Over the past several decades mycotic keratitis has been considered a rare sequel to hydrogel contact lens wear. In 2005–2006 an upswing in the incidence of *Fusarium* keratitis was associated with a disproportionate use of one multipurpose contact lens solution (MPS, ReNu with MoistureLoc, Bausch & Lomb, Rochester, NY). The MPS, as manufactured and marketed, was sterile and met regulatory guidelines for antimicrobial activity. A multivariate interaction of poor hygienic practices and the contact lens paraphernalia were associated with a mostly selective contamination in or on the lens storage case by members of the *F. solani*/*F. oxysporum* species complexes from the environment of the user. A decline of the anti-fusaria properties of the MPS in the lens case appeared related to its dissociation from drying, or dilution and the potential for sorption of antimicrobial solution components (e.g., alexidine) to various hydrogel lenses. These factors and capacities of the fusaria for rapid amplification by microcycle conidiation, production of dormant resistant cells, and potential for attachment and penetration of hydrogel lenses, were linked to the occasional selective fungal survival and growth during storage of the lens in MPS. Lack of a manual rubbing-cleaning step in the MPS disinfection process was considered a risk factor for keratitis.

**Keywords** *Fusarium* keratitis, contact lenses, multipurpose contact lens solution, *Fusarium solani*, *Fusarium oxysporum*
recognized for their capacities that permit invasion of compromised cornea and other tissues.

The FSSC-FOSC, as defined on a morphological and plant host basis, may be difficult to distinguish [1,15]. Historically, conidiophore and conidia morphology on potato dextrose (PDA) or Sabourauds (SAB) agars have been a major characteristic for separation of the two groups. For example, FSSC typically produces distinctly long (30–50 μm) septate monophialides with terminal globose to allantoid or kidney shaped microconidia (5–9 μm in false heads, Fig. 1 A, B) whereas the FOSC generally has shorter (10–20 μm) more inflated monophialides (Fig. 1, C, D). The two complexes, however, overlap in phenotype and include a variety of distinct genotypes, perhaps 25 or more overall in FSSC, many of which will probably be elevated to species status upon further taxonomic investigations.

Two different teleomorphic genera producing perithecia-type sexual states and seven biological species or mating types have been identified for isolates in the FSSC complex. No teleomorph has been demonstrated for the FOSC but the mating type loci are present [3]. Mehl and Epstein [16] confirmed that representative FSSC group 1 haplotypes from the keratitis outbreak were conspecific with and sexually compatible with mating type strains of plant pathogenic *F. solani* f. sp. *cucurbitae* race 2. These investigators confirmed that FSSC group 1, anamorphs of *Nectria haematococca*, were potential pathogens of humans and plants. For details of the status of the complex systematics of the genus *Fusarium* and aspects of its epidemiology in association with keratitis see Summerbell [1], Leslie et al. [15], Zhang et al. [5], O’Donnell et al. [4] and Mehl and Epstein [16].

![Micromorphology of F. solani GSU AFR4 and F. oxysporum GSU AFR9 on SAB. (A) GSU AFR4 elongate septate conidiophore with globose clusters of conidia; (B) GSU AFR4 feather-like arrangements of polyblastic microconidia; (C) GSU AFR9 microconidia produced singly on lateral monophialides and (D) on phialides on short branched conidiophores.](https://academic.oup.com/mmy/article-abstract/46/5/397/1022848)
Fusarium keratitis

Historically, *Fusarium* keratitis has been most commonly observed in male agricultural or construction workers in subtropical to tropical regions following ocular trauma by vegetable matter [17]. More recently, *Fusarium* keratitis has been reported as a secondary ocular infection following antimicrobial therapy for bacterial or viral keratitis [18, 19–21].

Since about 1980, contact lens wear has been increasingly recognized as a risk factor for mycotic keratitis [18, 21–25]. The estimated overall yearly incidence of microbial keratitis with hydrogel lens wearers ranges from about 1.5–20 per 10,000 wearers. Overnight wear is a risk factor, and *Pseudomonas aeruginosa* (<1% incidence) is the most common etiological agent [26–29]. The incidence of *Fusarium* keratitis in contact lens wearers has been historically lower than that of *P. aeruginosa* and has not been clearly differentiated from the incidence in non-contact lens wearers in most parts of the world [20, 23, 30–32].

