

Contact lens-related microbial keratitis: how have epidemiology and genetics helped us with pathogenesis and prophylaxis

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CAMBRIDGE OPHTHALMOLOGICAL SYMPOSIUM

Abstract

Contact lens wear is a common predisposing factor in microbial keratitis and is one of the two preventable risk factors for corneal infection in a working age population. Our understanding of the prevention and prophylaxis of contact lens-related corneal infection is informed by recent epidemiological studies describing the incidence of and risk factors for the disease, the effect of causative organism on disease severity, and an appreciation of individual immune profiles in susceptibility to and severity of the disease. Although contemporary contact lenses have not reduced the overall incidence of keratitis, a reduction in morbidity may be achievable through recognition of appropriate risk factors in severe disease, including avoiding delays in presenting for appropriate treatment, and attention to storage case hygiene practise. Severe keratitis is most commonly associated with an environmental causative organism, and daily disposable lenses are associated with less severe disease. *Pseudomonas aeruginosa* remains the commonest cause of contact lens-related corneal infection probably because of its unique virulence characteristics and ability to survive in the contact lens/storage case/ocular environment. In two recent outbreaks of contact lens-related infections, there has been a strong association demonstrated with particular contact lens solutions. Since the recall of these specific contact lens solutions, the rate of *Acanthamoeba* keratitis has remained above the expected baseline, indicating unidentified risk factors that may include environmental

exposures. Individual differences in susceptibility to microbial keratitis may be partly explained by differences in single-nucleotide polymorphisms in certain cytokine genes, particularly those with a proven protective role in corneal infection.

Eye (2012) 26, 185–193; doi:10.1038/eye.2011.288; published online 2 December 2011

Keywords: corneal infection; contact lens; microbial keratitis

Microbial keratitis is a potentially blinding corneal infection, which occurs rarely in the normal eyes.^{1–3} Predisposing factors have included ocular surface disease, ocular trauma, contact lens wear, systemic diseases, and ocular surgery.^{2,4–7} In a working age population, the two major preventable predisposing factors are ocular trauma and contact lens wear,^{5,7} each accounting for 1/3 of new cases presenting to a tertiary referral centre in Australia.⁷

Our understanding of prevention and prophylaxis of contact lens-related microbial keratitis has been informed by several recent well-designed prospective epidemiological studies describing incidence rates and risk factors, and recent evidence for causative organisms, pathophysiology, and the differences between individuals. This paper aims to summarise information relevant to limiting the morbidity associated with this condition.

Epidemiology of microbial keratitis with contemporary contact lenses

Tables 1–3 summarise the incidence estimates from a range of studies with hydrogel, silicone

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Received: 10 October 2011
Accepted: 12 October 2011
Published online: 2 December 2011

This work was presented at the Cambridge Ophthalmological Symposium, September 2011.

Table 1 Studies describing the unadjusted annualised incidence of presumed microbial keratitis and vision loss in hydrogel contact lens wear, stratified by selection of controls (adapted from Stapleton *et al*⁷⁸)

