

*Clinical & Refractive Optometry* is pleased to present this continuing education (CE) article by Dr. Brian Levy and Dr. Gary Orsborn entitled **Clinical Risks: Myths and Truths—Interpreting the Evidence-Based Data about Contact Lens Care**. This 1-hour Council of Optometric Practitioner Education (COPE) approved CE credit course is being provided free of charge by Bausch & Lomb Canada. Please refer to page 170 for complete instructions.

## Clinical Risks: Myths and Truths— Interpreting the Evidence-Based Data about Contact Lens Care

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### ABSTRACT

There has been a recent increased focus on what some researchers consider to be risk factors for contact lens-related microbial keratitis.

On the one hand, many admit that there is still much we don't understand concerning contact lens care and effective disinfection. Yet, on the other hand, many leap to conclusions that have no evidence-based support from clinical studies or laboratory research.

This article challenges a significant paradigm relating to contact lens-related microbial keratitis. A further challenge relates to the textbook teachings for the past 30 to 40 years versus data from well-designed studies that contravene the conventional wisdom that many hold.

Here we will review the data that challenge recent articles and presentations regarding the observation of in vivo corneal staining and its clinical interpretation.

In this article, we will cover topics related to solutions, contact lenses, and their relative risks and benefits; microbiology, compliance, toxicity, epidemiology and pathophysiology.

### MICROBIOLOGY

To give some perspective, Fig. 1 exhibits results of basic U.S. FDA and International Organization for Standards (ISO) stand-alone biocidal efficacy testing. These results demonstrate that these solution systems do relatively well against the standard American Type Culture Collection (ATCC) strains.

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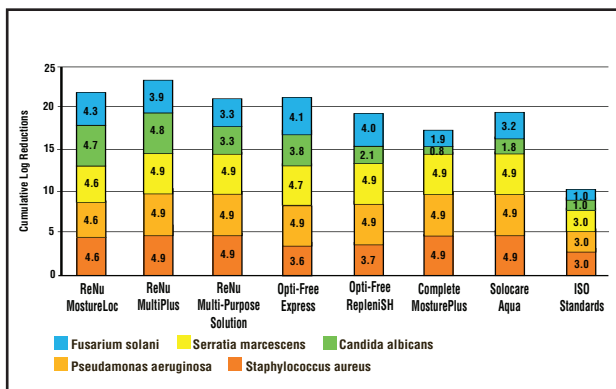
The FDA and the ISO have outlined specific procedures to evaluate the inherent microbiocidal activity of a disinfecting solution using a stand-alone test. The stand-alone method provides a quantitative measure by which disinfecting solutions are evaluated against FDA- and ISO-established performance criteria, and this method may be used to assess the relative antimicrobial efficacy of different disinfecting solutions.

The FDA and ISO require evaluation of a standard set of microorganisms, and at least a 3-log reduction for bacteria and a 1-log reduction for fungi (*Fusarium solani* and *Candida albicans*) in the minimum disinfecting time as specified according to the manufacturer's label. Bausch & Lomb's ReNu with MoistureLoc, now discontinued, met the FDA and ISO stand-alone primary acceptance criteria for all required microorganisms within the manufacturer's recommended disinfection time of four hours.

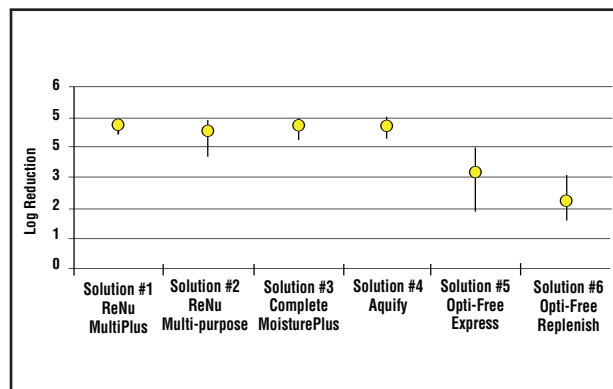
During the B&L investigation of the *Fusarium* issue in 2006, a new finding was the difference in adaptability between the standard ATCC strain compared to a clinical isolate of *F. solani* from New Jersey. According to internal B&L laboratory testing that focused on the possible impact of some noncompliant habits,<sup>1</sup> a polymer film can form under certain patterns of misuse, such as exposing a solution to evaporative conditions, and topping off. Could such a film support or protect *F. solani*?

