Contact Lens Update
CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

Understanding Clinical and Contact Lens Related Risk Factors for Corneal Inflammatory Events

September 10, 2019

Dr. Szczotka-Flynn is an optometrist and epidemiologist, and currently serves as Professor in the Departments of Ophthalmology & Vision Science and Population and Quantitative Health Sciences at CWRU. She is also the Director of the Contact Lens Service and Director of the Vision Research Coordinating Center at the University Hospitals Eye Institute in Cleveland, Ohio.

Contact lens associated corneal infiltrative events (CIEs), also referred to as corneal inflammatory events, are exactly that, inflammatory responses that are self-limiting, and represent either the host response to infection, or part of the innate or adaptive immune response to antigens in the absence of live organisms.[1,2] Up to about 50% of CIEs may be asymptomatic, while the others can disrupt normal contact lens wear and require intervention. The more serious CIEs can be difficult to distinguish from severe keratitis due to other causes, including infectious microbial keratitis which also presents with focal or diffuse corneal infiltration. CIEs have been described to represent a continuum of inflammatory responses including those present as part of the host response to microbial keratitis; this review, however, will limit discussion to CIEs that are presumed to be sterile or thwarted bacterial infections. In fact, there is evidence that infiltrates presumed to be sterile have been proven culture positive.[1,2] CIES are 22X more common than full corneal infection,[3] and are important to understand and limit occurrence because of pain, discomfort, inconvenience and costs associated with them.[4] Repeated occurrences will discourage continued contact lens wear on both the part of the practitioner and wearers.

The incidence of symptomatic CIEs during extended soft lens wear ranges from 2.5 – 6%; when asymptomatic CIEs are included, the incidence can be as high as 20-25%.[5] In daily soft lens wear, the annual incidence of symptomatic CIEs is about 3%, and in daily disposable soft lens wear the incidence nears zero.[6] Many factors, both modifiable and non-modifiable, influence the incidence and overall risk of CIE development.

Lens Factors

Extended wear not only increases the incidence of infectious microbial keratitis but CIEs as well.[7-15] Nonetheless, about 25% of patients continue to report the use of lenses in an overnight modality at least occasionally.[16] Most studies report a 2-7X increased risk for CIEs when comparing extended wear vs daily wear modalities.[9, 11, 13] Clinically, there are many patients that appear to be successfully able to wear lenses problem-free for many weeks at a time without removal. In fact, one study reported that longer (> 3 weeks) compared to fewer days of continuous wear was associated with decreased risk of CIEs,[17] reflecting increased success in this subgroup. Currently, we have no markers that can identify such patients proactively.

Lens material has been well described to influence the incidence of CIEs. Despite all the known corneal physiological improvements with silicone hydrogel lenses compared to traditional hydrogels (i.e. decreased corneal epithelial microcysts, edema, neovascularization, and limbal hyperemia), the risk of CIEs has increased with the use of silicone hydrogel materials worn on a reusable basis.[18] Relative to traditional polyHEMA-based hydrogel materials, silicone hydrogel materials have doubled the risk of CIEs, which is reproducible across lens brands, reusable wearing schedules, extended wear modalities and concomitant lens product usage.[13,18,19] The relative risk ranges between 1.85 and 2.18 fold[9,13,18, 19] across the various studies. Bacterial adhesion

properties to silicone hydrogel materials may be a contributing factor.[20-23] Additionally, deposition properties of low Dk hydrogel lenses which absorb significantly more active antimicrobial non-denatured proteins, particularly lysozyme, compared to silicone hydrogel materials may be a positive aspect that diminishes microbially driven complications with this class of materials.[24]

Indeed, bacterial bioburden has been linked to CIE development, and thus lens materials, solutions, and replacement schedules that limit bacterial presence and adhesion to lenses and cases are desirable. The odds of a CIE increase by 2.78X for every 1 log increase in colony forming units/mL on the lens surface.[25] On a population level, lens bioburden increases CIE risk between 4- to 8-fold during extended wear.[26-28] Although live organisms can certainly stimulate the immune mechanisms to overcome bacterial invaders, microbial breakdown products can also activate an inflammatory response. For example, key activators such as lipopolysaccharides found on (live and dead) Gram negative bacteria, can activate Toll-like receptors in the corneal epithelium and stimulate infiltration of leucocytes into the corneal tissue.[29]

Preserved multipurpose solutions (MPS) have been hypothesized to increase the risk of CIE development, in combination with both silicone hydrogel and traditional hydrogel classes of materials, yet in some studies no such relationship was identified.[8,30] Multiple reports have documented such a relationship, in that the rate of CIEs was increased with MPS when compared to the rate with peroxide based solutions.[9, 14, 31-33] More specifically, residual case contamination, particularly with Gram negative organisms that are residual within cases of specific MPS systems may be linked to risk of CIE development.[34] In fact, continual re-use of lens storage cases, presumably resulting in greater storage case contamination, results in a nearly 8-fold greater risk of CIEs.[14]

