

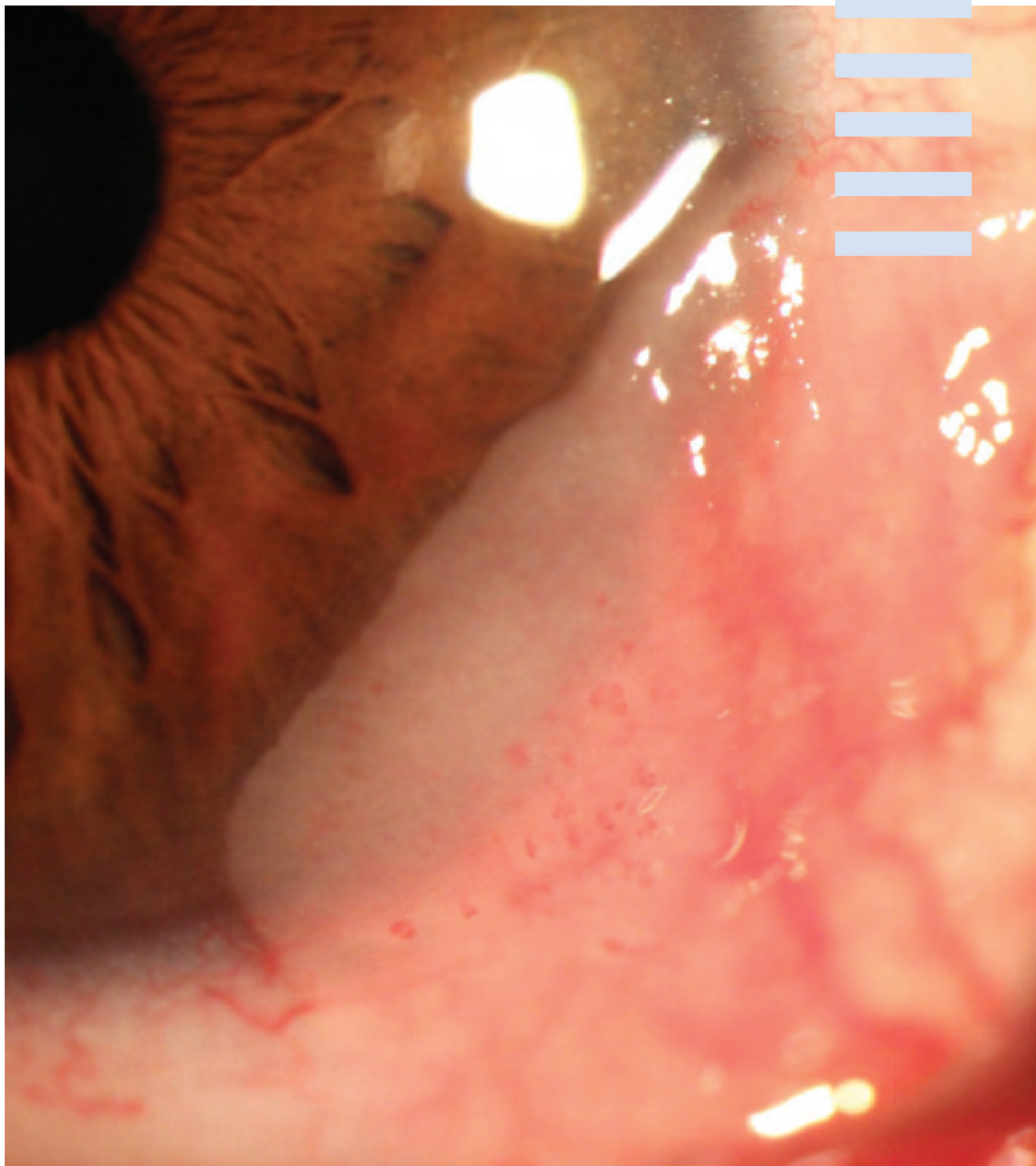
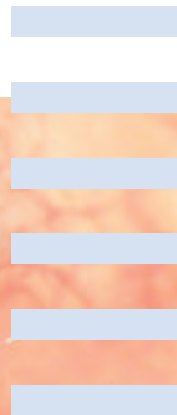
Supplement to

AUSTRALIAN

OPTOMETRY

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SEPTEMBER 2011



- Follicular-like conjunctivitis
- Glaucoma and interpreting OCT scans
- Levetiracetam and diplopia
- Ocular allergy
- Toxoplasmosis
- Keratitis, SiHy lenses and multipurpose solutions

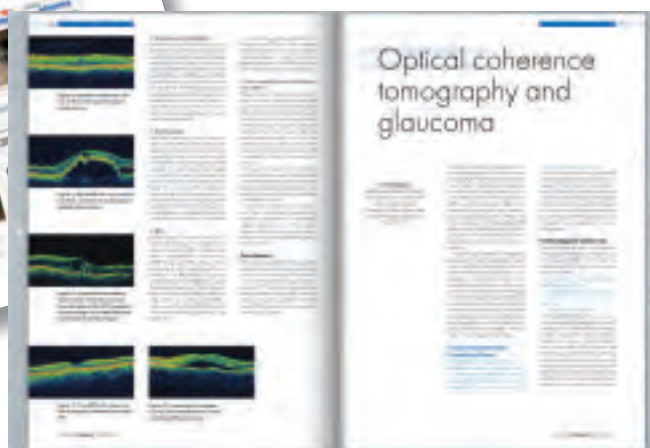
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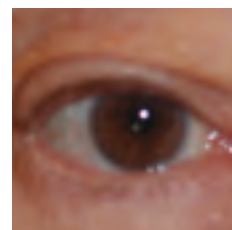
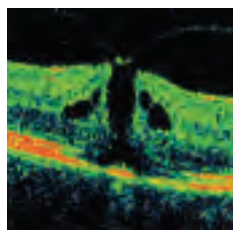
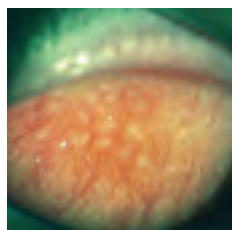
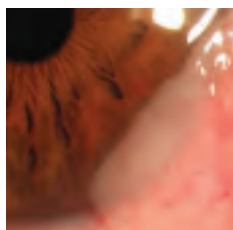


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Editor: **JEFF MEGAHAN**

National Publications Manager:
SANDRA SHAW

Journalist: **JENNIFER KELLET**

Advertising: **SANDRA SHAW**

Clinical Editor:

Associate Professor **MARK ROTH**
Department of Optometry and
Vision Sciences, The University of
Melbourne

Optometrists Association Australia
ABN 17 004 622 431

204 Drummond Street

Carlton VIC 3053

Tel (03) 9668 8500

Fax (03) 9663 7478

j.megahan@optometrists.asn.au

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FoCoSi

Michael Wyss
MScOptometry FAAO
Kontaktlinsen Studio Bärtschi
Bern, Switzerland

A new clinical finding sheds light on follicular-like conjunctivitis associated with silicone hydrogels

Abstract

Aim

The purpose of this article is to describe follicular-like conjunctivitis associated with silicone hydrogels (FoCoSi) in silicone hydrogel contact lens wearers as a novel subtype of the well-described contact lens induced papillary conjunctivitis (CLPC).

Methods

A total of 1,211 patients who wore silicone hydrogels were included in this prospective, non-randomised, single centre study. Subjective symptoms and clinical signs were evaluated for daily wear (DW) and continuous wear (CW) populations for several (lotrafilcon A, lotrafilcon B, senofilcon A, galyfilcon A) silicone hydrogel lens types. The CCLRU and other specifically developed grading scales were used for evaluation. Grading of 2 and above was rated as clinically significant.

Results

The clinical presentation of FoCoSi could be confirmed and showed an incidence of 3.8 per cent. Lotrafilcon A followed by senofilcon A on a CW modality presented, with a risk ratio of 2.49 and 1.53, respectively, the highest affinity for developing FoCoSi. Fluorescein positive spots showed the closest correlation with subjective symptoms reported by patients and divided FoCoSi into an active and dormant form. Besides deposition on the contact lens surface, air pollution like ozone or fine and ultrafine particles seems to be an important factor in developing FoCoSi.

Conclusion

FoCoSi is a novel and relevant subtype of CLPC. Further studies should be performed to validate these findings and answer

several questions about the aetiology of FoCoSi and CLPC.

Key words

Contact lens-induced papillary conjunctivitis (CLPC), follicular-like conjunctivitis associated with silicone hydrogels (FoCoSi), giant papillary conjunctivitis (GPC)

Introduction

Contact lens-induced papillary conjunctivitis (CLPC),¹ also known as giant papillary conjunctivitis (GPC), is a well-described condition and a major cause of discontinuation of contact lens wear.² It is an inflammatory and usually reversible condition that is characterised by enlarged papillae, hyperaemia of the palpebral conjunctiva and excessive mucous discharge. Symptoms include discomfort, pruritus or itching, foreign body sensation, excessive movement, decentration and deposits on the contact lens, resulting in blurred vision and decreased visual acuity.³⁷ CLPC can occur bilaterally or in 10 per cent of cases truly unilaterally.¹⁷ Epidemiological studies demonstrated that the presentation of CLPC in hydrogel contact lens wearers has a mean onset time between 4.3 and 31 months after commencing contact lens wear.^{11,16,38} Gender was not found to be a relevant associated factor for CLPC.¹¹ Patients with a history of allergy have been reported to be more susceptible to CLPC.^{8,9} Of further significance is the distribution in time of diagnosis of CLPC, with peaks in spring and late summer to early autumn, which was assumed to correlate with ragweed pollen season.⁹

The condition was first reported in 1970 in a patient wearing rigid contact lenses⁶ and later by Spring¹⁰ in 1974 in patients wearing hydrophilic contact lenses, and has since been frequently reported in wearers of both rigid and soft contact lenses.¹¹⁻¹⁵ The

incidence of CLPC varies but is greatest with soft contact lens wear (from 1.9 per cent to 45 per cent),^{16,21} especially while wearing conventional extended wear (EW) soft contact lenses.²² Disposable soft contact lenses, especially if wearing time is less than three weeks, showed a significantly lower incidence of CLPC than conventional soft lenses.^{13,14,19} No CLPC at all was found in patients wearing their contact lenses on a one-week or one-day replacement cycle.²³ Preliminary studies and case reports by Stern and Skotnitsky²¹ suggest that there is a greater occurrence of CLPC with silicone hydrogel (SiHy) lenses. When comparing six nights of extended wear to 30 nights of extended wear with SiHy, there was no difference in the occurrence of CLPC.¹⁸

Aetiology

Papillae are small protuberances with nerve endings that respond to stimulation. A vascular supply is observed radiating from a vessel occupying the central fibrotic core of each papillae.²⁵⁻²⁷ The conjunctival epithelium overlying the giant papillae is thickened and irregular, with many invaginations into the stroma. Excised papillae consist of conjunctival epithelial cells, goblet cells, mucous granules in non-goblet epithelial cells, inflammatory leucocytes including mast cells, plasma cells, lymphocytes, eosinophils, basophils and neutrophils in the epithelium, basophils in the substantia propria and newly-formed vessels among excessive fibrosis.²⁸⁻³⁵ Recent immuno-histochemical studies have demonstrated an increase in the number of CD4+ T cells, memory T cells, eotaxine and cytokine production in GPC specimens compared with normal tissue.³⁶⁻³⁹

Sulfidopeptide leukotriens produce increased microvascular permeability in a variety of tissues, which results in oedema formation due to the extravascular ac-

cumulation of plasma. Leukotriens (LT) are found in a higher concentration in patients with CLPC and in patients with allergies, and LT acts independently of histamine.⁶⁴ Immunoglobulin (IgE and IgG) antibodies in the tears and degranulated mast cells in ocular tissue were increased in patients with CLPC.^{40,41} All those results indicate that it is an immunoglobulin mediated type 1 hypersensitivity reaction.

There have been reports of prescribing differences in the distribution of papillae across the tarsal conjunctiva with different contact lens types.^{42,43} EW Studies with SiHy have indicated that there are two distinct categories of CLPC: general and local.^{17,19} CLPC involving enlarged papillae across the entire palpebral conjunctiva is classified as general, and papillae confined to one or two areas, generally in the central region nearest the lid margin, are termed local. Patients with general CLPC typically experience more serious clinical symptoms and have more lens deposits than do patients with local CLPC.¹⁹

Additionally, CLPC is thought to be an immunologic response to deposits (lipid, protein and mucin^{44,45}) on the contact lens surface.^{38,46} Studies have provided valuable information about deposit composition and formation mechanisms. Tear protein identified includes lysozyme, lactoferrin, protein-G, pre-albumin, albumin and immunoglobulines.⁴⁷⁻⁵³ Protein deposition varies in amount and activity and is driven primarily by contact lens polymer composition, water content, pore size and mainly ionic nature. Lysozyme is mainly deposited

on negatively charged substrates, whereas albumin is deposited on neutral and/or positively-charged materials.

Higher water content contact lenses graded from the US Food and Drug Administration (FDA) group II and group IV have a tendency to have more deposits than lower water content lenses. Ionically charged contact lens polymers (FDA group III and group IV) tend to attract proteins, such as lysozyme. Contact lenses of FDA group IV tend to have the greatest deposition of protein.

Whereas protein is taken into the aqueous phase, lipid becomes associated with the polymer matrix itself, independent of material ionicity. Interestingly, the protein deposition is largely unrelated to subjective differences, whereas lipid deposition is related to both material composition and inter-subject differences in tear film components, blink factors and environmental factors.^{50,53} SiHy materials have deposition profiles different from those seen with conventional hydrogel lenses. The surfaces of SiHy materials are characteristically hydrophobic, with typically significantly lower quantities of protein and higher levels of lipid deposition being measured.^{54,58}

In vitro study⁵⁹ and *in vivo* study found the highest amount of lipid adsorption (non-polar cholesterol and polar phosphatidylethanolamine) in SiHy with senofilcon A, followed by galyfilcon A, (FDA group I), and balafilcon A (FDA group III), whereas the lowest adsorption was with lotrafilcon A and B (FDA group I). However, lipids alone do not appear to be antigenic.⁶⁰ On the other

hand, interaction among depositing materials may play a role because it has been shown that lipid deposits on FDA group IV lenses may inhibit deposition of lysozyme.⁶¹

There were no differences in lysozyme accumulation between five different SiHy materials until five days of wearing time, but increases consistently after a longer period of wearing time, without reaching a plateau like the FDA group IV materials.⁶² Jones and co-workers^{50,51} found approximately 50 per cent denatured lysozyme on balafilcon A *ex vivo* lenses and 80 per cent on lotrafilcon A *ex vivo* lenses. Galyfilcon A lenses denatured only about 25 per cent of the lysozyme *in vitro* but approximately 50 per cent *in vivo*.

This difference in denaturation suggests *in vivo* factors such as the presence of other tear components (for example, lipid), lens surface drying during the interblink period, and shear forces during blinking may all contribute to denaturation of surface proteins during in-eye wear. Another study has demonstrated that protein denaturation may play an important role in the development of CLPC.⁴³ This study is of significant interest, because of CLPC being reported at higher levels with silicone-based lenses than with conventional lens materials.²¹

Pollen and other allergenic substances adhere to the surface of the contact lens, too, especially in patients with a poor tear film and poor contact lens wetting.²³ Additionally, the coated contact lens induces physical trauma to the conjunctival epithelium, resulting in the release of chemotactic factors, such as neutrophilic chemotactic factor (NCF), causing the influx of various inflammatory cells.⁶³

In CLPC patients, NCF was increased 15 times the level of asymptomatic patients. Biochemical characterisation of the conjunctival factors showed that NCF are proteins of high molecular weights and are capable of producing a GPC-like inflammatory reaction in the upper tarsal of rabbits when they are injected daily for seven days.⁶⁸ Furthermore, the eventual activation of lipoxigenase results in the release of LK, too.⁶⁴

So far, there has been no correlation between CLPC with a particular contact lens type or specific deposits. There have been no studies that have shown a biochemical or morphologic difference between the coating on contact lenses from patients with and without CLPC. Ballow and colleagues⁶⁵ have shown that when coated contact lenses from patients with CLPC are placed on monkey eyes, a papillary

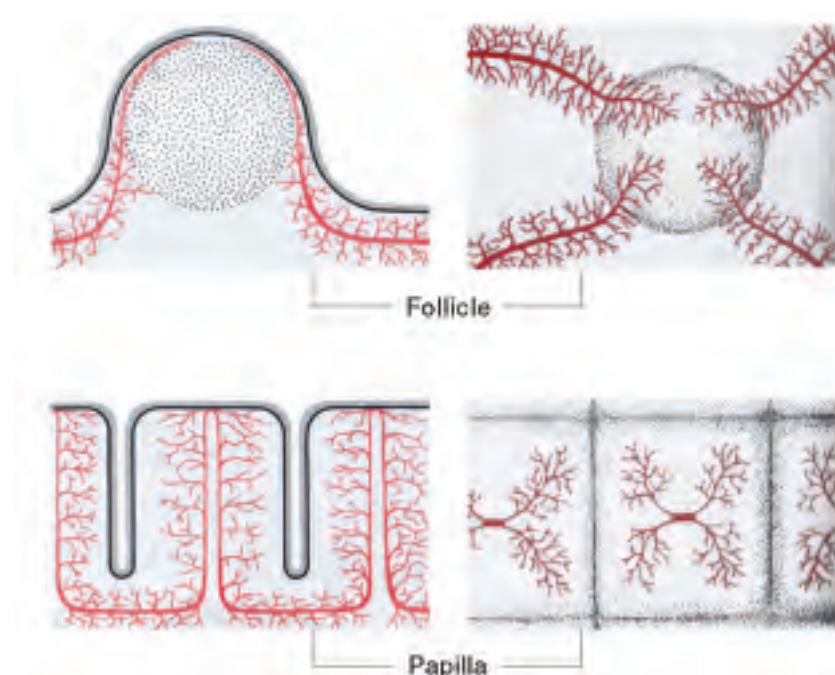


Figure 1. Papilla versus follicle. GOH Naumann. *Pathologie des Auges* 1980; 12: 252

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FoCoSi

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tarsal reaction develops with more of IgE and IgG. However, if coated contact lenses from asymptomatic patients are placed on the eyes of monkeys, a papillary reaction does not occur; neither is there an increase of tear immunoglobulin.

The second most prevalent sign of CLPC, after the inflammation of the conjunctiva, is excessive mucous. There is no increasing of the number of mucous secreting goblet cells;⁶⁶ moreover, the mucus vesicles in non-goblet epithelial cells contribute dramatically to the increase of mucous production.⁶⁷⁻⁶⁸ Excess mucous in the tear film interferes with vision by coating the contact lens surface and increased contact lens movement. Patients may report accumulation of mucous in the nasal corner of the eye, especially on waking.⁴⁸

In summary, the origin of CLPC appears to be a combination of mechanical irritation and immunological hypersensitivity reaction.⁴⁸

Purpose of this study

Papillae consist of a vascular supply that is observed radiating from a vessel occupying the central core of each papilla.^{22-24,48} In contrast, as a differential diagnosis, follicle has a white centre obscuring underlying vessels²² (Figure 1).

