age 15 or 16 years, children are less likely than adults to gain full myopic correction from their spectacles. As the child's cornea returns to normal curvature during the initial adaptation, the glasses don't over-correct the increasing myopia as much as they would in an adult with a stable, full myopic prescription in glasses. Children also adapt more easily to overcome the over-minused condition, so soft contact lenses with half of the baseline prescription are less necessary for children compared with adults. Children also do not drive, meaning they lodge far fewer complaints than adults of haloes around lights at night. However, children are just as at risk for microbial keratitis as adults, especially since the contact lenses are worn during sleep, so they should be educated about symptoms of corneal infections.

BIFOCAL CONTACT LENSES
Children are increasingly being fit with soft bifocal contact lenses for myopia control. However, fitting a child with soft bifocal contact lenses is nothing like fitting a presbyopic adult; in fact, fitting a child with soft bifocal contact lenses for myopia control is more like fitting a child with single vision contact lenses, primarily because they accommodate even while wearing bifocal lenses. Even the highest add powers rarely result in complaints from children, presumably because they typically accommodate better than adults, even when wearing a soft bifocal lens. Young convergence excess patients may even benefit from soft bifocal lens wear, presumably because they accommodate less with soft bifocal lenses. This may be because human body is adept at adjusting to uncomfortable situations, and these children may learn to relax accommodation to alleviate symptoms caused by convergence excess.

CONCLUSION
Children experience a range of visual and non-visual benefits from contact lens wear beyond those experienced by adults, without increased risks due to adverse physiological effects or irresponsibility. With additional considerations towards alleviating a child's anxiety and making the fitting process as fun as possible, children are as easy to fit with contact lenses as teenagers and adults.

Many practitioners love the additional challenge and free advertising that children bring to the practice. Children are extremely social beings; they participate in sports and recreational activities and hang out with their friends. Because they are not yet completely independent, parents often congregate around them, opening up the possibility for a discussion between adults regarding a child’s sudden independence from glasses. In some
cases, such a discussion may result in a referral, benefiting both the new patient and the practice. So, don’t be afraid to offer contact lenses to your young patients!

A ‘Coherent’ Strategy for Fitting Scleral Lenses

OCT: it’s not just for retina anymore!

If you are new to scleral contact lens fittings and own an optical coherence tomography (OCT) device, you have an amazing tool at your fingertips that can help make your job significantly easier. OCT has long been used to assess the posterior segment of the eye and has more recently gained popularity for anterior segment uses as well.

Global pachymetry features have given us the ability to measure the thickness of the cornea, which is great for monitoring the progression of diseases like keratoconus and pellucid marginal degeneration. Additionally, the “angle” feature allows us to view the iris configuration and angle measurement in degrees, helping us determine if a patient may be at greater risk for narrow angle glaucoma. Now, OCT can also assist with specialty contact lens fittings.

AUGMENTING THE SLIT LAMP

When fitting scleral contact lenses, it is of utmost importance to obtain proper corneal and limbal clearance. This can be assessed with a slit lamp and sodium fluorescein by comparing lens thickness to the tear layer thickness. If you only have access to a slit lamp, this is a completely acceptable method of fitting scleral lenses—but what if you could compare your slit lamp findings with your OCT scans? This could lead to better overall assessment of scleral lenses and is a great way to improve confidence (for both you and the patient) when fitting scleral lenses.

It is advisable to first insert the scleral lens and immediately evaluate it with the slit lamp. If the amount of clearance looks acceptable, let the lens settle for at least 20 to 30 minutes before reevaluation. Keep in mind the central clearance will decrease around 100µm during this time. Then, use the anterior segment feature of your OCT to measure the amount of central, limbal and edge clearance. You can do this either before or after your reevaluation of the lens under the slit lamp.