Understanding the effect of bacterial bioburden on CIEs intuitively suggests that the more frequent lens replacement afforded with daily disposability, including lack of bioburden from lens storage cases, should reduce CIE development. In that regard, daily disposable lenses have indeed produced a reduction in risk for CIEs. One study prospectively assessing incidence of CIEs with silicone hydrogel and non-silicone hydrogel daily disposable lenses found near zero incidence of CIEs, with a rate of 0.4% per year in silicone hydrogel daily disposables, and 0% in hydrogel daily disposables.[6] A large reduction in risk of CIE was demonstrated in a large retrospective multicenter case control study which reported re-useable lenses posed a 12.5x higher risk of CIEs compared to daily disposable lenses when worn for daily wear.[8]

One of the less well known associations with CIE development that is material or patient dependent, or both, is mucin ball formation. Mucin balls are spherical, translucent, insoluble tear film derived bodies composed of ocular surface mucins that are shed from the epithelial surface during contact lens wear. The mucus layer covers the corneal and conjunctival epithelial apical surfaces and acts as a barrier to pathogen penetrance and multiplication. With contact lens use, especially extended wear, shear forces from the mechanical interaction between contact lenses and the ocular surface contribute to mucin ball formation in some patients. Although mucin balls can be formed with most contact lens materials, a heightened presence was clinically noted when silicone hydrogels were first introduced on the market because of the higher material modulus and minimal protein deposition with these materials that were thought to contribute to their formation.[35] The relationship between mucin ball development/presence and CIEs is complicated in that there is both protective as well as increased risk for inflammatory events depending on when the mucin balls are observed in the course of fitting in the various studies. My research team performed two studies where the association between mucin balls and CIEs were modeled during extended wear with silicone hydrogel lenses. When mucin balls were noted during wear over a 1 year period of follow-up, their presence was found to decrease the risk of CIEs, and the effect was greatest when they were repeatedly present over time.[35,36] This effect is hypothesized to occur because the mucin balls may act as a “ball bearing” physical barrier between the lens and corneal surface, preventing upregulation of the immune response in the presence of lens-adhered bacterial antigens. However, provocative stimulation of mucin balls (as during a run-period with high modulus silicone hydrogel lenses) has been shown to significantly increase the rate of CIEs during a subsequent 12 month follow-up phase by 470%.[35] It was assumed that the early

mucin ball response represented disrupted homeostasis of the mucus layer, which later predicted subsequent risk for CIE during extended wear with various other silicone hydrogel lenses. This sort of rapid onset mucin ball formation likely identifies those "mucin ball formers" that are prone to disruption of their ocular surface mucins, which can overwhelm the mild protective response when the mucin balls are continuously present over time. From these studies we infer, and promote to the clinical community, that if early mucin ball production is noted during the fitting process it should be considered a marker for CIE risk, and continued extended wear should be discouraged.

Our clinical study findings regarding early appearance of mucin balls in heightening the risk for CIEs is supported by other studies that have demonstrated a subclinical inflammatory response in the anterior stroma beneath mucin balls. Grupcheva has shown that dendritic cells accumulate in the anterior corneal stroma beneath mucin balls when imaged on confocal microscopy.[37] We hypothesized that these dendritic cells can in fact prime the immune response, rendering it "hypersensitive" to subsequent corneal infiltrative events under the right conditions. Furthermore, mucin balls have also been shown to activate stromal keratocytes immediately beneath the mucin ball embedded in the epithelial surface.[38]

Lastly, there are a few other associations noted with CIE risk that are worth mentioning. These patient oriented factors are good tools for the clinician to consider as they monitor and fit patients with lenses, particularly for extended wear. Smoking status, age and previous history of CIEs are important demographic and previous ocular history markers that should be recorded in every medical record. Smoking is associated with a greater risk for developing a CIE and this elevated risk holds true even for former smokers when compared to patients who report never having been a habitual smoker.[12] The increased risk associated with smoking may be related to increased bioburden, toxins, pathogens in the subject's resident microbiota, or changes in mucous membranes. Additionally, it may be a simple confounding effect with other unmeasured risk-taking behavior. Age is also a known contributing factor. Younger lens wearers have been shown to be at higher risk of adverse contact lens-related events, with the highest risk within the 15-29 age range.[8, 9, 19, 33] It's been proposed that this may be attributed to the higher risk behaviors apparent in this population including noncompliant overnight use, neglectful hand washing, noncompliant lens case care, and poor decisions regarding lens replacement. Fortunately, the youngest contact lens wearers seem to be better off in this regard. Bullimore reported the overall incidence of CIEs in children aged 7-17 was 0-335 per 10,000 years of contact lens wear,[39] which is less than the reported annualized incidence of symptomatic CIEs in adults, that ranged from 316-2,061 per 10,000 patient years. Recurrence of CIEs has been demonstrated in studies where those with a previous history of CIEs present with a 4-7 fold greater risk of a repeat event.[14, 40] From a clinical standpoint, it is important to closely examine and document previous corneal scarring representing a past presumed infiltrative event as these patients may not be good candidates to remain in the same lens or in extended wear. In fact, the recurrent nature of these events in some individuals suggests genetic susceptibility to such inflammation.

