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Recent Outbreaks of Atypical Contact Lens-Related Keratitis: What Have We Learned?

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Abstract

Purpose—To examine the public health implications of two recent outbreaks of atypical contact lens-related infectious keratitis.

Design—A perspective based on the literature and authors' experience.

Results—The contact lens-related fusarium and acanthamoeba keratitis outbreaks were both detected by dramatic rises seen in tertiary care centers in Singapore and the US, respectively. Case control studies in both outbreaks each were able to identify a strong association with the use of different contact lens disinfection solutions. Their respective recalls resulted in a steep decline of *fusarium* keratitis, but not of *acanthamoeba* keratitis. Early investigations into each solution association implicate components not directly related to their primary disinfectant, but the true pathogenesis remains unknown. However, the number of *Acanthamoeba* cases individually attributed to each of almost all available disinfection systems exceeds previously understood *total* US incidence, suggesting other risk factors. Current standards do not require demonstration of anti-acanthamoebal activity. Yet, despite the inclusion of fusarium in mandatory testing for solutions, current pre-market testing was not predictive of the outbreak.

Conclusions—The two recent outbreaks of atypical contact-lens related keratitis have reinforced the value of tertiary care eye care centers in detecting early rises in rare infections and the power of adaptable, well-designed epidemiologic investigations. While *fusarium* keratitis has significantly declined with the recall of Renu with Moisturelоc, the persistence of Acanthamoeba keratitis begs fundamental changes in contact lens hygiene practices, inclusion of *acanthamoeba* as a test organism and contact lens disinfectant test regimens for all contact lens–related pathogens which are verifiably reflective of end user contact lens wear complications.

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Recent years have seen two significant outbreaks of contact lens related infection, each associated with the use of a particular contact lens disinfection system.[1–7] At a glance, these outbreaks have marked similarities in their recognition and investigation which have provided a greater understanding of the influence of these systems on contact lens-related infectious keratitis. At the same time, they have revealed wide gaps in knowledge as to their practical efficacy against infection. Ultimately, however, it is the striking differences which characterize each individual outbreak that provides the most valuable information in their current use and the future design of these systems.

Recognition and Investigation of the Contact lens-Related Fusarium Outbreak

These two respective outbreaks of contact lens-related infectious keratitis have been previously well documented. Briefly, the outbreak of *Fusarium* keratitis was first described in Asia, in particular Singapore, beginning in March of 2005 with concerns raised later that year by Hong Kong health officials.[1, 2] At that time, Khor et al. reported 68 eyes of 66 patients developing *Fusarium* keratitis in Singapore, 98% of which wore soft contact lenses. All but 4 of the patients (93.9%) reported using any Renu-branded disinfection solution (Bausch & Lomb) with a remarkably high percentage (63.6%) reporting the use of Renu with Moistureloc, only recently introduced into worldwide use in late 2004.2 Scattered cases were also reported in the United States during the same time frame after its introduction there in 2005.8 A case-control study of 164 US cases by the Centers for Disease Control and Prevention (CDC) found similarly that 154/164 cases (93.9%) were soft contact lens wearers. Of the 116 patients reporting single solution use, 94 reported Renu with MoistureLoc use (57%). In all, only 13% denied any use of Renu with MoistureLoc.9 Its use was strongly associated (OR 13.3; 95% CI 3.1–119.5) with contact lens related *Fusarium* keratitis. This resulted in a regional recall involving Singapore and Hong Kong of Renu with MoistureLoc in February, 2006 followed by voluntary recalls in the US (April, 2006) and globally (May 15th, 2006).

