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Fungal Keratitis in Contact Lens Wearers

Brett A. Levinson, Kristin M. Hammersmith, and Elisabeth J. Cohen

Contact lenses are widely used for correction of refractive error and for cosmetic purposes. Over 30 million Americans use contact lenses, and the risk of infection, while low, is well known to eye care professionals.[1] Infections secondary to contact lens use are most commonly associated with bacterial pathogens. Fungal keratitis, while less common, is an increasingly recognized risk of contact lens use, and often with devastating visual outcomes. Recently, increased attention has been focused on fungal infections due to an outbreak of *Fusarium* keratitis associated with one brand of a multipurpose contact lens solution. However, in addition to the recent *Fusarium* outbreak, an overall increase in rates of fungal keratitis has been noted in the past several years. This chapter will review fungal keratitis associated with contact lens wear.

Fungi may be commensal organisms of the ocular surface, and studies of normal eyes have found fungal isolates in 3% to 28% of conjunctival cultures. Fungal keratitis is less common than bacterial keratitis, comprising 6% to 20% of infectious keratitis cases, depending on the study. Fungal keratitis is more common in subtropical or tropical climates, such as southern Florida and India. In the temperate areas of the United States, *Candida* sp. and *Aspergillus* sp. have been the most common isolates with *Fusarium* sp. more common in the south.[2] However, recently, an increase in *Fusarium* related infections due to contact lens use have been reported across the country and worldwide.

Clinically, fungal keratitis can present similarly to other types of microbial keratitis with an epithelial defect, stromal infiltration and edema, conjunctival hyperemia, and anterior chamber

reaction and hypopyon, but often with a more indolent course, at least initially. Several characteristic findings of filamentous fungi include elevated, branching, grey-white ulcers, feathery margins, satellite lesions, and endothelial plaques (Fig. 1).<fig1> Yeasts can appear clinically similar to bacterial infections. The onset of fungal keratitis is typically subacute compared to the acute onset of bacterial keratitis.[2]

Trauma has been reported as the most common cause of fungal keratitis from filamentous organisms, whereas *Candida* is more common in eyes with chronic disease and in immunocompromised patients. A review of fungal keratitis cases seen between 1982 and 1992 at the Bascom Palmer Eye Institute in Miami examined 125 cases of fungal keratitis, of which 44% were due to trauma. In this series, *Fusarium* was the most common isolate and was seen in 62% of the patients.[3] A study in Singapore examined 29 cases of fungal keratitis seen between 1991 and 1995. Over half of the cases were associated with trauma, whereas only two patients had a history of contact lens use.[4] A review of fungal keratitis at the New York Eye and Ear Infirmary between 1987 and 2003 identified 61 cases, of which 29 (48%) were due to *Candida albicans,* and nine other cases due to other *Candida* species. The most common risk factors in this study included HIV positivity and chronic ocular surface disease, whereas trauma as an etiology was less common. In contrast to studies in Miami, *Fusarium* was uncommon, accounting for only six of 61 cases.[5]

Historically, fungal keratitis has been infrequently associated with contact lens use. In a review of fungal keratitis from 1972 to 1987, Wilhemus reported that four of 90 patients (4%) wearing cosmetic contact lenses and four of 15 patients (27%) wearing therapeutic contact lenses

developed fungal infections.[6] A review of cases seen at Bascom Palmer between 1969 and 1977 found only three cases of contact-lens-associated fungal keratitis.[7] A follow-up study at the same institution reviewed 573 cases of infectious keratitis from 1977 to 1982. Of the 64 culture-positive cases associated with contact lens use, only two (3%) were caused by fungi. In contrast, of the 264 culture-positive cases not associated with contact lens use, 63 (24%) were caused by fungal organisms. This finding led the authors to postulate that contact lenses may have a protective effect against the development of fungal keratitis.[8] Similarly, between 1982 and 1992, only five cases of fungal keratitis associated with contact lens use was noted at Bascom Palmer. Four patients wore extended wear contact lenses, and one patient had a therapeutic bandage lens.[3]