Four percent of 90 cases of contact lens-associated microbial keratitis among cosmetic and aphakic contact lens wearers examined by Wilhelmus et al. [33] between ∼1972 and 1987 were caused by fungi. Two cases among the cosmetic group involved *F. solani*. Wilson and Ahearn [34] reported two instances of mycotic keratitis; one by a *Fusarium* sp. associated with hydrogel contact lens wear among 450 patients with contact lens-associated adverse events. Sankaridurg et al. [35], in a study of asymptomatic contact lens wearers involving 4203 lenses, found an incidence of *Fusarium* sp. of about 0.1% at a density range of only 5–6 colony-forming units per positive sample. No *Fusarium* sp. was isolated from 118 lenses associated with corneal infiltrative events. Tanure et al. [20] noted only 4 infections with *Fusarium* sp. associated with hydrogel contact lens wear among 24 mould-associated keratitis cases, examined retrospectively over the years 1991–1999. Mah-Sadorra [36] reported among all keratitis events examined an increase in contact lens-associated corneal ulcers from 12% for 1996–1999 to 30% for 1999–2002. Of the 51 cases reported from 1999–2002, where cultures were available, 17 were identified with *P. aeruginosa* and only two identified with *Fusarium*. All keratitis among contact lens wearers were associated with conventional frequent replacement and disposable lenses. The majority of patients practiced overnight wear and, where data were available, over 60% of the patients practiced some type of improper lens care. Ritterband et al. [37], in a review of the history of fungal keratitis between 1987 and 2003 at the New York Eye Infirmary, found a 1.2% incidence of fungi among 5083 positive corneal cultures. Fusaria were isolated from only five patients, three of whom ‘. . . had spent significant time in Florida immediately before presentation . . .’ [37]. *Candida albicans* (n = 29 of 61 cultures) was the principal organism isolated. This species is essentially an obligate commensal and adventitious pathogen of man and warm-blooded animals, and we believe it is the most common cause of mycotic keratitis and endophthalmitis among non-contact lens wearers.

Iyer et al. [24] reported trauma (51%) and contact lens wear (40%) as major risk factors for 84 patients diagnosed with fungal keratitis in Florida between 1999 and 2006, with contact lens wear (52%) surpassing trauma (29%) after 2005, as the most common risk factor. Overall of the 84 cases, the percentage of fungal ulcers associated with non-therapeutic contact lens use showed a progressive increase from 21% (n = 6) between 1999–2001, to 32% (n = 8) between 2002–2004, and to 45% (n = 14) between Jan 2005–Jun 2006. About 75% of the patients within the first two time periods were males but females comprised 65% of the last time group. *Fusarium* (41% with FOSC and FSSC prominent) was the most commonly isolated genus for all time spans followed by similar incidences (12–14%) of *Candida, Curvularia* and *Aspergillus* [24].

**Outbreak: 2005–2006**

Khor et al. [25] reported an outbreak of 66 cases of confirmed *Fusarium* keratitis among contact lens wearers in Singapore (34 females) between March 2005 and May 2006. The vast majority of these patients reported the use of one type of multipurpose contact lens solution (MPS), ReNu with MoistureLoc® (RML, Bausch & Lomb, Rochester, NY) and no traumatic event. A high percentage (~81%) admitted to poor lens hygiene practices. A case control study of 61 of the patients indicated that the use of RML significantly increased the risk of *Fusarium* keratitis [38]. The incidence of contact lens-related *Fusarium* keratitis in Singapore, among an estimated 224,800 contact lens wearers, was 2.35 per 10,000 contact lens wearers per year.

*Fusarium solani* associated with RML in Singapore and Hong Kong in 2005–2006 was attributed primarily to FSSC group 2-d genotype [23]. Gene sequencing (28s-rRNA) of 15 isolates and 37 of 38 isolates of fusaria from Singapore patients in the respective investigations of Khor et al. [25] and Saw et al. [38], gave 100% matches with the sequence from *F. solani* CBS 490.63, a group 2 haplotype isolate [5]. Amplified fragment length polymorph typing of the 37 isolates of
Fusarium did not show a single identical clone and no point source of contamination was indicated [38].