In vivo confocal microscopy showed in follicular conjunctivitis, a hyporeflective core containing hyporeflective round cells surrounded by a hyper-reflective capsule and vessels,⁶⁹ so follicles appear as round to oval elevations measuring between 0.5 and 1.5 mm in diameter with a grey-white centre. They can be seen in the inferior and superior tarsal conjunctiva and less often, on bulbar or limbal conjunctiva. Patients may complain of ocular itching, foreign body sensation, tearing, redness and photophobia.

Typical signs of viral conjunctivitis include preauricular adenopathy, epiphora, hyperaemia, chemosis, subconjunctival haemorrhage, follicular conjunctival reaction and occasionally a pseudo-membranous or cicatricial conjunctival reaction.⁷⁰⁻⁷⁶ The disease typically begins in one eye and progresses to the fellow eye over a few days. The second eye is usually less significantly involved.^{77,78} Presumed diagnosis with clinical findings, especially follicles, scanty watery discharge and preauricular adenopathy were consistent with laboratory

findings in 76 per cent of cases.⁷⁹

Viral conjunctivitis is typically characterised by a mononuclear cellular response with preponderance of lymphocytes or monocytes. In early stages neutrophils can be numerous.⁸⁰ Interestingly, there is a seasonal variation in the aetiology of acute adenoviral conjunctivitis, reaching the peak in summer, followed by winter and spring, whereas Herpes simplex infections showed no seasonal peaks.⁷⁹ The reason for these differences remains unclear in the studies. Three to four days after onset of the symptoms, the cornea shows a diffuse epithelial keratitis, followed at one week by a focal epithelial keratitis that persists for up to two weeks.

Around this time, subepithelial infiltrates may be noticed beneath the focal epithelial lesions. They exhibit a round or nummular shape, may persist for months or years,⁸⁰ and represent an immune response to adenoviral antigens deposited in the corneal stroma. Follicles are most seen in viral (adenovirus and herpes simplex virus) or chlamydial infections^{77,78,81,82} but were never described as a finding in CLPC.

There are few papers in literature prescribing a follicular-like response of the upper conjunctiva in CLPC^{22,37,43,81} besides the response of papillae formation. This reaction was presumed in severe cases with a longer period of time to be a cicatrization of the conjunctiva surface at the apex of the papillae and appear in a cream/white colour.^{22,81} Sugar and co-workers⁸² presumed a thickening of the overlaying conjunctiva as the reason for a milky appearance in some cases of GPC after keratoplasty. In earlier stages the papillae apex can display infiltrates, which appear in a whitish colour as well.

Fluorescein staining occurs with epithelial cell damage and frequently occurs with papillae with apices that are flattened or crater-like.^{21,37,81} The reason for those alterations was presumed to be the initiating

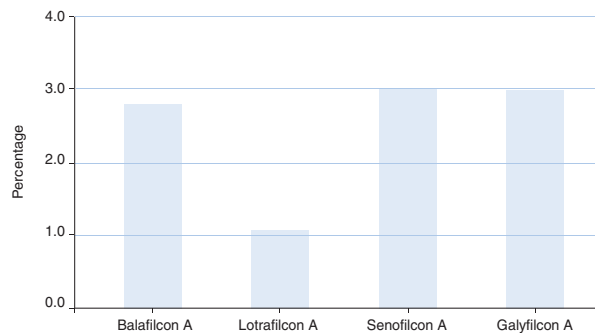


Table 1. Contact lens material

mechanical trauma. Greiner⁴³ in contrast found no fluorescein staining over those whitish papillae in GPC due to an epithelialised foreign body. Despite the importance of differential diagnosis of contagious viral or chlamydial infection, risk factors and aetiology of this specific condition are not well understood.

After the introduction of silicone hydrogel contact lenses, we thought we saw more of those whitish apices of papillae in patients with CLPC. The purpose of this study was to examine the distinct clinical presentations of follicular-like conjunctivitis associated with silicone hydrogels (FoCoSi) in cases with CLPC in a large number of silicone hydrogel lens wearers.

The study involved prospectively collected data from subjects wearing their contact lenses on a regular modality and replacement schedule. The data were compared with an asymptomatic control group.

Materials and method

The study was conducted from the kontaktlin-senstudio baertschi in Bern, Switzerland. A prospective, non-randomised, single centre study design was chosen for this research project. A total of 1,211 active silicone hydrogel contact lens wearers were included for the current analysis. Subjects with prior contact lens experience, as well as subjects with no prior contact lens wear experience (neophytes) were included. They had to have actively worn their lenses in their usual wearing mode, extended wear (EW) or daily wear (DW), between 1 January 2007 and 31 December 2007.

Demographic statistics

All subjects who wore silicone hydrogels in the period of the analysis were considered for the study. No exclusions due to age were made. Subjects ranged in age from 10 to 80 years with a mean of 34.09 and 63 per cent of them were female.

Materials

The contact lens materials included in the study were four different types of silicone hydrogel contact lenses: lotrafilcon A, balafilcon A, galyfilcon A and senofilcon A. All possible variations, such as toric or multifocal designs were included as well. The distribution of the used contact lens materials are listed in Table 1: 29.9 per cent of all subjects used senofilcon A, galyfilcon A material was used by 29.7 per cent, followed by balafilcon A with 28 per cent, lotrafilcon A was used by 12.3 per cent.

Method

The cornea, bulbar conjunctiva, upper and lower tarsal conjunctiva were examined. Examination was made under both white light and cobalt blue light with a yellow fluorescein enhancement filter using a wide range of magnification levels.

Fluorescein was used to detect corneal and conjunctival staining and to enhance the contrast in papillary size and definition. The reported symptoms were graded as well as tearing at the moment of FoCoSi. Additionally, preauricular lymph nodes were palpated and graded, and the anterior portion of the eye was observed to rule out any associated viral infections.

Finally, predominance to pollen allergy reaction was noted as well. Clinical diagnosis of CLPC and FoCoSi was based

on biomicroscopic findings of papillary changes of the upper and lower palpebral conjunctiva. All subjects with enlarged papillae presenting a follicular-like appearance were classified as FoCoSi. An example of a FoCoSi event is shown in Figures 2 and 3. Notice the numerous white spots with the absence of the central vascular tuft, whereas the surrounding papillae are present with a central vessel. This conjunctival change can be seen using the slitlamp biomicroscope; however, with Adobe Photoshop 7.0 software modified colour presentation, the FoCoSi differences can be observed much better.

Grading for follicular-like papillae presented in the upper and lower lid was divided into several subdivisions. Quantity of present follicular-like papillae, fluorescein positive spots, hyperaemia and oedema, and the character of tear secretion were graded from zero to 4.

Contact lens examination

To describe possible correlations of the appearance and frequency of FoCoSi, various contact lens parameters and wearing modalities were noted. Besides the type of the contact lens used, additionally listed were the age of the contact lens, wearing modality, movement and appearance of any material defects, and care solution used were noted with specifically developed grading

scales from zero to 4. As deposits on the surface of a contact lens are an important factor in the comfort of wearing contact lenses and can trigger CLPC, five different types of deposits (lipid, mucin, hydrophobic spots, cosmetics and mixed deposits) were noted and graded, too.

Statistical analyses

Data were included in this study from subjects who began EW or DW and attended at least one scheduled EW or DW visit. The first adverse response to contact lens wear during EW or DW was used to categorise the subject eyes into groups. Eyes that did not develop any adverse response to contact lens wear during the follow-up period were retrospectively categorised as asymptomatic controls. The adverse response groups included FoCoSi only. Clinical and subjective variables were collected at scheduled and unscheduled visits. Data for all events in the right or left eye or both eyes were recorded for clinical variables. All continuous variables were compared for differences among controls and the FoCoSi group using analysis of variance with mixed and random effects. Multiple comparisons were performed with Tukey HSD post hoc analysis. Categorical variables such as percentage of reported symptoms were compared between the groups using the chi-squared test and followed by Fisher exact test for multiple comparisons. Statistical significance was set at $p \leq 0.05$ for clinical variables.

Results

General results

A total of 46 FoCoSi subjects were seen, which was an incidence of 3.8 per cent. Subjects ranged in age from 19 to 63 years with a mean of 31.98 years of age and 56.5 per cent of them were female. Gender ($p = 0.058$) and age ($p = 0.633$) are not significant factors for the development of FoCoSi. For gender there was a tendency for males to be more prone to developing FoCoSi than females. Seasonal differences in occurrence of FoCoSi events showed peaks in January, April and essentially during June until August (Table 2).

Allergies against pollen were associated in only 50 per cent of all subjects with FoCoSi. There was no correlation between reported allergy propensity and the seasonal distribution of FoCoSi events ($p = 0.108$).

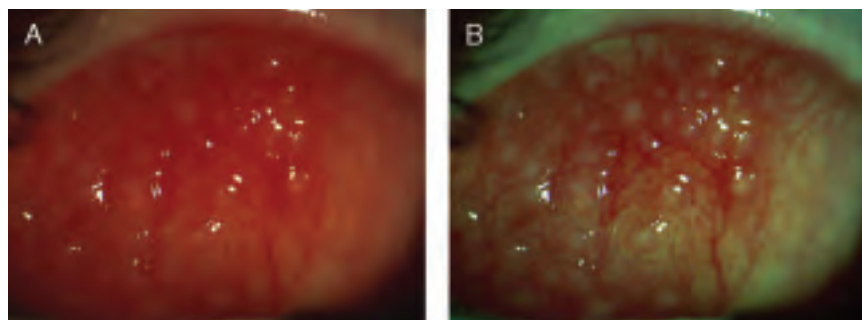


Figure 2. FoCoSi example as original picture (A) and as a software modified version (B)

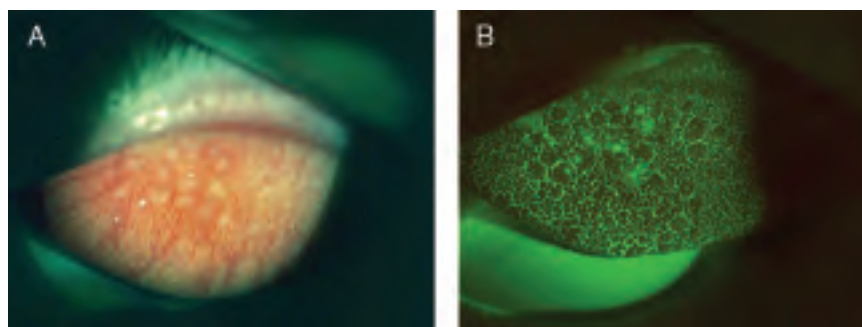


Figure 3. FoCoSi of one eye presented on slitlamp under normal light (A) and with fluorescein staining (B)

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FoCoSi

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Results of slitlamp examination of cornea and conjunctiva

None of the subjects with FoCoSi showed either positive preauricular lymphadenopathy finding or any viral reaction or conspicuousness of the cornea or conjunctiva. None of the subjects exceeds grading 2 in the lower palpebral conjunctiva for papillae. In the superior palpebral conjunctiva, only 15.3 per cent showed moderate to severe papillae formation with severe hyperaemia and oedema of the palpebral conjunctiva. The FoCoSi reaction was exclusively found in the superior palpebral conjunctiva. Of the subjects, 22.8 per cent showed monocular FoCoSi response. Observing the superior palpebral conjunctiva for each eye separately, 33.7 per cent showed from one to five, 26.1 per cent showed from six to 10, 13.0 per cent had from 11 to 20 and 4.3 per cent showed more than 20 FoCoSi spots.

Classification into local and general form of appearance was performed. All subjects presenting fewer than 11 follicular-like papillae formations were labelled as local, whereas the others were labelled as general form of distribution; 83.6 per cent were classified as local and 16.4 per cent of the subjects showed the general form of distribution. FoCoSi subjects with the general form reported significantly ($p = 0.003$) more symptoms.

Fluorescein staining was performed for two reasons: first, papillae are more visible and easier to grade; and second, to reveal persisting FPS on the apex of FoCoSi. Not all of the FoCoSi subjects showed FPS; 36.6 per cent presented the whole superior conjunctiva as fluorescein negative, 23.9 per cent had one FPS, 22.5 per cent had from one to three fluorescein positive spots, 11.3 per cent had from four to six FPS and 5.6 per cent had more than six FPS. Observing the correlation between the numbers of FoCoSi spots found and the amount of FPS showed that for the group with more than 20 FoCoSi spots, the highest amount of FPS was noted as well. This finding was statistically significant ($p = 0.020$).

A similar result was found for oedema,

so that the oedema was more severe in the group with more than 20 FoCoSi spots. Again, this is a statistically significant finding ($p = 0.015$) (Table 3). Additionally, the correlation between the reported subjective symptoms and objective findings of FoCoSi in the meaning of the amount of FoCoSi spots, the oedema and the amount of FPS in the superior palpebral conjunctiva was calculated. Interestingly, all three parameters presented similar results.

If the objective findings of FoCoSi were worse, the reported symptoms were worse, as well. In detail, if the oedema was graded worse, the symptoms were graded worse as well. That finding was strongly significant ($p = 0.002$). For the amount of FoCoSi spots in general, the same statistically significant correlation was found as it was for oedema findings ($p = 0.003$) (Table 4).

Finally, the more FPS observed in superior palpebral conjunctiva, the more severe subjective symptoms were described. Statistically, this correlation showed the weakest significance ($p = 0.032$) from the observed three findings. In comparing subjects without FPS reaction and those with more than six spots, there was a strong statistical correlation ($p = 0.001$) indicating that a higher FPS

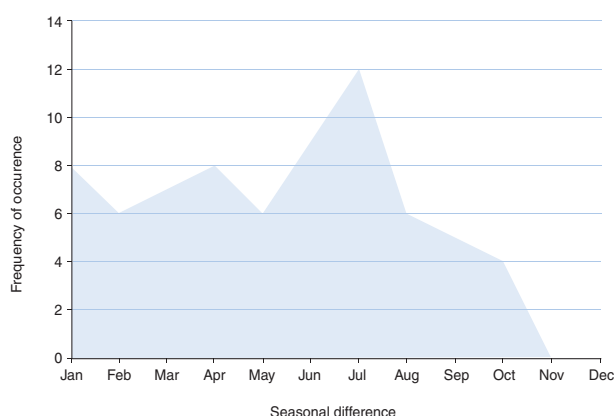


Table 2. Seasonal difference in occurrence of FoCoSi events

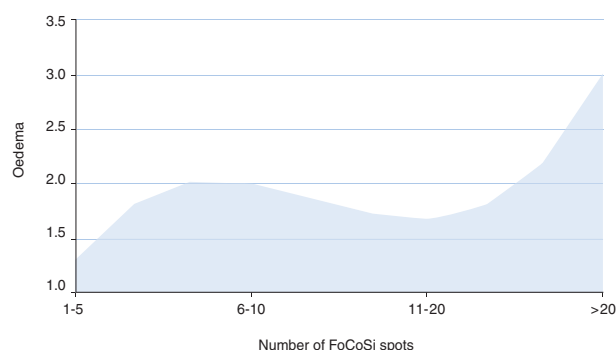


Table 3. Correlation between the amount of FoCoSi and oedema

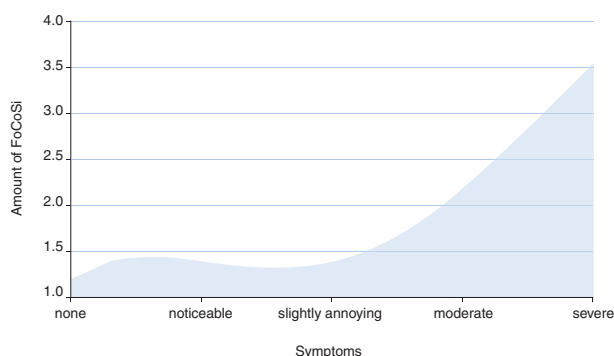


Table 4. Correlation between symptoms and amount of FoCoSi in the superior palpebral conjunctiva

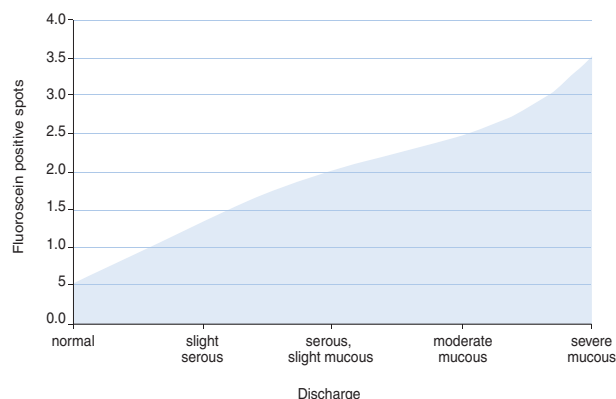


Table 5. Correlation between discharge and FPS

grading results in more severe symptoms.

There was a statistically significant correlation between the character of the noted tear secretion and the conjunctival oedema and FPS, respectively ($p < 0.050$). If the subjects had severe oedema or a higher amount of FPS, the discharge was more severe and more mucous-like (Table 5).

Results of the contact lens section

The contact lens types most often involved in FoCoSi were senofilcon A (45.7%), lotrafilcon A (26.1%), balafilcon A (19.6%) and galyfilcon A (8.7%); and none of the subjects presenting FoCoSi used lotrafilcon B. Due to the small number in the cohort, lotrafilcon B was not considered for statistical evaluation. These results were statistically significant ($p = 0.005$) compared with the asymptomatic control group. To be clearly evident, the risk ratio for developing FoCoSi for each contact lens material used was calculated and can be seen in Table 6. Lotrafilcon A (2.12) and senofilcon A (1.53) showed the highest risk ratio, followed by balafilcon A (0.70) and galyfilcon A (0.29).

The contact lenses were worn in different modalities; 56.5 per cent used their contact lenses on CW basis, up to one month as a

maximum, with the exception of one week for senofilcon A material. Wearing modality and contact lens material did not differ significantly ($p = 0.338$). Life span of each contact lens worn, at the time of FoCoSi happened, was reported; 61.9 per cent of the contact lenses were over the half-time of their life span.

Solution and deposits analysis

None of the findings in the solution category was statistically significant for a correlation with FoCoSi. The degree of deposits and type of material deposited on the surface were reported for each subject. Lipids are a common deposition for SiHy. In this study 22.8 per cent did not have any visible lipid deposits, 44.6 per cent had slight lipid deposition, 20.7 per cent had mild deposition and 12.0 per cent had moderate deposition. Interestingly, no subject had severe lipid deposition. While mucin is heavily produced in CLPC, deposition of mucin material would be logical, but 76.7 per cent of subjects showed no mucin deposits at all, 13.3 per cent showed slight deposition, 7.8 per cent had mild and 2.2 per cent moderate mucin deposition. Again, none of the subjects showed severe deposition.