A retrospective study at Wills Eye Hospital in Philadelphia examined records from 1991 to 1999 and found 24 cases of fungal keratitis, of which seven cases were associated with contact lens use. Five patients were using frequent replacement hydrophilic soft contact lenses, one patient was wearing a daily-wear rigid gas permeable, and one patient was wearing a bandage contact lens. All patients in the study using contact lenses for refractive errors developed *Fusarium* keratitis. This study found *Candida* to be the most common fungal isolate overall, whereas *Fusarium* was the most common filamentous species.[9]

Koidou-Tsiligianni et al. reviewed 658 cases of ulcerative keratitis at Bascom Palmer. No fungal keratitis was found in the contact lens group as compared to 40 cases (17%) in the noncontact lens group. (Koidou-Tsiligianni, 1989) In a case-controlled study published in 1997 comparing bacterial keratitis to fungal keratitis, Wong et al. reported that bacterial keratitis was more likely

to be associated with contact lens use, whereas fungal keratitis was significantly more likely to be associated with ocular trauma and less likely to be associated with contact lens use.[10]

Studies from the 1980s examined the susceptibility of extended wear soft contact lenses to fungal growth. Yamaguchi et al. exposed contact lenses with water-contents of 45% and 73.5% to *Fusarium solani* and *Aspergillus flavus* on Sabouraud agar. Penetration of the contact lenses occurred in both types of lenses, but the fungi grew more vigorously in the lenses with the higher water content.[11] (Current soft lenses have higher water contents than the prior generation of lenses.) Wilson and Ahearn described fungal growth on 11 extended wear contact lenses, which in most cases were known to have been contaminated while on the eye.[12] A follow-up study examining these 11 contact lenses with electron microscopy found that a contact lens with greater than 55% water content created a suitable environment for saprophytic fungi. In vitro tests of these lenses demonstrated that fungi could penetrate the lens in 4 to 7 days of continuous exposure.[13]

ReNu with MoistureLoc Fungal Keratitis

Recently, however, a paradigm shift has occurred in the thinking about fungal keratitis and contact lens use in part due to an outbreak in contact lens-associated *Fusarium* keratitis. An insurgence of *Fusarium* keratitis in Singapore was first recognized in February 2006, at which point, 54 patients were identified over the previous 12 months.[14] The Centers for Disease Control (CDC) first received a report from a New Jersey ophthalmologist about three patients in March of 2006 with contact-lens-associated *Fusarium* keratitis. An association between cases

and use of a particular multipurpose solution, ReNu with MoistureLoc (Bausch & Lomb, Rochester, NY) was noted, prompting an investigation of Bausch & Lomb's manufacturing plant, and a review of contact lens related *Fusarium* cases. After the initial reports from the Pacific Rim, several physicians from geographically diverse locations in the United States began to report an increasing incidence of contact lens-related *Fusarium* keratitis. Similar to the reports from East Asia, the incidence was significantly out of proportion to previously noted rates of disease.[14,15]

Khor et al. reviewed the experience of *Fusarium* keratitis in Singapore from March 2005 to May 2006. During this time period 42 (64%) of patients were known users of ReNu with MoistureLoc. Five patients required emergent penetrating keratoplasty. Contact lens hygiene was noted to be suboptimal in over 80% of patients including the use of contacts past the replacement date, overnight use of daily lenses, and swimming with lenses. A cluster of 33 patients with contact lens-associated *Fusarium* keratitis was also reported in Hong Kong, and Bausch & Lomb suspended sale of the ReNu brand solutions in the Pacific Rim in February 2006.[14]

In the United States, Alfonso et al. reported 34 cases between January 2004 and April 2006 at Bascom Palmer.[16] Bernal et al. documented four cases during a 5-week period in 2006 at the University of California, San Francisco.[17] Gorscak et al. reported on 11 cases of contact lens-associated *Fusarium* keratitis between October 2005 and April 2006 at the University of Medicine and Dentistry of New Jersey and the Wills Eye Hospital.[18] Jeng et al. reported three cases of contact lens related *Fusarium* keratitis in MoistureLoc users in Cleveland, Ohio, from November 2005 to March 2006.[19] Twenty cases were noted in Puerto Rico between October