As of 18 May 2006, the National Centers for Disease Control and Prevention (CDC) had received reports of 130 confirmed cases of Fusarium keratitis within 26 states of the USA and Puerto Rico with an onset after 1 June 2005 [39]. None of these patients (67% female) had a history of ocular trauma, and 125 were contact lens wearers. Seventy-five reported using RML alone and an additional 14 used RML in combination with some other solution.

By 30 June 2006, these data had been expanded to 154 confirmed Fusarium keratitis cases among contact lens wearers of 164 fusarial cases analyzed. Of 39 isolates of Fusarium examined, at least 10 different phylogenetic species and 19 unique multilocus genotypes (3 loci) were present. Nineteen of 30 isolates associated with the use of RML [40]. Five of the patients had corneal lesions culture positive for F. solani and the one patient who had suffered vegetative trauma to the cornea required penetrating keratoplasty. Four additional symptomatic but culture-negative cases in this study responded to antifungal therapy.

Bernal et al. [41] reported on four of the USA cases of Fusarium keratitis in 2006 from San Francisco, California. All four were female contact lens wearers; three of whom had no noted risk factors for infection other than soft contact lens wear and stated use of RML. Prior to this 2006 series of cases, only 2 of 8 fusarial keratitis cases seen in the preceding 30 years had been associated with contact lens wear.

Alfonso et al. [22] reviewed 34 contact lens patients (20 females) with recognized keratitis between 1 January 2004 and 15 April 2006, who were culture positive for Fusarium species. Thirty-one of the patients received antibacterial antibiotics prior to diagnosis of mycotic keratitis, initially presumed to be caused by FOSC (20 cases), but later, mostly positioned in the FSSC [4]. Only two of the cases were associated specifically with RML use, but an additional nine patients were probable users. Three of the last-used contact lens cases (n = 3) and 10 of the last-used lenses (n = 11) from these 20 patients were culture positive for Fusarium spp. Lens solution bottles tested (n = 5) were all culture negative. Prior to January 2004, spanning the years 1990–1992, less than 10 cases of contact lens associated mycotic keratitis had been reported from the Bascom Palmer Eye Institute in Miami, Florida [22].

The above cases of Bernal et al. [41], Alfonso et al. [22], and Donnio et al. [40] were represented in the epidemiological study by Chang et al. [23].

O'Donnell et al. [4] compared sequences from 3 loci of 191 isolates (91 corneal, 100 from contact lens and lens cases) obtained from the outbreak associated with use of RML. Approximately 60% of the isolates were FSSC (mostly haplotypes 1-a and 2-d) and 30% FOSC (mostly 3-a). Each of these 3 haplotypes represented distinct phylogenetic species and each represented the most common clinical and environmental isolates among the patients. These authors indicated that their data supported the initial suggestion of Chang et al. [23] that contamination of RML occurred during use. Overall the epidemiological data for the 2005–2006 outbreak indicated that the source of the fusaria was from the immediate environments of the individual patients.

Taken together, these published studies suggest a gradual shift in the epidemiology of Fusarium keratitis from a disease associated with trauma in southern agricultural workers to one associated with daily contact lens wear in both warm and temperate environments. Continued documentation of the incidences of Fusarium keratitis with hydrogel contact lens wear will be needed to confirm this suggestion.

Why Fusarium?

The 2005–2006 outbreak of Fusarium keratitis was associated statistically with the use of RML. This association persisted, even after adjusting the analysis for poor lens hygiene, such as re-use of solution (‘topping off’) and extended wear of disposable lenses [23,38]. Unused solutions of RML in their containers obtained from patients were not found to be contaminated with Fusarium spp. and fresh solutions were inhibitory when challenged with fusaria in stand-alone type tests [25,42–45]. After Bausch & Lomb withdrew RML from the market on 15 May 2006, there was a decrease in the incidence of Fusarium keratitis [23].