There was no statistically significant correlation between the severity of conjunctival oedema, or FPS in the superior palpebral conjunctiva, and the amount of the previously discussed specific depositions on the contact lens surface ($p > 0.050$). Finally, the amount of mixed depositions was noted; 57.6 per cent showed no deposition at all, 19.6 per cent slight, 12.0 per cent mild, 5.4 per cent moderate and 5.4 per cent severe mixed depositions. Subjects with more severe follicle-like papillae formations (oedema $p = 0.021$, staining $p = 0.008$ and FPS $p = 0.032$) were observed with significantly more mixed deposition (Table 7).

Comparing the different contact lens materials and the type of deposition noted, there were no significant differences found for the different depositions, except for lipid. Balafilcon A material does attract statistically significantly more lipids ($p = 0.012$) than the other materials.

Conclusion and discussion

This study confirms the clinical presentation of follicular-like conjunctivitis associated with silicone hydrogels in cases with CLPC.

Aetiology

The incidence was 3.8 per cent lower than reported in events with CLPC.^{16,21} Gender and age were not a significant factor in developing FoCoSi which correlates to CLPC.¹¹ Whitish appearance in severe CLPC or GPC cases with a longer period of time was presumed to be a cicatrization of the conjunctiva surface at the apex of the papillae and appear in a cream/white colour.^{22,81} The onset time for FoCoSi after the first introduction to SiHy contact lenses was between four months and eight years. This indicates that for FoCoSi to occur it is not a matter of time or a chronic pathway. On the contrary, it seems to be an acute reaction. Sugar and colleagues⁸² presumed a thickening of the overlying conjunctiva as the reason for a milky appearance in some cases of GPC after keratoplasty. In earlier stages the papillae apex can display infiltrates, which appear in a whitish colour as well. These observations better match the appearance of FoCoSi than a cicatrization of the conjunctiva. If the immunohistochemical studies for CLPC³⁶⁻³⁹ represent the same findings in subjects with FoCoSi, infiltration of inflammatory leucocytes could give an explanation for the whitish appearance of FoCoSi. Sulfido peptide LK increases microvascular permeability,⁶⁷ which has the potential for creating oedema in the

Material	Cohort (%)	Events (%)	Risk ratio
Balafilcon A	28.0	19.6	0.70
Lotrafilcon A	10.5	26.1	2.12
Senofilcon A	29.9	45.7	1.53
Galyfilcon A	29.8	8.7	0.29

Table 6. Risk ratio for developing FoCoSi for different contact lens materials

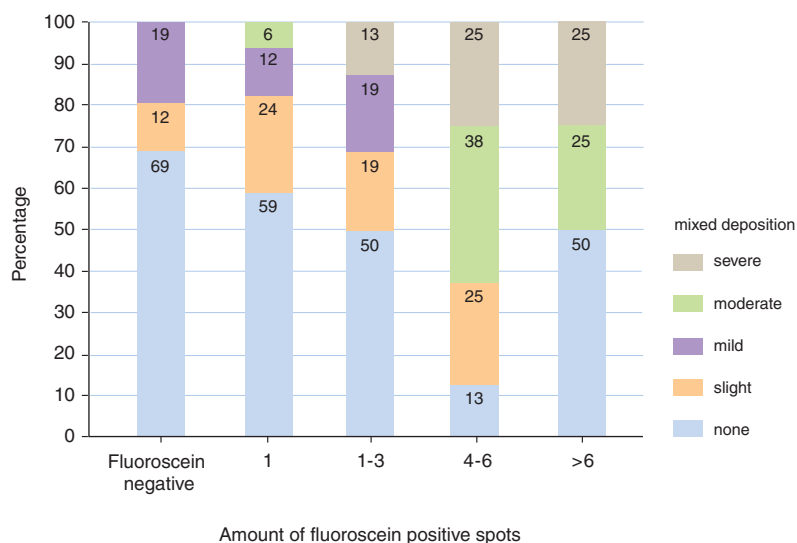


Table 7. Correlation between mixed deposition and FPS

Continued page 8

FoCoSi

From page 7

surrounding conjunctiva, leading to the characteristic shape of FoCoSi.

Environmental influence

An interesting finding was the seasonal distribution of FoCoSi events with peaks in January, April and during summer until August. Even if studies have shown that patients with a history of allergy seem to be more susceptible to CLPC,^{8,9} our findings did not correlate properly with allergies to pollen reported by the subjects. Fifty per cent of all FoCoSi subjects did not report any known allergy at all, and the January reports during winter in particular cannot be explained with pollen counting. Other factors like high pollution of the air could provide an answer to that question.

During the winter season, long periods of atmospheric inversion are common in Switzerland.⁸³ While the lower parts of Switzerland are predominantly covered by fog, the higher areas enjoy longer periods of sunny days. During atmospheric inversion, temperatures in the lower areas are cooler than in the higher alpine regions, resulting in minimal air exchange between both layers, and the pollution of the air rises dramatically. Other meteorological factors such as ozone (O₃) and temperature could have an impact on FoCoSi development. From April until August 2007, ozone frequently exceeded the limit value (120 µg/m³) published by Swiss federal emission control.⁸⁴

Pollution characterised by elevation of oxides of nitrogen (NO_x), ozone, tobacco smoke, fine and ultra-fine particulate and diesel exhaust particles seems to enhance allergic disease.⁸⁵ Additionally, the bioavailability of grass pollen allergens may be modulated by air pollutants. Interestingly, cleaning pollen from air pollutants reduces the allergic reaction significantly.⁸⁶ We have further studies arranged to resolve these questions.

Unilateral versus bilateral presentation

CLPC was reported only in 10 per cent of the cases as a truly monocular event,¹⁷ whereas a study with data from Australia and India¹⁹ showed with 78.4 per cent the highest amount of unilateral CLPC events reported so far in a study. In our cohort 22.8

per cent of FoCoSi events were unilateral. This phenomenon cannot be explained with unilateral different mechanical irritation as it clearly is in cases with foreign bodies on the ocular surface. All of the FoCoSi subjects have worn the same contact lens material on both eyes and only two lenses had minor material defects that could have introduced unilateral mechanical irritation to the tarsal conjunctiva.

On the other hand, immunological responses were discussed as a reason for CLPC; the fact that there were a great number of unilateral FoCoSi events may indicate that factors other than general immunologic responses may contribute to the pathogenesis of FoCoSi condition. Additionally, ocular viral infections are often unilateral in the beginning but with all the negative corneal and conjunctival findings related to viral infections and negative preauricular lymphadenopathy as well, viral involvement can be ruled out. We have not found a rational explanation for those unilateral findings, so far. Further studies should be conducted on that topic.

Local versus general form

As described in Australia there are local (81.8 per cent) and general (18.2 per cent) presentations of CLPC.¹⁹ FoCoSi showed a similar distribution (83.6 per cent local versus 16.4 per cent general). In very close agreement with CLPC, FoCoSi subjects with the general form reported significantly ($p = 0.003$) more symptoms; however, the mechanisms of action and aetiology of local versus general CLPC are poorly understood and clinical variables such as physiologic parameters of limbal and bulbar redness, lens surface and lens-fitting parameters could not differentiate between the subjects who developed either local or general CLPC.¹⁹ For FoCoSi, no correlation between local or general form and contact lens material, wearing modality, lifespan of contact lens, movement of contact lens, corneal reaction, or limbal and bulbar redness could be found as well. In summary, none of the included parameters of our study design showed an explanation for the different distribution of local and general FoCoSi form.

Fluorescein positive spots

In the FoCoSi study, fluorescein positive spots (FPS) appeared as the most relevant objective clinical parameter. Subjects presenting with FPS had more severe symptoms and mucous discharge and as a consequence, heavier coated contact lenses. These spots were always observed

on the apices of follicular-like papillae. In contrast, there was no FPS in normal papillae formation. Due to FPS, the FoCoSi syndrome can be divided into an active and a dormant stage of presentation. The active form only, with FPS, was responsible for the subjective symptoms patients noted, whereas the dormant form, without FPS, was detected only through previously described objective findings. Interestingly, the dormant form was observed only in patients who had previously presented an active form once in their lifetime.

FPS or whitish areas in CLPC or GPC have been discussed in only a few studies so far.^{22,37,43,81} Fluorescein staining occurs with epithelial cell damage and frequently occurs with papillae with apices that are flattened or crater-like. The reason for those alterations was presumed to be the initiating mechanical trauma.^{22,37} In contrast, Greiner⁴³ found no FPS over those whitish papillae in GPC due to an epithelialised foreign body.

Lotrafilcon A, with the highest modulus (1.4) of the studied materials, supports that presumption, but mechanical trauma alone as reason for FoCoSi and FPS seems to be unlikely, because senofilcon A material with a very low modulus (0.6) had the second highest incidence of FoCoSi events. Additionally, senofilcon A contact lenses showed the lowest amount of movement on the bulbar conjunctiva, which should have a positive effect from the mechanical point of view. Finally, in the majority of cases no defects in contact lens edge design—which could have induced FoCoSi or FPS—were found.

Another approach is to recognise FPS as a consequence of an inflammation or immunological process rather than the cause for FoCoSi. The immunohistochemical studies for CLPC³¹⁻³⁷ not only give an explanation of the whitish appearance of FoCoSi caused by inflammatory leucocytes infiltration, it also gives an explanation for FPS as well. Those processes promoting better infiltration of leucocytes can enhance the permeability of the overlying epithelium as well, resulting in possible staining with fluorescein.

Contact lens influence

Subjects wearing lotrafilcon A (2.12) and senofilcon A (1.53) contact lenses, respectively, had the highest risk ratio for developing FoCoSi, especially if the contact lenses were worn on a CW modality.

Deposition on contact lens surface

FoCoSi events may indicate an immunologic response to deposits that accumulate on

the contact lens surface as it was reported for CLPC in several studies. It is believed that these deposits or the exposure of the upper lid to allergens, especially denatured protein,⁵¹ on the contact lens surface is the initiating factor and subsequent immunologic reaction occurs in CLPC. If oedema, the number of FoCoSi spots and especially FPS got worse, mixed deposition on the contact lens surface was increased, which was more likely to be the consequence of the increased mucous discharge rather than the cause.

A shorter replacement schedule of contact lenses, discussed in former studies, was found to be preferable to avoid CLPC,^{13-14,19} and especially a one-week replacement cycle showed no CLPC formation at all.¹⁹ These findings make sense to prevent the ocular environment from coming in contact with a high amount of denatured protein depositions; however, 20.1 per cent of FoCoSi events were found in patients wearing their contact lenses one week CW (53.9 per cent of subjects in the CW group: 46.2 per cent senofilcon A and 7.7 per cent galyfilcon A). This finding suggests that another deposition or mechanism hypothesised for CLPC so far may play a role in the aetiology of FoCoSi, if any. On the other hand, the older the life span of the contact lenses, the more prone the subjects were to FoCoSi. This indicates that before FoCoSi can occur, a certain period of interaction between the eye and the contact lens is needed.

SiHy materials have different deposition profiles from those seen in conventional hydrogel lenses and can be summarised as less accumulative to protein but with a higher percentage of denatured protein^{50,51} and a significantly higher affinity to lipids.^{54,58} Lipid depositions are progressive, cumulative and do not plateau like protein. Because of great intersubject variability in lipid deposition, it was suggested that protein deposition is driven primarily by contact lens material, whereas lipid deposition is related to both material composition and intersubject differences in tear film components, blink factors and environmental factors.⁵⁸

In the present study, the deposition profiles were equal between the different contact lens materials. Only the amount of lipids was greater in balafilcon A than for the other materials, but in contrast this material showed only a low incidence of FoCoSi. It must be said that the amount of deposition was judged only by using slitlamp impression. Subjects with more severe follicle-like papillae formations (oedema $p = 0.021$, staining $p = 0.008$ and FPS $p = 0.032$) were observed with significantly more mixed

deposition, but this indicates more the result rather than the cause of FoCoSi.

Especially in subjects with FPS a severe mucous discharge was frequently observed. Concentrating on lotrafilcon A and senofilcon A with the highest incidence of FoCoSi, in former studies lotrafilcon A showed the highest amount for denatured protein and senofilcon A the lowest. For lipids, senofilcon A showed the highest and lotrafilcon A the lowest amount. Additionally, the two materials are extremely different over a great variety of parameters, for example modulus or coating.

These findings indicate that there is not an easy explanation of how FoCoSi occurs. One may suggest that denatured protein depositions alone are not responsible for FoCoSi; lipid depositions must be considered as well. Even though lipids alone do not appear to be antigenic,⁶⁰ they can be transformed or influenced, for example with ozone. These are new ideas to clear up the questions of aetiology of FoCoSi and perhaps give a new approach to solving the questions around CLPC as well. Further studies should be done on that topic.

Care solution

The contact lens care solution most related to FoCoSi was Opti-Free express (Alcon); however, in comparison with the control group, this finding was not statistically significant ($p > 0.05$) as it is the predominantly used solution in that group. Furthermore, while looking at the high amount of CW subjects who did not use any care solution at all, it seems that the care solution plays a minor role in FoCoSi development and the follicular-like changes are not a reaction to certain solution components.

Treatment of FoCoSi

The study design was not specifically made for evaluating the treatment of FoCoSi; however, two major treatments, changing wearing modality to DW or wearing daily disposable contact lenses for a two-week to four-week period, seem to be successful in solving the subjective symptoms during FoCoSi. If the subject was in CW, reducing wearing modality to DW was mostly effective enough. If the subject already was in DW, discontinuation of contact lens wear or changing to a daily disposable contact lens was successful. All FoCoSi subjects were able to resolve the syndrome and could continue with contact lens wear after treatment. FPS and oedema were completely resolved but the FoCoSi spots remain with a follicular-like whitish appearance. This was described as the dormant form of

FoCoSi and remains without any subjective complaints. Due to the juridical situation in Switzerland, we were not allowed to use medications for treatment. Further studies on that topic should be done to determine which, if any, medication could bring the dormant FoCoSi back to normal palpebral conjunctival appearance.

Summary

FoCoSi is a novel and relevant subtype of CLPC. The aetiology seems to be unclear to date and raises new questions about the aetiology of CLPC as well. The theory of a combination of mechanical irritation and immunological hypersensitivity reaction is questionable, because the mechanical irritation of senofilcon A can be classified as very low. On the other hand, lipid deposition on contact lenses rather than protein deposition and air pollution like ozone and fine and ultra-fine particles are a new approach in finding the cause of FoCoSi or CLPC. Fluorescein staining of the apices has shown the highest correlation with subjective symptoms. This is new and clinically interesting knowledge as well.

Finally, the different presentation of FoCoSi, such as local versus general, or bilateral versus unilateral, correlates very well to the reported findings in CLPC but our study design could not give an explanation for the aetiology of those findings. Further studies should be performed to answer all those new questions.

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References are available from the author at mwyss@kontaktlinsenstudio.ch.

Interpreting OCT scans

Dr Simon Chen

MBBS BSc FRCOphth
FRANZCO Retinal Specialist
Vision Eye Institute, Sydney

Top tips show you how to extract the wealth of valuable information in retinal OCT scans

Optical coherence tomography (OCT) is a safe, non-invasive, fast, reliable test that provides high resolution, cross-sectional images of the retina and vitreoretinal interface. It is an increasingly important tool for the diagnosis and monitoring of a wide range of vitreoretinal conditions.

Current commercial OCT machines use a near infrared broadband light source (not a laser) to illuminate the retina. Differences in echo time and intensity between the reflected light and that from a reference path are measured and converted into three to 10 micron resolution retinal images. This is analogous to the use of sonar waves to image the ocean floor. The resulting image can be considered to be like an optical biopsy of the retinal layers. The layers that appear in an OCT image represent changes in optical reflectance within the retina, which do not necessarily correlate with familiar histological layers.

The latest spectral domain OCT (SD-OCT) machines use complex Fourier analysis techniques to increase signal processing speed, resulting in faster scan acquisition and higher image resolution than is possible with older, time-domain OCT (TD-OCT) systems such as the Zeiss Stratus OCT.

Colour or greyscale

Colour images

Changes in optical reflectance are illustrated in a colour-coded fashion in which warm colours (red, yellow, white) indicate high reflectivity and cold colours (green, blue) indicate low reflectivity.

Greyscale images

Brighter shades are used instead of warm colours to indicate high reflectivity. Absence of reflection appears black.

Greyscale images are better than colour images for visualising epiretinal membranes (ERM), photoreceptor (PR) and retinal pigment epithelium (RPE) morphology. Colour images can be misleading as the displayed colours are false colours and dramatic changes in colour can be misinterpreted as large changes in OCT reflectivity.

Normal macula OCT scan

Familiarity with the appearance of a normal macular OCT scan (Figure 1) is important to

confidently identify pathological changes. Features to note (from anterior to posterior) include:

- The anterior signal originates from the inner limiting membrane (ILM) and retinal nerve fibre layer (RNFL). This has a smooth, relatively flat outline peripherally and a

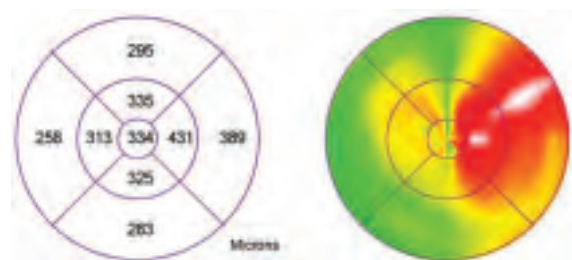
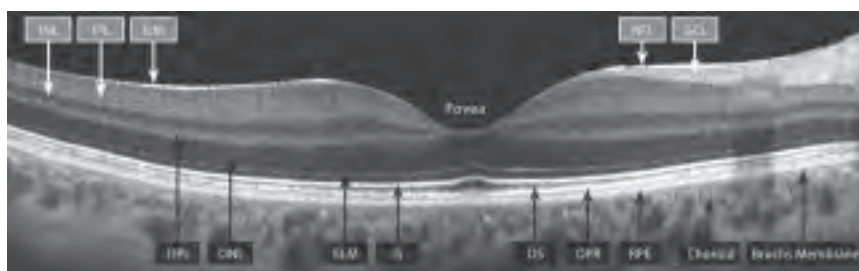


Figure 2. Macular thickness map showing macular oedema due to wet AMD

characteristic central dip at the fovea (referred to as the foveal pit).

- Posterior to the ILM/RNFL, subtle changes in reflectance are seen as alternating bands of hyper- (lighter) and hypo- (darker) reflectance representing the ganglion cell bodies, the inner plexiform, inner nuclear, outer plexiform and outer nuclear layers.
- Posterior to the outer nuclear layer, a series of three adjacent and increasingly hyper-reflective lines may be visible, representing the external limiting membrane (ELM), photoreceptor inner segment/outer segment junction (IS/OS junction), and RPE. A focal elevation of the ELM and IS/OS junction lines beneath the foveal pit is normally present. The ELM and IS/OS junction lines are often absent in SD-OCT scans of suboptimal image quality and in older TD-OCT scans.
- The signal posterior to the RPE arises from the choroid as patchy areas of high reflectivity.