2005 and April 2006.[20]

In a landmark paper in the *Journal of the American Medical Association*, physicians from the CDC reviewed cases of contact lens-associated *Fusarium* cases between June 2005 and July 2006 and identified 164 confirmed cases, of which 55 (34%) required corneal transplantation (Fig 2).<fig2> The only statistically significant association found after multivariable analysis was use of MoistureLoc multipurpose solution in the month prior to symptom onset. MoistureLoc was manufactured in one location for distribution to the United States, Hong Kong, and Singapore. No evident cause of contamination in the production of MoistureLoc was noted. No fungus was cultured from the bottles of MoistureLoc at the site of production or from bottles submitted by patients with *Fusarium* keratitis in the CDC investigation.[15]

Genetic analysis of the *Fusarium* cultured from infected corneas found several different species and multiple different genotypes of *Fusarium* species, suggesting that there was not one isolated source of contamination in the manufacturing process. Also, if the production was contaminated, one would expect the other ReNu products produced at the same site to have an increased association with *Fusarium*, which was not found. On multivariable analysis, no single contact lens hygiene practice was independently associated with a disease state – both cases and controls reported suboptimal contact lens hygiene. Univariate analysis found that infected patients were more likely than controls to have reused multipurpose solution already in the contact lens case.[15]

Bausch & Lomb's previous formulation of multipurpose solution, ReNu MulitPlus has been sold without changes in formulation for approximately 10 years. MoistureLoc was introduced to the

United States market in the fall of 2004 and achieved an approximately 40% market share in the United States by the first quarter of 2005. The first cluster of contact lens-associated *Fusarium* keratitis cases in the United States was reported in the third quarter of 2005. By the first quarter of 2006, MoistureLoc had an approximately 60% of the U.S. market share, and cases of contact lens-associated *Fusarium* keratitis had more than doubled. MoisutreLoc was withdrawn from the United States market on in April 2006, and the CDC had 27 reported cases of *Fusarium* keratitis that month. In May 2006, the CDC had two reported cases, and one case was reported in June (Fig. 2).[15]

Because no single source of contamination has been found, the cause of the *Fusarium* outbreak appears to be a multifactorial interaction between MoistureLoc, *Fusarium* in the environment, and possibly the contact lens material or the case. MoistureLoc has properties unique from the multipurpose solutions currently available. It contains two chemicals not found in other multipurpose solutions – alexidine, a disinfectant, and polyquarterium 10, a moisture-retaining polysaccharide designed to hold water close to the surface of the contact lens. In vitro studies validated that MoistureLoc met current FDA requirements against *Fusarium,* a one-log reduction in colony forming units. However, it was suspected that an interaction between the novel ingredients in MoistureLoc, biofilm formation on the contacts or the lens case, and *Fusarium's* ability to penetrate soft contact lenses were causal in this insurgence of disease.[15]

Zhang et al. collected contact lens cases with and without contact lenses and multipurpose solution containers from patients with known or suspected *Fusarium* keratitis. Growth of *Fusarium* isolates were inhibited by fresh multipurpose solutions, however, *Fusarium* survived

in drying films of multipurpose solution. All four multipurpose solutions, ReNu with MoistureLoc, ReNu MultiPurpose, Complete, and Opti-Free, had visible fungal elements in drying solution, but ReNu had significantly higher amounts of recovered fungal elements by a factor of 10 to 100.[21]

A study performed for Bausch and Lomb by Levy et al. investigated the efficacy of MoistureLoc in a simulation of real-world conditions, including evaporation of the solution and re-use of old solution in the contact lens case. Both MoistureLoc (alexidine), and MultiPlus (polyhexamethethylene biguanide or PHMB) demonstrated a fivefold log reduction in colony forming units of *Fusarium solani* at their full strengths. However, when alexidine was allowed to evaporate to simulate the removal of one half and three fourths of the water content, the antifungal activity was only a 1.5 and 1.0 log reduction, respectively. PHMB, however, showed no decrease in antifungal activity with dehydration.[22]