Levy et al. [46] and Dyavaiah et al. [43] reported that the biocidal efficacy of RML, under simulated conditions of patient reuse (drying and concentration), was reduced, particularly against an isolate of Fusarium from a case of RML-associated keratitis. Rosenthal et al. [47] found that lens storage in contact lens cases, with discarding of lenses daily through one week of testing, significantly reduced the antimicrobial activity in the residual of biguanide-type MPS’s. In particular, alexidine-containing RML was markedly reduced in anti-fusaria activity with storage time. Similar
decreased activities were not reported for the polyquad-based products studied. Sorption of the antifungal components of RML by the contact lens during storage in the case and subsequent release of the potentially eye-irritating biguanide (alexidine) from the lens while it was worn were implied as co-factors in the outbreak [47]. These implications were based on reports of fluorescein staining of the ocular surface in wearers of lenses disinfected with alexidine, although the supposition that fluorescein staining is evidence of increased susceptibility to microbial keratitis has been questioned [48,49]. Zhang et al. [42] demonstrated discrete regions of fungal colonization on the outer surfaces of contact lens cases and, to a lesser extent, on RML containers from patients with RML-associated *Fusarium* keratitis. Representative haplotypes FSSC GSU ARF4 1-a; GSU ARF12 1-b and FOSC GSU AFR9 (sen-su [4]) demonstrated the capacity to undergo rapid amplification by microcycle conidiation [i.e. the germination of a conidium directly to a conidiophore with conidiogenesis [50] and to produce resistant chlamydospores in drying RML. Microcycle conidiation by *F. solani* has been observed in drying MPS on plastic [45] and on hydrogel lens surfaces in *in vitro* tests and on deposits on *ex vivo* hydrogel lenses [51] (Fig. 2). These properties were proposed to facilitate the selective survival and growth of the fungus in drying and stressed MPS, mainly RML to the exclusion of most bacteria within the contact lens case [44].

**Hydrogel lens penetration**

Multiple lens types, including both conventional hydroxyethylmethacrylate (HEMA) and high oxygen diffusion silicone hydrogel (SH), were involved in the recent outbreak of *Fusarium* keratitis (Table 1, Disposable lenses used beyond their manufacturers’ recommended use time appeared a preeminent stress factor [22,23,25,42,44,52]. Contamination of used hydrogel contact lens cases by bacteria and fungi during consumer use, in conjunction with a role of the lenses as fomites in the transportation of microorganisms to the eye, have been commonly noted as risk factors for the development of keratitis [53–57]. The hydrogel lenses from a number of patients in the 2005–2006 were cultured only for *Fusarium*, but little information was available as to whether the lenses served as passive carriers transporting the fungus from contaminated lens cases to the eye, or if the matrix of the lens was actually invaded by the fungi [51,58] (Fig. 3). The latter case could be expected to increase the risk of keratitis, as the fungus would probably be maintained on the eye for longer periods of time and at higher densities during lens wear.

The invasion of the matrices of non-therapeutic hydrogel contact lenses by a variety of fungi is not uncommon, although reported events are more often associated with eye irritation rather than the development of keratitis [21,34,58–61]. Ahearn et al. [52] examined the capacity of selected isolates of *Ulocladium* and *Fusarium* for their ability to attach to and penetrate the matrices of SH and conventional HEMA hydrogel lenses suspended in phosphate buffered saline (PBS). *Ulocladium atrum*, a melanized fungus similar in morphology to *Alternaria* spp., has been implicated as a casual agent in keratitis of a non-contact lens wearer [62], and the genus has the potential for contact lens wear.
spoilage [52]. Also, *Ulocladium* spp. have occasionally been misplaced in the genus *Alternaria*, a genus occasionally associated with mycotic keratitis [63].