Recognition and Investigation of the Contact lens-Related Acanthamoeba Outbreak

Less than a year later at the American Academy of Ophthalmology meeting in November 2005, an increasing number of *Acanthamoeba* keratitis cases (19) identified over the prior year at the Wills Eye Institute were reported. We identified a statistically significant increase in cases at the University of Illinois Eye and Ear Infirmary dating back to June 2003 (RR 6.67; 95% CI 3.05 to 17.52), and published an exploratory analysis of the first 40 cases at our institution presenting through November, 2005.[3] In this, we identified a unique geographic distribution of cases in which the population-based rate ratio was higher in peripheral collar counties of Chicago (RR 3.59; 95% CI 1.44–8.39) inconsistent with previously known risk factors.3 Consequently, we initiated a single-center case-control study to investigate the outbreak origins, designing the study to allow for analysis of both environmental and more common lens-related/hygiene risk factors. Through our ongoing discussions with the Illinois Department of Public Health and the CDC, the CDC eventually concluded from a survey of 10 U.S. ophthalmology centers conducted in early 2007 that an increase in culture positive cases was evident beginning in 2004. In May, 2007, both an interim analysis of our ongoing case control study, and an exploratory analysis by the CDC using historical *Fusarium* keratitis study controls, identified the use of AMO Complete Moisture Plus as a statistically significant risk factor for the development of contact lens-related *Acanthamoeba* keratitis (OR 16.67; 95% CI 2.11 – 162.63), leading to an immediate worldwide recall (May 29th, 2007).[4, 10]

Case Ascertainment and Aggregation of Infectious Outbreaks

The initial reports of *Fusarium* and *Acanthamoeba* keratitis were remarkably similar in that both were first identified at tertiary care ophthalmology centers: Singapore National Eye Center, in addition to the University of Illinois Eye and Ear Infirmary and the Wills Eye Institute, respectively.[2, 3, 7] The reasons are for this are both obvious and important, with several factors driving these two diseases in particular towards tertiary care facilities and ultimately driving outbreak identification. First, the standard treatment for each infection involves medications not widely available. Although a commercial preparation of natamycin 5% is widely available for the treatment of fungal keratitis, the rate of clinical resistance for *Fusarium* sp., specifically, is significant.[11] Similarly, standard therapy for *Acanthamoeba* keratitis either consists of commercial medications unavailable in the U.S. and/or compounded biguanides. Second, the infections are known to masquerade as other either infectious or non-infectious conditions, often requiring the expertise of clinicians and microbiologic facilities familiar with their diagnosis. Third, these infections are often highly symptomatic, with poor outcomes if not promptly and appropriately treated; 17% of the University of Illinois Eye and Ear Infirmary *Acanthamoeba* keratitis patients and 34% of U.S. *Fusarium* keratitis patients required corneal transplantation. [9, 12]

Finally, the rarity of each disease, prior to the outbreaks, facilitated more rapid recognition. Although *Fusarium* keratitis is the most common filamentous fungal infection in non-contact lens users, it was previously uncommon with contact lens use.[13, 14] And while *Acanthamoeba* keratitis is primarily restricted to contact lens users, the previous annual U.S. incidence estimates, based on the outbreak of the late 1980's and roughly our pre-outbreak experience, was ~2 cases per million contact lens users.[3, 15] These infections have remained rare even in the midst of the outbreaks. The annual *Fusarium* keratitis incidence in Singapore was estimated at 2.4 cases per 10,000 contact lens wearers,[2] and while no comparable *Acanthamoeba* keratitis incidence rates have been calculated, our gross estimates from the Chicago outbreak approach 20 annual cases per million contact lens users. Hence, it is unlikely that a single ophthalmologist, or even cornea specialist, would be able to acutely detect an outbreak; thus, the importance of tertiary care centers in large metropolitan areas to provide case aggregation and the perspective of a more "population-based" comparison of disease trends with time.

Taken together, these four factors made possible a relatively complete case ascertainment at the tertiary care facilities that led to the identification of each outbreak. Without a structured surveillance system for contact lens-related keratitis, or any microbial keratitis, the absence of any of the above characteristics would mask or significantly delay the detection of outbreaks of 1) milder, more easily diagnosed disease; 2) diseases with widely available, effective therapy; or, 3) diseases that are significantly more common than these. The historical recognition that extended wear use of contact lenses was significantly associated with bacterial infectious keratitis,[16] for example, may have been delayed if efficacious antibiotics were available in the community at the time, obviating the need for fortified antibiotics compounded at specialty hospitals where case aggregation could occur. Looking to the future, we likely will have no ability to identify a substantial outbreak of a more common, fluoroquinolone-sensitive, contact lens-related microbial keratitis, due to the successful nature of community-based empiric antibiotic treatment as well as the non-specificity of the utilization patterns for these drugs which have a wide range of both non-therapeutic and non-corneal indications.