Polymer films are created when solutions are allowed to evaporate and dissolved solids in the solution are allowed to precipitate on the contact lenses or their cases. MoistureLoc polymer films inoculated with *Fusarium solani* were compared with polymer films created from MultiPlus. As the concentration of alexidine decreased from 100% to 50%, the number of colony forming units (CFU) of *Fusarium* increased from 20 to 228 in the presence of a polymer film. In contrast, PHMB in the presence of a polymer film had no detectable CFU at any concentration.[22]

Rosenthal et al. from Alcon compared alexidine and PHMB with the active biocides in Opti-Free Express and Optifree Replenish (Alcon, Fort Worth, TX), polyquaternium-1, polyquad, and

myristamidopropyl dimethylamine, aldox . When these biocides were placed in contact lens cases without contact lenses, they maintained their antimicrobial activity. However, when placed in lens cases with an Acuvue 2 lens (etafilcon A, 58% water content, Johnson & Johnson Vision Care, Jacksonville, FL), significant uptake of the alexidine and PHMB into the lens was noted. The uptake of the biocide into the lens material corresponded with a decrease in antifungal activity. Alexidine was noted to have lost 37% of its biocidal activity against *Fusarium* after 6 hours and PHMB demonstrated 71% less fungicidal activity after 6 hours. The Optifree solutions, polyquad and aldox, retained between 90% to 100% activity against *Fusarium* after 7 days.[23]

The CDC noted that 14% of the patients with confirmed cases of *Fusarium* keratitis did not self-report using MoistureLoc. Some explanations for this include that the CDC only asked patients if they had used MoistureLoc prior to 30 days before onset of symptoms; patients may have used MoistureLoc prior to 1 month before symptom onset. Also, the packaging for MoistureLoc and MultiPlus was very similar – two patients who denied using MoistureLoc submitted bottles of MoistureLoc to the CDC for analysis, implying that the use of MoistureLoc may have been under-reported.[15]

Trends in Fungal Keratitis

Some of the cases of *Fusarium* keratitis of patients not using MoistureLoc may represent increasing background levels of disease. In recent journal articles and conference presentations, several authors have noted increasing rates of fungal keratitis in contact lens users. Colby and

Jurkunas presented a paper at the American Academy of Ophthalmology Joint Meeting in 2006 comparing rates of fungal keratitis from 2004 to 2006 with rates from 1999 to 2002 at the Massachusetts Eye and Ear Infirmary. Between 2004 to 2006, 89% of fungal keratitis cases were due to filamentous fungi and 55% occurred in soft contact lens users as compared with 30% and 18%, respectively, in 1999 to 2002.[24] Alfonso et al. reviewed culture-positive cases of microbial keratitis at Bascom Palmer between 2004 and 2006 and compared the results with prior case series from their institution. Fungal keratitis cases increased from two to 12 cases per year, which was a 500% increase.[25]

Iyer et al. also reported on the increasing rate of fungal keratitis in contact lens users. The authors reviewed 84 cases of fungal keratitis at the University of Florida between 1999 and 2006. Between 1999 and 2004, trauma was the leading cause of fungal keratitis, 51%, with contact lens use the second most common cause, 40%. However, between 2005 and 2006, 52% of fungal ulcers were due to contact lens use, whereas trauma was the etiology in 29% of cases. The incidence of fungal keratitis associated with nontherapeutic contact lens use increased from 21% in 1999 to 2001, 32% in 2002 to 2004, and 45% in 2005 to 2006. Filamentous fungi isolated in 86% of cases, with *Fusarium* as the most common genus, isolated in 46% of the patients.[26]

A parallel increasing trend of bacterial and amoebic ulcers in contact lenses has also been noted. Mah-Sadorra et al. found that 30% of corneal ulcers seen at Wills Eye were associated with contact lens use from 1999 to 2002 compared with 12% from 1996 to 1999.[27] Rocha et al. reported an increase in *Acanthamoeba* keratitis associated with contact lens use. Between January 2004 and December 2005, 19 patients with *Acanthamoeba* ulcers were seen at Wills Eye

in contact lens users as compared with 11 cases in the previous 8 years.[28]