ILM: Inner limiting membrane
IPL: Inner plexiform layer
INL: Inner nuclear layer
OPL: Outer plexiform layer
ONL: Outer nuclear layer

ELM: External limiting membrane
IS: Photo receptor inner segment
OS: Photo receptor outer segment
OPR: Outer PR/RPE complex

NFL: Nerve fibre layer
GCL: Ganglion cell layer
RPE: Retinal pigment epithelium & Bruch's membrane

Figure 1. Greyscale SD-OCT scan of a normal macula

Protocols for assessment

The most useful scanning protocols for assessing vitreoretinal disease are:

High-resolution line scan

This is a single high-resolution cross sectional scan, typically passing through the foveal centre, although the position of the scan can be changed to image areas of focal pathology outside of the fovea. This type of scan is good for making a diagnosis and assessing the retinal layers in detail (Figure 1).

Composite thickness map

This is a topographical display providing quantitative information about the thickness of the retina in a colour-coded map (Figure 2). Warm colours (red, yellow, white) indicate areas of thicker retina and cold colours (green, blue) indicate areas of thinner retina. The normal macula thick-

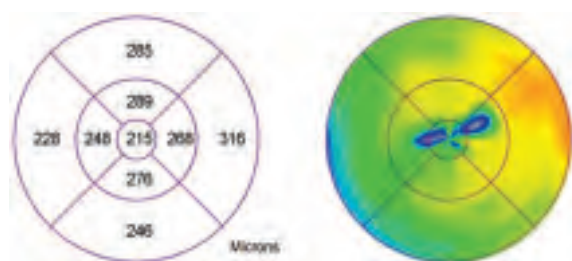


Figure 3. Macular thickness map showing partial resolution of macular oedema following intravitreal anti-VEGF treatment for wet AMD (same eye as in Figure 2)

ness is approximately 150 to 250 microns; this figure varies according to the specific machine and manufacturer's normative database. Thickness maps are good for quickly identifying and localising areas of diffuse retinal pathology that may be missed on individual high resolution line scans. The quantitative data provided by serial thickness maps is useful for monitoring progress and response to treatment over time, particularly in conditions such as macular oedema associated with diabetic retinopathy, retinal vein occlusions, ERMs or choroidal neovascularisation associated with wet age-related macular degeneration (AMD)(Figure 3).

En face and 3D scans

These provide impressive-looking images demonstrating the three-dimensional appearance of the vitreoretinal interface, which can be useful for educating patients and spicing up lecture presentations. Their clinical usefulness is relatively limited (Figure 4).

Top interpreting tips

Be systematic in your approach to reviewing OCT scans. I typically start by reviewing the macular thickness map to gain a quick overall view of the macular topography. Look for areas of retinal thinning (often associated with atrophic AMD, high myopia or chorioretinal scarring) or thickening (commonly associated with epiretinal membranes, wet AMD or macula oedema due to retinovascular disease) (Figure 2).

Next, I look at the high resolution line scans in greyscale, specifically reviewing each anatomical layer from anterior to posterior looking for the following:

1. Posterior vitreous face

This is a thin, curved or horizontal line of hyper-reflectivity visible anterior to the retinal surface. It is often not visible if the vitreous is still completely attached to the macula or if it has detached anteriorly beyond the area visualised by the OCT scan. When visible, the vitreous face may be completely detached from the macula or partially detached with residual attachment to the central macula and fovea; this is a common normal appearance called a perifoveal posterior vitreous detachment and represents the early stages of a posterior vitreous detachment (Figure 5).

If the attachment between the vitreous and the fovea is abnormally strong, pathological changes due to vitreomacular traction may be visible as a change in the shape of the normal foveal pit (the pit may be absent, shallower than usual, irregular or have underlying cystic structures visible) or splitting/cystic changes within the neurosensory retina (Figure 6). Advanced vitreomacular traction can lead to a full-thickness defect in the central neurosensory retina known as a macular hole (Figure 7).

2. Vitreoretinal interface

Look at the anterior surface of the retina for features of an epiretinal membrane (ERM). These are common and identified as a distinct hyper-reflective line in close contact with the retinal surface. ERMs can cause a wrinkling of the retinal surface, which can be visible as irregular saw-tooth shaped undulations in the retinal surface. ERMs may cause a reduction in depth or even complete loss of the normal foveal dip (Figure 8).

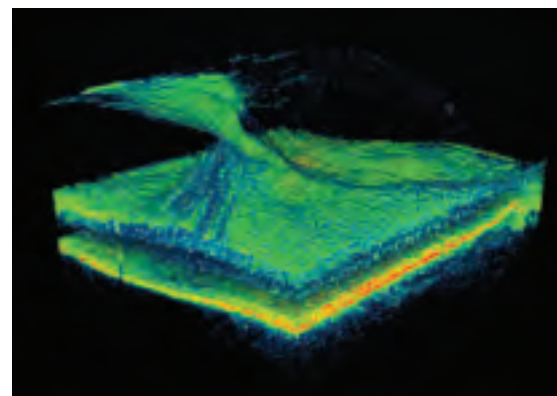


Figure 4. Three-dimensional macular scan showing vitreomacular traction

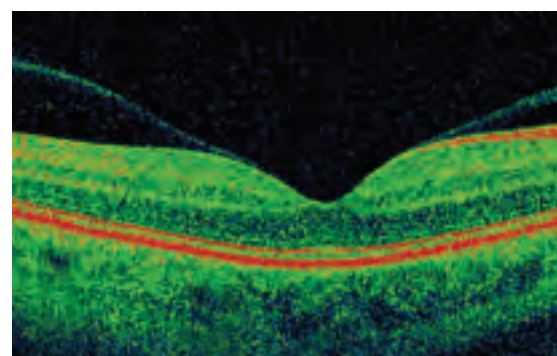


Figure 5. Perifoveal posterior vitreous detachment

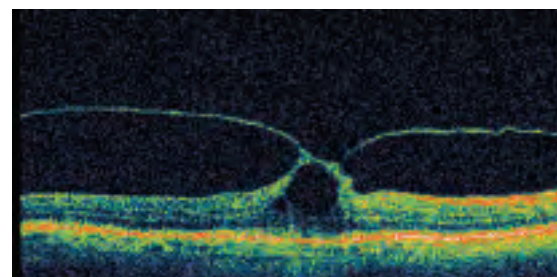


Figure 6. Vitreomacular traction with secondary foveal cyst

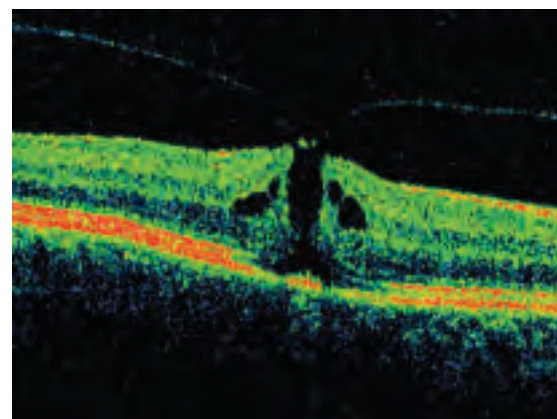


Figure 7. Full thickness macular hole due to vitreomacular traction. Free-floating operculum visible anterior to macular hole.

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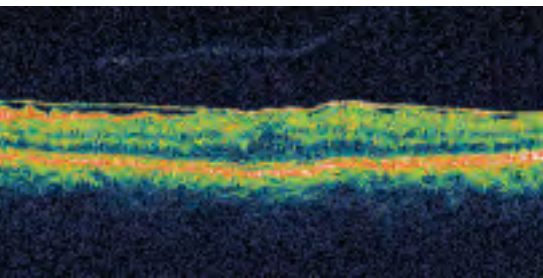


Figure 8. Epiretinal membrane with loss of the foveal pit and irregular retinal contour

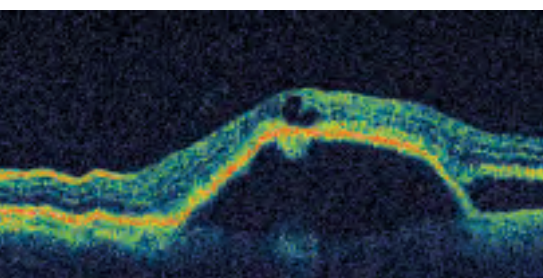


Figure 9. Wet AMD with cystic intraretinal fluid, subretinal fluid and pigment epithelial detachment

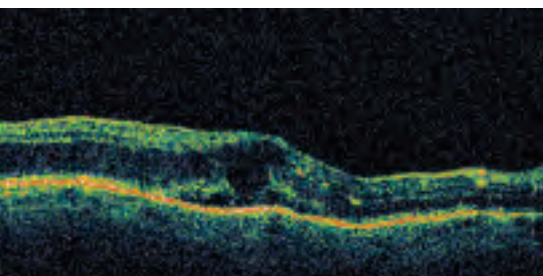


Figure 10. Cystoid macular oedema due to branch retinal vein occlusion. Note disruption of the IS/OS junction in the foveal region associated with poor visual acuity of counting fingers.

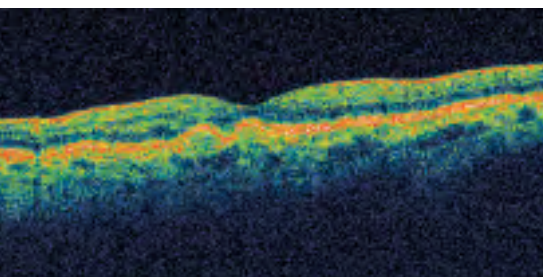


Figure 11. Dry AMD with drusen visible as irregular protuberances of the RPE

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3. Neurosensory retinal layers

Qualitatively assess the thickness, regularity and continuity of the retinal layers. Look specifically for hyporeflective cystic changes indicating fluid that may be intraretinal, subretinal (between the neurosensory retina and the RPE) or sub-RPE (below the RPE). Common causes of cystic fluid accumulation include wet AMD (Figure 9), diabetic macula oedema and retinal vein occlusions. Exudates may be seen as focal areas of hyper-reflectivity within the neurosensory retina in diabetic maculopathy, retinal vein occlusions and wet AMD.

4. IS/OS junction

Specifically assess the visibility and continuity of the IS/OS junction because the integrity of this structure often correlates with visual acuity in many retinal conditions. If the IS/OS junction is clearly visible and unbroken, the visual acuity is often good but if the IS/OS junction is disrupted, the visual acuity is often correspondingly poor (Figure 10). Thus the IS/OS junction can be considered to be a surrogate marker for retinal photoreceptor viability and provides prognostic information in monitoring or predicting response to treatment of conditions such as epiretinal membranes or wet AMD.

5. RPE

Look for areas of elevation, variation in thickness (thickening or thinning), and fluid above or below the RPE or discontinuity. AMD is associated with a wide variety of RPE changes on OCT, such as drusen appearing as small dome-shaped protuberances in the RPE (Figure 11), pigment epithelial detachments (PED) seen as larger dome-shaped elevations, fibrosis (areas of RPE thickening) atrophy (area of RPE thinning). Central serous retinopathy (CSR) is often associated with small PEDs, typically

in association with overlying subretinal fluid (Figure 12).

The choroid is poorly visualised with current generation OCTs but future machines will achieve greater choroidal resolution, enabling changes in conditions such as degenerative myopia, CSR, PCV and inflammatory choroidopathies to be analysed.

6. Assess quality of scan, look for common artifacts

Poor-quality scans may appear grainy, irregular in contour, colour and intensity, and may result from ocular surface disease (dry eyes, blepharitis, corneal disease), poor fixation, small pupils or extreme refractive error. Prior to performing an OCT scan, the ocular surface should be examined, the patient should be asked to blink, artificial tear-drops may be used in patients with dry eye, and fixation should be monitored or assisted with the use of an external fixation light.

Review scan placement (is the fovea centred or does the scan include the area of pathology?) and algorithm performance (do the computer-generated boundary lines used to calculate retinal thickness correlate with ILM/PR location?).

Movement artifacts are common due to poor fixation, poor patient co-operation or nystagmus, and appear as an undulating irregular appearance of all retinal layers. Shadow artifacts posterior to retinal vessels are a common and unavoidable feature of many normal scans.

Conclusion

OCT scanning provides detailed qualitative and quantitative information about the retinal structure in a wide range of retinal conditions. A familiarity with the appearance of a normal OCT scan and a systematic approach to evaluating retina OCT scans will enable practitioners to glean the maximum amount of clinically useful information when interpreting OCT scans.

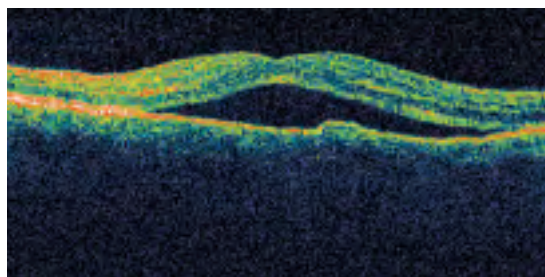


Figure 12. Central serous retinopathy with subretinal fluid and a small underlying RPE detachment



OCT and glaucoma

The most appropriate clinical diagnoses of glaucoma rely on thorough analysis and examination, not on imaging alone

Dr Tim Roberts

MBBS MMed FRANZCO FRACS
Vision Eye Institute, Chatswood;
Sydney Medical School
University of Sydney;
Department of Ophthalmology
Royal North Shore Hospital

Glaucoma is a group of diseases characterised by degeneration of the optic nerve with cupping of the disc and corresponding visual field loss. The definition of glaucoma has evolved over the past decades. Prior to the 1980s, elevated intraocular pressure (IOP) was almost exclusively used as the diagnostic criterion and clinical measure of progression. During the 1980s, the definition evolved to include elevated IOP and visual field (VF) defects. By the 1990s, optic disc and retinal nerve fibre layer defects were incorporated into the clinical definition.

The current gold standard for diagnosing glaucoma and identifying disease progression is optic disc photography (structure) and visual field testing (function). Structural changes at the optic disc usually occur before functional loss is seen on VF testing. The relationship between structural damage of the retinal nerve fibre layer (RNFL) and optic nerve axons and functional visual field loss continues to be extensively studied. The early diagnosis of glaucoma and the detection of progression are critically important as much of the functional damage is asymptomatic until late stages of the disease.

Ocular Hypertension Treatment Study

Of the patients with elevated IOP who developed glaucoma after five years, 57 per cent were diagnosed based on optic disc changes, 33 per cent based on visual field

changes and 10 per cent with co-existing visual field and optic disc change.

Visual field testing has been the mainstay of detecting glaucoma and progression; however, there is a small but significant group of patients in which accurate fields are unobtainable. Imaging technologies can now provide an objective assessment of the retinal nerve fibre layer which can be used by the ophthalmologist as part of the overall clinical assessment of patients with glaucoma.

Technological advances

The past decade has seen the introduction of imaging technologies, particularly retinal tomography (HRT), optical coherence tomography (OCT) and scanning laser polarimetry (GDx).

The development of imaging technologies was driven by the desire to:

- improve the diagnosis of glaucoma
- predict disease progression (risk modelling)
- detect disease progression.

OCT produces high-resolution, cross-sectional tomographical images of the retina. It is analogous to ultrasound B-mode imaging but OCT uses light rather than soundwaves. It projects a narrow slit (20 microns) of near infra-red (850 nm) light across the fundus; images are obtained by detecting optical back-scattering (interferometry). The original time domain scans comprised 400 A-scans per second and

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OCT and glaucoma

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measured the RNFL thickness around the optic nerve head along three high-density circular scans of 3.4 mm diameter. The new spectral OCT system captures 26,000 scans per second. Ultra-high speed OCT is able to capture 70,000 to 312,000 scans per second. OCT offers the advantage of objectivity in measurement reproducibility and ability to quantify change over time and measure the rate of change.

Spectral-domain OCT

Spectral-domain (SD) scanning is the newest generation of OCT technology and has largely replaced time-domain (TD) scanning. The faster image acquisition and better axial resolution gives better quantitative measurements of the peripapillary RNFL.

The larger 6x6 mm² zone increases the diagnostic capability as RNFL defects can now be identified in areas that would have been missed using the conventional circle scanner 3.4 mm. Acquisition time is

less than one second and the raw scans are captured and the distribution around the clock hours printed and compared to a normative database. RNFL parameters are printed with inter-eye differences recorded and a symmetry graph provided (Figure 1).

Optic disc anatomy

One of the difficulties in providing an accurate normative database is the significant variability in the optic disc appearance in humans. The average area is 2.2 - 2.4 mm² with a vertical cup-to-disc ratio of 0.34. The neuro-retinal rim follows the ISNT rule (thicker inferiorly then superiorly, nasally and temporally). There is a linear correlation between optic disc cupping and the overall disc diameter, with larger discs commonly having a physiologically larger cup. Clinically, it is important not to overlook early glaucoma in small hypermyopic discs (Figure 2).

What is the role of OCT?

There is a reasonable correlation between OCT and RNFL measurements and visual field loss detected with standard automated perimetry; however, it is important to remember that not all statistically significant change is clinically significant, nor is it always related to the disease process.

Imaging tests should be done as part of a clinical work-up, not as a screening test, as the false positive rate will result in an unacceptable number of 'suspect' cases. As with most studies, the gold standard reference for glaucoma is based on visual field defects, which tends to exclude early glaucoma and can result in the sensitivity and specificity of OCT being over-represented in early glaucoma.

