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REVIEW

The Epidemiology of Contact Lens Related Infiltrates

FIONA STAPLETON, MCOptom, PhD, FAAO, LISA KEAY, BOptom, PhD, FAAO, ISABELLE JALBERT, OD, PhD, FAAO, and NERIDA COLE, PhD

Vision Cooperative Research Centre, University of New South Wales, Sydney, Australia (FS, LK), Institute for Eye Research, University of New South Wales, Sydney, Australia (FS, LK, IJ, NC), and School of Optometry and Vision Science, University of New South Wales, Sydney, Australia (FS, LK)

ABSTRACT

With estimated numbers of contact lens wearers worldwide exceeding 140 million, even complications with a low incidence will affect a significant number of individuals. Although contact lenses clearly have many advantages for wearers, certain risks have been associated with their use. Differences in risk for different types of contact lenses and wearing patterns have been demonstrated for both rare and common lens related complications. This review particularly focuses on the incidence and etiology of contact lens related corneal infection and inflammation. An understanding of the risks and contributory factors to these conditions is important for practitioners and will enable an informed choice of safer lens wear modalities, wear schedules, and hygiene regimes to be made.
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Key Words: contact lenses, microbial keratitis, corneal infiltrates, epidemiology

Epidemiological studies of contact lens related complications provide information on their frequency and distribution and on their associated risk factors. Estimates of the total number of contact lens wearers worldwide in 2005 were as high as 140 million, such that even complications with a low incidence may affect a large number of individuals. Knowledge of the incidence and risk factors of individual contact lens complications enables practitioners to accurately inform their patients on the risks of developing these conditions. This information may also assist in the management and in understanding the pathogenesis of contact lens related disease.

Contact lens related complications occur because of a wide range of causes, and clearly the epidemiology of complications with different pathogenesis will be different. Attempts at classifying contact lens related complications have previously been made on the basis of the underlying etiology,[1–3] the primary location of the condition,[4] or the clinical subtype.[5] Because of the diversity of classifications used by different authors, it is difficult to give an exact estimate of the overall complication rate associated with contact lens wear, although one study has estimated that 6% of contact lens wearers develop a complication each year.[4] This review will focus on the epidemiology of inflammatory/infectious complications of contact lens wear, including (1) microbial keratitis and (2) sterile/aseptic keratitis.

Microbial Keratitis

Corneal infection is a rare but severe complication of contact lens wear. In severe cases, it is associated with visual loss because of scarring and perforation. Less severe cases may also be associated with significant morbidity, for example, in hospital admission, the cost of treatment, outpatient visits, time off needed from work, inability to wear contact lenses, severe pain, and temporary visual loss experienced.[6]

Microbial keratitis in contact lens wearers predominantly appears to be a bacterial process,[7] although amoebae, particularly *Acanthamoeba* have been associated with contact lens related infections. Historically, fungal infections in contact lens wearers have been infrequently reported, although a recent series of contact lens related cases in Singapore[8] and across multiple states in the United States[9] have been reported in association with use of a particular multipurpose solution. The association between viruses and contact lens related keratitis is poorly understood.

The Epidemiology of Contact Lens Related Microbial Keratitis. Before the widespread use of contact lenses, microbial keratitis was predominantly associated with trauma, ocular surface disease, ocular surgery, or with contact lens wear for aphakic or therapeutic indications. During the 1970s and 1980s, there was increased anecdotal reporting of cases of lens related infections.[10–15] In studies of hospital cases, the proportion of cases of microbial keratitis because of contact lens wear varies with the severity of disease. In severe disease requiring hospital admission, 20 to 44% of cases were caused by contact lens wear.[16–18] In studies which have examined all cases of microbial keratitis, 34 to 65% of cases could be attributed to contact lens wear for the correction of low refractive errors.[19–22]

In determining the incidence of contact lens related microbial keratitis, several study designs have been proposed.[23] Randomized

clinical trials provide the gold standard in level of research evidence and these designs reduce the effects of confounding factors by randomly allocating a treatment or exposure. Randomized trials are only feasible when the complication of interest is not rare and there are no randomized trials of contact lens related microbial keratitis as these would require an unfeasibly large sample size. For example, given a rate of microbial keratitis of 0.2% per year in EW lenses, to measure a reduction of 0.1% with a certain exposure, with a power of 80%, the required sample size would be in excess of 24,000.