Unique Epidemiology of the Individual Outbreaks

Despite these similarities, there are distinct differences in the epidemiology of each outbreak that offer important lessons in their respective outbreak study design and implementation. In a rare disease such as microbial keratitis, the case-control study design is preferred as it is highly efficient; however, appropriate selection of controls is critical to maintain study validity and prevent the introduction of systemic error, biasing results. Because of the rarity of *Fusarium* keratitis among contact lens users, baseline incidence and historical risk factors were generally unknown. However, a simple evaluation of the percentage of cases using the recalled solution, as well as a comparison against market share, strongly implicated the role of a single solution.[2] As such, a case-control study designed to investigate contact lens solutions, as well as the potential role of general lens-related keratitis risk factors including lens hygiene, was launched.[9] Controls were selected to allow for analysis of these factors: controls were matched to the neighborhood of cases restricted to contact lens users over the age of 17. Results identified the strong association of Renu with MoistureLoc with *Fusarium* keratitis as well as the relatively smaller contribution of "topping off" or solution reuse. This strong association contributed to a worldwide recall, with an immediate reduction in *Fusarium* keratitis cases identified through both active and passive surveillance techniques.[17]

The independent investigations (CDC, the University of Illinois Eye and Ear Infirmary) of the *Acanthamoeba* keratitis outbreak provide further insight.[10, 18] Our initial publication identified a unique geographic distribution of cases in Chicago, suggesting the need for a case-control study design that allowed for analysis of factors that can vary by geography, with solutions potentially less relevant in this outbreak.[3] More reliable *Acanthamoeba* keratitis incidence estimates further suggested a problem beyond just a single solution: despite a potential signal, no single solution accounted for a strong majority of cases, indicating as much as a five-fold increase in disease regardless of type of solution used (arm-chair epidemiology: 2 vs. 20–30 annual cases in Chicago, 40% of cases without AMO Complete MoisturePlus use, hence now 8–10 annual cases with all solutions, so up to a 5x increase).[10] Further, *Acanthamoebae* are found commonly in water and soil, but are considered largely a waterborne pathogen in humans. While many forms of infectious keratitis have been linked to temperature and climate, only *Acanthamoeba* keratitis has been consistently linked to alterations in the quality of the domestic water supply.[19–21] Because our initial analysis identified a unique geographic distribution of cases, hypothesized as related to the water supply, we selected a case-control study design in which controls were clinic-based, matched on age and date of visit in order to be able to analyze the effect of geography and the potential effects of water supply, which is inherently impossible when controls are matched by neighborhood.[10] To our benefit, our single-center study design not only allowed for analysis of typical lens-related risk factors, but also restricted potential confounding factors (i.e., Miami weather is more conducive in the winter than Chicago to water-related activities that increase risk of infection).

In comparison, the CDC investigation closely mirrored the study design conducted for the *Fusarium* keratitis outbreak.[9, 18] The initial MMWR alert in May 2007, in which 46 culture positive (39 soft contact lens wearers) *Acanthamoeba* cases were identified, was based on control data collected during the *Fusarium* keratitis outbreak the year prior.[4] The potential pitfall is that solution market share changes with time and might not reflect contemporary use, especially given the interim recall of Renu with MoistureLoc solution. Their subsequent outbreak investigation that recruited new controls retained the same study design as the *Fusarium* keratitis study, with the recruitment of controls that were neighborhood-matched to identified cases.[18]

Nevertheless, both independent studies confirmed the significant association of the use of AMO Complete MoisturePlus with *Acanthamoeba* keratitis (OR 16.67; 95% CI 2.11 – 162.63).[10, 18] Not surprising, given the high frequency of cases that reported use of solutions other than the recalled solution, the number of *Acanthamoeba* keratitis cases in Chicago and nationally has not returned to baseline, unlike the *Fusarium* keratitis outbreak that occurred one year prior serving as a wonderful baseline comparison for the *Acanthamoeba* keratitis outbreak.[22] This indicates the contribution of other, yet unidentified risk factors to the *Acanthamoeba* keratitis outbreak.

