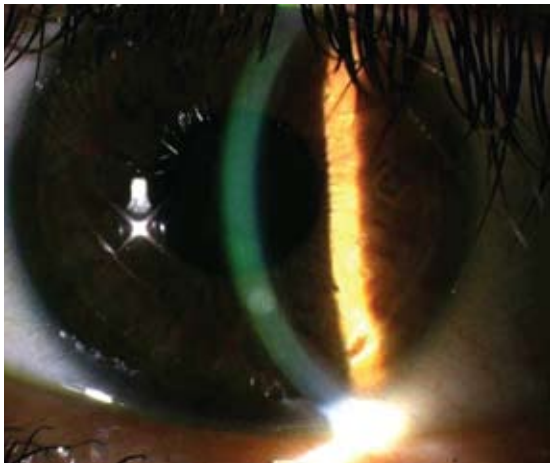
Risk factors for non-infectious corneal inflammatory events

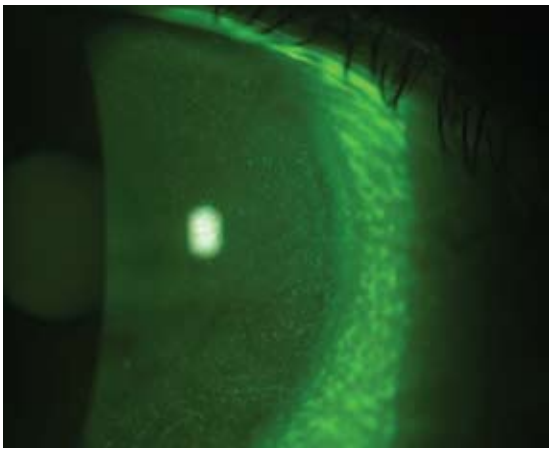
In part two of a three-part series, **Dr Paul Karpecki** explores the agreement and discrepancies between eye care professional beliefs and evidence in the scientific literature on corneal staining, corneal infiltrative events and other contact lens complications

As previously discussed in Part 1 of this series (*Optician* 03.06.11), there has been an ongoing, and sometimes heated, debate regarding the clinical significance of asymptomatic corneal staining (CS) with use of sodium fluorescein dye in contact lens (CL) users; especially in multipurpose solution (MPS) users, where high levels of hyperfluorescence are observed approximately two hours following CL insertion.[1] Some eye care professionals (ECPs) have tried to suggest that this transient hyperfluorescence or 'solution-induced corneal staining (SICS)' is damage to the cornea.

Part of the confusion may be related to two studies published in 2007 that found an association of CS during continuous wear (CW) and transient hyperfluorescence 'SICS' was associated with an increased risk of corneal infiltrative events (CIEs). However, as laid out in the first instalment of this three-part series, there are no other signs or symptoms associated with the transient hyperfluorescence observed in MPS users. Recently, the findings of an association between CIEs and asymptomatic CS in CW and corneal hyperfluorescence in MPS users has been retracted by the original authors due to new more rigorous studies or re-analysis of the original data showing confounding factors are responsible for the increase in CIEs rather than the hyperfluorescence.



Small scar from old infiltrative event



Superficial punctate epithelial staining thought to be related to care system

New research suggests that the transient hyperfluorescence observed in MPS users is a benign phenomenon that is different from CS in physiological and pathological situations. These new data support the beliefs that the corneal hyperfluorescence in MPS users (what my colleagues and I have termed preservative-associated transient hyperfluorescence [PATH]), is an artefact with no known sequelae or associated risk factors for CIEs. While my many colleagues and I believe PATH does not signify a pathological process, it seems ECPs still believe that PATH is predictive of CIEs, even with the new findings by the authors. It was of interest to determine how prevalent the belief that asymptomatic CS and/or PATH is predictive of CIEs and whether this belief is based upon scientific evidence in the literature. Additionally, curious to determine what other factors ECPs believed were predictive of CIEs, this topic was explored as well.