Only a few conidia from inocula of about $10^4$ conidia/ml of both *Ulocladium* sp. and *F. solani* were observed to germinate on the hydrogel lens surface and penetrate the lens matrix [44,52]. The sites of attachment and degree of penetration were irregular and varied with the strain of fungus and type of lens. *Ulocladium* sp. penetrated HEMA lenses more rapidly than most SH lenses, whereas specific isolates of FSSC, including GSU AFR4 from an RML-associated case of keratitis, attached to and invaded several SH lenses suspended in PBS to a greater extent and more rapidly than an etafilcon A (HEMA) lens. The FSSC group 1 and group 2-d haplotypes appeared predominant in association with the documented RML-associated outbreak of *Fusarium* keratitis [4,23,25]. Preliminary screening of representatives of major haplotypes associated with the *Fusarium* outbreak suggests that FSSC group 1 isolates attach to and penetrate hydrogel lenses suspended in PBS more readily than most FSSC group 2-d isolates. The penetration of lenses by the majority of examined FSSC group 2 and 3 (particularly the standard ATCC 36031- haplotype group 2-c, an FDA acceptable challenge isolate) did not achieve *in-vitro* the extent of penetration observed in several lenses from patients with RML-associated keratitis [44,52, Ahearn unpublished data]. We speculate, however, that given appropriate environmental conditions most fusaria could express some degree of hydrogel lens penetration.

Exposure of select lenses to full-strength RML prior to exposure to FSSC GSU AFR4 delayed or inhibited lens penetration, but exposure to FSSC GSU AFR4 first and then RML resulted in lens penetration. In contrast, isolates of FOSC when suspended in PBS, expressed negligible or only latent capacities to invade the matrices of several hydrogel lens types [44,52]. However, when lenses were soaked first in SAB for 2 h prior to suspension in PBS, multiple isolates of FOSC attached to and invaded an expanded spectrum of SH and HEMA lenses, nearly to an extent previously observed only with lenses from patients [44]. Additionally, once penetrated, the lenses (some with resistant chlamydospores on and within the lens matrices) were recalcitrant to an MPS disinfection process even when a vigorous rinsing and rubbing procedure was included [44,52]. Upon transfer of these lenses to PBS with 0.03% SAB, regrowth of fusaria in lenses treated with certain MPS, particularly RML and Complete® MoisturePlus™ (CMP, Advanced Medical Optics, Santa Ana, CA) occurred within 48 h [44] (Fig. 5). These observations suggest that in-situ penetration of lenses by fusaria, especially FOSC, may have followed infrequent or inappropriate disinfection regimens that permitted sorption of organics into or on the

<table>
<thead>
<tr>
<th>Table 1 Some lens types used by patients with RML-associated keratitis</th>
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<tr>
<td>Lens type or brand name</td>
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<td>--------------------------</td>
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<tr>
<td>Etafilcon A</td>
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<td>Galyfilcon A</td>
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<tr>
<td>Senofilcon A</td>
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<td>Alafilcon A</td>
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<tr>
<td>Lotrafilcon B</td>
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<tr>
<td>Nelfilcon</td>
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<tr>
<td>Monthly disposables&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>2 wk daily wear&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>30 day extended wear&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7 day extended wear</td>
</tr>
<tr>
<td>Daily disposable</td>
</tr>
<tr>
<td>Frequent or planned replacement</td>
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<sup>a</sup>Includes etafilcon A lenses. <sup>b</sup>Includes lotrafilcon A and balafilcon A lenses.

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Fig. 3 Coiled penetration pegs of *Fusarium* sp within matrices of (A) HEMA- (*in vitro*) and (B) silicone hydrogel lenses (*ex vivo*).
lens prior to exposure of the lens to appropriate disinfection [44]. Such a situation could be created by wear of disposable lenses beyond their intended usage (e.g., with build up of tear film) in conjunction with topping off of the disinfection solutions.

Risk factors for RML-associated keratitis

The literature, combined with anecdotal comments on the recent keratitis outbreak, suggest that some lenses had been stored in MPS for 2 days or more in potentially contaminated lens cases and then placed directly on the eye without exposure to fresh MPS or a rub or rinse. Lens care practices that might increase the risk of Fusarium keratitis are listed below:

- Failure to discard used disinfection solution after disinfection process or upon lens storage, particularly with lenses used beyond their recommended discard time.
- ‘Topping off’ disinfection solutions.
- Failure to rub lenses manually as part of the disinfection procedure. [Combination of these first 3 practices in the bathroom environment and the susceptibility of the stressed and drying RML to colonization by selected fusaria are proposed as a major cause of the 2005–2006 outbreak [8,42].
- Occasional addition of water or a different MPS to the lens case.
- Failure to empty, rinse and store contact lens cases in fresh MPS under conditions that restricted evaporation and drying between uses.
- Failure to expose lenses to disinfection solutions for the recommended amount of time.
- Insufficient cleaning and rinsing of contact lens case and outside of container bottle for removal of ‘sticky’ (partially-dried) residue between disinfections.
- Failure to replace or sterilize (by boiling or with H₂O₂) contact lens cases frequently (perhaps weekly).
- Failure to wash hands prior to handling contact lenses and other lens care paraphernalia.
- Routine care of contact lenses in environments likely to be contaminated by Fusarium.

We believe that various combinations of the above practices contribute to the increase in the incidence of fungal keratitis that has been seen over the years. Although the statistical association between Fusarium keratitis and a contact lens disinfection solution has been established only for RML, we hypothesize that there is probably an overall increase in the incidence of infectious keratitis from other fungi and with other disinfection products, especially those containing relatively weak disinfectant formulations that are used without rubbing.

We also note that there is a trend, at least in the USA, for contact lens-associated keratitis to be associated with females. Contact lens wear may be more common among females than males. Also females, because of routine manipulation of the outer eye with more diverse products, occasionally with high densities of contaminant microorganisms [64], may increase the risk of epithelial abrasions and subsequent infections [65,66] (Fig. 6).

In vitro assessment of disinfection

The association of Fusarium keratitis with RML raises questions about the appropriateness of in vitro tests used by FDA and other regulatory agencies to determine the efficacy of contact lens disinfection systems. Independent testing by several investigative groups (although in conflict as to relative efficacies of specific MPS) indicated that various MPS’s, including RML, demonstrate fungal efficacies that meet FDA guidelines for the ‘stand-alone’ and ‘regimen’ tests [46,47,67]. The stand-alone criteria include a one log average reduction in fungal densities of designated isolates of Fusarium solani (ATCC 36031) and Candida albicans within the manufacturer’s recommended disinfection time. An additional criterion of the stand-alone test is a reduction or stasis among survivors at 25, 50, 75, 100 and 400% of the prescribed disinfection time [68,69].

The regimen test evaluates the efficacy of the MPS as it performs within the manufacturers detailed regimen,
i.e., rubbing, rinsing, storage, etc. The test involves representative hydrogel lens groups (total of 24 lenses), organic soil (killed *Saccharomyces cerevisiae* in inactivated bovine serum) with an overall reduction to no more than 10 surviving colony-forming units (cfu) per lens, per lens group, and per organism. The initial inoculum, as per the stand-alone test, is from 0.5 to $2 \times 10^6$ cells per challenge organism. All MPS approved by the FDA have been manipulated successfully within these parameters by experienced laboratory technicians. However, in our experience, to consistently meet the FDA guidelines (even with the approved challenge strains of *F. solani* (ATCC 36031, a group 2-c haplo-type), and particularly *Candida albicans*, the total organic load, i.e. inocula mass, organic soil, rinsing process and choice of lens etc., needs to be optimized.

Fig. 5  (A) Growth and attachment after 6 d to balafilcon A silicone hydrogel lens that had been suspended in SAB (2 h) and transferred to PBS with $10^4$ conidia of *F. oxysporum* GSU AFR 9; (B) lens after vigorous cleaning with manual rub using RML; (C) surface of cleaned lens with penetration pegs immediately after cleaning; (D) regrowth of GSU AFR9 from lens that had been cleaned and soaked in RML for 6 h then transferred to PBS with 0.03% SAB and incubated for 48 h.
Although MPS may pass in-vitro testing requirements, stress of the hydrogel disinfection system during lens storage, mainly from inappropriate hygienic practices of the consumer, will eventually result in contamination of solutions in the wells of the case and other contact lens paraphernalia. In fact, microbiological surveys of in-use contamination of hydrogel lens cases typically show overall microbial incidences of 20–60%, with fungi present about 20% of the time [53,55,70]. Probably near 100% of contact lens users are delivering potentially harmful microorganisms to the eye at some time during their contact lens wear [23,25,70,71]. Nevertheless, keratitis related to contact lens wear, particularly by fungi including fusaria, remains a rare event.