Consequently, one of the important clinical factors to keep in mind when assessing new technologies is that the sensitivity of structural testing may not be as good in early glaucoma as in moderate to advanced

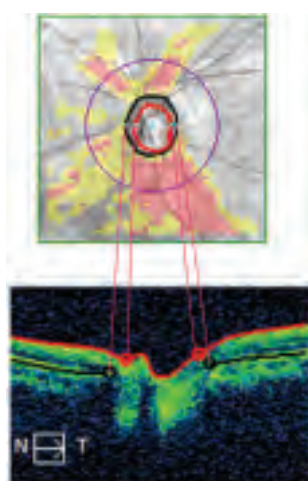


Figure 1. OCT print-out

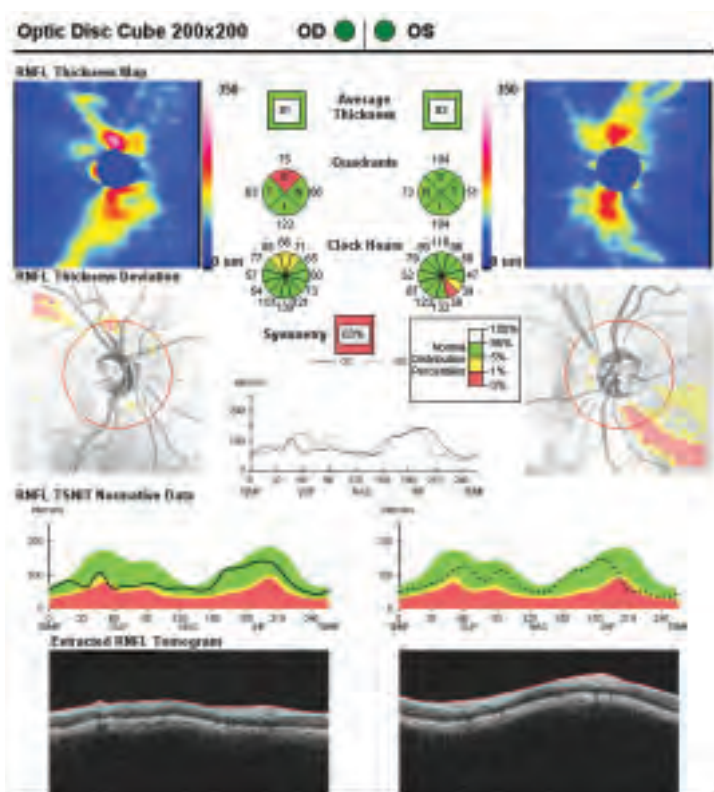


Figure 2. Optic nerve head calculations

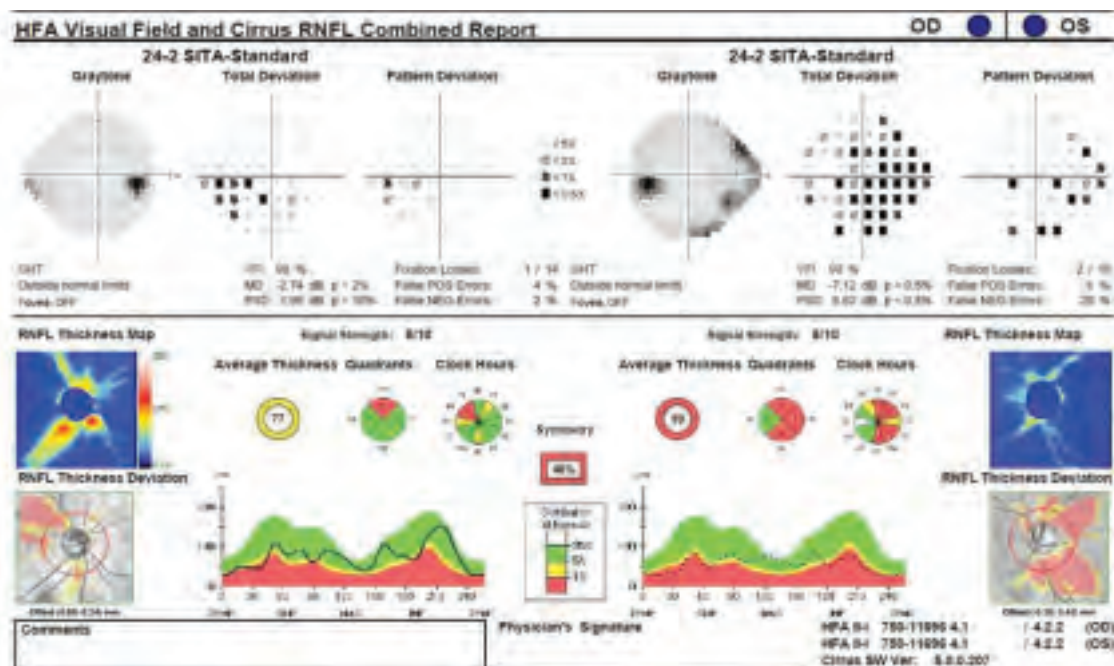


Figure 3. Correlation between visual field defect and OCT scan

glaucoma where the degree of neural tissue loss is significantly greater (Figure 3).

While the evolution of new technology is exciting, careful analysis of the clinical utility of these emerging tests is needed. The new SD-OCT images cannot be compared to images taken with the earlier TD-OCT technology. As progression is a key determinate of glaucoma control and the need for accelerated treatment, caution is required not to mistake the thinner RNFL images obtained with SD-OCT for glaucoma progression.

A limitation of OCT is the inability to identify optic disc haemorrhages, which are an important risk factor and have been shown to precede RNFL loss and field defects. They are an important sign for glaucoma diagnosis and progression, and highlight the reality that imaging alone cannot replace a careful examination of the optic disc. Any patient found to have a haemorrhage should be referred to an ophthalmologist for assessment even if an OCT scan is apparently normal.

When is imaging helpful?

1. Abnormal optic disc and reliable visual field with corresponding defect

The diagnosis is evident and imaging is not required to either make the diagnosis or for follow-up.

2. Abnormal optic disc and normal visual field

OCT imaging is not unreasonable to evaluate for pre-parametric glaucoma by seeking evidence of focal RNFL defects.

3. Abnormal optic disc and unreliable visual field

'Objective perimetry' was developed in an effort to provide reliable quantitative measurements in this subgroup of patients unable to accurately and reproducibly perform visual field testing. OCT can be cautiously used as a surrogate for field testing in these patients; however, clinical assessment of the optic nerve head by ophthalmoscopy remains the gold standard of monitoring progression.

4. Normal optic disc and suspicious visual field

A normal OCT scan may support a decision not to treat and to keep the patient under observation with repeat VF testing. The abnormal VF may be due to non-glaucomatous pathology.

Summary

The clinical diagnosis of glaucoma is made by an ophthalmologist or optometrist, not by a machine in isolation. Careful examination of the optic disc through a dilated pupil is crucial and allows for identification of patients with possible optic nerve head damage who can then be referred. A high index of suspicion should be observed in those with a family history of glaucoma or recorded episode of elevated IOP. Optic disc changes should be identified clinically and correlated with visual field loss. Most cases are diagnosed clinically with imaging tests providing secondary support if evident.

Thoughtful application of imaging technologies in appropriate individuals may help identify those with healthy optic nerves or those who are already showing signs of optic nerve damage. Cross-sectional assessment of an individual is obtained by comparison to a normative database but the limitations of the database need to be carefully understood to prevent erroneous interpretations. Longitudinal assessment using change-analysis software uses the patient's own scan as a baseline and is becoming more sensitive as the noise of the scans is reduced and the inter-test reproducibility and reliability improves.

Levetiracetam and diplopia

Norman Smith

BS

Leonid Skorin Jr

OD O MS FAAO FAOCO

Mayo Clinic Health System,
Ophthalmology and Optometry
Albert Lea, Minnesota, USA

Among the rare adverse effects of anticonvulsants, ocular complications are among the most common. While adverse reactions occurring in the hepatic and haematological systems attract considerable practitioner attention, ocular side-effects are, by comparison, more common, more annoying and frightening to patients and often cause patients to discontinue their medications. Discussion of adverse ocular effects with the patient plays an important role in patient overall satisfaction, compliance and informed consent.

A 79-year-old Caucasian male presented complaining of double vision. He reported he had taken only three one-half doses of a recently-prescribed anticonvulsant, levetiracetam before his double vision began.

Case report

His physician immediately discontinued the medication after he reported this complication to him. At our examination, the patient was alert, co-operative and oriented to person, place and time. His visual acuities were 6/6 corrected in each eye. Pupils were round and reactive to light, with no afferent pupillary defect. Confrontational visual fields with finger counting were full. A cover test with correction revealed a left esotropia of 12 prism dioptres. Motility testing showed right lateral rectus palsy with the right eye not progressing beyond the midline during right gaze (Figures 1-3).

Diagnosis

Diplopia resulting from right lateral rectus palsy secondary to anticonvulsant therapy with the oral medication, levetiracetam.

Discussion

Anticonvulsants have long been a primary treatment for a variety of neurological disorders. Levetiracetam (Keppra, UCB Pharmaceuticals, Inc.) has been available as a generic brand since 2008. Levetiracetam is approved in Australia as an add-on therapy for patients with partial onset seizures with or without secondary generalisation. It has been approved in the European Union and the United States as a monotherapy treatment for epilepsy in the case of partial seizures or as an adjunctive therapy for partial, myoclonic and tonic-clonic seizures.



Figure 1. Left gaze exhibiting no restriction

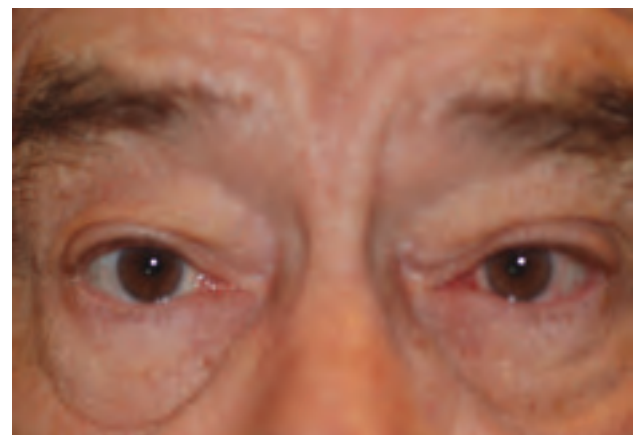


Figure 2. Primary gaze exhibiting mild right lateral rectus palsy

While levetiracetam is a useful treatment in reducing the frequency of seizures in some patients, the ocular side-effects suggest that precautions prior to use are warranted.

Studies show that levetiracetam is a better adjunctive therapy than placebo but its long-term safety is unknown. There is no information about its use in children or how it compares with the other add-on anticonvulsant therapies. Specific data on ocular side-effects are both sporadic and inconsistent. For example, the reported incidence of diplopia or blurred vision with use of the much more widely studied anticonvulsant drug carbamazepine ranges from four per cent to 58 per cent.^{1,2}

Mechanism of action

The mechanism of action of levetiracetam is unknown but it does not act in the same way as other antiepileptic drugs. Mainly excreted in urine, it is unlikely to have significant interactions with drugs metabolised by the liver. It does not inhibit the cytochrome P450 system. The drug binds to a synaptic vesicle protein, SV2A, which is believed to impair nerve conduction across synapses.^{3,4} The pharmacokinetics of levetiracetam are unchanged by other anticonvulsants, such as phenytoin, carbamazepine, phenobarbitone, lamotrigine and gabapentin. A double-blind trial compared levetiracetam with placebo as add-on therapy for 294 patients with refractory partial seizures.⁵ The frequency of seizures was halved in 33 per cent of patients taking levetiracetam

1000 mg daily and in 40 per cent of patients taking 3000 mg daily.⁵ Only 11 per cent of the placebo group had similar reductions in seizure frequency.⁵ Patients taking the higher dose of levetiracetam had a 30 per cent reduction in the weekly frequency of seizures relative to placebo.⁵

Prevalence

One hundred per cent of people who develop diplopia as a side-effect do so in less than one month when on levetiracetam. Sixty-four per cent are female and 46 per cent are between the ages of 40 and 49 years with only approximately eight per cent being either older than 60 years or younger than 30 years. The most common patient conditions involving the use of levetiracetam are, in order of frequency: epilepsy, multiple myeloma, convulsion, partial seizures and rheumatoid arthritis. The most common anticonvulsive drugs for which levetiracetam is used as add-on therapy are tegretol, lamotrigine, carbamazepine, depakote and vimpat.⁶

Conclusion

Anticonvulsants overall have a good safety record and often have excellent results compared to other drug categories. Nevertheless, some precautions prior to the use of these medications do appear warranted.

An initial, baseline ophthalmic examination is desirable if there is a history of pre-existing ocular conditions. Careful monitoring is particularly important in this case as subtle eye changes are often a precursor to more severe pathology.⁷ Ocular reactions in most cases can be averted or reversed with careful dose titration and monitoring.

Clinicians should try to use the lowest dose that achieves the desired therapeutic effect minimising the side-effect threshold that seems to vary greatly from person to person.⁸

Possible side-effects, including ocular reactions should be fully discussed with the patient. Truly informed consent not only protects the clinician but more importantly, minimises the chances of non-compliance.

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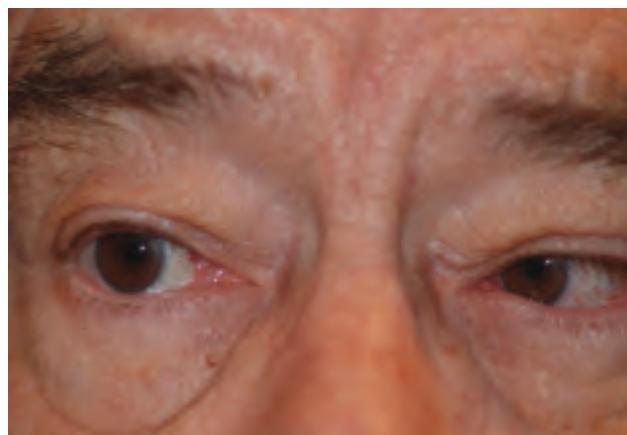


Figure 3. Right gaze exhibiting prominent right lateral rectus palsy

Contact lens material, contact

A rising number of cases of infiltrative keratitis and contact lens-associated infiltrates/infiltrative keratitis may be associated with the growing popularity of daily wear silicone hydrogel lens fittings

Dr Thomas Kislan

OD

Director, Stroudsburg
Eye Specialists, Hazleton
Eye Specialists and the
Dry Eye Clinic of
Northeastern PA, USA

The contact lens market grew substantially with the advent of soft contact lenses (SCL), which unlike their predecessors, rigid gas permeable lenses, do not require an initial adjustment period to achieve maximum comfort.¹ The trade-off for comfort with SCL wear has been

an increase in the rate of certain adverse events, including microbial keratitis and non-infectious infiltrative keratitis.²

The introduction of disposable silicone hydrogel (SiHy) lenses was expected to reduce the incidence of adverse events experienced with hydrogel CLs. While the incidence of hypoxic events (that is, neovascularisation) has decreased with the introduction of SiHy lenses, rates of microbial keratitis have remained the same^{2,4} and milder adverse events, such as non-infectious corneal inflammatory events (CIEs), increased.⁵ With nearly one million contact lens wearers residing in Australia, clinicians need to be concerned with these complications, both for the health of their patients and their practices.

The association between certain multi-purpose solutions (MPS) and infiltrative keratitis (IK) in daily SiHy lens wearers was first noted in 2007. Previously, the majority of urgent care visits for IK were in those who wore lenses on an extended wear (EW) basis.⁶

In an effort to ascertain whether the increase was due to a specific brands of contact lenses or solutions and whether there were any other characteristics in common among the cases of IK, a chart review was performed of all cases of IK that presented for urgent care visits to a large private interdisciplinary practice setting in 2008.

Methods

Patients who presented with infiltrative keratitis for an urgent care visit and concomitant acute pain, photophobia or decreased visual acuity (VA) during 2008 were included in this chart review. Factors assessed were: brand of lens and lens care solution system used at symptom onset; number, appearance, and location of infiltrates; conjunctival injection (graded on a scale of 1 to 4 where 1 = trace, 2 = mild, 3 = moderate and 4 = severe); treatment; resolution; and post-treatment management. To confirm solution used at onset, patients were instructed to bring their solution

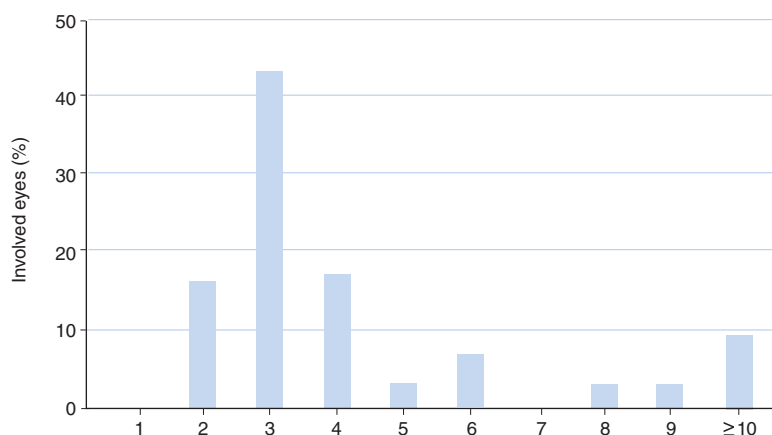


Figure 1. Distribution of the number of infiltrates noted on initial slitlamp examination

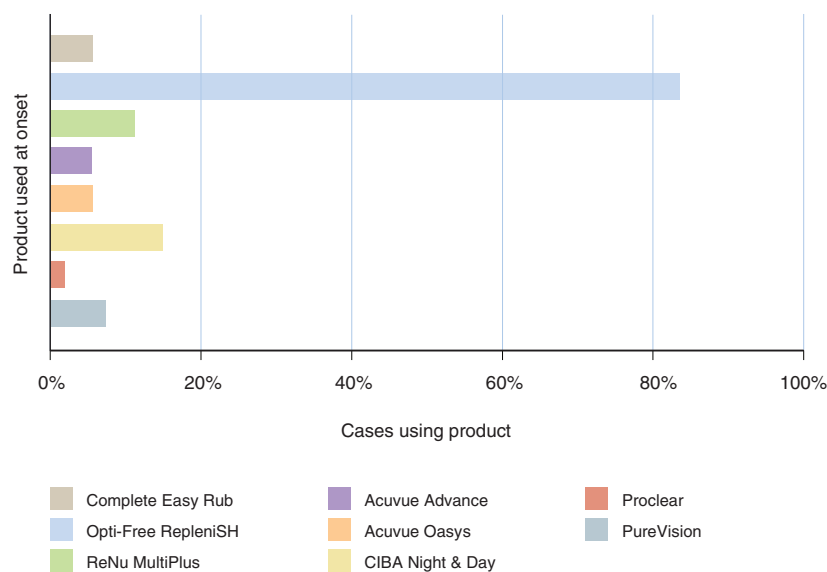


Figure 2. Distribution of the lens material worn and lens care solution used at presentation of symptoms

lens solutions and infiltrative keratitis

	Infiltrative keratitis	CLAIK
Number of infiltrates	≈ 50% with a single infiltrate ^{7,8}	100% Multiple infiltrates
Appearance of infiltrates	Round, hazy, grey-white, cloudy or amorphous opacities ⁹	Course, grainy/granular and grey opacities
Location of infiltrates	Corneal periphery or mid-periphery ^{9,11}	Central or paracentral
Severity with regard to location	Lower severity toward periphery ¹⁰	Severity independent of location
Symptoms	Mild to moderate ^{8,9,12}	Mild to moderate
Eye involvement	Most often unilateral ^{7,8,11}	Most often bilateral
Corneal fluorescein staining	Absent in about 50% ^{7,11}	Absent in > 90% of cases
Modality	DW, ^{6,10-13} EW ^{6,10,12} (risk greater ^{6,7,13})	DW
Lens material	Hydrogel, silicone hydrogel ^{5,10}	Silicone hydrogel, most commonly with Acuvue Oasys
Lens solution in DW	MPS ¹⁴	Most with Opti-Free RepleniSH ¹⁵⁻¹⁷

Table 1. Characteristics of commonly observed in patients sterile infiltrative keratitis (IK) compared with those observed in patients with contact lens-associated infiltrates/infiltrative keratitis (CLAIK)

bottle to their appointment. Treatment was individualised depending on the severity at the initial visit.

Results

A total of 54 patients presented for urgent care with the above signs and symptoms over the 12-month period. No patients presented with an epithelial defect or fluorescein staining. The mean conjunctival injection score was 1.8, and was ≥ grade 2 in 59 per cent (32/54) of cases (data not shown). Ninety-four per cent of cases (51/54) were bilateral. No involved eyes had a singular focal infiltrate. The mean number of infiltrates was 4.5 (range: 2 to 20) (Figure 1); had a greyish, granular appearance; and were centrally located on the cornea. VA loss of 6/12 or greater with ≥ 6 infiltrates and conjunctival redness of ≥ grade 2 occurred in 37 per cent (20/54) of eyes.