To assess the consistency between beliefs held by ECPs and the available scientific evidence regarding predictive factors for CIEs, a survey and systematic review of the literature was performed. This second part of the three-part series explores the findings regarding factors predictive of or associated with CIEs; Part three of the series will explore our understanding of the risk factors for infectious infiltrative events, and will be published in subsequent months.

Methods

A global web-based survey of ECPs was performed to assess the level of knowledge and beliefs regarding risk factors for CIEs, including CS. Statistical analyses were performed to determine the differences between beliefs when appropriate; statistical significance was set to <0.05. Briefly, as previously reported, a systematic review of the literature (peer-reviewed, trade journals, and professional meeting abstracts) on CS during CL wear was performed that included all pertinent primary references up to February 28, 2011.[1] A separate systematic review of corneal infiltrative events from 2007 until August 31, 2011 was performed. The year 2007 was chosen since two comprehensive reviews[2,3] on epidemiology and risk factors for CIEs and the two studies that showed an association of CS and PATH with CIEs were published. The only difference in criteria was in regard to the inclusion of reviews that contained more than 50 references. The review findings were compared with the survey respondent's beliefs to determine the extent these beliefs are based on company marketing or supportive research.

Results and discussion

Demographics of the survey

A total of 1,136 ECPs answered questions regarding predictive factors

for CIEs. Of the respondents, 4.9 per cent practise in Australia, New Zealand or the Asia Pacific region, 1.2 per cent in Africa or the Middle East, 31.7 per cent in the UK and Europe, and 62.1 per cent in the United States.

ECPs believe the factors predictive for CIEs are:

Over 50 per cent of respondents chose eight factors that are predictive for CIEs. As shown in Figure 1, the factor believed by the greatest number of total respondents was poor lens care compliance (94.3 per cent), followed by duration of continuous wear (>seven days/nights) (85.1 per cent), history of CIEs (80.8 per cent) and contact lens-induced acute red eye (CLARE) (74.6 per cent), high bacterial bioburden or contamination (66.9 per cent), smoking (62.0 per cent), certain MPS (60.1 per cent), and corneal hyperfluorescence/PATH (53.3 per cent).

While several factors are believed to be predictive for CIEs by the same proportion of respondents from the UK/EU and the US, there were several factors that more respondents from one region choose than the other. Factors chosen more frequently by the UK/EU were high bacterial bioburden and contamination (77.9 per cent vs 60.3 per cent; p <0.0001) and low socioeconomic class (31.0 per cent vs 17.2 per cent; p <0.0001) (Figure 2). Of those factors that have been shown to significantly increase the risk for CIEs, history of CLARE, use of certain MPS, and silicone hydrogel (SiH) lens use, (see below) were chosen more frequently by respondents from the US compared with those from the UK/EU (77.4 per cent vs 70.4 per cent; p = 0.01, 67.8 per cent vs 46.1 per cent; p < 0.0001, and 24.5 per cent vs 15.1 per cent; p = 0.0005, respectively). Of the factors that are not associated with an increased risk of CIEs (see discussion below), only one factor, PATH, was chosen by a significantly different proportion of respondents from each region. A significantly greater number of respondents from the US believe that PATH increases the risk for CIEs compared with those from the UK/EU (55.5 per cent vs 48.1 per cent; p = 0.03) (Figure 3).

Systematic review

A total of 1,198 primary unique references were identified in the systematic search on CS; 41 had pertinent information regarding CIEs. An additional 24 were identified from the search of risk factors for CIEs and their bibliographies.

Figure 1 Beliefs of ECPs regarding risk factors for CIEs and their association based on the literature