As an alternative to randomized trials, observational studies allow estimation of the incidence of disease, where the investigator observes the outcome of contact lens wear on a suitably large number of individuals without assigning contact lens type and mode of wear.[24] The numerator (incident cases of disease) and denominator (number of wearers in the cohort) by the duration of wear experience are used to establish the incidence of disease (new cases per 10,000 wearers per unit time). This approach requires a large cohort of individuals wearing the lens type or types of interest.[23]

A farther approach involves surveying all practitioners or primary eye care centers involved in the management of disease, in a selected area to determine the number of new cases of microbial keratitis over a period of time. An estimate of the total contact lens wearing population in that area is used as the denominator. The denominator can be derived from surveying the population in the area, where a representative sample may be derived, for example, from the relevant postcode regions, general practitioner patient lists, or electoral registers. Other strategies for deriving the denominator might include manufacturers' contact lens sales data or from data from local contact lens practitioners, which may be applied to estimates of the total population in the region of interest. Different methods are associated with different sources of bias. For example, surveys of contact lens prescribing reflect entry of lens modalities into the community and such estimates show trends in advance of community surveys. This has been illustrated in the United Kingdom where community surveys have shown the penetrance of silicone hydrogel lenses to be 7% of wearers and contact lens prescribing surveys have shown silicone hydrogel lenses are prescribed for 13% of refits.[25] Conversely, lens types or modalities which are infrequently prescribed (such as hydrogel EW) would show a low penetrance in fitting surveys, but a higher penetrance in the lens wearing community. Surveys of lens wearers in the community are preferred because of greater accuracy for modalities with low penetration rates and reflection of actual wear practice.[26]

An additional consideration in all study designs is the diagnostic criteria used. Inclusion criteria are usually based on a diagnosis of presumed microbial keratitis, rather than a positive corneal culture, because of the low sensitivity of microbial investigations,[27] and more recently, the diminishing reliance on culture in the management of mild and moderate disease.[28] Table 1 describes the diagnostic criteria and derivation of the denominator in studies of the incidence of presumed microbial keratitis.[29–35] Given the morbidity associated with microbial keratitis, it would seem reasonable to include equivocal diagnoses as presumed microbial keratitis. The impact of diagnostic criteria on calculated incidence rates has been illustrated by applying diagnostic criteria retrospectively to an existing data set[36] and this clearly supports the need for rigor in methodological considerations and for the use of criteria which are in place prospectively and for which specific variables have been collected.

In addition to diagnostic difficulties, there has been confusion in terminology between studies.[37] The term "ulcerative keratitis" may include both presumed infected and presumed sterile lesions and "suppurative keratitis" describes a spectrum of corneal infiltrative lesions.[27,34,38] Morgan et al., in 2005[34] used a scoring system, modified from that proposed by Aasuri et al., 2003,[38] to stratify corneal infiltrates into "nonsevere" and "severe" keratitis, where "severe" keratitis is likely to be analogous to the historical definitions of presumed microbial keratitis. Schein et al., 2005[39] recently used an endpoint adjudication committee to classify infiltrative events by severity. Outcome measures (vision loss, disease duration, and direct and indirect cost of disease) have also provided a means to validate grading of disease severity.[40]

Studies from the United States,[29] Sweden,[35] the Netherlands,[32] and Hong Kong[33] estimated incidences of ulcerative keratitis in daily wear (DW) soft contact lens users and EW hydrogel contact lens users based on identifying new cases within a defined area and using population based studies to estimate numbers of contact lens wearers in the region to establish the denominator. These studies all showed incidences that were broadly similar (Table 1). Minor differences between estimates across studies may be based on the study methodology, selection of cases and controls, and diagnostic criteria. On the basis of the results from such studies, approximately 1 in every 2500 daily wear soft lens users and 1 in every 500 EW soft lens users will develop presumed microbial keratitis every year.

Since these early studies, high oxygen transmissibility silicone hydrogel and daily disposable contact lenses have been released in many markets. Although a cause relation effect has not been convincingly demonstrated between hypoxia and corneal infection,[41] the higher risk of disease in overnight lens wear has led to speculation that contact lens induced corneal hypoxia predisposes contact lens wearers to a greater rate of corneal infection because of compromised corneal epithelial integrity,[42] impaired wound healing,[43] and an increased susceptibility of corneal epithelial cells to bacterial binding.[44–46] All contact lens wear slows normal corneal epithelial homeostasis by suppressing cell proliferation,[47] impairing cell migration,[48] and by reducing the rate of cell exfoliation.[49–51] These effects are reduced but not eliminated with highly oxygen permeable contact lenses made from silicone hydrogel materials.[47,52] Compared with other soft contact lenses, silicone hydrogel contact lenses do provide considerably improved corneal oxygen permeability and significantly reduce the overt clinical manifestations of corneal hypoxia.[53] However, the impact of this reduced hypoxia on either the absolute risk or severity of microbial keratitis with silicone hydrogel lens wear could only be investigated in large scale epidemiological studies.