First author	Total cases	Definition of microbial keratitis	Study design	Location	Incidence per 10 000 (95% CI). Daily wear	Incidence per 10 000 (95% CI). Extended wear
<i>Denominator derived from random telephone survey of the community to identify penetrance of contact lens wearers.</i>						
Stapleton ¹¹	285	Clinical diagnosis of microbial keratitis with either a positive corneal culture or infiltrate with overlying epithelial defect, with one or more of: lesion in the central cornea; anterior chamber response; and pain	12-month prospective surveillance of practicing ophthalmologists and optometrists	Australia	1.9 (1.8–2.0) Vision loss 0.4 (0.4–0.4)	19.5 (14.6–29.5) Vision loss 4.0 (2.9–6.6)
Cheng ⁹	92	Clinical diagnosis of microbial keratitis in cosmetic contact lens wearers, excluding viral keratitis. Self-limiting small corneal lesions excluded	3-month prospective surveillance of all practicing ophthalmologists	Netherlands	3.5 (2.7–4.5)	20.0 (10.3–35.0)
Seal ⁷⁴	27	Presumed non-viral microbial keratitis	8-month prospective, population surveillance via 8 hospitals	Western Scotland	2.7 (1.6–3.7)	—
Poggio ¹⁶	195	Corneal stromal infiltrate with an overlying epithelial abnormality (ulceration) clinically diagnosed as microbial keratitis, received antibiotic treatment	4-month prospective surveillance of all practicing ophthalmologists	Five states in northern United States	4.1 (2.9–5.2)	20.9 (15.1–26.7)
<i>Denominator derived from fitting surveys. CL type and modality by matched controls</i>						
Morgan ⁷⁵	38	Prospective identification of corneal infiltrative events associated with CL wear. 'Severe' keratitis defined as cases with clinical severity score > 8/22 National fitting data applied to estimated hospital catchment population	12-month prospective study of patients presenting to hospital accident and emergency clinic	Royal Eye Hospital, Manchester, UK	6.9 (6.3–7.5)	96.4 (37.5–245.2)
Lam ¹⁰	59	Clinical diagnosis, corneal stromal infiltrate > 1 mm ² usually but not necessarily with an overlying epithelial defect, excluding inflammatory, herpetic and adenoviral keratitis. Retrospective fitting survey data (1994) applied to 1998 census data	17-month prospective survey of two hospitals and 27 private ophthalmologists	Hong Kong	3.1 (2.1–4.0)	9.3 (4.9–13.7)
<i>Denominator derived from practitioner fitting surveys</i>						
Nilsson ⁷⁶	26	CL induced keratitis, defined as full epithelial defect with a stromal infiltrate or full ulcer.	3-month prospective national surveillance of all ophthalmologists	Sweden	2.2 (0.4–3.9) Vision loss 0.5 (0.3–0.8)	13.3 (4.1–22.6)

Abbreviations: CI, confidence interval; CL, contact lens.

hydrogel, and daily disposable contact lenses, respectively. Incidence rates appear not to be appreciably different with contemporary contact lens materials and wear modalities. Two key findings are that the incidence rate for microbial keratitis with overnight use of silicone hydrogel lenses is no different to that of hydrogel contact

lenses (1 per 500 wearers per year), and that daily disposable contact lenses were not associated with a lower risk for all microbial keratitis than daily wear frequent replacement contact lenses.

Independent risk factors for microbial keratitis show some variation between studies, possibly due to

Table 2 Studies describing the annualised incidence of presumed microbial keratitis in silicone hydrogel contact lens wear, stratified by selection of controls (adapted from Stapleton *et al*⁷⁸)

Author (total cases)	Definition	Study design	Location	Incidence per 10 000 (95% CI). Daily wear	Incidence per 10 000 (95% CI). Extended wear
<i>Denominator derived from random telephone survey of the community to identify penetrance of contact lens wearers</i>					
Stapleton ¹¹	Clinical diagnosis of microbial keratitis with either a positive corneal culture or infiltrate with overlying epithelial defect, with one or more of: lesion in the central cornea; anterior chamber response; pain	12-month prospective surveillance of practicing ophthalmologists and optometrists.	Australia	11.9 (10.0–14.6) 44 cases Vision loss 1.1 (0.9–1.4)	25.4 (21.2–31.5) 92 cases Vision loss 2.8 (2.3–3.5)
<i>Prospective cohort study, 6245 participants using a silicone hydrogel lens on an extended wear schedule, 5561 wearer years of experience</i>					
Schein ⁷⁷	Presumed microbial keratitis based on presenting signs and symptoms and review by endpoint adjudication committee	12-month prospective cohort postmarket surveillance study	131 clinical practices widely distributed across North America	N/A	18.0 (8.5–33.1) 10 cases Vision loss 3.6 (0.4–12.9)
<i>Denominator derived from fitting surveys, CL type and modality by matched controls</i>					
Morgan ⁷⁵	Prospective identification of corneal infiltrative events associated with CL wear. 'Severe' keratitis defined as cases with clinical severity score >8/22. National fitting data applied to estimated hospital catchment population	12-month prospective study of patients presenting to hospital accident and emergency clinic	Royal Eye Hospital, Manchester, UK	0.0 (0.0–210.1) 0 cases	19.8 (6.7–58.0) 3 cases

Abbreviations: CI, confidence interval; CL, contact lens.