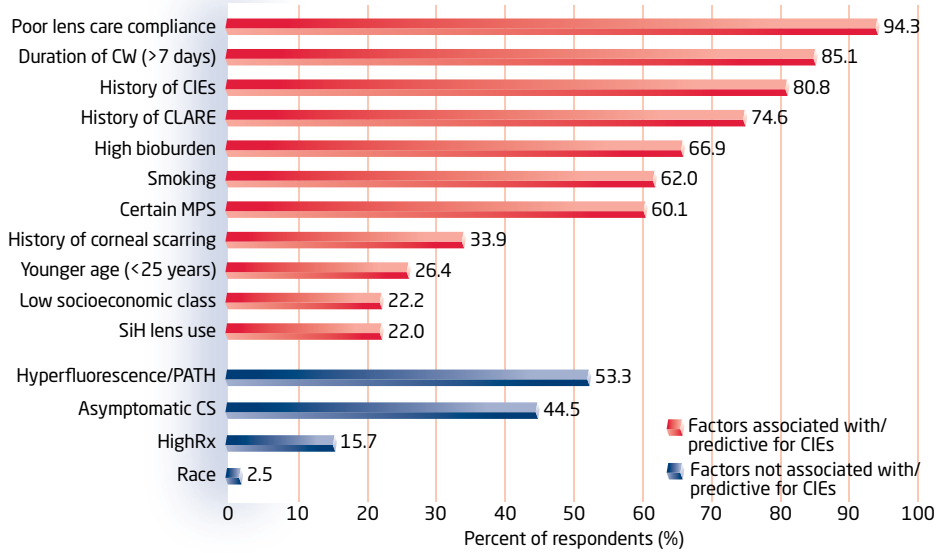
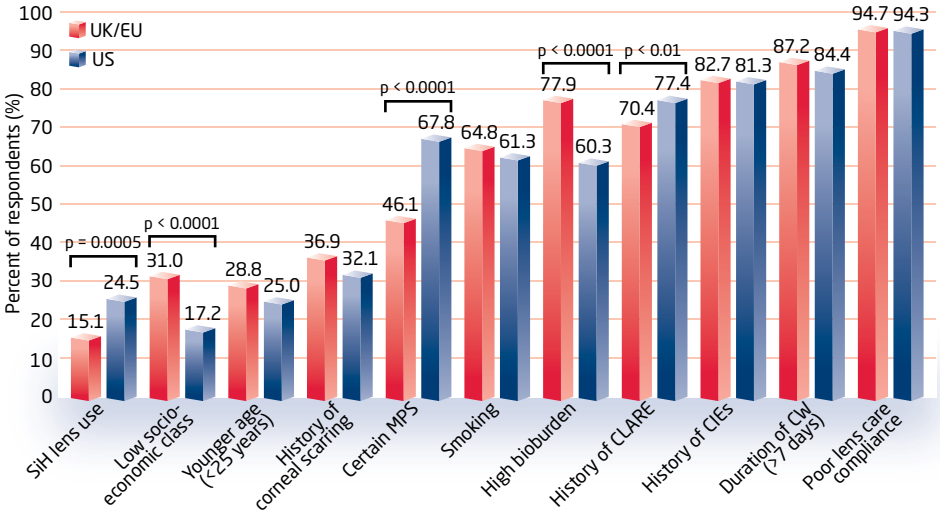
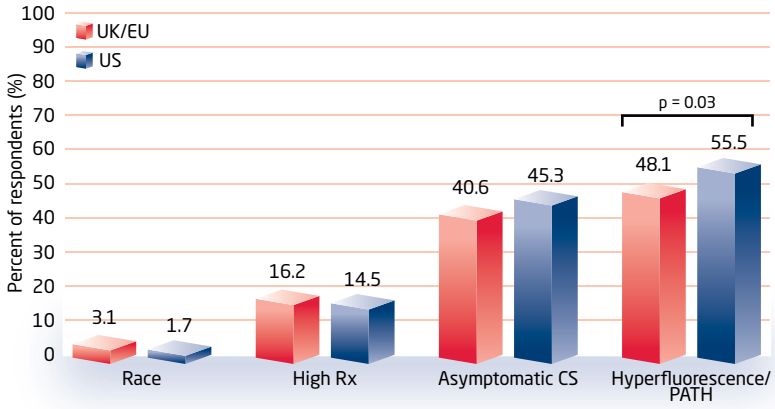


Figure 2 Beliefs of ECPs from the UK/EU and the US regarding risk factors for CIEs based on the literature