In summary, the incidence of CIEs had not decreased with the introduction of new lens types and modalities until recently with the introduction of daily disposable lenses. Continued work in the areas of antimicrobial lenses, novel materials, and genetics will surely uncover new data and pathways to limit the occurrence of these non-serious, but unwanted contact lens complications.

REFERENCES

1. Donshik PC, Suchecki JK, Ehlers WH. Peripheral corneal infiltrates associated with contact lens wear. *Trans Am Ophthalmol Soc*. 1995;93:49-60; discussion 60-44.
2. Wu P, Stapleton F, Willcox MD. The causes of and cures for contact lens-induced peripheral ulcer. *Eye & CL Lens*. 2003;29(1 Suppl):S63-66; discussion S83-64, S192-194.
3. Szczotka-Flynn L, Ahmadian R, Diaz M. A re-evaluation of the risk of microbial keratitis from overnight contact lens wear compared to other life risks. *Eye & CL*. 2009;35(2):69-75.

4. Robboy M, Comstock T, Kalsow C. Contact Lens Associated Corneal Infiltrates. *Eye & CL*. 2003;29(3):146-154.
5. Steele K, Szczotka-Flynn L. Epidemiology of contact lens-induced corneal infiltrates: an updated review. *Clin Exp Optom.* 2017;100(5):473-481
6. Chalmers RL, Hickson-Curran SB, Keay L, et al. Rates of adverse events with hydrogel and silicone hydrogel daily disposable lenses in a large postmarket surveillance registry: the TEMPO Registry. *Invest Ophthalmol Vis Sci*. 2015;56(1):654-663.
7. Efron N, Morgan PB, Hill EA, et al. Incidence and morbidity of hospital-presenting corneal infiltrative events associated with contact lens wear. *Clin Exp Optom*. 2005;88(4):232-239.
8. Chalmers RL, Keay L, McNally J, Kern J. Multicenter Case-Control Study of the Role of Lens Materials and Care Products on the Development of Corneal Infiltrates. *Optometry Vision Sci.* 2012;89(3):316-325.
9. Chalmers RL, Wagner H, Mitchell GL, et al. Age and Other Risk Factors for Corneal Infiltrative and Inflammatory Events in Young Soft Contact Lens Wearers from the Contact Lens Assessment in Youth (CLAY) Study. I*nvest Ophthalmol Vis Sci*. 2011;52(9):6690-6696.
10. Morgan PB, Efron N, Hill EA, et al. Incidence of keratitis of varying severity among contact lens wearers. *Brit J Ophthalmol.* 2005;89(4):430-436.
11. Morgan PB, Efron N, Brennan NA, et al. Risk factors for the development of corneal infiltrative events associated with contact lens wear. *Invest Ophthalmol Vis Sci.* 2005;46(9):3136-3143.
12. Cutter GR, Chalmers RL, Roseman M. The clinical presentation, prevalence, and risk factors of focal corneal infiltrates in soft contact lens wearers. *Cont Lens Ant Eye*. 1996;22(1):30-37.
13. Radford CF, Minassian D, Dart JKG, et al. Risk Factors for Nonulcerative Contact Lens Complications in an Ophthalmic Accident and Emergency Department A Case-Control Study. *Ophthalmology*. 2009;116(3):385-392.
14. Richdale K, Lam DY, Wagner H, et al. Case-Control Pilot Study of Soft Contact Lens Wearers With Corneal Infiltrative Events and Healthy Controls. *Invest Ophthalmol Vis Sci*. 2016;57(1):47-55.
15. Sorbara L, Zimmerman AB, Mitchell GL, et al. Multicenter Testing of a Risk Assessment Survey for Soft Contact Lens Wearers With Adverse Events: A Contact Lens Assessment in Youth Study. *Eye & CL.* 2018;44(1):21-28
16. Jansen ME, Chalmers R, Mitchell GL, et al. Characterization of patients who report compliant and non-compliant overnight wear of soft contact lenses. *Contact Lens Ant Eye*. 2011;34(5):229-235.
17. Chalmers RL, McNally JJ, Schein OD, et al. Risk factors for corneal infiltrates with continuous wear of contact lenses. *Optom Vision Sci*. 2007;84(7):573-579.
18. Szczotka-Flynn L, Diaz M. Risk of corneal inflammatory events with silicone hydrogel and low dk hydrogel extended contact lens wear: a meta-analysis. *Optom Vis Sci*. 2007;84(4):247-256.
19. Chalmers RL, Keay L, Long B, et al. Risk factors for contact lens complications in US clinical practices. *Optom Vis Sci*. 2010;87(10):725-735.
20. Dutta D, Cole N, Willcox M. Factors influencing bacterial adhesion to contact lenses. *Mol Vis.* 2012;18:14-21.
21. Henriques M, Sousa C, Lira M, et al. Adhesion of Pseudomonas aeruginosa and Staphylococcus epidermidis to silicone-hydrogel contact lenses. *Optom Vis Sci*. 2005;82(6):446-450.
22. Kodjikian L, Casoli-Bergeron E, Malet F, et al. Bacterial adhesion to conventional hydrogel and new silicone-hydrogel contact lens materials. *Graefes Arch Clin Exp Ophthalmol.* 2008;246(2):267-273.
23. Willcox MD, Harmis N, Cowell, et al. Bacterial interactions with contact lenses; effects of lens material, lens wear and microbial physiology. *Biomaterials*. 2001;22(24):3235-3247.
24. Brennan NA, Coles ML. To the editor: risk of corneal inflammatory events with silicone hydrogel and low dk hydrogel extended contact lens wear: a meta-analysis. *Optom Vis Sci*. 2008;85(5):364; author reply 364-365.
25. Ozkan J, Mandathara P, Krishna P, et al. Risk Factors for Corneal Inflammatory and Mechanical Events with Extended Wear Silicone Hydrogel Contact Lenses. *Optom Vis Sci.* 2010;87(11):847-853.
26. Szczotka-Flynn L, Lass JH, Sethi A, et al. Risk Factors for Corneal Infiltrative Events during Continuous Wear of Silicone Hydrogel Contact Lenses. *Invest Ophth Vis Sci.* 2010;51(11):5421-5430.
27. Willcox M, Sharma S, Naduvilath TJ, et al. External Ocular Surface and Lens Microbiota in Contact Lens Wearers With Corneal Infiltrates During Extended Wear of Hydrogel Lenses. *Eye & CL-Science and Clinical Practice*. 2011;37(2):90-95.
28. Holden BA, La Hood D, Grant T, et al. Gram-negative bacteria can induce contact lens related acute red eye (CLARE) responses. *Cont Lens Ant Eye*. 1996;22(1):47-52.