First, check the amount of central clearance by centering the OCT image over the pupil (Figure 1). Then, use the ruler application to measure from the posterior portion of the scleral lens to the anterior portion of the cornea to determine the amount of central clearance in microns. You can then compare your findings with the slit lamp to see how accurate you are.

If you know which area of the cornea has the highest elevation, you can also center the OCT image over that portion of the lens and measure the amount of clearance in that location. To check limbal clearance, center the OCT image over the limbus. Clearance here should be significantly less than central clearance in most scleral lens designs.

Edge alignment can also be viewed using an OCT. Have the patient look to the left and the right to capture images of the edge of the scleral lens (Figure 2). You can also check the alignment of the conjunctiva with the scleral lens edge to see if there is any compression. OCT imaging can
also be useful when fitting hybrid lenses—you can view both the soft skirt and GP lens junction, as well as the lens-to-cornea fitting relationship (Figure 3).

CASE #1
A 28-year-old female was refit into scleral lenses due to her high -10.00D OU Rx. She was fit in a design for conventionally shaped corneas and had been wearing the scleral lenses successfully for about two weeks. She stated that insertion and removal were becoming easier each day and that comfort and wear time were excellent. However, she noted appearance of a strange glare in her right eye only and reported that her vision wasn’t as sharp in the right eye as it was in the left eye.

Visual acuity was 20/30 OD and 20/20 OS. There was no significant spherocylinder over-refraction. Lens fit in both eyes was good: the central and limbal clearance of both lenses appeared appropriate, as well as the lens edge. Both lens surfaces appeared to be wetting well with no deposits or scratches. Upon OCT evaluation, the posterior surface of the right lens appeared slightly distorted, and it was determined the lens was defective: the lathe had not properly cut the posterior lens surface, leading to an uneven surface. This was causing the patient symptoms of poor vision and glare (Figure 4). The laboratory refabricated the OD lens and, upon dispensing, the patient reported 20/20 vision and no glare.

CASE #2
A 40-year-old white female was fit into scleral lenses for treatment of dry eye disease. She had been wearing the lenses successfully for about one month, but complained of decreased wear time, stinging upon removal and increasing eye redness throughout the day. She also noticed a compression ring upon removal. While wearing the lenses, she could see 20/20 OD and 20/20 OS. There was no significant spherocylinder over-refraction.

Slit lamp evaluation showed central clearance of about 200µm in each eye, but limbal clearance was difficult to assess. The edges did show some blanching at 360 degrees. Evaluation of the edges with the OCT showed minimal limbal clearance and poor edge alignment.

With lenses removed, there was limbal staining OU, indicating inadequate clearance. To remedy the poor lens fit, the limbal vault was increased and the edge design was flattened slightly to help with the limbal staining and edge compression, respectively (Figure 5). She has now worn the lenses successfully for six months with no corneal staining or edge compression.

As optometrists, we typically think of OCT imaging for the posterior segment, but we should also remember there are some excellent anterior segment applications. OCT imaging definitely helped me become more confident with fitting scleral contact lenses when I was first learning about this special lens design. Keep in mind that you do not need an OCT to successfully fit scleral lenses, but if you do have this device on hand, the information it can give you can be very valuable for your scleral lens fittings.

**IS OCT BILLABLE FOR SCLERAL LENS FITTING?**
Currently, I roll topography, specular microscopy and any OCT evaluations into my specialty lens fitting fee. The pricing reflects a bundled service, and I do not bill each procedure separately. Hopefully, in the future, CPT codes will be able to be billed to insurance during specialty contact lens fittings.

![Distortion of posterior lens surface.](image1)

![Fig. 4. Distortion of posterior lens surface.](image2)

![OCT before (top) and after (bottom) lens modifications.](image3)

![Minimal limbal clearance](image4)

![Improved limbal clearance](image5)

![Edge compression](image6)

![Edge alignment](image7)
Many contact lens wearers experience perennial symptoms of ocular allergy that can eventually lead to dropout if not addressed, but some patients are only affected during certain times of the year and thus may not be symptomatic when they come in for their exam. These patients often neglect to mention their symptoms or use of over-the-counter treatments when reviewing their eye history with you. In cases like these, it is important to ask the right questions—you may be surprised what you hear.