Table 3 Studies describing the annualised incidence of presumed microbial keratitis in daily disposable contact lens wear

Study	Number of cases	Incidence of presumed microbial keratitis per 10 000 (95% CI).
Stapleton <i>et al</i> ¹¹	12	1.9 (1.8–2.0)
Morgan <i>et al</i> ⁷⁵	8	4.9 (2.5–9.6)

Abbreviation: CI, confidence interval.

differences in study design, differences in wear practises, and power to detect differences; however, modifiable risk factors that have been consistently reported include extended wear,^{2,8} a longer duration of extended wear;^{8–10} occasional overnight lens use;¹¹ poor hygiene,^{8,10} including omission of or infrequent lens disinfection,^{2,12} omitted or infrequent case cleaning,^{11,13} and omission of handwashing before handling lenses¹⁴ and smoking.^{10,11,15} Non-modifiable risk factors reported include younger age, males, and socioeconomic class.^{2,14–16} Systemic risk factors include self-reported poor general health,¹⁷ diabetes⁸ and thyroid disease¹⁷ Most recently, an increased exposure (number of days of wear per week) in daily wear, hypermetropia, obtaining lenses via the

Internet or mail order, and the early period of lens wear have been identified as additional risk factors with contemporary lens types.^{11,14} Despite a higher unadjusted incidence rate for daily use of silicone hydrogel contact lenses compared with hydrogel contact lens use (Table 1), multivariable analyses have not identified lens material as an independent risk factor.^{11,14} Within such multivariable models, the risk factors identified typically accounts for 70–80% of the total risk. It is conceivable that other behaviour traits, not evaluated in these studies, including risk taking propensity¹⁸ and individual differences in susceptibility also contribute to this unexplained risk of disease.

Disease severity

Given the limited impact of new lens modalities in reducing the overall risk of contact disease, an alternative approach may be to examine disease severity and specific risk factors, which may predispose to a more severe phenotype. Disease severity is frequently reported as the rate of vision loss and 10–14% of cases lose two lines of best-corrected spectacle acuity (Tables 1 and 2). Vision loss is strongly associated with keratitis caused by an

environmental organism (Gram-negative bacteria, *Nocardia* sp, fungi or *Acanthamoeba*), rather than with other Gram-positive bacteria or a culture-negative outcome (11.4 ×, 95% CI 4.2–30.9) and with remoteness to healthcare (5.1 ×, 95% CI 1.6–16.6).¹⁹ Disease severity may also be measured by cost and duration of disease. Both of these outcome measures are associated with the corneal culture result and with a delay in receiving appropriate treatment.¹⁹

While the risk of infection associated with daily disposable contact lenses is of a similar magnitude to that of other daily use lenses, the low rate of severe/moderate keratitis in daily disposable contact lenses (0.5 (CI 0.5–0.6) per 10 000 wearers per year) compared with frequent replacement daily wear contact lenses (1.1 (CI 1.1–1.2) per 10 000 wearers per year), and low risk of vision loss with this modality is of note.^{11,14} This is perhaps consistent with these lenses being disposed of after each wear rather than being exposed to risk factors associated with hygiene procedures. A preliminary study has described a greater proportion of culture-negative lesions in daily disposable wearers compared with other daily wear contact lens users.²⁰ This low rate of severe disease when daily disposable lenses are worn on a strict daily disposable wear basis would suggest an advantage in reduced morbidity.

An analysis of independent risk factors for moderate and severe microbial keratitis among daily wear contact lens users has specifically indicated the importance of poor storage case hygiene and infrequent case replacement.²¹ When assessing the contribution of risk factors to disease load, attention to storage case cleaning and replacement could reduce the disease load by over 60%.²¹ The significance of storage case hygiene practise in limiting severe disease would suggest the importance of microbial contamination of the storage case in microbial keratitis. Despite storage case contamination remaining common among asymptomatic wearers,²² there is evidence that the causative organism can be recovered from the storage case in microbial keratitis^{23–26} A recent study examining non-culturable organisms from the storage case has demonstrated a link between the number of bacterial species recovered and increased severity of keratitis.²⁷ Based on this evidence, elimination of the storage case via daily disposable contact lens use or elimination of contamination through antimicrobial technologies, easily cleaned case designs, frequent case replacement or simplified case hygiene practise would be effective approaches to limit disease severity.