To answer this question, B&L conducted a study in which researchers added an inoculum of *F. solani* to MoistureLoc (without the disinfecting active Alexidine) and allowed the product to dry, forming a polymer film containing *F. solani*. When dry, the product was challenged with different strengths of MoistureLoc and checked for viable *F. solani* after four hours. *F. solani* isolates showed viability in the MoistureLoc film, while in contrast, ReNu Multi- Plus performed well against both strains and did not show viable *F. solani* in the product film when similarly challenged.

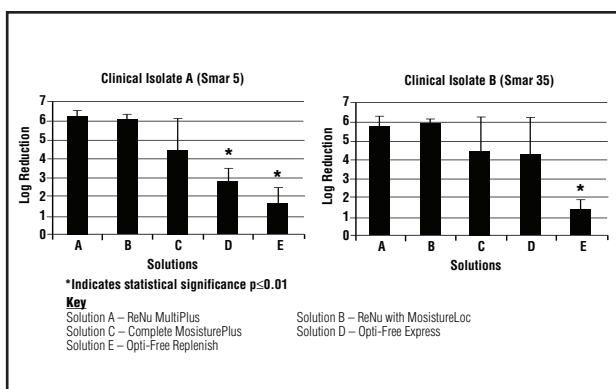
Solutions containing PHMB, such as ReNu MultiPlus and original ReNu Multi-Purpose solutions, demonstrate better overall activity against a battery of clinical isolates of *Staphylococcus aureus* than solutions containing polyquaternium 1, such as Alcon's Opti-Free Express and Opti-Free Replenish (Fig. 2).<sup>2</sup>



**Fig. 1** Contact lens care solutions all perform quite well when compared to the ISO standards for stand-alone biocide.



**Fig. 2** Variability in biocidal efficacy of different solutions against *Staphylococcus aureus* clinical isolates. Graph depicts the mean (dot) and the range of values (line).



**Fig. 3** Variability in biocidal efficacy of different solutions against *Serratia marcescens* clinical isolates.

In addition, in a study conducted at the Institute for Eye Research in Australia, researchers compared the susceptibilities of clinical isolates of *Serratia marcescens* and the standard ISO ATCC strain to five multipurpose solutions (Fig. 3). Results show the average (with standard deviation) log-reduction of viable bacteria for *S. marcescens* clinical isolates A (Smar 5) and B (Smar 35) after disinfection for the minimum recommended disinfection time for five commercially available multipurpose disinfection solutions. The authors found that solutions containing biguanides (such as ReNu MultiPlus) were the most effective and conclude, “Clinical isolates of *S. marcescens* may show increased resistance to disinfection with polyquatrenium.”<sup>3</sup>

## COMPLIANCE

Another topic that has received a lot of attention is the matter of patient noncompliance.

## Noncompliant behavior includes:

- Not cleaning lens case regularly
- Not replacing lens case regularly
- Poor cleanliness with bottle caps
- Open bottle caps and/or lens cases
- Poor hand washing/incomplete rinsing of hands
- No rinsing of lens
- Topping off solution

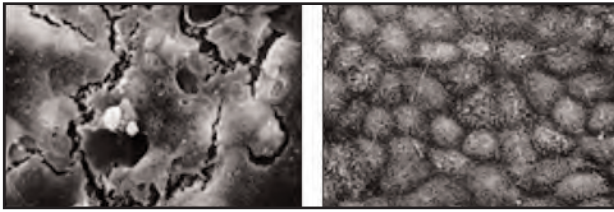
In the Singapore cases of *Fusarium* keratitis, lens hygiene was found to be suboptimal in 81.8% of patients.<sup>4</sup> Each had at least one predisposing factor for *Fusarium* infection, including failure to replace contact lenses at the planned replacement date (43.9 percent), overnight use of daily wear contact lenses (19.7 percent) and wearing contact lenses often without using goggles in swimming pools (30.3 percent).