At the onset of symptoms, four SiHy lens materials were noted as being worn: Acuvue Advance (galyfilcon A, Vistakon); Acuvue Oasys (senofilcon A, Vistakon); Focus Night & Day (lotrafilcon A, CIBA Vision);

and PureVision (balafilcon A, Bausch + Lomb). Only one hydrogel lens material, Proclear (omafilcon A, CooperVision), was worn at symptom onset. Acuvue Oasys lenses were the most commonly noted lens, with 70.4 per cent (38/54) of cases wearing these lenses at symptom onset (Figure 2). Only three solutions were used by the patients at onset, with Opti-Free RepleniSH (Alcon) being used by the vast majority of patients as 83.3 per cent (45/54) used this solution at the time of the infiltrative event (Figure 2). Additionally, 64.8 per cent (35/54) of patients were using both Opti-Free RepleniSH and Acuvue Oasys lenses at symptom onset.

Mild cases did not require pharmacological treatment and were controlled with palliative measures such as artificial tears and cold compresses. To aid in quick resolution, moderate to severe cases were treated with steroids and non-steroidal anti-inflammatory drugs. When corneas were clear and all signs and symptoms had resolved, contact lens wear was managed by changing to a hydrogen peroxide-based care system and switching the lens material from a SiHy to

a hydrogel lens. The new combination of lenses and lens care product was successful in preventing a recurrence of keratitis in all cases. No long-standing vision loss occurred in any of the patients.

The distinct clinical picture described in this case series, including bilateral involvement, infiltrate number, location and appearance, from that commonly observed with IK,⁵⁻¹⁷ (Table 1) has led my colleagues and me to name this entity contact lens-associated infiltrates/infiltrative keratitis (CLAIK) in an effort to improve diagnosis and management.

Previous studies have shown evidence that CL material, CL solution and lens-solution interactions may lead to clinical observations on the cornea. While some combinations show higher levels of asymptomatic preservative-associated transient hyperfluorescence (PATH) with sodium fluorescein dye,^{18,19} other lens-solution combinations have led to clinically significant ocular events such as IK and CLAIK.^{15-17,20}

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CLAIK

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The first report in the literature of 'intolerance' to Opti-Free RepleniSH in SiHy lens wearers was by a Sydney-based optometrist, Narelle Hine, who stated: 'Recently several patients successfully using Opti-Free with their silicone hydrogel lenses (O₂Optix and Acuvue Oasys) developed intolerance to lens wear within weeks of swapping to the new Opti-Free RepleniSH solution.'²⁰ Similarly to Ms Hine, I have observed a predilection for infiltrative events with Opti-Free RepleniSH when combined with Oasys lenses, although I have not observed the same trend with O₂Optix lenses.

The anecdotal reports of an increase in IK in users of Opti-Free RepleniSH, such as this case review, are supported from work at the Brien Holden Vision Institute, based in Sydney, and the Institute for Eye Research, based in Kensington, Victoria. Their studies have shown that the incidence of infiltrative events in subjects participating in clinical trials who used Opti-Free RepleniSH were at a statistically greater risk of experiencing an infiltrative event than those using either a hydrogen peroxide or a PHMB-based solution.^{15,16} In their studies, almost 17 per cent of subjects using RepleniSH experienced an infiltrative event, of which more than 70 per cent were symptomatic (that is, infiltrative keratitis).¹⁵

Two trends in contact lens fittings may



Figure 3. Percentage of silicone hydrogel daily wear lens fittings globally, in Australia and the USA^{22,23,32,33}

explain why CLAIK was first noticed as more than an atypical case in 2007-2008 in my practice and by colleagues in Australia. While globally, SiHy lens fittings for DW remained below 20 per cent from 2006 to 2008, in Australia and the USA, this practice grew from 22 per cent and 27 per cent, respectively, in 2006 to 36 per cent and 46 per cent, respectively, by 2008 (Figure 3).^{21,23} During this time, in an attempt to address the needs of daily lens wearers left by the two solution recalls, ECPs recommended Opti-Free RepleniSH, which contains a novel moisturising agent, TearGlyde, which led to a subsequent increase in market share.^{24,26}

While both Opti-Free RepleniSH and Oasys lenses most commonly worn by the patients in this case series have the highest market shares, their estimated market shares are significantly less than the incidence

observed in this analysis^{26,27} and cannot fully account for the observed rate of infiltrates. The estimated market share of Opti-Free RepleniSH was approximately 25 per cent in 2008,²⁶ where > 80 per cent of cases were confirmed as using Opti-Free RepleniSH at the onset of symptoms in this series (Figures 4 and 5). The same can be said for Acuvue Oasys as the entire global Johnson & Johnson (Vistakon) contact lens franchise, which includes Oasys lenses, has only a 43 per cent market share for all of its contact lens brands,²⁷ where > 70 per cent of cases in this chart review used Oasys lenses.

All cases in this series were free of fluorescein corneal staining. This finding is not unexpected as Dr Mark Willcox, the chief scientific officer at the Brien Holden Vision Institute, reported at the 2008 FDA Ophthalmic Devices Committee Meeting that PATH (also known as SICS) is not associated with inflammatory events. He stated 'reliance on [PATH] as a measure of inflammation is questionable and clinical consequences of [PATH] are not known.'²⁸ Additionally, a recently-published study by Dr Loretta Szczotka-Flynn showed that even in CW, which carries the highest risk for complications, asymptomatic corneal staining is not associated with corneal inflammation.²⁹ Previous findings of an association between 'staining' and CIEs by these same authors in 2007^{30,31} have since been reassessed due to the co-linearity of observing transient hyperfluorescence or CIEs and MPS usage.²⁹

All but one patient presented wearing SiHy lenses, which has led to all patients who wore SiHy lenses being refitted with hydrogel lenses after resolution of the keratitis. Similarly, all patients were changed out of



Figure 4. Worldwide market share of leading soft lens care products^{27,32-34}

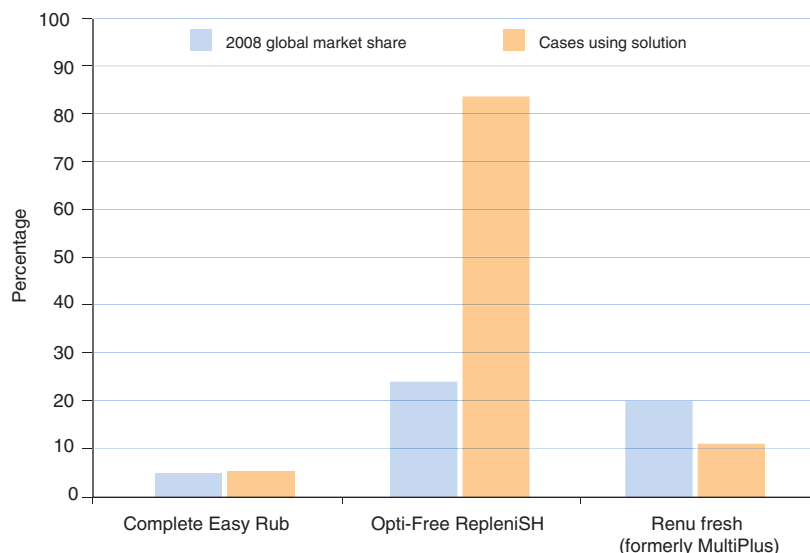


Figure 5. Worldwide market share of soft lens care products in 2008 and the percentage of CLAIK cases using the soft lens care products

the care systems used at the onset of their symptoms. While all the patients in this case series were changed to a peroxide system, other management strategies include changing to an MPS with a PHMB preservative, daily disposable lenses, especially for those with allergies, or LASIK for appropriate candidates.

Although the cases in this series are all from 2008, the problem persists in our practice (data from cases during 2009 and 2010 were presented at the 2011 annual meeting of the Association for Research in Vision and Ophthalmology in May). This does not come as a surprise as more than 50 per cent of fittings are DW SiHy lenses in the USA and the estimated market share of Opti-Free RepleniSH was greater than 25 per cent during both 2009 and 2010 (Figure 4).^{27,32-34} Similar trends in the use of SiHy DW fittings in both Australia and the USA^{22,23,32,33} (Figure 5) based on the annual international survey of contact lens prescribing, can be expected to result in practitioners of both nations noticing a significant rise in the cases of IK and CLAIK, if they have not already.

The question of the cause of IK in these cases cannot be fully determined here, as this study is a retrospective case series and patient factors that have been associated with CIEs, such as contact lenses,²⁹ lens case bioburden,³⁵ smoking²⁹ and other potentially confounding factors were not assessed. While causality cannot be directly determined, the high prevalence of CLAIK with certain MPS and SiHy material

combinations is of great concern, and warrants further study and vigilance in all regions, especially those with a high rate of DW SiHy lens fittings, such as occurs currently in Australia.

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Management of ocular allergy

Patanol combines antihistamine activity with stabilisation of conjunctival mast cells, offering patients relief from the discomfort and inconvenience of allergic response

Dr Arthur B Epstein

OD FAO

North Shore Contact Lens
and Vision Consultants,
Roslyn Heights NY, USA

In the United States, The National Institute of Allergy and Infectious Diseases (NIAID) reports that more than 50 million people have allergic diseases, which are the sixth-leading cause of chronic illness in the USA. The cost to the health-care system exceeds US\$18 billion a year and that does not take into account other economic losses such as wages, lost work days or other life disruptions.

Despite the cost and suffering, allergy is frequently ignored or minimised, except by those affected by it. As a result, many patients are left to their own devices when it comes to managing their own condition. Many allergy patients suffer in silence and many practitioners miss a golden opportunity to make a substantial positive difference in their patients' lives.

Hygiene hypothesis and genesis of allergy

An important concept in allergy is what allergists and immunologists refer to as the 'hygiene hypothesis'. It states that growing up in relatively antiseptic urban environments shields individuals from natural pathogens and shifts their T helper cell populations to those more sensitive to allergic stimuli. This increases the likelihood of developing allergies later in life. Conversely, growing up in an underdeveloped country or rural environment with greater exposure to pathogens decreases the chances for allergy later. This is believed to be the reason for allergy increasing in industrialised nations and being much less evident in underdeveloped countries.

Although we commonly perceive allergy as an annoying but essentially harmless reaction to common things like ragweed or cat dander, the origins of the allergic response are of far greater systemic significance. Allergy is a type 1 immediate hypersensitivity reaction designed to deal with serious threats immediately and decisively. The characteristic allergic over-reaction to normal environmental elements is yet another paradox, which explains why allergy patients suffer so much during allergy season.

Mechanism of allergy

An allergic reaction occurs in steps—some initiate, some follow. The first step is sensitisation, where an allergen is processed into a template for the creation of antigen-specific IgE molecules. This newly-created IgE populates a mast cell thus preparing it to respond to subsequent contact with the specific allergen.

Mast cells are the primary cells involved in ocular allergy. There are normally about 50,000 of them in human conjunctiva. When not exposed to allergens, mast cells reside deeper within conjunctival tissues; however, during allergy season, mast cells typically migrate to more superficial layers to be better positioned to react to allergens. Mast cells contain all of the components of allergic response including histamine and many other chemicals that mediate the full-blown allergic response.

Although most clinicians are unaware of this important fact, mast cells differ in function, morphology and chemistry, depending on where in the body they reside. Medications that stabilise mast cells are typically effective only on the specific subset of mast cells they are designed to stabilise. Mast cell stabiliser medications designed for rhinitis or asthma are likely to be ineffective when treating seasonal allergic conjunctivitis.

Early-phase response describes the immediate hypersensitivity reaction when a

sensitised mast cell encounters an allergen. Mast cell activation initiates the release of histamine and numerous other preformed and stored inflammatory mediators, followed by the synthesis of a variety of proinflammatory and messenger molecules such as cytokines and leukotrienes.

There is a second, late phase reaction that occurs in the rest of the body marked by a cellular response, but this is an insignificant part of acute ocular allergy with which most optometrists deal.

Allergy medications

Antihistamines used for ocular allergy are H-1 antagonists. They function as reversible competitive blockers of H-1 histamine receptors. Depending on the specific medication, the therapeutic effect can take up to several minutes to kick in and provide relief. Most antihistamines provide several hours of relief, particularly the modern agents. Antihistamines work in a straightforward way. They possess much greater affinity for histamine receptors than histamine does and on instillation, simply attach H-1 receptors on nerve endings and vascular smooth muscle, blocking attachment of histamine. Antihistamines are functionally inactive and prevent any physiologic response.

Although antihistamines are perceived as itch-stoppers, they have other clinically important properties. In 1960, Mota and DaSilva described the biphasic effect, an intrinsic property of all antihistamines that is unrelated to histamine blocking. Mota and DaSilva discovered that, at low drug concentrations, antihistamines stabilise all cell membranes. At higher concentrations, the antihistamine suddenly and catastrophically disrupts the cell membrane releasing cell contents. This occurred in a predictable, dose-dependent fashion.

This antihistamine effect on cells was found to be non-specific, affecting all cell membranes. In the context of allergy, low concentrations of antihistamines stabilise

mast cell membranes similarly to a function-specific mast cell stabiliser and with the same result: prevention of the release of histamine and other allergic mediators.

Commonly-prescribed ophthalmic antihistamines, such as ketotifen (Zaditen, Novartis Ophthalmics) are marketed as a combination antihistamine-mast cell stabiliser. These agents derive initially from systemic use. While the systemic concentrations never reach critical membrane disruptive levels, this is not the case with the vastly higher concentrations of their topically administered ophthalmic counterparts.

Tests using human conjunctival mast cells have demonstrated that at commercially formulated concentrations, these classical antihistamines cause sudden and rapid destabilisation of mast cell membranes and the subsequent release of histamine and all other allergy mediators.^{1,2} While all of these medications are potent H-1 antagonists, they have no effect on the other mediators that they release.

Olopatadine (Patanol, Alcon Laboratories) is the only exception among the currently marketed ophthalmic anti-allergy medications. It effectively combines antihistaminic activity (with no biphasic effects) and effective stabilisation of human conjunctival mast cells.³ First introduced in 1997, Patanol was developed specifically for treatment of allergic conjunctivitis and tested on human conjunctival mast cells during its development. All other currently available ophthalmic medications were first introduced for rhinitis, asthma or other systemic allergy.

Well over a dozen published, peer-reviewed, well-controlled human-subject studies have compared Patanol to other topical allergy medications. Patanol has consistently been shown to be more effective, more comfortable and better tolerated in all clinical outcome measures. The predominance of Patanol is likely to be due to its dual action as both a potent H-1 blocker as well as an effective stabiliser of human conjunctival mast cells.

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Clinical QUIZ

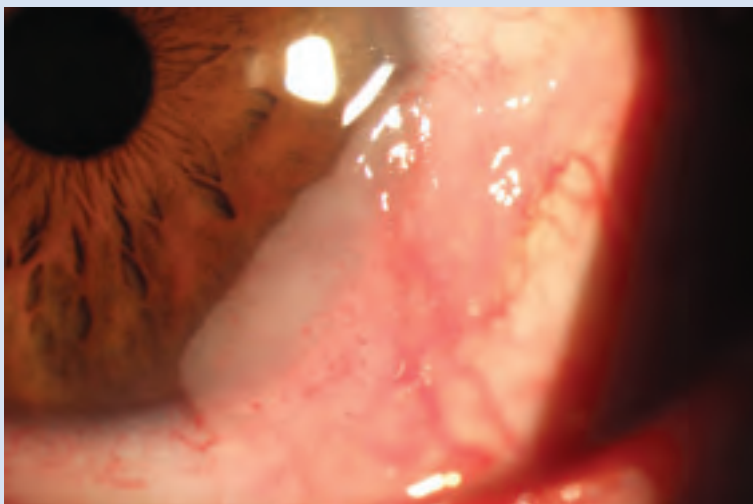


Photo: Matthew McLennan

What is your diagnosis and management?

ANSWER PAGE 26

Monthly ranibizumab injections better than quarterly

Best-corrected visual acuity (BCVA) is shown to most significantly improve among patients who receive monthly as opposed to quarterly ranibizumab injections for AMD.

An Austrian study, supported by Swiss pharmaceutical company Novartis, divided 293 patients into three groups—those receiving quarterly injections of 0.3 milligrams of ranibizumab, those receiving quarterly injections of 0.5 milligrams of ranibizumab and patients given monthly injections of 0.3 milligrams of ranibizumab.

Patients were monitored over a 12-month period. Patients all received three consecutive monthly injections as part of the 'loading phase' of treatment before moving into the 'maintenance phase' of treatment involving either monthly or quarterly injections.

Over the 12-month period, patients in the monthly injections group enjoyed an average BCVA improvement of 8.3 letters, compared with 4.9 and 3.8 letters for the 0.3 milligram and 0.5 milligram quarterly groups, respectively.

All patients recorded significant and relatively similar increases in BCVA within the first three months of their respective treatment regimens, yet those in the quarterly

injections groups suffered BCVA reductions in the subsequent nine months.

Patients receiving monthly injections demonstrated a mean increase in BCVA of 0.8 letters in their final nine months of treatment.

Ranibizumab, which is known by the trade name Lucentis, is used in the treatment of wet AMD.

Schmidt-Erfurth U et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE Study. *Ophthalmology* 2010; e-publication 9 Dec.

Medical industry website

A new website launched by the Australian Medical Industry hopes to raise awareness of the organisation's contribution to the health and economy of Australia.

The website, launched in July, includes information about making and using medicines as well as career advice.

Visit www.ausmedindustry.com.au.

Effect of contact lens solutions on tear film

Dr Ami Abel Epstein

OD

Eye Do Family Eye Center

Birmingham AL, USA

Lens care solutions that remove denatured proteins while maintaining certain proteins in their native state may help to reduce bacterial infections

The ocular environment is a sensitive system that has many components. One important element of this system is tear film which, in addition to providing a smooth optical surface,¹ also protects and lubricates the surface that is exposed to the environment.² There are four physical attributes of healthy tear film: pH, osmolality, viscosity and surface tension.² Tear film also has inherent antimicrobial properties. This article will review the physical attributes and antimicrobial abilities of tear film and how they may be affected by contact lens solutions.

Tear film attributes

pH level is the measure of a solution's acidity, alkalinity or neutrality. A pH level of 7.0 is neutral; those that are lower are considered acidic and those above it are alkaline. Osmolality is the concentration of dissolved particles in a solution.³ Viscosity is the ability of a fluid to resist a force that would cause it to flow.^{4,5} Surface tension is a property of liquids where, due to unbalanced molecular forces at or near the surface, the surface contracts and takes on properties resembling those of a stretched elastic membrane. The healthy tear film values for each of these attributes are contained in Table 1.