CIE = corneal infiltrative events; CLARE = contact lens-induced acute red eye; CW = continuous wear; MPS = multipurpose solutions; SiH = silicone hydrogel

Figure 3 Beliefs of ECPs from the UK/EU and the US regarding factors not predictive for CIEs based on the literature



CS = corneal staining; PATH = preservative-associated transient hyperfluorescence; Rx = refractive error (prescription)

Survey vs the literature

Out of the 15 possible choices of factors predictive of CIEs, only 11 have significant support as a risk factor. As demonstrated in Figure 1, these factors include poor lens care compliance,[4,5] longer duration of continuous wear,[4,6] history of inflammatory events (CIEs and CLARE)[7-10] and scarring,[10] high bioburden/contamination of contact lenses[11-17] and lens storage cases,[14,18] smoking,[4,10,15,19,20] the use of certain MPS,[21-28] younger age (<25 years),[20,29,30] and SiH lens use compared with non-SiH soft lenses.[4,31-33]

The remaining four possible survey choices either have no evidence of an association (race) or have previously been implicated in an increased risk of CIEs but the most recent studies by the same authors show no predictive value for these factors (high ametropia, asymptomatic corneal staining during CW, and corneal hyperfluorescence/PATH in users of MPS) actually exists. Few respondents believed that race or degree of ametropia increased the risk of CIEs (Figures 1 and 3). Interestingly, a large proportion of respondents believed that corneal hyperfluorescence/PATH in users of MPS is predictive of CIEs, though only one study from 2007 showed any association with CIEs and only when asymptomatic.[34]

Factors associated with CIEs Identified in the survey

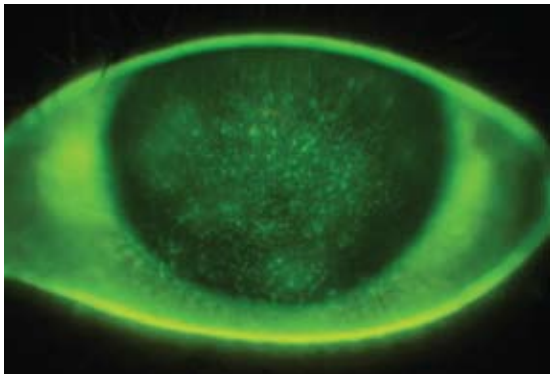
Non-modifiable factors including younger age (≤25 years)[20,29,30] and a history of inflammatory events (CIEs and CLARE) and scarring have been found to increase the risk of CIEs in lens wearers. Several studies by one group of researchers have demonstrated that younger age (≤25 years),[20,29,30] which seems to peak between 15 and 25 years of age[30] increases the risk for inflammatory events. A history of corneal adverse events may alter the ocular surface response[35] and pre-dispose lens wearers to additional events or these wearers may already have a predilection for these events due to their physiological make-up.[36]

Poor lens care compliance, including not washing one's hands prior to lens handling,[4] infrequent disinfection, cleaning or use of enzyme tablets,[5,18] are well-known risk factors for CIEs. These practices are likely to play a role in the increased bacterial bioburden of contact lenses and storage cases, with substantial evidence implicating these factors in an increased risk for CIEs.[11-18] This is especially true for gram-negative bacteria, which were seen in few cases during asymptomatic wear, however, their incidence during CIE in comparison to asymptomatic wear was substantial and significant (23.7 vs 3.8 per cent; p <0.0001).[11] Interestingly, increased levels of protein and other lipid deposits were not associated with CIEs.[37] This may explain why a lower level of deposit removal with different MPS does not correlate to an increased incidence of CIEs with each lens care solution.[38] Reduction of CL bioburden by adsorption of antimicrobial peptides onto lenses resulted in a reduction of corneal infiltration and prevention of CIEs in animals models.[39,40] These findings are of concern considering studies show that bacterial bioburden is found on the majority of CLs and on storage cases.[41,42]

Another factor that has been shown to possibly increase the risk for CIEs in silicone hydrogel (SiH) lens wearers is a greater duration of CW past seven days.[6] However, this study only measured 30 day CW and seven-day CW and a separate study showed no increase in risk for CIEs past seven days of CW in wearers of non-SiH lenses,[5] so the effect of duration of lens wear greater than seven days but less than 30 in SiH lens wearers is unclear. A separate study showed that participants prescribed 30 nights of CW who wore the lenses for ≥3 weeks were less likely to have an infiltrative event (0.45x [0.25– 0.81]).[20] This may suggest a 'survivor effect', where those who are vulnerable to inflammatory complications are less likely to achieve the intended wearing schedule rather than wearing lenses for the longer duration being beneficial.