Noncompliant behavior raises the risk of infection, as shown in a study from the *Indian Journal of Ophthalmology*.<sup>5</sup> These researchers took corneal scrapings from 35 patients who had culture-proven contact lens-associated microbial keratitis and found that the corneal scrapings bacteria were the same as bacteria found in their lens storage cases. This is evidence that the source of contamination could be the contact lens storage cases.

## TOXICITY

The industry has seen and heard over the past several years the terms solution toxicity and cytotoxicity. It’s important to gain an understanding of what cytotoxicity really means and how the term is used in the context of corneal staining.

Cytotoxicity is assessed through standard assays performed not only in the contact lens industry but also



**Fig. 4** Physiologic effect on cell cultures following exposure to non-PHMB (left) and PHMB (right) solutions.

throughout other industries. Assays are used to determine the effect of different compounds on cells from different tissues. Before a manufacturer moves to human clinical testing with any product, researchers must determine if a cytotoxic component exists. If so, the manufacturer would not proceed to human testing with that particular compound.

It's somewhat troubling to us that the terms cytotoxicity and solution cytotoxicity are being used indiscriminately with respect to the clinical finding of micropunctate transient corneal staining to imply that some lens care systems are inferior to others. The use of this terminology as it pertains to this type of staining flies in the face of the morphological findings with classic cytotoxicity assays. PHMB solutions have been reported to be clinically associated with higher levels of low-grade micropunctate transient staining compared to Aldox/Polyquad-based systems. Yet in several studies the cytotoxicity index is always higher for Aldox/Polyquad systems vs. PHMB in the classic cytotoxicity assays.<sup>6</sup> Clearly these findings indicate that staining doesn't appear to be a cytotoxic response and needs further investigation with respect to morphological characteristics.

Tchao and coworkers (2002) reported on the use of sodium fluorescein permeability assays *in vitro* to study the effects of various disinfecting solutions on the integrity of the epithelium.<sup>7</sup> Fig. 4 shows the physiologic damage done to the cell cultures following exposure to PHMB and non-PHMB solutions. The image on the left shows that tight junctions between the cells of the epithelial culture were compromised with a non-PHMB solution but were not compromised with a PHMB-based solution. This study was performed on kidney cell cultures. In this standard cytotoxic assay, the effect on cells seems to be worse with a non-PHMB solution.

Also in 2002, Mowrey-McKee and co-workers published a paper on ocular toxicity.<sup>8</sup> They determined the cytotoxicity potential of soft lens disinfecting solutions by looking at three different USP elution tests. One test looked at the effect from the direct contact of that solution on the cells; another looked at the uptake of dye by these

cells, which increases when the cell membrane is damaged. The third test measured the cell's ability to re-grow after exposure to the solution.

In addition, results of a study presented at the 2007 British Contact Lens Association meeting demonstrated that silicone hydrogel contact lenses (balafilcon A) treated with Opti-Free Express had a greater effect on the cell membranes and tight junctions of rabbit corneal epithelium cells after two hours of lens wear than balafilcon A (PureVision, B&L) contact lenses treated with ReNu MultiPlus.<sup>9</sup> Corneas of rabbits that wore balafilcon A contact lenses treated with ReNu MultiPlus exhibited morphology very similar to the untreated control cornea.