Proposed Pathogenesis of Contact-lens Related Atypical Keratitis

The role of the contact lens disinfection systems in each outbreak is still not fully understood. It has been established that no evidence exists in either outbreak to support solution contamination in sealed production lot testing.[9, 18] PCR testing of unsealed solution bottles is not supportive of lot contamination, because it lacks confirmation of the source as well as the viability of the genetic material detected.[23] Further, the diversity of fungal isolates in the CDC study and of *Acanthamoeba* isolates in the Chicago study makes it highly unlikely that a single source contamination occurred with either solution.[9, 24]

Two theories have been proposed to explain the mechanism for an increase in *Fusarium* keratitis with Renu with MoistureLoc use. In vitro studies indicated that the practice of "topping off" (solution reuse) concentrates the solution residua in the contact lens case.[25] The resultant film protects the *fusarium* from disinfection, allowing proliferation and exposing the lens to a sufficient burden of pathogenic fungi. Another theory suggests disinfection efficacy is degraded by high temperature storage, especially since the balance of cases was sourced to a single production/ distribution channel.[26] A lower, but significant number of cases were also seen, however, in other geographic areas, including Europe.[27, 28] Interestingly, compliance with contact lens hygiene is universally, repeatably poor even among healthy controls[9, 29] and cannot change at the population level to cause an outbreak, yet contact lens-related *Fusarium* keratitis was rare prior to the introduction of Renu with MoistureLoc to the market.[9] The magnitude of the disease increase implied that potentially, a specific solution property may have promoted and amplified the incidence of *fusarium* infection not previously seen even in severely non-compliant patients, making it unlikely that a lack of efficacy alone would be sufficient to cause this change. This would be most consistent with the theory of "topping off" facilitated proliferation, but some combination of other factors is also likely.

The mechanism of action also remains unclear for the increase in *Acanthamoeba* keratitis with AMO Complete MoisturePlus use. Speculation has revolved around the additional "comfort" components added to the prior generation product (AMO Complete) to create AMO Complete MoisturePlus and, in particular, propylene glycol and the amino acid taurine, which, at sufficient concentrations, is well-known to microbiologists to induce transformation of the organism into the highly disinfectant resistant cyst form.[30, 31] Further, results of in vitro testing suggest a relative lack of efficacy of the base disinfectant in AMO Complete MoisturePlus (polyhexamethyl biguanide (PHMB)) when compared to other available systems varying somewhat with testing methodology.[30, 32] Of note, the CDC did not find any indication that a particular lens material was associated with disease, which is important as the substantially new silicone hydrogel contact lens type was also introduced during this time frame.[18]

The role of contact lens solutions should not be minimized, but it has become clear that other, more global, risk factors likely underlie the most recent *Acanthamoeba* keratitis outbreak. As previously mentioned, *Acanthamoeba* keratitis as compared to all contact types

of lens-related infections has been more closely associated with water exposure such as hot tub use,[29] as well as contamination of municipal water.[20] Because *Acanthamoeba* is not a surveillance organism, the previous levels of *Acanthamoeba* in domestic water is not well known, but interim results from the University of Illinois Eye and Ear Infirmary study have shown that greater than 18% of all homes tested harbored *Acanthamoeba* (Joslin, CE, et al. IOVS 2010;51:ARVO E-Abstract 1309), far higher than any prior study except one (30%) which tested only taps of infected patients.[21] The only other study performed in the U.S. showed a 2.8% level in South Florida in a normal population.33 We have previously hypothesized that changes in EPA regulations implemented nationally between 2002 – 2004 could potentially change the microbiologic configuration of the domestic water supply.3 Regardless, both the initial finding of the non-random distribution of cases in the peripheral collar counties as well as the subsequent shifting distribution of *Acanthamoeba* keratitis cases over time towards the city are consistent with a geographic risk factor which follows the pattern of water distribution in the Chicago metropolitan area.[3, 22]