Causative organisms

The spectrum of causative organisms in all microbial keratitis varies by climate and predisposing factor.

In general, Gram-positive bacteria are more frequently recovered in temperate climate regions,^{5,7,28} and Gram-negative bacteria and fungi in tropical or sub-tropical climates.^{6,29–31} Fungi account for 5–40% of culture proven infections.

In non-contact lens-related disease, Gram-positive bacteria predominate, specifically *S. aureus*, coagulase-negative staphylococci, *Strep. pneumoniae* and *viridians*.^{5,7,28} In contrast, *Pseudomonas aeruginosa* is the most commonly recovered causative organism in contact lens-related disease, followed by Gram-positive bacteria, fungi and *Acanthamoeba*.^{32–36} Severe microbial keratitis with vision loss in contact lens wearers is more likely to be caused by an environmental pathogen, and to occur in tropical regions in association with high daytime temperatures.³⁶ There is a further strong association between *Acanthamoeba* and contact lens-related disease, with up to 95% of *Acanthamoeba* keratitis cases attributed to contact lens wear.³⁷

Why *P. aeruginosa*?

The strong association between *P. aeruginosa* and contact lens-related infection is intriguing. Although *P. aeruginosa* can elaborate a wide range of cell associated and extracellular virulence factors, which can initiate and potentiate the infection process and activate the host defence mechanisms (see Willcox³⁸ for a review), the link with contact lens wear has not been fully elucidated. The lens, storage case, and ocular environment may offer a suitable survival niche for this environmental organism. *P. aeruginosa* can adhere to and colonise lens materials during wear and survive in contact lens storage cases (see Szczołka-Flynn *et al*³⁹ for a review), partly through its ability to grow as a resistant biofilm on lenses and cases,⁴⁰ and partly due to innate⁴¹ or acquired resistance to contact lens disinfectants.⁴²

The initiation of microbial keratitis probably requires a combination of unique bacterial virulence characteristics plus the physiological impact of contact lens wear on the cornea. Physiological changes as a result of contact lens wear, which are likely to affect resistance to infection, include inhibition of normal corneal epithelial cell shedding,⁴³ corneal epithelial thinning,⁴³ increased binding of bacteria to corneal epithelial cells⁴³ possibly through exposure of specific bacterial adhesins on basolateral cell membranes,⁴⁴ increased internalisation of bacteria through expression of membrane lipid rafts on corneal epithelial cells,⁴⁵ reduced tear exchange,⁴⁶ and disruption to the normal lid/cornea/tear resurfacing mechanism.

During lens wear, the relatively static post-contact lens environment may protect organisms from host defences and may prolong retention time of organisms at the

ocular surface, allowing organisms to replicate. This environment may preferentially select for certain virulence characteristics. Evidence for this includes the change in genotype of organisms associated with contact lens-related infections. *P. aeruginosa* strains are differentiated by the presence of particular Type III secretion system genes to either *exoS* or *exoU*, encoding for exoenzymes S and U, respectively. The exoenzymes are injected into the host cell and initially locate to the plasma cell membrane. The *exoS* gene is associated with an invasive phenotype, where strains possessing this gene invade epithelial cells, replicate intracellularly and produce cell death through disruption of the host cell actin cytoskeleton.⁴⁷ Exoenzyme U is a potent cytotoxin that damages the host cell membrane, and causes overwhelming inflammation and host tissue damage through intracellular phospholipase A₂ activity.⁴⁸ ExoU-producing strains replicate extracellularly. The majority of non-ocular clinical isolates (70–80%) contain the *exoS* gene,⁴⁹ which is consistent with the findings in non-contact lens-related microbial keratitis. In contact lens-related disease, however, there is a greater representation of strains containing the *exoU* gene.⁵⁰ (Figure 1) The genotypic selection of *exoU* isolates in contact lens-related infections perhaps suggests that cytotoxicity is a more important and specific virulence factor in contact lens-related keratitis than in other *P. aeruginosa* infections.

Severe disease caused by *P. aeruginosa* results from the specific virulence factors of the organism and an extreme host inflammatory response initiated via a host–bacteria interaction between host pattern-recognition receptors (eg, Toll-like receptors) and the respective pathogen-associated molecular pattern.⁵¹ Strategies directed towards microbial virulence characteristics⁵² may be more successful in preventing or limiting disease severity rather than attempting to modulate the host response. Biofilm prevention or disruption, or inhibition of *P. aeruginosa* quorum sensing may limit disease severity.