CASE #1
A 31-year-old male patient presented for a comprehensive eye exam and update of his contact lens prescription. He did not have any comfort complaints, but was having some trouble focusing while using the computer throughout the day. He was wearing monthly disposable contact lenses and replacing them as prescribed. He also reported using the same multi-purpose solution he had been using for several years and denied any other ocular or medical changes since his last eye exam.

I (Dr. Miller) performed a refraction on this patient to see if we had over-minused him during his last appointment, but found no such issues. With slit lamp evaluation, I observed some mild limbal injection in both eyes (Figure 1). I instilled fluorescein and, upon observation of significant staining (Figure 2), asked him the following questions:

• Do you have seasonal allergies?
• Do you ever use OTC eye drops?
• How often do your eyes itch, water or turn red?
• Do your contact lenses ever become more difficult to wear or less comfortable during certain times of the year or in your work environment?

The patient admitted to using self-prescribed OTC Visine eye drops every few hours per day for approximately the last six months with his contact lenses in. He did not think anything was wrong with his regimen; in fact, he believed it was helping to clear up the redness in his eyes. We gradually tapered the Visine, and he was able to safely return to contact lens wear with no further issues after a couple weeks. I did refit him into daily disposable contact lenses, which eased daily irritation due to long hours on the computer.

CASE #2
An 18-year-old female patient presented with ocular discomfort and itching, which she reported increased in severity after taking her contact lenses out each night. To alleviate this discomfort, she had taken to wearing her daily lenses overnight. Her symptoms started approximately one month ago and she stated that she had not been using any eye drops.

Her slit lamp exam demonstrated a moderate amount of conjunctival injection and edema (Figure 3), and her inferior palpebral conjunctiva revealed diffuse G3 papillae throughout (Figure 4), suggesting the presence of...
allergic conjunctivitis. I discontinued her contact lens wear so that I could get her allergic conjunctivitis under control, first using an ophthalmic steroid and later an antihistamine/mast-cell stabilizer for maintenance. She was able to return to using her daily disposable contact lenses and is no longer sleeping in them overnight.

Asking the right questions and treating patients appropriately can often help you to more easily manage common cases like these. By identifying those contact lens wearers who experience intermittent—rather than constant—visual or symptomatic discomfort, you can proactively help improve all of your patients’ experiences with contact lenses, thus reducing the potential for dropouts and improving the profitability of your practice.

**TREATMENT OPTIONS**

Allergies are a common cause of contact lens discomfort. If the allergic response is seasonal and patients know when their allergy symptoms typically begin, consider starting them on an antihistamine/mast-cell stabilizer a week or two prior to that time. I prefer to use a prescription (instead of an OTC) product because it can be challenging to ensure the patient will purchase the correct OTC product.

Types of antihistamine/mast-cell stabilizer combination drops include: Astelin (azelastine hydrochloride ophthalmic solution 0.05%, Optivar); Elestat (epinastine hydrochloride ophthalmic solution 0.05%, Allergan); Zaditor (ketotifen fumarate ophthalmic solution 0.025%, Novartis); ketotifen fumarate (Alaway, Bausch + Lomb); Patanol (olopatadine hydrochloride ophthalmic solution 0.1%, Alcon); and Bepreve (bepotastine besilate ophthalmic solution 1.5%, Bausch + Lomb). All should be used twice daily. Pataday (olopatadine hydrochloride ophthalmic solution 0.2%, Alcon), Lastacaft (alcaftadine, Allergan) and the new Pazeo (olopatadine hydrochloride ophthalmic solution 0.7%, Alcon) are all used once daily.