None of the currently available multipurpose solutions have significant efficacy against acanthamoebal cysts with current one-step hydrogen peroxide solutions demonstrating only partial efficacy.[30] This lack of in vitro activity is supported by the clinical observation that the individual number of cases attributed to each separate multipurpose solution in our study would, in itself, represent an increase over the previously estimated total outbreak incidence of the late 1980's, when tap water was incorrectly utilized in lens care. The increasing number of cases that we have seen in our cohort with all soft lens solution systems, both multipurpose and one-step hydrogen peroxide solutions, as well as in gas permeable rigid lens users, which utilize different disinfection schemes, suggests that an increasing environmental load is overwhelming the limited ability of existing systems to limit the exposure of pathogenic *Acanthamoeba* organisms during contact lens wear.

The Role of Pre-market Testing of Contact Lens Disinfection Systems

A specific test regimen is mandated by the Federal Drug Administration for approval of contact lens disinfection systems. Briefly, testing involves disinfection efficacy for five organisms, *Pseudomonas aeruginosa, Staphylococcus aureus, Serratia marcescens, Candida albicans,* and *Fusarium solani*. Standalone efficacy is determined by a >3 log reduction of bacteria or > 1 log unit reduction of fungi in a test tube. A second regimen test which includes a case, contact lens and organic soil may be required if the solution does not pass the stand-alone test, but passes lower criteria for that test. These established standards had not required testing against *Acanthamoeba* presumably because of the previously low incidence of disease and controversy over appropriate testing methods.

Existing testing methods for contact lens disinfection systems were, however, unable to predict either of these outbreaks. As a new formulation, Renu with Moistureloc passed all required tests and was highly efficacious against the *Fusarium* species specified. In the hands of contact lens wearers, the majority of whom are variably non-compliant with lens hygiene, a dramatic rise in *Fusarium* keratitis resulted, demonstrating that in vitro solution efficacy results did not adequately reflect solution effectiveness, or its performance in the "real world". Further, small, changes seemingly unrelated to a solution's main disinfectant function may alter its risk for infection. For example, the formulation changes which did not alter the solution's base disinfectant may have been responsible for unforeseen changes in a solution's performance against *Acanthamoeba* organisms. These two outbreaks, which highlighted gaps in existing efficacy testing, were the first steps towards establishing new testing methods initiated at an FDA-hosted workshop in 2009. The implementation is expected to include an expansion in the number of bacterial and fungal test organisms,

addition of *acanthamoebal* strains and changes in testing methodology leading to new disinfection systems.

Even still, scant evidence supports a correlation of in vitro testing results and a reduction in infectious keratitis primarily as these relationships have not been, and are difficult, to study. As contact lens wear is the primary risk factor for *Acanthamoeba* keratitis and also more general forms of bacterial keratitis, a carefully-designed system of post-market surveillance that not only explores solution, lens, and lens hygiene factors, but also carefully explores the contribution of environmental causes, would lead to earlier detection of subsequent outbreaks and help to validate and refine pre-market testing. Further, it may be the only way to detect a significant lack of effectiveness against bacterial organisms not included in the testing panel.

Considerations for Current Contact Lens Wearers

Various hygiene-related risk factors were evaluated in case-control studies of both outbreaks. While the practice of solution reuse or “topping-off”, where used solutions are incompletely discarded before refilling the contact lens storage case, was found to be associated with a higher risk of Acanthamoeba keratitis on multivariate analysis in only the CDC study,[18] a role for this practice in the pathogenesis of both contact-lens related *Fusarium* and *Acanthamoeba* keratitis has been suggested in multiple studies.[9, 10] These studies also suggest a number of other hygiene-related practices may have a role including a lack of rubbing of contact lenses during the cleaning process, showering in contact lenses, and using lenses beyond their replacement date.[10, 34] These factors may have some clinical utility, but it should be understood that the magnitude of their contributions are likely substantially less than either the identified contact lens solution associations or yet to be identified environmental associations for these outbreaks. As evidence, the recall of Renu with Moistureloc, despite the widespread deficiencies in hygiene found in both cases and controls, was successful in reducing the number of cases of Fusarium keratitis to near baseline.[9, 17]