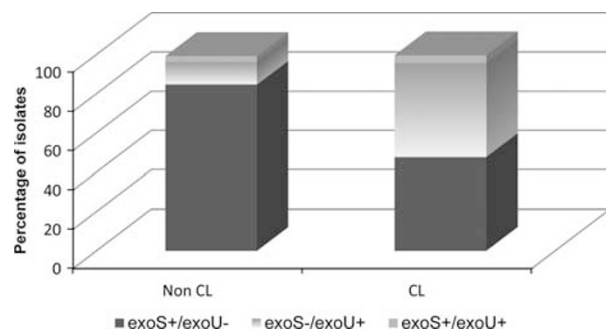


Figure 1 Distribution of type III secretion toxin genes *exoU* and *exoS* for *P. aeruginosa* strains from both non-contact lens and contact lens-related keratitis (after Choy *et al*⁵⁰).

Recent trends

Certain contact lens care solutions were recently associated with outbreaks of *Fusarium* and *Acanthamoeba* keratitis, namely ReNu MoistureLoc (Bausch & Lomb, Rochester, NY, USA) and Complete MoisturePlus (Abbott Medical Optics, Santa Ana, CA, USA), respectively. The *Fusarium* outbreak was initially detected via case series in Singapore⁵³ and in the United States,⁵⁴ and was subsequently described in two case control analyses.^{55,56} Independent risk factors are reported in Table 4 and both the studies confirmed the excess risk associated with ReNu MoistureLoc. The solution was recalled worldwide by May 2006. Laboratory studies demonstrated reduced fungicidal activity with this solution under conditions of prolonged increased temperatures,⁵⁷ evaporation,^{58,59} and reuse.⁵⁸ A recent retrospective multicentre case series (2001–2007), reported on 695 cases of fungal keratitis including 283 contact lens wearers.⁶⁰ Although the rate of *Fusarium* keratitis among contact lens wearers had reduced to the pre-outbreak levels, the rates of non-*Fusarium* fungal keratitis remained elevated.⁶⁰

A year after the *Fusarium* outbreak, there was a similar pattern of increased reporting of contact lens-related keratitis in daily wear soft contact lens use due to *Acanthamoeba*.^{61–63} Independent risk factors were established in two case control studies (Table 5) and both

Table 4 *Fusarium* keratitis: risk factors

Risk factor	Singapore ⁵⁶ Multivariate analysis (61 cases, 345 controls)	US: CDC ⁵⁵ Multivariate analysis ^a (22 cases, 32 controls)
<i>Contact lens solution</i>		
Brands other than ReNu	1.0 Referent	1.0 Referent
ReNu MoistureLoc only	99.3 (18.4–535.4)	22.3 (3.1–∞)
ReNu MultiPlus	21.5 (4.0–115.5)	NS
<i>Contact lens replaced on schedule</i>		
Yes	1.0 Referent	Not examined
No	4.8 (1.7–13.8)	
Reuse solution	NS	— ^b
Did not 'rub' lenses	Not examined	NS ^b
Hand washing	Not examined	NS
Case replacement	Not examined	NS
Extended wear	NS	NS
Swim in lenses	NS ^b	NS
Demographics:	Age: NS, male (3.3 ×), age, gender, high income (3.8 ×), income, ethnicity	NS
	Malaysian (3.8 ×)	

Abbreviations: CI, confidence interval; NS, not significant.

^aControlling for reuse of solution.

^bSignificant in univariate analysis.