Tear film proteins

Tear film comprises the mucin component, the aqueous component and the lipid component. Abnormalities within any of these components can result in tear film instability and hyperosmolality.^{18,19} The aqueous component, which is the most voluminous portion of tear film, contains almost 500 proteins.²⁰ Many of these proteins are present in very small, almost negligible quantities (< 0.1 mg/mL⁻¹), but there are four that are present in large concentrations: lactoferrin, lipocalin, lysozyme and secretory immunoglobulin A.¹⁸ Table 2 lists their concentration in tear film and the roles that they play.

Attribute	Healthy tear value	Supplemental notes
pH	7.30 to 7.70 ⁶	The pH range of healthy tear film can vary depending on each individual's ocular physiology⁶
Osmolality	244 to 344 mOsm/kg ^{7,8}	- Osmolality levels can vary depending on the method by which the tear film is collected and the location on the eye from which the sample was collected^{7,8} - Osmolality levels decrease at night, when eyes are closed, due to a reduction in tear film evaporation. During the day, with the eyes remaining open, levels rise due to increased evaporation of the tear film^{3,9,10} - In patients experiencing dry eye, osmolality levels can increase due to an increased concentration of electrolytes³
Viscosity	1 to 10 cP	- Shear stress, also known as shear thinning, can cause viscosity levels to decrease^{11,12} - When the eyes are open, tear film has a higher level of viscosity and thus, is less prone to damage and tear film break-up. When the eyes are closed, such as during blinking, tear film has a low viscosity level, which helps to prevent damage to the epithelial layers¹³
Surface tension	42 to 46 mN/m ¹⁴	- The surface tension of healthy tears is lower than that of water (72 mN/m) due to the presence of proteins, electrolytes, lipids and other substances¹⁵ - Patients experiencing dry eye have higher levels of mean surface tension than those without dry eye^{16,17}

Table 1. Healthy tear values for pH, osmolality, viscosity and surface tension

Protein	Concentration ¹⁹	Tear film role
Lactoferrin	1.65 mg/mL ⁻¹	• Binds to Gram-positive and Gram-negative membranes²¹ • Inhibits the spread of <i>Escherichia coli</i>, <i>Haemophilus influenza</i>, and species of <i>Pseudomonas</i>, <i>Staphylococcus</i> and <i>Streptococcus</i>²¹ • Possible synergistic connection with lysozyme²²
Lipocalin	1.55 mg/mL ⁻¹	• Binds with lipids and has a strong affinity for fatty acids²³ • Indirectly enhances tear film antimicrobial abilities by maintaining lysozyme, which is accomplished by binding between fatty acids and preventing the presence of long-chain fatty acids that can inactivate lysozyme²⁴
Lysozyme	2.07 mg/mL ⁻¹	• Delivers its antibacterial effect by hydrolysing the bonds in the outer walls of bacteria²⁴ • Has a special affinity for bacteria that are Gram positive, and its principal targets in tear film are species of <i>Streptococcus</i> and <i>Staphylococcus</i>²⁵
Secretory immunoglobulin A (secretory IgA)	1.93 mg/mL ⁻¹	• Prevents bacteria from forming on the ocular surface²⁶ • Makes bacteria targets for phagocytosis²⁶

Table 2. Concentration and role of the major proteins of tear film

These proteins maintain their greatest antimicrobial properties when they are in their natural state. A protein becomes denatured, or altered from its natural state, when there is a change in its secondary or tertiary structures. This can occur as a result of temperature changes,²⁷ surface hydrophobicity,²⁸ peroxidising lipids²⁹ and when pH becomes strongly acidic.³⁰ Proteins lose much of their antibacterial properties when denatured. Another consequence of denatured proteins is that their presence may lead to their development of diseases, such as papillary conjunctivitis.³¹

Contact lens solutions and tear film

The main functions of a contact lens solution are to clean and disinfect the contact lens and to make lens wear as comfortable as possible. Lens solutions have different formulations, which can result in varying solution characteristics, such as pH levels and degrees of antibacterial efficacy.¹⁵ The physical attributes of tear film and its proteins can be affected by contact lens care solutions.

A contact lens solution's pH is affected by the buffering agents (for example, boric acid, sodium phosphate, taurine) contained in the formulation.¹⁵ Solutions with pH levels < 6.6 and > 7.8 can cause ocular discomfort and stinging.¹⁵ Tear film osmolality levels in patients experiencing dry eye tends to be higher than average (305 mOsm/kg)^{16,32,33} and because most contact lens solutions have osmolality levels lower than this, patients may experience discomfort due to these differences in osmolality.²

Different agents contained in contact lens solutions have different levels of viscosity. For instance, the cleansing agents are more viscous than the solutions' lubricants, which are more viscous than the soaking agents.³⁴ These viscosity levels have the potential to influence patient comfort on lens insertion or at end of day.¹⁵ Surface tension is also an important part of contact lens wear, as the lens floats within the tear film above the cornea.³⁵ Contact lens solution components that reduce the surface tension of tear film, such as surfactants, may lead to increased movement of the lens on the cornea and a reduction in patient comfort.¹⁵ Contact lens solutions that do not closely align with the four properties of healthy tear film may have a negative impact on the comfort of contact lens wear, either on insertion or throughout the wearing period.²

Tear film contains almost 500 proteins, some of which have antimicrobial abilities. Contact lens solutions are very effective at removing proteins, both natural and denatured, from contact lenses. A study by Williams and colleagues (2003) casts doubt on whether patients are better off having all proteins removed from their lenses.³⁶ In this study, contact lenses that had been previously worn and therefore had components of tear film adsorbed by them, were compared with new contact lenses. The authors found that the worn lenses contained less viable bacteria for certain strains of *P. aeruginosa* and Gram-negative bacteria than the new lenses.³⁶ The Williams study poses an interesting question. If lenses that were coated in proteins that occur naturally in tear film presented with fewer viable bacterial strains, then would it be beneficial to

keep them active rather than automatically removing all proteins as many contact lens solutions currently do?

Conclusions

The eye has many attributes that can be adopted and incorporated into lens care solutions. As scientists continue to unravel the complexities of the ocular system, additional elements will be discovered that may make solutions an even more effective part of contact lens care.

For now, we know that tear film is vital to keeping the eye comfortable and healthy. Healthy tear film has specific parameters for pH, osmolality, viscosity and surface tension. Developing lens care solutions that closely match these values will help maintain the balance that exists within the ocular environment.

Certain proteins in tear film have antimicrobial properties when in their natural state, and developing lens care solutions that dissolve and remove denatured proteins, while maintaining certain proteins in their native state, may help to reduce the amount of viable bacteria that can form on the lens. While it may be beneficial to incorporate as many attributes of the eye as possible into future contact lens solutions, manufacturers should still take every opportunity to augment these properties, particularly with regard to disinfection.

References are available from j.megahan@optometrists.asn.au, subject: Epstein tear film 2011.

Clinical QUIZ

ANSWER

Inflammatory hypertrophy

Management

Squamous cell carcinoma was suspected. The lesion was biopsied and found to be consistent with inflammatory hypertrophy. Treatment was initiated with mitomycin to reduce the size of the lesion.

Bradley Deece and
Matthew McLennan

IOP higher in first eye

Intraocular pressure measured in the first eye, whether right or left, is higher than IOP measured in the fellow eye, which may be partially due to ocular squeezing.

These are the findings of a study conducted by researchers at the University of California, USA. The researchers say that traditionally doctors measure the right eye first, which may have led to other studies suggesting that IOP might be higher in the right eye.

They advocate that multiple measurements should be taken over several visits, with the order varied.

One hundred and five healthy volunteers from the eye clinic and staff at Washington University were randomised into two groups. Group 1 underwent three sets of two IOP measurements per eye, starting with the right eye (right eye twice, left eye twice, right eye twice). Group 2 underwent similar measurements, starting with the left eye.

After two weeks, the order of IOP measurements was reversed between the groups.

A mixed-model repeated-measures analysis of variance analysed the association of IOP measurement with the order measured between first and second eyes, between first and second visits, between right and left eyes, and with ocular squeezing.

IOP measured high in first eyes compared with fellow eyes, regardless of whether right or left was measured first. IOP measurements decreased between first and second visits. No difference was found in IOP measurements between right and left eyes.

Moderate and severe ocular squeezing were associated with higher IOP measurements, and occurred more during earlier than later IOP measurements within a set and between sets.

Archives of Ophthalmology 2011; 129: 3: 276-281; doi: 10.1001/arch.ophthalmol.2011.33

Antioxidants

High dietary intake of antioxidants may be associated with a lower risk of early age-related macular degeneration (AMD) in genetically susceptible individuals, according to research conducted at the Erasmus Medical Centre in the Netherlands.

The study examined the relationship between a healthy diet, genetic risk and early AMD in 2,167 individuals over the age of 55 years who were at risk of the disease.

Researchers advised that fortified cereals, dark-green leafy vegetables and oily fish are some of the best sources of antioxidants, and doctors and optometrists should provide associated dietary advice to those at high risk of AMD.

Archives of Ophthalmology 2011; 129: 6: 758-766.

iPhone app

A new government-funded iPhone app has been launched in the hope of counteracting the challenges faced by patients who take one or more medicines.

Currently ranked as the number one medical app in Australia, the NPS Medicine List app allows users to keep photos and essential information about medicines on hand, including active ingredients, dosage and branding.

Health professionals can help their patients be medicine-wise by encouraging them to download the app and recording their medicine details.

The NPS iPhone app is available as a free download from iTunes.

An obligate parasite causes infection with ocular manifestations

Toxoplasmosis infection has worldwide distribution.¹ Estimates suggest that up to 20 per cent of the world's population may be infected. While this may sound like an epidemic, the ocular manifestations are much lower in prevalence. A recent review of the literature has offered guidelines for recommending treatment in the event of ocular involvement.²

Discussed here are the presentation, management and risks for developing ocular toxoplasmosis. The organism involved is *Toxoplasmosis gondii*, an obligate intracellular parasite. Vectors are numerous, as will be seen below.

Let us address risks first. A central toxoplasmosis laboratory has been established at Stanford University in the USA. Its most recent publication has indicated newly-discovered risks for developing toxoplasmosis infection. In addition to the well-known risks of eating raw or undercooked meat and proximity to cat, rodent or farm-animal faeces, the newly-enumerated risks include:

- eating locally-produced cured, dried or smoked meat
- working with meat
- drinking unpasteurised goat's milk
- having three or more kittens
- eating raw oysters, clams or mussels was significant in a separate model among persons asked this question.³

With the somewhat universal and daunting list, it may seem that exposure to *T. gondii* is almost inevitable. The purpose is not to instil fear in our patients but to enumerate the risks for the purpose of minimising exposure and the possibility of infection.

While seropositivity is rampant, ocular involvement rests on recognition of an active lesion. Ocular presentations often involve reactivation of previous lesions. Inflammation secondary to *T. gondii* ocular infection is the most frequent cause of posterior uveitis—30-50 per cent by some estimates.^{2,4} The appearance of the fundus may be obscured by the overlying uveitis/vitritis. The observation of the optic nerve in these situations is the origin of the clinical term 'headlights in the fog' (Figure).

Toxoplasmosis

Dr Leo Semes
OD FAAO FACMO
UAB School of Optometry
Birmingham AL, USA

When a teenager presents with reactivation of a lesion, the possibility of HIV infection or AIDS should be ruled out.⁵ Retinal involvement primarily involves the inner retina. The inflammatory response can extend to the outer retina as well as the choroid.⁶

Referring to the accompanying case, several classic clinical aspects are present. First, there is a pre-existing, post-inflammatory lesion. It is likely that the current infection represents a reactivation. Next, consistent with inner retinal involvement, there is an accompanying vitritis. This obscures the view of the optic disc on the nasal side. The history of blurred vision suggests that the process had been in place for some time before the patient attended a clinic. Treatment is indicated when the posterior pole is involved. Specifically, this would include macular involvement or threat by proximity to the optic nerve.⁷ This is the rationale for offering treatment in the present case. The reason to observe rather than treat is based on visual acuity outcome. No difference in VA was seen when lesions were observed but not treated in the periphery.⁷ Each case should be evaluated based on risks and benefits of treatment.

Interpretation of studies on reactivation is confusing. On the surface, the longer patients go with an interval free from reactivation, the less likely reactivation becomes. That optimism is somewhat counterbalanced by increasing risk of reactivation as the patients age.^{8,9}

There are many management options. The classic treatment includes pyrimethamine and sulfadiazine with folic acid supplementation. A contemporary treatment of choice is Bactrim or other trade name (sulfmethoxazole 400 mg + trimethoprim 80 mg). Remember, this would be contraindicated in sulfa-sensitive individuals; caution is also advised for women of child-bearing age who may become pregnant or who are nursing. Alternatives include clindamycin and azithromycin, both of which are available as generics. These two options have lower risk of side-effects among pregnant women. Controversy remains regarding the balance of efficacy, ease of dosing and cost,^{10,11} so the jury is still out on oral management in immunocompetent patients.

Intravitreal injection of clindamycin plus dexamethasone may emerge as the optimal treatment strategy.¹² Two internet resources that may be useful to clinicians to share with patients include information from the CDC (USA) and Feline Advisory Board (UK).^{13,14}



The left posterior pole of a 16-year-old white male who complained of a two-week history of blurred vision in that eye. VA is 6/12. Note the blurred appearance of the fundus due to vitritis; and the pigmented post-inflammatory scar adjacent to the optic nerve head, which is likely to represent a reactivation. The patient was prescribed Bactrim DS and sent for HIV testing but was lost to follow-up.

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New Zealand fights on

The attainment of therapeutic prescribing rights for New Zealand optometrists has been a gradual process. Numerous legislative changes have occurred over the past 30 years leading up to the gaining of these rights.

Early legislation

The original act that governed the practising of optometry in New Zealand contained a section that specifically prohibited the use of cycloplegic agents in measuring refractive status, or the use of any drug for the treatment of ocular diseases (Section 44, *Optometrists and Dispensing Opticians Act 1976*).¹ The *Medicines Act* of 1981² gave the government the ability to classify medicines and specify who could use them, the details of which appear monthly in the government newsletter the *Gazette*. The *Medicines Regulations* of 1984,³ through the 1981 *Medicines Act*, gave New Zealand optometrists the right to apply local anaesthetics 'for the use in his practice as an optometrist'.

In 1996, an amendment to the 1976 *Optometrists and Dispensing Opticians Act* gave optometrists the right to use cycloplegics for the purpose of refraction;⁴ however, it was not until 1998 that cyclopentolate was published in the *Gazette* for use by optometrists. Prior to 1998, the use of cycloplegics by optometrists had to be under the direction of or a prescription from a medical professional (GP or ophthalmologist).

Dr Geraint Phillips

Clinic Director,
University of Auckland Clinics,
Department of Optometry and
Vision Science,
The University of Auckland

Dr Simon Backhouse

New Zealand Association of
Optometrists Education and
Research Fund Post-doctoral
Fellow, Department of
Optometry and Vision Science,
The University of Auckland

Current legislation

Changes in legislation began with the New Zealand Government's introduction of the *Medicines Amendment Bill* in 1998, and in 2002 led to the New Prescribers Advisory Committee hearing applications for the extension of prescribing rights to new groups of health practitioners.

The process of acquiring optometric prescribing rights was gradual. Submissions were made on behalf of optometrists by the Department of Optometry and Vision Science at The University of Auckland and the New Zealand Association of Optometrists (NZAO). Unlike the attainment of nurse prescribing, for which a dedicated team of Ministry of Health staff had been working on the process, optometry had only the NZAO.

The initial submission to the New Prescribers Advisory Committee was rejected as the committee would accept only applications from health professional registration bodies and not from the professions themselves; however, the legislation that covered the Optometrists and Dispensing Opticians Board (ODOB) at that time did not provide avenues for promoting or furthering the profession. After much lobbying the NZAO and the Department of Optometry and Vision Science, with the support of the ODOB, were finally permitted to submit an application in May 2002.

The decision on the question of which classes of medicines optometrists could prescribe was made independently of the development of the guidelines for the use of the different classes of medicine. The application was accepted and optometrists were included as registered health practitioners in the 2003 *Health Practitioners Competence Assurance Act*.⁵ The act was passed on 11 September 2003 and came into full effect on 18 September 2004.

Within the act, the ODOB is required to specify the Scope of Practice for optometrists in New Zealand and the qualifications required to attain these scopes. The scope defines what an optometrist can do, compared with the old act that defined what optometrists could not do. Optometrists with therapeutic pharmaceutical agents (TPA) endorsement are allowed to prescribe therapeutic agents as detailed in the *Gazette*.

Undergraduate therapeutic training

The New Zealand ODOB prescribes the qualifications necessary to register as a TPA endorsed optometrist. From 1999, the Optometry Council of Australia and New Zealand required that existing education programs in optometry begin the process of including training in therapeutic pharmaceutical agents in their courses as a condition of maintaining their accredited status. The Department of Optometry and Vision Science at The University of Auckland began the process of changing its undergraduate Bachelor of Optometry course to incorporate therapeutic training in 2000. The first students eligible to be selected into the modified BOptom program began their university studies in 2002. Since 2006 all newly graduated optometrists have had TPA endorsement.

Postgraduate therapeutic training

Postgraduate training in ocular therapeutics was initially provided by The Auckland Program in Ocular Therapeutics (TAPIOT). This program was designed in 2002-2003 to meet the accreditation requirements of the Optometrists Registration Board of

for anti-glaucoma drugs

The profession has come a long way since winning the right to use topical anaesthetics in 1984

Victoria, the only board able to accredit any therapeutics courses in Australasia. TAPIOT was modelled after the established course at The University of Melbourne. The first cohort of optometrists completed this postgraduate level program in 2004. In 2006 the program was restructured by dividing the content into three standard postgraduate courses. This enabled government funding to support the training.

On-going competence in ocular therapeutics

All TPA-endorsed optometrists are required to maintain competence through biannual requirements for continuing professional development hours, many of which are facilitated through seminars provided by local ophthalmologists.

Optometrist numbers

As of 31 March 2010, there were 685 optometrists holding practising certificates from the ODOB, of whom 276 were TPA endorsed (40.29 per cent).⁶ This was an increase from 225 of 675 registered optometrists (33.33 per cent) at 31 March 2009.

Current medications

Since 1998, registered optometrists have been able to use diagnostic pharmaceutical agents within their practice (topical local anaesthetics, mydriatics and cycloplegics). Since 2004, TPA-endorsed optometrists have been able to prescribe a number of therapeutic agents.⁷

Initially, optometrists were able to prescribe 22 medications covering antiviral (acyclovir), antibacterial (chloramphenicol, ciprofloxacin, framycetin, fusidic acid, gentamicin, gramicidin, neomycin, polymyxin B, tobramycin and trimethoprim), anti-inflammatory (betamethasone, dexamethasone, diclofenac, fluorometholone, flubiprofen, ketorolac and prednisolone), anti-allergy (olopatadine at subsidised prescription rate), and cycloplegic (atropine, homatropine, and hyoscine) modalities.

In August 2007, tropicamide and cyclopentolate were added to the list of medicines able to be prescribed by TPA-endorsed optometrists. In April 2009, chloramphenicol was reclassified by the government to a

restricted medication, meaning that both pharmacists and registered optometrists could maintain stock and sell it to patients without having to write them a prescription.