Recent epidemiological studies evaluating contact lens related presumed microbial keratitis have included newly introduced lens types (Table 2). A 12-month prospective cohort study involving 5561 patient years of wear of a silicone hydrogel lens on a 30-night EW basis, has reported an overall risk of 18.0 per 10,000 wearers per year.[39] Morgan et al., in 2005[34] reported similar absolute risk data of 19.8 per 10,000 wearers per year developing "severe" keratitis, which is likely to be analogous to presumed microbial keratitis. These data were based on a 12-month prospective study of patients presenting to a hospital accident and emergency clinic, with controls derived from fitting study estimates extrapolated to an estimate of the hospital catchment population. Preliminary analysis from the Australian and New Zealand surveillance studies complement these early estimates.[54] These

TABLE 1.
Summary of studies estimating the annualized incidence of presumed microbial keratitis in hydrogel contact lens wear, stratified by derivation of the denominator

Study (number of cases)	Definition	Study design	Location	Years	Incidence per 10,000 (95% CI); daily wear	Incidence per 10,000 (95% CI); extended wear
Denominator derived from random telephone survey of the community to identify penetrance of contact lens wearers						
Poggio[29] (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	5 States in northern USA	1987	4.1 (2.9–5.2)	20.9 (15.1–26.7)
Seal[30] (27)	Presumed microbial keratitis (nonviral)	8-month prospective, population surveillance via 8 hospitals	Western Scotland	1995	2.7 (1.6–3.7)	—
Cheng[31] (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 Telephone surveys carried out in 1994 and 1997	Netherlands	1996	3.5 (2.7–4.5)	20.0 (10.3–35.0)
Denominator derived from compilation of premarket clinical studies						
Macrae[32]	Corneal ulcers, without distinction between microbial and sterile lesions	Compilation of adverse responses from pre-market clinical studies	USA	1990	5.2 (0–15.4)	18.0 (8.2–27.8)
Denominator derived from fitting surveys, CL type, and modality by matched controls						
Lam[33] (59)	Clinical diagnosis, corneal stromal infiltrate $>1mm^2$ usually but not necessarily with an overlying epithelial defect, excluding inflammatory, herpetic adenoviral keratitis Retrospective fitting survey data (1994) applied to 1998 census data	17-month prospective survey of 2 hospitals and 27 private ophthalmologists	Hong Kong	1997–1998	3.1 (2.1–4.0)	9.3 (4.9–13.7)
Morgan[34] (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	2003	6.9 (6.3–7.5)	96.4 (37.5–245.2)
Denominator derived from fitting survey						
Nilsson[35] (26)	CL induced keratitis, defined as full epithelial defect with a stromal infiltrate or full ulcer Concurrent survey of 71% of contact lens fitters	3-month prospective national surveillance of all ophthalmologists	Sweden	1993	2.2 (0.4–3.9)	13.3 (4.1–22.6)

TABLE 2.
Summary of studies estimating the annualized incidence of presumed microbial keratitis in silicone hydrogel contact lens wear, stratified by derivation of the denominator

Study (number of cases)	Definition	Study design	Location/Years	Incidence per 10,000 (95% CI); daily wear	Incidence per 10,000 (95% CI); extended wear
Prospective cohort study, 6245 participants using a silicone hydrogel lens on an extended wear schedule, 5561 wearer years of experience					
Schein[39] (10)	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/2002–2003	N/A	18.0 (8.5–33.1) Vision loss 3.6 (0.4–12.9)
Denominator derived from fitting surveys, CL type and modality by matched controls					
Morgan[34] (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/ 2003	0.0 (0.0–210.1) 0 cases	19.8 (6.7–58.0) 3 cases

latter studies involved national surveillance studies which identified all new cases of keratitis occurring over a 12-month period,[55] where the denominator was derived from national telephone surveys. In the Australian study, 286 cases were identified and 1798 contact lens wearing controls from a survey of 35,914 individuals aged 15 to 64 years old.[54]