While smoking as a risk factor for CIEs has been known for over 15 years,[19] evidence has continued to mount regarding its deleterious effects on the ocular surface[43] predisposing lens wearers to inflammatory events.[4,10,15,44]

SiH lenses have been shown in several studies, including a meta-analysis, to increase the odds of experiencing a CIE by approximately two-fold compared with other soft lens materials.[4,30-32] While some studies found SiH lenses did not increase the risk for CIEs when compared with non-SiH soft lenses,[3,45-47] several of those that found an increased risk are in real world use.[4,29,30] Additionally, some studies show that some SiH materials are associated with a higher incidence of CIEs than others.[23,24,48]



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Similarly, a certain MPS, Opti-Free RepleniSH, has been implicated in several clinical studies and case series over the past five years,[21-28] to be a risk factor for CIEs, especially contact lens-associated infiltrative keratitis (CLAIK), which is a distinct clinical entity versus peripheral infiltrates commonly observed with extended wear lenses.[26,49] An Alcon sponsored study presented at the 2011 AOA meeting, which has since been published this year, showed that CL wearers who used Opti-Free RepleniSH MPS are 63 per cent more likely to develop symptomatic CIEs than those using other MPS brands.[31,50] Additionally, these studies show that CIEs, including CLAIK, in users of Opti-Free RepleniSH occur predominantly when combined with SiH lenses, and most commonly with Acuvue Oasys lenses.[22,23,25,26] While Oasys lenses are a commonly used brand, one potential reason Oasys lenses, which are a two-week replacement (2W) lens, may increase wearers' risk is due to poorer compliance with the manufacturers' recommended replacement schedule with 2W lenses compared with monthly replacement lenses.[51,52] One possible reason that fewer ECPs in the UK and Europe did not chose certain MPS and SiH lenses as risk factors for CIEs compared with respondents from the US may be due to the substantially lower number of DW fits with SiH lenses in the years just prior to performance of this survey in this region.[53,54]

Additional factors associated with CIEs identified in the systematic search

Several additional risk factors were identified during the systematic search including, extended/overnight wear[2-5,30,31,48,55] whether habitual or occasional,[4] adaptation period[7] or within the first 3-6 months of CL wear,[56] limbal and bulbar redness,[9,57] corneal vascularisation during CL wear,[16] tight lenses/reduced lens movement,[16,58] older (>50 years) ▶

age,[20] working in outdoor or non-ideal environment,[16,59] mucin balls (protective),[36] MPS use,[8,30,31,58] use of certain daily disposable (DD) lenses,[4] and fall and winter months (Table 1).[29,44]

A few interesting findings will be explored further. It is well known that extended lens wear[2-5,30,31,48] as well as occasional overnight wear[4] is associated with an increased risk of CIEs. The advent of DD lenses was to circumvent the need for cleaning and reduce the risk of CIEs due to non-compliance. While DD lenses may reduce the risk of CIEs,[30] the most commonly used brand of DD lenses was associated with increased risks of sterile keratitis (2.7x; 95 per cent CI, 1.7– 4.1; $p < 0.001$).[4]

ECPs recognize that CLs, especially soft CLs when compared with rigid lenses,[4,33] are associated with an increase in risk for CIEs. One mechanism that CLs make the cornea more susceptible to inflammation may be via the downregulation of mucin gene expression after long-term wear.[60] This hypothesis is further supported by a recent report by Szczotka-Flynn and colleagues (2011),[36] where the finding that mucin balls, especially the repeated presence of mucin balls, were associated with an 84 per cent decreased risk of experiencing a CIE. The authors hypothesise that presence of mucin balls represents a thicker mucus layer that prevents an immune response against bacteria. One study showed mucin balls are associated with an increased risk for CIEs;[58] however, the reason for this is unclear and may be a consequence of mechanical forces of too tight lenses,[16,58] which was also found to be associated with increased risk for inflammatory events, rather than the presence of mucin balls themselves.