Early prescribing

When optometrists first began prescribing, the New Zealand legislation did not cover the prescriptions under the HealthPac subsidy scheme available to other health practitioner prescribers. This meant that a pharmacist could not claim back part of the cost for subsidised medicines prescribed by an optometrist, and patients were forced to pay the full cost of the medication. The same prescription coming from an ophthalmologist was covered under the subsidy scheme. This duality was the result of the way in which the pharmaceutical budget was independently managed by PHARMAC, the Pharmaceutical Management Agency of New Zealand.

PHARMAC agreed to review the process of patient access to subsidies and changed its protocol to base access on patient and clinical attributes instead of being based on prescriber status as it had been. In March 2006, the Ministry of Health changed the HealthPac payment and claiming system to allow pharmacists to claim the subsidies against scripts prescribed by optometrists and from 1 October, 2007 PHARMAC allowed access to subsidised eye preparations for all prescribers.

One of the conditions associated with the granting of prescribing rights to optometrists was that a record of all steroid prescriptions made was kept by each prescribing optometrist. These were collected by the Ministry of Health for monitoring purposes to ensure steroids were not being over-prescribed. This requirement was abolished in March 2006. The latest annual report from the ODOB⁶ found that 'optometrists are prescribing responsibly with no excessive use of antibiotics or steroids'.

The number of prescriptions written by TPA-endorsed optometrists has increased since the board first began collecting reports from the HealthPac reporting system in 2006. The majority of prescriptions in the quarter to 31 March 2010 were for antibacterial drugs (45 per cent), closely followed by anti-inflammatory drugs (19 per cent for

steroids and 16 per cent for non-steroidal anti-inflammatory drugs).⁸

Future medications

The class of medicines that was absent from the initial list of allowed medicines was the anti-glaucoma preparations. The accreditation requirements of both the graduate and undergraduate TPA courses means that optometrists trained in New Zealand have the knowledge, skills and observational experience in the use of these medications that satisfies boards in Australia. The profession is still keen to have this class added to the therapeutic scope of practice. The on-going discussions about the addition of the anti-glaucoma class of medicines to the TPA-endorsed scope of practice are again occurring independently of the discussions about the guidelines for the use of this class.

While still in its infancy, ocular therapeutic prescribing by optometrists in New Zealand has grown rapidly from the desire to provide the highest quality primary eye-care service possible to our patients.

1. New Zealand Legal Information Institute http://www.nzlii.org/nz/legis/hist_act/oadoa19761976n61444/ (accessed March 2011).
2. New Zealand Legal Information Institute http://www.nzlii.org/nz/legis/hist_act/ma19811981n118120/ (accessed March 2011).
3. New Zealand Legislation <http://www.legislation.govt.nz/regulation/public/1984/0143/latest/whole.html> (accessed March 2011).
4. New Zealand Legal Information Institute http://www.nzlii.org/nz/legis/hist_act/oadoa19961996n138524/ (accessed March 2011).
5. New Zealand Legislation <http://www.legislation.govt.nz/act/public/2003/0048/latest/whole.html> (accessed March 2011).
6. New Zealand Optometrists and Dispensing Opticians Board http://www.odob.health.nz/cms_show_download.php?id=79 (accessed March 2011).
7. New Zealand Legislation <http://www.legislation.co.nz/regulation/public/2005/0256/latest/whole.html#d1m348602> (accessed March 2011).
8. New Zealand Optometrists and Dispensing Opticians Board via the New Zealand Ministry of Health Pharmaceutical Collection (Pharms) <http://www.moh.govt.nz/moh.nsf/indexmh/dataandstatistics-collections-pharms> (accessed April 2010).

Abstracts

Flixotide use in children with asthma

The long-term, intermittent treatment of asthma with inhaled fluticasone propionate has been shown to not significantly alter cataract formation, corneal ectasia, dry eye, ocular hypertension or glaucoma in paediatric patients.

A study group consisted of pre-pubertal children ($n = 266$; age range: 7-11 years) who had periodically used inhaled fluticasone propionate spray (mean daily dosage: 323 μg) for between three and six years. Controls ($n = 160$) were children who were newly-diagnosed asthmatics who had not received any treatment.

Ocular integrity was determined using Schirmer tests, central corneal thickness, visual acuity, intraocular pressure, slitlamp examination and tear break-up time. There were no statistically significant differences observed for any of the measured ocular parameters over the investigation period, suggesting that fluticasone propionate does not affect the majority of eye functions.

Steroids 2011; 76: 6: 548-552.

Pre-seasonal Patanol suppresses symptoms

Treatment with topical olopatadine eye-drops prior to the onset of allergy symptoms has been demonstrated to be beneficial in suppressing the subjective symptoms of seasonal allergic conjunctivitis (SAC).

A prospective, interventional case series involved 11 patients with SAC who received topical olopatadine in one eye, two weeks prior to the onset of allergic symptoms; the fellow eye served as a control. At the onset of symptomatic allergy, both eyes received treatment. A visual analogue scale was used to evaluate subjective symptoms. Tear levels of histamine and substance P were also measured.

At the onset of symptoms, pre-treated eyes had significantly less allergic symptoms than the untreated eye; this effect persisted even four weeks after bilateral treatment was commenced. The effectiveness of treatment was found to correlate with the tear level of substance P.

Am J Ophthalmol 2011; 151: 4: 697-702.

Neuropeptide tear levels increase after allergen exposure

A study suggests that locally-released neuromediators may modulate allergic responses at the ocular surface.

Dr Laura Downie

PhD(Melb) BOptom
PGCertOcTher
DipMus(Prac) AMusA
Eyetechn Optometrists,
Melbourne VIC

Patients with established allergic conjunctivitis in non-active phase ($n = 15$) and age-matched, healthy controls ($n = 10$) underwent a conjunctival provocation test (CPT), involving ocular exposure to an allergen. At baseline, there were no significant differences in neuropeptide tear levels between the groups ($p > 0.05$).

CPT induced conjunctival hyperaemia and itching in all patients with a history of allergic disease; no reaction was evident in controls. In allergic patients, tear content of the neuropeptides substance P, calcitonin-related peptide and vaso-active intestinal peptide was significantly ($p < 0.05$) elevated compared with controls, suggesting a role for locally-released neuromediators in modulating allergic reactions at the ocular surface.

Mol Vis 2011; 7: 17: 47-52.

Role for contact lenses in relieving ocular allergy

Daily disposable contact lenses have been shown to provide a barrier to airborne antigens.

Ten patients with skin prick- and ocular-provocation confirmed allergic sensitivity to grass pollen were recruited (mean age: 27.4 ± 7.7 years). The following parameters were assessed both pre- and five minutes post-allergen exposure: subjective ocular symptoms, bulbar and limbal conjunctival injection, palpebral conjunctival hyperaemia, corneal and conjunctival fluorescein staining. The procedure was repeated three times, separated by 72 hours, with patients wearing etafilcon A, nelfilcon A with enhanced lubricating agents or no contact lenses, in a randomised order.

Daily disposable contact lens wear reduced both subjective symptomatology and the clinical signs of ocular allergy; this

effect was reported to be more pronounced in lenses with enhanced lubricating agents.

Cont Lens Anterior Eye 2011; 27 (Epub ahead of print).

Smoking affects ocular inflammation

Results from a large, retrospective cohort study conducted on patients with ocular inflammation (uveitis, scleritis and/or inflammation of the ocular surface) and a known smoking history (total subjects = 2,676) indicate that smoking adversely affects ocular outcomes.

Current smokers were more likely to present with bilateral ocular inflammation (64%; 95% CI, 60%-68%) than both former-smokers (55%; 95% CI, 50%-60%) and non-smokers (56%; 95% CI, 54%-8%). Current smokers also experienced a significantly longer time before adequate inflammatory control was achieved (median time to resolution: 1.7 months), compared with former-smokers (1.3 months, $p = 0.04$) and non-smokers (1.4 months, $p = 0.02$).

The investigators concluded that smoking has adverse effects on patients with ocular inflammation, including a 17 per cent to 27 per cent higher risk of relapse of inflammation. These data suggest an opportunity for clinically-meaningful improvement in the course of ocular inflammation on cessation of smoking.

Curr Allergy Asthma Rep 2011; 11: 3: 185-186.

Keratoconus is associated with systemic immune disorders

A recent study conducted in Israel has identified strong associations between keratoconus and several auto-immune diseases.

A retrospective, observational case-control study was performed on patients diagnosed with keratoconus at a central health service ($n = 426$) and a group of age- and gender-matched controls ($n = 1,704$). A statistically significant association was identified between keratoconus and the following conditions: rheumatoid arthritis (odds ratio [OR]: 8.1; 95% confidence interval [CI]: 1.5-44.2), ulcerative colitis (OR: 12.1, CI: 1.3-116), asthma (OR: 2.1, CI: 1.4-3.2), environmental allergy (OR = 1.3, CI: 1.02-1.75) and irritable bowel syndrome (OR: 5; CI: 2.1-12.1).

The authors suggest that these findings may indicate a role for the immune system in the pathogenesis of keratoconus.

Cornea 2010; 29: 11: 1261-1264.

Schedule 4 medicines that optometrists with a scheduled medicines endorsement are qualified to prescribe

12 August 2011

Anti-infectives

Aciclovir[†]
Azithromycin^{†§}
Bacitracin[†]
Cephazolin^{†§}
Ciprofloxacin[†]
Framycetin
Gentamicin[†]
Gramicidin[§]
Neomycin
Ofloxacin[†]
Polymyxin
Tetracycline
Tobramycin[†]
Vidarabine[†]

Anti-inflammatories

Cyclosporin^{†§}
Dexamethasone[†]
Diclofenac
Fluorometholone
Flurbiprofen
Hydrocortisone
Ketorolac
Prednisolone[†]

Anti-glaucomas

Apraclonidine
Betaxolol
Bimatoprost
Brimonidine
Brinzolamide
Carbachol
Diprivatefrin
Dorzolamide
Latanoprost
Levobunolol
Pilocarpine
Timolol
Travoprost

Decongestants/anti-allergics

Olopatadine

Local anaesthetics

Amethocaine
Lignocaine[†]
Oxybuprocaine
Proxymetacaine

Miotics, mydriatics and cycloplegics

Atropine
Cyclopentolate
Homatropine
Pilocarpine[†]
Phenylephrine
Tropicamide

[†] Not available in ACT

[§] Not available in Tasmania

PBS list of medicines for optometrists

12 August 2011

	Product	Max qty	Repeats	
Antiglaucoma preparations				
Betaxolol eye-drops, suspension, 2.5 mg (as hydrochloride)/mL, 5 mL	Betoptic S	1	5	
Betaxolol eye-drops, solution, 5 mg (as hydrochloride)/mL, 5 mL	Betoptic			
	BetoQuin	1	5	
Bimatoprost eye-drops 300 micrograms/mL, 3 mL	Lumigan	1	5	
Bimatoprost with timolol eye-drops containing 300 micrograms bimatoprost with timolol 5 mg (as maleate)/mL, 3 mL	Ganfort 0.3/5	1	5	
Brimonidine eye-drops containing brimonidine tartrate 2 mg/mL, 5 mL	Alphagan			
	Enidin	1	5	
Brimonidine Tartrate eye drops 1.5 mg per mL (0.15%), 5 mL	Alphagan P 1.5	1	5	
Brimonidine with timolol eye-drops containing brimonidine tartrate 2 mg with timolol 5 mg (as maleate)/mL, 5 mL	Combigan	1	5	
Brinzolamide eye-drops 10 mg/mL, 5 mL	Azopt			
	BrinzoQuin	1	5	
Brinzolamide with timolol eye-drops containing brinzolamide 10mg/mL with timolol 5mg (as maleate)/mL, 5mL	Azarga	1	5	
Dorzolamide eye-drops 20 mg (as hydrochloride)/mL, 5 mL	Trusopt	1	5	
Dorzolamide with timolol eye-drops containing dorzolamide 20 mg (as hydrochloride) with timolol 5 mg (as maleate)/mL, 5 mL	Cosopt			
		1	5	
Latanoprost eye-drops 50 micrograms/mL, 2.5 mL	Xalatan	1	5	
Latanoprost with timolol eye-drops 50 micrograms latanoprost with timolol 5 mg (as maleate)/mL, 2.5 mL	Xalacom	1	5	
Pilocarpine eye-drops containing pilocarpine hydrochloride 10 mg/mL, 15 mL	Isopto Carpine			
	Pilopt	1	5	
	PV Carpine			
Pilocarpine eye-drops containing pilocarpine hydrochloride 20 mg/mL, 15 mL	Isopto Carpine			
	Pilopt	1	5	
	PV Carpine			
Pilocarpine eye-drops containing pilocarpine hydrochloride 40 mg/mL, 15 mL	Isopto Carpine			
	Pilopt	1	5	
	PV Carpine			
Timolol eye-drops 2.5 mg (as maleate)/mL, 5 mL	Tenopt			
	Timoptol	1	5	
Timolol eye-drops 5 mg (as maleate)/mL, 5 mL	Tenopt			
	Timoptol	1	5	
Timolol eye-drops (gellan gum solution) 2.5 mg (as maleate)/mL, 2.5 mL	Timoptol XE	1	5	
Timolol eye-drops (gellan gum solution) 5 mg (as maleate)/mL, 2.5 mL	Timoptol XE	1	5	
Timolol eye gel 1 mg (as maleate)/g, 5 g	Nyogel	1	5	
Travoprost eye-drops 40 micrograms/mL, 2.5 mL	Travatan	1	5	
Travoprost with timolol eye-drops 40 micrograms travoprost with timolol 5 mg (as maleate)/mL, 2.5 mL	Duotrav	1	5	
By writing a PBS prescription for an antiglaucoma agent, the prescriber is certifying that the criteria set out in the PBS guidelines are satisfied				
	Product	Restriction	Max qty	Repeats
Anti-viral eye preparations				
Aciclovir eye ointment 30 mg per g (3%), 4.5 g	Zovirax	Restricted: Herpes simplex keratitis	1	0
Antibiotics				
Chloramphenicol eye-drops 5 mg/mL (0.5%), 10 mL	Chlorsig	Unrestricted	1	2
	Chloromycetin		1	2
Chloramphenicol eye ointment 10 mg/g (1%), 4 g	Chlorsig		1	0
	Chloromycetin		1	0
Framycetin sulfate eye-drops 5 mg/mL (0.5%), 8 mL	Soframycin		1	2
Sulfacetamide sodium eye-drops 100 mg per mL (10%), 15 mL	Bleph-10		1	2
Anti-inflammatory agents				
Fluorometholone eye-drops 1 mg/mL (0.1%), 5 mL	Flucon	Unrestricted	1	0
	FML Liquifilm		1	0
Fluorometholone acetate eye-drops 1 mg/mL (0.1%), 5 mL	Flarex		1	0
Flurbiprofen sodium eye-drops 300 µg/mL (0.03%) single dose units 0.4 mL, 5	Ocufen		1	0
Hydrocortisone acetate eye ointment 10 mg/g (1%), 5 g	Hycor		1	0
Anti-allergy agents				
Sodium cromoglycate eye-drops 20 mg/mL (2%), 10 mL	Cromolux	Restricted: Vernal keratoconjunctivitis	1	5
	Opticrom		1	5

Continued

	Product	Restriction	Max qty	Repeats
Tear supplements				
Carbomer eye gel 2 mg/g (0.2%), 10 g	Geltears	Restricted: Severe dry eye including Sjögren's syndrome	1	5
	PAA		1	5
	Viscotears		1	5
Carmellose sodium with glycerin eye-drops 5 mg-9 mg per mL (0.5%-0.9%), 15 mL	Optive		1	3
Carmellose sodium eye-drops 10 mg/mL (1%), 15 mL	Refresh Liquigel		1	5
Carmellose sodium eye-drops 5 mg/mL (0.5%), 15 mL	Refresh Tears plus		1	5
Hypromellose eye-drops 3 mg/mL (0.3%), 15 mL (contains sodium perborate)	In a Wink Moist'ing		1	5
	Gentel		1	5
Hypromellose eye-drops 5 mg/mL (0.5%), 15 mL	Methopt		1	5
Hypromellose with carbomer 980 ocular lubricating gel 3 mg-2 mg/g (0.3-0.2%), 10 g	HPMC PAA		1	5
	Gentel gel		1	5
Hypromellose with dextran eye-drops 3 mg-1 mg/mL (0.3%-0.1%), 15 mL	Poly-Tears		1	5
	Tears Naturale		1	5
Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); 15 mL	Systane		1	5
Polyethylene glycol 400 eye drops 2.5 mg per mL (0.25%), 15 mL	Blink Intensive Tears		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL	PVA Tears		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL	PVA Forte		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL	Liquifilm Tears		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL	Liquifilm Forte		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative)	Vistil		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative)	Vistil Forte		1	5
Unpreserved tear supplements				
Carbomer 974 ocular lubricating gel 3 mg/g (0.3%), single dose units 0.5 g, 30	Poly Gel	Authority required: Severe dry eye syndrome in patients sensitive to preservatives in multi-dose eye-drops	3	5
Carbomer eye-gel 2 mg per (0.2%) , single dose units 0.6 mL, 30	Viscotears Gel PF		3	5
Carmellose sodium eye-drops 5 mg/mL (0.5%), single dose units 0.4 mL, 30	Cellufresh		3	5
Carmellose sodium eye-drops 10 mg/mL (1%) , single dose unit 0.4 mL, 30	Celluvisc		3	5
Carmellose sodium eye-drops 2.5 mg/mL (0.25%), single dose units, 0.6 mL, 24	TheraTears		4	5
Carmellose sodium ocular lubricating gel 10 mg/mL (1%), single dose 0.6 mL, 28	TheraTears		3	5
Carmellose Sodium with Glycerin eye drops 5 mg-9 mg per mL (0.5%-0.9%), single dose units 0.4 mL, 30	Optive		3	5
Hypromellose with dextran eye-drops 3-1 mg/mL (0.3-0.1%), single 0.4 mL, 28	Bion Tears		3	5
Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); single dose units 0.8 mL, 28	Systane		2	5
Polyethylene glycol 400 eye drops 2.5 mg per mL (0.25%), single dose units 0.4 mL, 20	Blink Intensive Tears		5	5
Soy lecithin eye spray 10 mg/mL (1%), 10 mL	Tears again		2	5
Topical ocular lubricant ointments				
Paraffin compound eye ointment 3.5 g	Polyvisc	Unrestricted	2	5
	Duratears		2	5
Paraffin pack containing 2 tubes compound eye ointment 3.5 g	Polyvisc (2 pack)		1	5
Paraffin pack containing 2 tubes compound eye ointment 3.5 g	Ircal (2 pack)		1	5
	Lacri-Lube (2 pack)		1	5

PBS-listed medicines available to medical practitioners only

Anti-infectives

Ciprofloxacin
Gentamycin
Ofloxacin
Tobramycin

Anti-inflammatories

Dexamethasone
Prednisolone

Anti-glaucoma preparations

Apraclonidine

Mydriatics and cycloplegics

Atropine
Homatropine
Pilocarpine