However, if contact lens users are being exposed to a higher level of *Acanthamoebae*, the options for control are few. Limiting organism exposure should reduce disease incidence. Reducing the environmental load would be ideal, but *Acanthamoebae* are highly resistant to chlorine-based disinfection and require filtration to exclude it from the water supply. Once ensconced in the water supply, it is unclear whether this remains a modifiable risk factor because of the difficulty in eradicating established biofilms from water distribution systems. Daily disposable contact lens use would limit the potential contamination of contact lens cases as well as minimize hygiene-related water exposure, but other sources of water exposure would remain, including showering. Reusable contact lens users would require contact lens solution systems that are effective against *Acanthamoebae*. Heat and two-step hydrogen peroxide systems are highly effective against *Acanthamoebae* as well as most other organisms, but are more complicated to use which may itself further lower compliance.[35] While systems are not expected to completely sterilize lenses, it is evident that none of the current disinfection systems are sufficiently effective to limit *Acanthamoeba* keratitis under current environmental conditions with existing hygiene standards. Nevertheless, strict adherence to the guidelines of contact lens solution manufacturers which include rubbing of lenses, changing cases at regular intervals, avoiding solution reuse and limiting water exposure (e.g. Showering, hot tub use, swimming) are reasonable cautions to reduce the risk of infection.

Conclusions

For many years, contact lens users enjoyed a period of stability with relatively low rates of largely treatable bacterial keratitis and even lower rates of *Acanthamoeba* keratitis. The outbreaks of 2006 and 2007 have been a harsh reminder of the unanticipated dangers of contact lens use but have in turn provided us with valuable insights. They have demonstrated the value of tertiary care centers in the early identification of outbreaks of rare keratitides, but raise concerns regarding the future recognition of a similar surge of a more easily treated bacterial keratitis. Both also demonstrate the power of epidemiologic studies in rapidly identifying modifiable risk factors to avert disease, as well as illustrate the need to consider historical risk factors, disease pathogenesis, and early outbreak characteristics in the design of epidemiologic studies. Finally, small changes in the formulation of contact lens solutions may have profound effects on real world effectiveness that may be nearly impossible to account for in studies designed for pre-market testing. Current testing methods were inadequate to predict these two outbreaks, and indicate the need not only for additional, more comprehensive testing, but also methods, including post-market surveillance, to evaluate the validity of these pre-market tests when applied to real consumer use.

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References

1. Ma SK, So K, Chung PH, Tsang HF, Chuang SK. A multi-country outbreak of fungal keratitis associated with a brand of contact lens solution: the Hong Kong experience. Int J Infect Dis Jul; 2009 13(4):443–448. [PubMed: 19019715]
2. Khor WB, Aung T, Saw SM, et al. An outbreak of Fusarium keratitis associated with contact lens wear in Singapore. JAMA Jun 28;2006 295(24):2867–2873. [PubMed: 16804153]
3. Joslin CE, Tu EY, McMahon TT, Passaro DJ, Stayner LT, Sugar J. Epidemiological characteristics of a Chicago-area Acanthamoeba keratitis outbreak. Am J Ophthalmol Aug;2006 142(2):212–217. [PubMed: 16876498]
4. Acanthamoeba keratitis multiple states, 2005–2007. MMWR Morb Mortal Wkly Rep Jun 1;2007 56(21):532–534. [PubMed: 17538529]
5. Fusarium keratitis--multiple states, 2006. MMWR Morb Mortal Wkly Rep Apr 14;2006 55(14): 400–401. [PubMed: 16617289]
6. Update: Fusarium keratitis--United States, 2005–2006. MMWR Morb Mortal Wkly Rep May 26;2006 55(20):563–564. [PubMed: 16723968]
7. Thebpatiphat N, Hammersmith KM, Rocha FN, et al. Acanthamoeba keratitis: a parasite on the rise. Cornea Jul;2007 26(6):701–706. [PubMed: 17592320]
8. Alfonso EC, Cantu-Dibildox J, Munir WM, et al. Insurgence of Fusarium keratitis associated with contact lens wear. Arch Ophthalmol Jul;2006 124(7):941–947. [PubMed: 16769827]
9. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of Fusarium keratitis associated with use of a contact lens solution. JAMA Aug 23;2006 296(8):953–963. [PubMed: 16926355]
10. Joslin CE, Tu EY, Shoff ME, et al. The association of contact lens solution use and acanthamoeba keratitis. Am J Ophthalmol Aug;2007 144(2):169–180. [PubMed: 17588524]
11. Lalitha P, Shapiro BL, Srinivasan M, et al. Antimicrobial susceptibility of Fusarium, Aspergillus, and other filamentous fungi isolated from keratitis. Arch Ophthalmol Jun;2007 125(6):789–793. [PubMed: 17562990]
12. Tu EY, Joslin CE, Sugar J, Shoff ME, Booton GC. Prognostic Factors Affecting Visual Outcome in Acanthamoeba Keratitis. Ophthalmology Nov;2008 115(11):1998–2003. [PubMed: 18571729]