**Prognosis and therapy**

The prognosis for *Fusarium* keratitis is dependent upon rapid diagnosis and appropriate treatment [21,22,24, 25,72]. Under optimal circumstances and early detection, treatment with topical natamycin and amphotericin B (AMB) frequently will resolve the infection, but residual visual loss from scarring is common [25,23]. Unfortunately, the diagnosis may be delayed and fungal growth enhanced by treatment with topical steroids [21,22,24]. The indolent nature of mycotic keratitis, particularly by some strains of the *Fusarium* complexes, is often not recognized until referral of the patient to a specialist. Moreover, the nature of the subsurface growth of the fungus in the corneal lesion, along with partial antibiotic treatment, may reduce the likelihood that initial scrapings will reveal a definitive mycosis [16,21]. In severe cases of *Fusarium* keratitis that do not respond promptly to topical natamycin, oral azoles ((ketoconazole, voriconazole, posaconazole; 200–400 mg 2 d) in conjunction with topical treatment have been suggested because of their capacity to attain therapeutic vitreous levels [72–75]. Although the triazoles voriconazole and posaconazole show relatively poor in-vitro activity against *Fusarium* sp. [76,77], therapeutic efficacy with these triazoles (notably posaconazole) has been achieved in several refractory *Fusarium* keratitis cases that had included unsuccessful topical and intravitreal AMB injections [72,78, 79]. Of the 66 confirmed keratitis cases reported by
Khor et al. [25] and the 154 summarized by Chang et al. [23] at least 7% and 34%, respectively, underwent keratoplasty.

In a few instances, *Fusarium* keratitis diagnosed by confocal microscopy or positive culture of the eye has been noted as self-resolving or responsive to topical fluoroquinolone therapy [25,80]. Whether these observations can be explained by strains with low virulence, vigorous host responses, or misdiagnoses remains unknown.

**Conclusions**

While we have noted an increase in the incidence of *Fusarium* keratitis, the incidence of bacterial keratitis has not noticeably decreased with increased MPS use, even among apparently compliant wearers [81]. This suggests that 'convenience labeling' is not achieving its intended goals.

During the same years of evolving ‘no-rub’ MPS and the increased wear of silicone hydrogel lenses, incidences of mycotic and amoebic keratitis apparently have increased [39,82]. Densities and incidences of *Fusarium* spp. in the indoor and outdoor environments are less common and more variable than those of *P. aeruginosa*, but the probability of encountering fusaria daily is high, particularly in subtropical to tropical regions. Both FSSC and FOSC are associated with both fresh and prepared foods as well as some household products, so occasional colonization of sink and shower drains can be expected [8,14]. Of particular note are the reports of conspecificity of FSSC and FOSC from drainage systems and hospital water systems with isolates from patients [8,14,16]. Although chance encounter with these fungi is not dependent upon their capacities to colonize moist habitats in households and medical facilities, their capacities to do so in bathrooms or moist ventilation systems would likely increase the probabilities of their contamination of and occasional survival in a contact lens case. Moreover, wearers’ compliance with manufacturers instructions apparently has not increased with the easy to use ‘no-rub’ solutions [23,25,38]. Sixty of 61 *Fusarium* keratitis patients reviewed by Saw et al. [38] practiced topping-off or reuse of solutions in the contact lens case.