H1>Multipurpose Solutions

The overall increase in fungal keratitis in contact lens patients may be related to the popularity of multipurpose solutions, and "no-rub" formulations, as suggested by Cohen in an editorial in *The Archives of Ophthalmology*.[29] Multipurpose solutions are more effective against bacteria than fungi and amoeba. The FDA only requires a 1-log reduction of fungal colonies for approval of a multipurpose solution. The addition of a cleaning solution in addition to a disinfecting solution increases the antimicrobial activity; however, in the name of patient compliance, this step has been largely abandoned. Also, small changes in formulations can lead to large changes in the antimicrobial effects. A reduction in the concentration of biguanide from 0.0001% to 0.00005% is associated with a 10-fold reduction in antimicrobial activity.[29]

As noted earlier, newer formulations of multipurpose solutions may not perform as well in real-world settings as in vitro. Also, patient compliance with contact lens cleaning regimens may be declining as contact lens use becomes more popular and accepted, leading to poor patient hygiene and increased overall risk of infection.[30] However, noncompliance may have always been widespread and under-reported. Bowden et al. examined the hygiene practices of contact lens patients in 1987 with microbial keratitis and found that 88% of patients did not follow standard cleaning protocols. Bacterial contamination was found on the contact lenses, cases, or solutions in 83% of samples, and 62% of the patients used solutions that were more than 3 months old.[31] Najjar reported a case series of 70 patients with contact-lens related ulcers

between 1999 and 2002, of whom 21 (30%) reported using a multipurpose solution and claimed compliance with contact lens hygiene. This finding may represent a failure of multipurpose solutions to adequately kill microorganisms under normal use or it may represent a reporting bias on the part of the patients who attest to better compliance than they actually achieve.[32]

Until more effective multipurpose solutions are available, in our clinical practice, we emphasize that daily disposable contact lenses remain the safest option to reduce the risk of bacterial and fungal keratitis. Daily disposable contacts are worn for at most one day, and then disposed. Because these lenses are not stored for re-use, there is no need for disinfection, and the risk for contamination is, therefore, reduced.[33] Infectious keratitis associated with daily disposable use remains rare and limited to case reports.[34]

Hydrogen Peroxide Disinfection

Other contact lens disinfection systems include 3% hydrogen peroxide systems and two-step chemical disinfection systems with a separate daily cleaner, which may provide more antifungal activity than multipurpose solutions. Current hydrogen peroxide disinfection solutions include AoSept, Pure Eyes and Clear Care (Ciba Vision, Duluth, GA) and Ultracare (AMO, Santa Ana, CA).[35] Richardson et al. compared two hydrogen peroxide systems, Aosept and Ultracare, against two multipurpose solutions, ReNu Multi-purpose and Opti-free against the mold, *Beauveria bassiana.* The study found that the hydrogen peroxide systems were much more effective antifungal activity than multipurpose solutions.[36]

New Medical Therapies

Natamycin 5% (Natacyn) is the only commercially available antifungal agent and is often used as the first-line choice for fungal keratitis. Natamycin has antifungal activity against *Fusarium* and many other filamentous fungi. Ketoconazole and fluconazole also have broad activity against filamentous fungi. Fortified amphoteracin B 0.15% is often the first choice for *Candida*, however, natamycin and the azoles also have antiyeast activity.[2]

Newer medical options are available for the treatment for fungal keratitis. One such option includes voriconazole, a triazole antifungal agent, which is a synthetic derivative of fluconazole. Voriconazole was approved by the FDA in 2002 and is available commercially in oral and intravenous formulations; it can be compounded for ocular use. Voriconazole for intravitreal or topical preparation can be made with a 1:20 dilution of voriconazole for intravenous administration, which creates a 50 mcg/0.1 mL solution.[37]