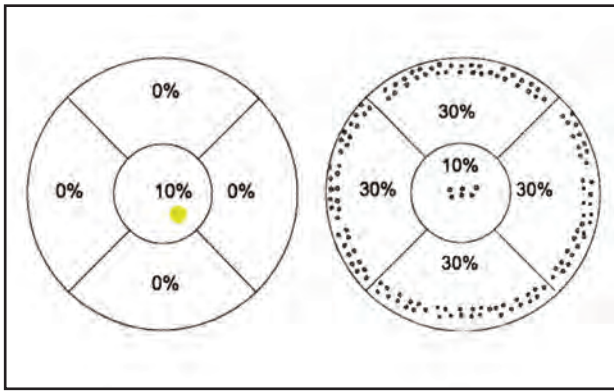
These studies raise questions and should offer more clarification on the use of the terms "cytotoxicity" and "solution cytotoxicity."

In another example of the differences between *in vitro* assays and *in vivo* clinical observations as they relate to the term cytotoxicity, Mowrey-McKee and coworkers (2002) from Wayne State University demonstrated a lack of correlation between staining and change in cell morphology after exposure to PHMB soaked lenses. In this study, researchers soaked soft contact lenses for 24 hours in either a PHMB-containing solution or a phosphate buffered saline (PBS). Lenses were fitted onto rat eyes and then removed at one, three and five hours.

The researchers instilled fluorescein into the rats' eyes and observed and photographed the degree of staining at a slit lamp. Animals were then sacrificed and the eyes enucleated and processed for scanning electron microscopic (SEM) observation. SEM showed no morphologically detectable effect of PHMB that would correlate with the slit lamp information and confirmed that the cellular architecture of the corneal epithelium did not differ between the two treatment groups. The researchers concluded "That corneal staining with fluorescein following contact lens disinfection with PHMB is not indicative of damage to the surface of the cornea and that staining is an artifact that disappears within hours."

## EPIDEMIOLOGY

Some researchers and clinicians have suggested that observations of higher levels of low-grade, transient, micropunctate corneal staining may increase risk of infection. We know of no study or data that's been published in a peer reviewed forum which shows micropunctate staining is a risk factor for contact lens-associated microbial keratitis.<sup>10</sup> It can be argued that there is only one sight-threatening event related to contact lens wear — infectious keratitis — and data continue to support extended wear as the primary risk factor for microbial keratitis. Peer reviewed papers evaluating



**Fig. 5** The Staining Grid and a potentially misleading area-estimate method.

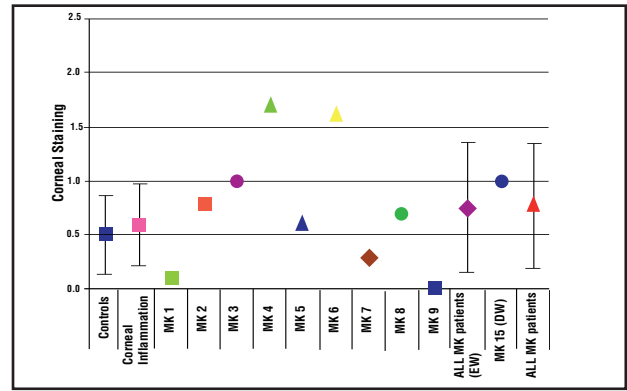
hydrogel and silicone hydrogel lenses confirm that rates have remained stable regardless of material type. Despite these findings, practitioners should base extended wear use on risk/benefit assessment between patient and practitioner, as rates of infection even with extended wear remain very low.

Interestingly, with extended wear being the primary risk factor, there's either no or minimal exposure to solution systems. This fact questions the alleged relationship between solution-related corneal staining and infectious keratitis.