The extent of adulterating stress that reduces the disinfection capacity of an MPS during storage in a contact lens case varies with formulation [43,47,83]. MPS formulations with complex viscosity and demulcent components (e.g., complexes of cellulose- and polyglycol derivatives), when adulterated, particularly during drying, may undergo phase separation, partitioning and self neutralization. Such alterations, in the case of RML, permit survival or growth of select *Fusarium* while inhibiting other microorganisms at various stages of the drying process [42,44,51, Zhang unpublished data]. (Fig. 7). Air-drying (including partial) of MPS with components such as the above polymers, sometimes followed by addition of a different MPS formulation or water, probably occurred among patients in the outbreak. CDC surveys suggest mixed MPS usage by *Fusarium* keratitis and *Acanthamoeba* keratitis patients was not unusual [39,82]. Adulterated RML, which became supportive of amplification and survival of selected FSSC and FOSC in or on the contact lens case, appears preeminent in the 2005/2006 *Fusarium* keratitis outbreaks. Multiple events seem to have affected the loss of antimicrobial activity of RML in the contact lens case including neutralization of the inhibitory components by organic debris, selective sorption of inhibitory components by the contact lens, and by the selective process of drying or dilution of the MPS with water or a different MPS formulation. Lenses stored in MPS under these compounded stress conditions, when placed directly on the eye, could be expected to associate with an increased risk of infection. Concerns for toxicity and compatibility with materials control the type and concentrations of disinfectants suitable for soft lens disinfection. Potential toxicities for the eyes are heightened for disinfectants active against fungi and amoebae because of their eucaryotic nature. Therefore, selection of appropriate disinfectants for products used around the eye is a compromise between preservative efficacy and hypersensitivity and toxic reactions that can vary with the individual. Species within the *Fusarium* complexes, because of their unique capacities to rapidly amplify...
Fusarium solani- F. oxysporum complex associated with hydrogel contact lens related fungal keratitis

Representative environments colonized by mould with variable types of conidia

Soils → Water

Plants

Indoor Fungi - Industrial Products

(A)erial dispersion of macroconidia, microconidia, and chlamydoconidia

1) Trauma from plants directly to eye or to contact lens.
2) Predominance of conidial or “spore” type is strain and substratum dependent; microcycle conidiation (MC) in case, on bottle or contact lens.
3) Hydrogel lens with fusaria occasionally with penetration pegs.
4) Amplification in case with soiled or stressed solution (diluted, concentrated, etc.)
5) Shaded area represents “stressed” solution and fungal growth.

Fig. 8  Overview cartoon (caption on figure).

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and to produce survival cells (features common to *Acanthamoeba* and the aspergilli [42,52], combined with virulence factors, are of particular concern.

Our *ex-vivo* observations of hydrogel lenses penetrated by FSSC and *in-vitro* observations suggest that lens penetration is usually a relatively slow (>96 h) lens-storage case phenomenon, which in rare instances may be stimulated by adulterated MPS. However, the unique environmental circumstances that permitted select fusaria to attach to and to occasionally penetrate the matrices of hydrogel lenses are still speculative. However, the attachment and penetration process probably occurred before the lens was exposed to full strength MPS. An epidemiological scheme for the association of *Fusarium* spp. with keratitis is given in Fig. 8.

The risk of *Fusarium* keratitis associated with contact lens wear appears related to a multi-variant interaction between MPS formulation, strain of fungus, type of lens, and improper hygienic practices as tempered by host defensive factors. Unfortunately, data on the outbreak are still insufficient to determine exact factors that resulted in early reports on recoveries of only outbreak are still insufficient to determine exact factors that resulted in early reports on recoveries of only lens wearers. This, in part, was probably due to host physical factors of an intact epithelium surface and blink mechanism in conjunction with significant ocular defense mechanisms, i.e., tear immunoglobulins.

It was initially thought that the introduction of ‘no-rub’ MPS, disinfection solutions that could be placed on the eye without neutralization, and wetting agents to increase the comfort of contact lenses might increase compliance and, therefore, reduce the risk of contact lens-associated microbial keratitis. Marketing advantages of the ‘no-rub’ claim led manufacturers to seek products that could qualify for this type of ‘convenience labeling’. However, it is clear to us that the reduced efficacy of the formulations (brought about, in part, to achieve greater comfort in lens wear), the lack of rubbing to remove adherent fungi, and the presence of films that support survival or growth on the surfaces of contact lens products combine to increase the likelihood of fungal keratitis.

It is also clear that current testing procedures fail to identify contact lens care products that will fail under conditions of actual use. We have recommended repeatedly that contact lens cases be cleaned and replaced on a regular basis and that a manual rubbing of the lens be used. With the broader recognition that contact lens wear is a risk factor for rare mycotic keratitis, a return to ‘efficacy labeling’ from ‘convenience labeling’, and education of consumers to comply with disinfection recommendations, should be undertaken as soon as possible.

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