13. Rosa RH Jr, Miller D, Alfonso EC. The changing spectrum of fungal keratitis in south Florida. Ophthalmology Jun;1994 101(6):1005–1013. [PubMed: 8008340]
14. Alfonso EC, Miller D, Cantu-Dibildox J, O'Brien TP, Schein OD. Fungal keratitis associated with non-therapeutic soft contact lenses. Am J Ophthalmol Jul;2006 142(1):154–155. [PubMed: 16815266]
15. Schaumberg DA, Snow KK, Dana MR. The epidemic of Acanthamoeba keratitis: where do we stand? Cornea Jan;1998 17(1):3–10. [PubMed: 9436873]
16. Poggio EC, Glynn RJ, Schein OD, et al. The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. N Engl J Med Sep 21;1989 321(12):779–783. [PubMed: 2770809]
17. Grant GB, Fridkin S, Chang DC, Park BJ. Postrecall surveillance following a multistate fusarium keratitis outbreak, 2004 through 2006. JAMA Dec 26;2007 298(24):2867–2868. [PubMed: 18159055]
18. Verani JR, Lorick SA, Yoder JS, et al. National outbreak of Acanthamoeba keratitis associated with use of a contact lens solution, United States. Emerg Infect Dis Aug;2009 15(8):1236–1242. [PubMed: 19751585]
19. Radford CF, Minassian DC, Dart JK. Acanthamoeba keratitis in England and Wales: incidence, outcome, and risk factors. Br J Ophthalmol May;2002 86(5):536–542. [PubMed: 11973250]
20. Mathers WD, Sutphin JE, Lane JA, Folberg R. Correlation between surface water contamination with amoeba and the onset of symptoms and diagnosis of amoeba-like keratitis. Br J Ophthalmol Oct;1998 82(10):1143–1146. [PubMed: 9924301]
21. Kilvington S, Gray T, Dart J, et al. Acanthamoeba keratitis: the role of domestic tap water contamination in the United Kingdom. Invest Ophthalmol Vis Sci Jan;2004 45(1):165–169. [PubMed: 14691169]
22. Joslin CE, Tu EY, Shoff ME, Anderson RJ, Davis FG. Shifting distribution of Chicago-area Acanthamoeba keratitis cases. Arch Ophthalmol Jan;128(1):137–139. [PubMed: 20065234]
23. Hasler S, Dedes W, Mathis A, Grimm F, Thiel MA. MoisturePlus contact lens solution as a source of acanthamoeba keratitis. Cornea Feb;2009 28(2):219–220. [PubMed: 19158570]
24. Booton GC, Joslin CE, Shoff M, Tu EY, Kelly DJ, Fuerst PA. Genotypic identification of Acanthamoeba sp. isolates associated with an outbreak of acanthamoeba keratitis. Cornea Jul;2009 28(6):673–676. [PubMed: 19512903]
25. Zhang S, Ahearn DG, Noble-Wang JA, et al. Growth and survival of Fusarium solani-F. oxysporum complex on stressed multipurpose contact lens care solution films on plastic surfaces in situ and in vitro. Cornea Dec;2006 25(10):1210–1216. [PubMed: 17172900]
26. Bullock JD, Warwar RE, Elder BL, Northern WI. Temperature instability of ReNu With MoistureLoc: a new theory to explain the worldwide Fusarium keratitis epidemic of 2004–2006. Arch Ophthalmol Nov;2008 126(11):1493–1498. [PubMed: 19001215]
27. Kaufmann C, Frueh BE, Messerli J, Bernauer W, Thiel MA. Contact lens-associated fusarium keratitis in Switzerland. Klin Monbl Augenheilkd May;2008 225(5):418–421. [PubMed: 18454384]
28. Gaujoux T, Chatel MA, Chaumeil C, Laroche L, Borderie VM. Outbreak of contact lens-related Fusarium keratitis in France. Cornea Oct;2008 27(9):1018–1021. [PubMed: 18812765]
29. Stehr-Green JK, Bailey TM, Brandt FH, Carr JH, Bond WW, Visvesvara GS. Acanthamoeba keratitis in soft contact lens wearers. A case-control study. JAMA Jul 3;1987 258(1):57–60. [PubMed: 3586292]
30. Shoff ME, Joslin CE, Tu EY, Kubatko L, Fuerst PA. Efficacy of contact lens systems against recent clinical and tap water Acanthamoeba isolates. Cornea Jul;2008 27(6):713–719. [PubMed: 18580265]
31. Kilvington S, Heaselgrave W, Lally JM, Ambrus K, Powell H. Encystment of Acanthamoeba during incubation in multipurpose contact lens disinfectant solutions and experimental formulations. Eye Contact Lens May;2008 34(3):133–139. [PubMed: 18463477]
32. Borazjani RN, Kilvington S. Efficacy of multipurpose solutions against Acanthamoeba species. Cont Lens Anterior Eye Dec;2005 28(4):169–175. [PubMed: 16332501]