### PATHOPHYSIOLOGY

Suzanne Fleiszig, OD, PhD, has performed the most research in trying to understand corneal infections related to contact lens wear.<sup>11</sup> She has shown that the cornea has a series of active and passive strategies to protect itself from infection — starting with the tear layer, moving into the epithelium and ultimately the basal lamina. Fleiszig's work confirms the complex multifactorial nature of the cornea's defense mechanisms. She has shown that even if one of those corneal defense mechanisms is intact, the cornea is unlikely to become infected. She states, "Even with massive staining, the cornea maintains its resistance to infection provided there is some level of defense."

Many practitioners are familiar with the staining grid developed by Gary Andrasko, OD, through support from Alcon. Fig. 5 shows an example of how misleading the staining grid can be. If you were to assess a small lesion (less than 1mm diameter) in the central cornea to stromal depth (beyond basal lamina), this eye would clearly be at a relatively high risk for infection. Using the staining grid. com philosophy, this same eye stained with fluorescein would have a low score (<10 percent) and green color assigned to it on the grid, indicating low risk for adverse outcome. On the other hand, an eye with SPK in the



**Fig. 6** Dr. Sweeney's work shows no correlation between the extent of corneal staining and microbial keratitis.

periphery impacting several quadrants (clearly an eye at low risk for adverse outcome) would be assigned a high score and red color indicating high risk (Figure 5). We believe this example clearly indicates that using the grid for assignment of risk is inconsistent with standard measures and is in fact misleading. Furthermore, the contention that the relative distribution of transient superficial staining is an indicator of biocompatibility is not borne out by the toxicology and epidemiological studies relating to contact lens/solution use.

Epidemiological studies conducted on lens-related corneal infections 10 years apart show the same rates. The 1989 Poggio study<sup>12</sup> and Cheng group 10 years later<sup>13</sup> ran similar studies and found similar rates. Infectious keratitis incidence over this 10-year period remained essentially the same. Keep in mind that during this period PHMB-based solutions made up 60 percent of the market and infections didn't increase along with the increased percentage of PHMB solutions in the market.

Fig. 6 illustrates the work of Deborah Sweeney, BOptom, PhD, which shows no relationship between the extent of corneal staining and microbial keratitis.<sup>14</sup> This figure shows the average corneal staining extent prior to a microbial keratitis (infection) event among 10 individuals. There is no pattern or trend of the extent of staining and these 10 events. In addition, when looking at the control group (n=658) and a group of subjects who had corneal inflammatory events (CIE) (n=419), it appears no significant difference was found in corneal staining extent between the control and those subjects who experienced any CIE.

If chronic staining is associated with higher risk for infection, then infections with 3 o'clock and 9 o'clock staining in GP contact lens wear should be common. Yet we're not aware of any reported cases of this in the

literature, even with severe 3 o'clock and 9 o'clock staining. Clinicians have observed examples of severe corneal staining with superior epithelial arcuate lesions (SEALs), yet, again, we couldn't find any reported cases of infections with SEALs. Co-author Dr. Levy has coined the term "Asian idiopathic pseudo-entropion," to describe the condition in which the superior lid margin in Asian patients is usually turned-in slightly with an extra layer of lashes that chronically rubs against the cornea. These patients exhibit chronic staining, which is observed when fluorescein is applied. Again, we're not aware of any reported cases of infection related to the chronic staining with this phenomenon. Just about every practitioner has seen keratoconus patients with central corneal abrasions, which often result in fibrosis. As well, we couldn't find a single case reported of microbial keratitis with GP lens wear in keratoconus.

### SUMMARY

As clinicians, we need to use scientific and clinical data to provide the best patient care. We need to weigh the risks and benefits of all treatments and make good clinical decisions. Corneal infection is complex and multifactorial and occurs at an extremely low rate; however, current data suggests that extended wear of contact lenses is a primary risk factor associated with infectious keratitis. Superficial, transient corneal staining occurs in lens and non-lens wearers, at a higher or lower rate depending on ocular condition and various solution/lens combinations. Based on scientific data, it's not a risk factor for lens-related corneal infection.

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