Table 5 *Acanthamoeba* keratitis: risk factors

Risk factor	Chicago ⁶⁴ Multivariable analysis (30 cases, 39 controls)	USA ⁶⁵ Multivariable analysis (72 cases, 140 controls)
<i>Contact lens solution</i>		
Brands other than Complete MoisturePlus	1.0 Referent	1.0 Referent
Complete MoisturePlus	18.50 (2.11–162.63)	16.9 (4.8–59.5)
<i>Reuse of solution/topping off</i>		
Reuse 0–5 × per month	1.0 Referent	1.0 Referent (no topping off)
Reuse <5 × per month	3.17 (0.82–12.33) ^a	2.8 (1.2–6.8)
<i>Rub to clean lenses</i>		
Rub <10 × per month	1.0 Referent	NS
Rub ≤10 × per month	9.05 (0.82–100.19) ^a	
<i>Wear duration</i>		
Lenses worn for <5 years	Not examined	1.0 Referent
Lenses worn for ≤5 years		2.8 (1.0–7.6)
Shower wearing lenses (<5 × per month)	NS	Not examined
Lens replaced (quarterly +)	NS	Not examined
Age of case at replacement (<3 month)	NS	Not examined
Extended wear	NS	Not examined
Lens material type	NS	NS

Abbreviation: NS, not significant.
^aConditional multivariable analysis, reporting factors significant at the $P < 0.1$ level.

confirmed the excess risk associated with Complete MoisturePlus (Abbott Medical Optics, Santa Ana, CA).^{64,65} Unlike the previous outbreak, however, <60% of cases used this product. A worldwide recall of the product was initiated in May 2007, however, since that time the disease has persisted,⁶⁶ suggesting the contribution of additional unidentified risk factors.

In terms of limiting disease morbidity, there is limited contribution of hygiene and compliance risk factors other than reuse or topping off of solutions. Ongoing surveillance facilitates early detection, and there has been no licensing requirement for contact lens solutions to demonstrate efficacy against *Acanthamoeba*, consequently this is now currently under consideration by the FDA.

Genetic factors in disease susceptibility and severity

Genetic mutations in the innate immune system may be involved in individual susceptibility to microbial

keratitis. Both susceptibility to and severity of inflammatory diseases have been linked to mutations of single bases (single-nucleotide polymorphisms, SNPs) and combinations of these bases (haplotypes) of cytokine and cytokine receptor genes.⁶⁷ In a mouse model of corneal infection, Th2-responsive animals show a less severe microbial keratitis response than Th1 designated animals.⁶⁸ In contact lens wearers with bacterial keratitis, there is a relationship between haplotypes of interleukin (IL)-10 and the severity of and susceptibility to keratitis.⁶⁹ The genotype of IL-6 (rs1800795) has been associated with severity of contact lens-related microbial keratitis, suggesting that IL-6 modulates disease severity.⁷⁰ Contact lens wearers carrying one copy of the SNP were 3.1 × (95% CI 1.1–8.3, $P = 0.03$) more likely to experience moderate/severe keratitis and those with two copies, were 6.4 × (95% CI 1.4–28.4, $P = 0.02$) more at risk compared with those without the mutation.⁷⁰ The biological relevance and functionality of this SNP has been demonstrated, with reduced IL-6 production in juvenile chronic arthritis sufferers with the SNP.⁷¹ Similarly, in mouse models of *P. aeruginosa*⁷² and *S. aureus*⁷³ keratitis, IL-6 is protective.

Individual immune profiles therefore can modulate the susceptibility and severity of corneal infections in contact lens wearers and may assist in predicting those at risk, particularly those wearers at risk of more severe disease.

Conclusions

Somewhat disappointingly, contemporary contact lenses appear to have not reduced the overall incidence of microbial keratitis. Risk factor analysis indicates that disease load is reduced by 60–70% by avoidance of overnight lens use and attention to lens hygiene factors. More severe disease is associated with an environmental causative organism and a delay in presentation for treatment. More significantly, a reduction in morbidity may be possible through recognition of appropriate risk factors, such as hygiene, specifically attention to storage case hygiene as both case cleaning and replacement reduces the risk of severe disease in daily contact lens use. Daily disposable lenses are associated with less severe disease. In two recent outbreaks of contact lens-related infections due to unusual organisms, the antimicrobial efficacy of specific contact lens solutions has been a causal factor. As the recall of these products, the rate of *Acanthamoeba* keratitis has remained above baseline levels, indicating the impact of as yet unidentified risk factors. Individual differences in susceptibility may be partly explained by differences in SNPs in certain cytokine genes, particularly those with a protective role in corneal infection.

Conflict of interest

The authors declare no conflict of interest. The Vision CRC and Brien Holden Vision Institute receive a royalty on the sales of certain contact lenses.

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