The standard dosage for oral voriconazole is 200 mg twice a day and a loading dose of 400 mg twice a day for the first day can be administered. Oral voriconazole has a 96% bioavailability and reaches peak plasma concentrations in 2 to 3 hours after dosing. Voriconazole is metabolized by the hepatic cytochrome P450 system, and it may interact with other CP450 metabolized medications. Dosage may need to be lowered in patients with reduced hepatic function. There are no known long-term ocular side effects of voriconazole, but the most common side effect, seen in up to 30% patients, is a reversible visual disturbance. These visual side effects include photopsias, blurry vision, changes in color vision, and photophobia. Skin reactions, including

rash, photosensitivity, facial erythema, and elevations in liver enzymes are the other common side effects.[37]

Bunya et al. reported treating nine patients with fungal keratitis refractory to other antifungal agents with topical and oral voriconazole. Of the seven patients where follow-up was available, resolution was noted in five patients.[38] Vemulakinda et al. determined that topical voriconazole reaches therapeutic concentration in the anterior chamber for a broad spectrum of yeasts and molds when dosed every 2 hours for a 24-hour period in the uninflamed eye.[39] Marangon et al. tested voriconazole in vitro against isolates from 421 cases of culture-positive fungal keratitis seen at Bascom Palmer. Species tested included *Fusarium*, the most common isolate, *Candida*, *Aspergillus* and *Paecilomyces*. All of these species were sensitive to voriconazole with a lower minimal inhibitory concentration for these isolates than amphoteracin B, fluconazole, itraconazole, and ketoconazole.[40]

Posaconazole, (Noxafil), is a new triazole antifungal agent similar to itraconazole and is dosed orally either 200 mg four times a day or 400 mg twice a day. Posaconazole has broad activity against yeasts and molds, and it has been found to have greater clinical efficacy against *Fusarium* than voriconazole. Tu et al. reported on three patients with *Fusarium* keratitis who did not respond to maximal medical or surgical therapy, including voriconazole. The patients were treated with oral posaconazole and had improvement of their ocular infections.[41]

Surgical Treatment

Surgical options for treatment of fungal keratitis have a role when medical therapy has failed due to progressive infection or perforation. Some authors recommend the use of amniotic membrane transplants during the active infective phase of refractory cases. Medical therapy must also be continued after amniotic membrane transplantation.[42] Other authors have reported successful treatment of nonresponsive fungal keratitis with penetrating keratoplasty. The corneal graft must be sized to resect the infected tissue in its entirety.[43] In our clinical practice, steroids are avoided or delayed after surgical treatment of fungal keratitis. Steroids may be added if no fungal organisms are noted on pathology or culture from the excised corneal button.

Conclusion

Fungal keratits associated with contact lens use was once quite rare, but has become more common in recent years. Although one recent outbreak was linked to a particular brand of multipurpose solution, the overall increase in this problem is multifactorial. Possible contributory factors include the use of multipurpose solutions, change in contact lens materials, poor contact lens hygiene, and increase in fungus in the environment. Several treatment options exist, which include new generation triazoles, such as voriconazole and surgical intervention. Although current generation multipurpose solutions are safe when used as directed, their efficacy is less than prior disinfection systems, and antimicrobial activity may be much less under real-world conditions. For patients in our practice, we recommend daily disposable contact lenses when available in the patient's prescription or frequent planned replacement lenses with a hydrogen peroxide disinfection system as our second-line choice.

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<FIG>**LEGENDS**

<DFIG>**FIGURE 1. A.** Left eye of 21-year-old soft contact lens user (2-week replacement), history of ReNu with MoistureLoc use, with *Fusarium* keratitis. Note the satellite lesions. Patient treated with topical voriconazole with resolution of infection and residual peripheral scarring. Final vision 20/20. **B.** Right eye of same patient, photo taken on the same day. Note the variability in clinical presentation in this patient with bilateral *Fusarium* keratitis. Resolution with topical voriconazole. Final vision 20/20.

<DFIG>**FIGURE** 2. Confirmed cases of *Fusarium* keratitis in the United States, June 2005 to July 2006. Month of illness onset of confirmed cases of *Fusarium* keratitis reported to the Centers for Disease Control and Prevention. (Reprinted with permission from Chang DC, Grant GB, O'Donnell K et al: Multistate outbreak of Fusarium keratitis associated with use of a contact lens solution. JAMA 296:956, 2006)