29. Pearlman E, Johnson A, Adhikary G, et al. Toll-like receptors at the ocular surface. *Ocul Surf.* 2008;6(3):108-116.
30. Szczotka-Flynn L, Jiang Y, Raghupathy S, et al. Corneal Inflammatory Events with Daily Silicone Hydrogel Lens Wear. *Optom Vision Sci.* 2014;91(1):3-12.
31. Carnt NA, Evans VE, Naduvilath TJ, et al. Contact Lens-Related Adverse Events and the Silicone Hydrogel Lenses and Daily Wear Care System Used. *Arch Ophthalmol-Chic*. 2009;127(12):1616-1623.
32. Zimmerman AB, Emch AJ, Geldis J, et al. Contact Lens Corneal Inflammatory Events in a University Population. *Optom Vis Sci*. 2016;93(1):42-49.
33. Lazon de la Jara P, Papas E, Diec J, et al. Effect of lens care systems on the clinical performance of a contact lens. *Optom Vis Sci*. 2013;90(4):344-350.
34. Willcox MD, Carnt N, Diec J, et al. Contact lens case contamination during daily wear of silicone hydrogels. *Optom Vis Sci*. 2010;87(7):456-464.
35. Szczotka-Flynn LB, Jiang Y, Stiegemeier MJ, et al. Mucin Balls Influence Corneal Infiltrative Events. *Optom Vis Sci.* 2017;94(4):448-457.
36. Szczotka-Flynn L, Benetz BA, Lass J, et al. The association between mucin balls and corneal infiltrative events during extended contact lens wear. *Cornea*. 2011;30(5):535-542.
37. Grupcheva C MT, Ivancheva V. The importance of the mucin balls. Poster session presented at BCLA 2013.
38. Ladage PM, Petroll WM, Jester JV, Fisher S, Bergmanson JP, Cavanagh HD. Spherical indentations of human and rabbit corneal epithelium following extended contact lens wear. *CLAO J* 2002;28:177-80.
39. Bullimore MA. The Safety of Soft Contact Lenses in Children. *Optom Vis Sci*. 2017;94(6):638-646.
40. McNally JJ, Chalmers RL, McKenney CD, Robirds S. Risk factors for corneal infiltrative events with 30-night continuous wear of silicone hydrogel lenses. *Eye & CL*. 2003;29(1 Suppl):S153-156; discussion S166, S192-154.