Typical steroids may also be an option for patients requiring topical medical treatment for their ocular allergy symptoms in more severe cases or those who are not responding to treatment with the antihistamine/mast-cell stabilizer. Alrex (loteprednol etabonate ophthalmic suspension 0.2%, Bausch + Lomb) and Lotemax (loteprednol etabonate ophthalmic suspension 0.5%, Bausch + Lomb) are two commonly prescribed steroid drops for allergic conjunctivitis. Topical steroids are often used for a pulse during a short period of time (one to two weeks), followed by use of an antihistamine/mast-cell stabilizer for sustained maintenance over a longer period of time.

**Fig. 3.** A slit lamp exam revealed moderate conjunctival injection and edema.

**Fig. 4.** Observation of diffuse G3 papillae, suggesting allergic conjunctivitis.
The disposable contact lens market has come a long way since 1987, when the first disposables intended for one week of continuous wear were introduced. Sold in a plastic clamshell box, the lenses came in lots of six. This meant that patients would need more than eight boxes per eye to allow them to wear these lenses as prescribed without interruption for one year. At the time, we were less concerned with a patient’s yearly lens supply and more apprehensive about sticking our toes back into the previously problem-filled waters of extended wear. The next lens on the market, which also had six lenses per box, was intended to be prescribed for two weeks of continuous wear, meaning a yearly supply consisted of less than five boxes per eye. It was at that time the “yearly supply” lightbulb went off for most of us and we started to recognize the patient (i.e., compliance) and practice (i.e., economic and logistic) benefits of prescribing and dispensing annual supplies of lenses. Yet, for many of us, dispensing a year’s supply of lenses is still a challenge. The most common reason is that patients balk at the up-front cost. Much has been written about how to overcome this objection and various techniques have been developed to increase the rate of annual supply purchase, including informing the patient they have been pre-approved for a year’s supply and offering them a tiered price structure with a discount based on number of boxes purchased. Lens manufacturers also offer rebates in an effort to stimulate the frequency of annual supply purchase. While collectively some of these techniques may be moderately effective, they are all largely unnecessary.

The easier solution? A rubber band. That’s the secret.

DON’T SHORTCHANGE YOUR PATIENTS
What would have happened if the first box of disposable one-week lenses had had seven lenses in it? What if it had had 11, 14 or 23? My guess is that doctors’ heads would have exploded, or they would have dispensed one, possibly two, boxes for each eye and waited for patients to call for more lenses, same as they did for the six-lens boxes. Similarly, what if the first box had 365 daily disposable lenses in it? The same thing would have happened, except that the patient would have called for replacements at a much later date. Manufacturers I’ve spoken to agree that putting more lenses into a single box helps with annual supply concerns and they agree that 365 daily lenses in a box is a great solution. But they also believe that many doctors would shy away from such a lens supply out of fear of price rejection from patients. That’s where they and I disagree, and the rubber band comes in.

I guarantee that no one reading this dispenses just the right lens and tells the patient to try it out for a few days before coming back to get the left eye fitted. The reason you fit both eyes at the same time, without even considering why, is because it’s perfectly logical to do so and rather silly not to. Plus, many of us would never consider doing otherwise because we’ve always done it this way and it works. So, how about the following logical and successful way to dispense more annual supplies without memorizing scripts, explaining rebates or trying to master tiered-pricing plans? Until the day comes when a manufacturer puts 365 daily disposable lenses into the box, simply put a rubber band around the appropriate number of boxes and present the annual supply of lenses as the default way that you dispense lenses in your practice. No apology necessary, no excuses needed. Just do it. Nine times out of 10, your patients will accept this as standard practice without argument.

It’s better for patients, since it eliminates their incentive to stretch the lens replacement cycle beyond what you prescribed. It’s also more convenient for them than having to keep ordering more lenses throughout the year. And just like fitting both eyes at the same visit, once you get in the habit of always doing it this way, you’ll wonder why you never reached for the rubber band sooner.
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