33. Shoff ME, Rogerson A, Kessler K, Schatz S, Seal DV. Prevalence of Acanthamoeba and other naked amoebae in South Florida domestic water. J Water Health Mar;2008 6(1):99–104. [PubMed: 17998610]

34. Saw SM, Ooi PL, Tan DT, et al. Risk factors for contact lens-related fusarium keratitis: a case-control study in Singapore. Arch Ophthalmol May;2007 125(5):611–617. [PubMed: 17502498]

35. Hughes R, Kilvington S. Comparison of hydrogen peroxide contact lens disinfection systems and solutions against Acanthamoeba polyphaga. Antimicrob Agents Chemother Jul;2001 45(7):2038–2043. [PubMed: 11408220]

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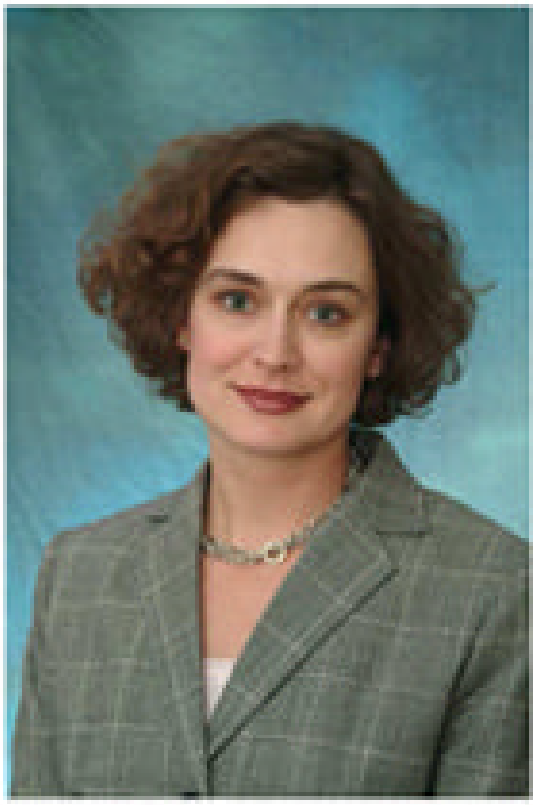

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