Since 2007: reversal of findings

In 2007, two studies identified 'corneal staining' with fluorescein as a risk factor for CIEs, one during daily wear SiH use[34] and the second during continuous wear of SiH lenses.[9] Since the publication of these two studies, newer more rigorous studies or re-analysis of the original data by the authors has shown that there is no association between asymptomatic corneal staining or PATH/hyperfluorescence and increased risk for CIEs.[15,61] Additional studies, including one recently published by Chalmers and colleagues (2010), further support the absence of an association between corneal staining/hyperfluorescence and inflammatory events.[29,62,63] Data reporting an absence of an acute inflammatory response measured by cytokine expression at two hours (when peak levels of PATH are observed) in eyes wearing lenses associated with high levels of PATH and lack of association of inflammatory mediator expression with the extent of PATH may explain the lack of association of PATH and CIEs.[64]

Another risk factor identified in 2007,[20] high ametropia, by Chalmers and colleagues, has been shown in several recent studies by the same authors to have no predictive value for CIEs.[29-31]

TABLE 1

Factors associated with/predictive for CIEs not included in survey

Factors	Referent
Extended/overnight wear[2-5,30,31,48,55]	No overnight use or DW
Any limbal/bulbar redness[9,57]	No limbal/bulbar redness
Any corneal vascularisation during lens wear[16]	No vascularisation
Early lens experience/adaptation period[7,56]	>6 months of experience with lens
Tight lenses/reduced lens movement[16,58]	Increase in units of lens movements
MPS use[8,30,31,58]	H_2O_2/saline use
Older (>50 years) age[20]	26-50 years of age
Working in outdoor or non-ideal environment[16,59]	Working in indoor environment
Inability to achieve intended wearing schedule (<3 weeks of 30 day CW)[20]	Achievement of intended wear schedule (≥3 weeks/up to 30 days) of CW
Autumn and winter months[29,44]	Summer (July)

CW = continuous wear; DW = daily wear; H_2O_2 = hydrogen peroxide lens care systems; MPS = multipurpose solution

Applying findings to clinical practice: more must be done

Although a large proportion of patients are aware of the risks of certain behaviours for adverse events including CIEs, many still perform them. In a study, only one behaviour was associated with having an adverse event, such as corneal infiltrates, which was replacement of lens cases (79 per cent of patients after event vs 53 per cent in the absence of an event).[65] Importantly, 21 per cent of patients still fail to replace their lens case despite having experienced a problem ($p = 0.002$). Of these subjects, 93 per cent reported using the recommended solution; however, only a fraction of patients recall whether their ECP made a recommendation with respect to their lens care system, suggesting that this number is probably a gross overestimate.[65]

After a CIE, many ECPs changed lens type or brand and patients ceased to routinely sleep in lenses, or wore lenses less often. Changes in lens-related behaviours of patients who have suffered from a CIE seem to be aimed at reducing the risk of a further occurrence[66] but proactive changes are necessary to reduce the risk for an infiltrative event in the first place.

It is important to address the factors that are modifiable and shown to be associated with inflammatory events based on strong evidence-based medicine rather than what marketing machines may tell you. In addition to changing lenses, do not prescribe solutions shown to be associated with inflammatory events, such as CLAIK, and sit down and discuss with patients the importance of proper lens care and cessation of smoking.

Know your patients' demographics and monitor those with risk factors for CIEs, especially within the first few months. This will enable you to manage these patients and reduce the chance that they will experience an inflammatory event, and if they do, how best to address their needs to prevent future occurrences.

References

A list of references is available from the clinical editor (william.harvey@rbi.co.uk).

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