Direct comparisons between different lens types and modalities, including silicone hydrogel contact lenses, have been made in several studies. One single center study has reported a 5-fold reduction in the incidence of "severe" keratitis with EW silicone hydrogel lenses when compared with hydrogel lenses.[34] The estimate of the incidence of "severe" keratitis in EW hydrogel lens use from this study (96.4 per 10,000 wearers) is not in good agreement with other reported incidence rates and may be a reflection of the indirect method of estimation of lens use in the community.[26] Preliminary analyses from both the incidence studies carried out in Australia and New Zealand[54] and a case–control study from Moorfields Eye Hospital in London[56] have demonstrated no difference in the risk of infection between EW hydrogel and EW of silicone hydrogel lenses. All three studies cited above indicate an increased risk with overnight lens use irrespective of lens material type. Interestingly, although studies of hydrogel lens use have consistently demonstrated the impact of degree of overnight lens use on increasing risk,[20,57] this effect was not confirmed in a cohort study of wearers of a silicone hydrogel lens.[39] Further, the point estimates for the incidence of microbial keratitis in 30-night EW of silicone hydrogel lens use[39] is remarkably similar to historical estimates of incidence in hydrogel 6-night EW suggesting that the increase in number of nights of continuous wear has not had a dramatic effect on the risk of disease.

Outcomes and Morbidity. The rate of visual loss (loss of two or more lines of best corrected visual acuity) caused by microbial keratitis is an important public health issue and 12 to 14% of cases of presumed microbial keratitis cases[6,32,35] have previously been reported to experience visual loss. For daily wear hydrogel lenses, this would represent around 5 per 100,000 wearers and 3 per 10,000 wearers in EW per year. More recently, Schein et al., 2005[39] estimated vision loss in EW silicone hydrogel lens use to occur in 3.6 per 10,000 wearers per year. These figures are particularly relevant when one attempts to compare the relative safety of the various modes of refractive correction available. While the rate of visual loss following refractive surgery varies with degree of refractive error, population studied, study design, type of surgery, and loss to follow up rates, vision loss of two or more lines has been estimated to occur in 0.5 to 1.5% of individuals during the intraoperative and early postoperative period,[58] although rates as low as 0.16% demonstrating a loss of one line or more, have been reported in a selected population of young service people.[59] Late postoperative vision loss (mean time to development 10 months postoperatively) has been attributed predominantly to ectasia and a loss in best corrected visual acuity because of ectasia has been estimated to occur in 1 per 2500 LASIK procedures.[60] The risk of vision loss following LASIK could conservatively be considered to be the equivalent to the risk following 20 years of EW hydrogel wear where lenses are used for 6 nights continuously or silicone hydrogel contact lens use where lenses are used for 30 nights continuously. However, population based studies are not currently available for visual outcomes after refractive surgery and such stud-

ies would be required for meaningful comparison of the risks associated with different correction modalities.

Other than the incidence of the disease and associated visual loss, other outcome parameters related to disease severity are of importance. Microbial keratitis may be associated with hospital admission, time off needed from work, and the cost of medications and back up spectacles. A population study has examined factors affecting the morbidity of contact lens related microbial keratitis.[6] Disease severity was strongly influenced by culture result and by a delay in receiving appropriate treatment. After adjustment for these factors in a paired analysis, wearers of silicone hydrogel lenses had a shorter disease duration (median 4, interquartile range 4 days) than those of hydrogel lens wearers (median 7, interquartile range 10 days), although the rate of vision loss and disease cost were similar. The distribution of disease severity in a study of symptomatic corneal infiltrates, including lesions presumed to be microbial, has also suggested that disease severity, based on a clinical scoring scheme may also be reduced in EW of silicone hydrogel lenses when compared with hydrogel lenses.[61]

Risk Factors for Disease. From these incidence data, it is clear that the risk of presumed microbial keratitis differs for different lens types and wear schedules and these relationships were investigated in the late 1980s to 1990s and recently in a series of studies in 2003 to 2005. Case–control studies have also been used to establish relative risk of microbial keratitis for different lens modalities and to estimate the impact of potential risk factors such as lens wear practice, patient demographics, and lens wear history.

Table 3 summarizes the crude relative risks for microbial keratitis for different lens types and modes of wear. Reliable differences in risk have not been reported between daily use of rigid gas permeable, PMMA, and daily wear soft contact lens use. In hydrogel contact lens use, a progressive increase in risk from daily wear, to occasional overnight to EW has been consistently reported.[20,54,56,57,66] Recent studies including silicone hydrogel contact lenses have confirmed the excess risk associated with overnight contact lens use when compared with daily use,[34,54,56,62] however, debate persists regarding differences between EW hydrogel and EW silicone hydrogel contact lenses.

Table 4 summarizes the risk factors identified in case series and case–control studies and Fig. 1 lists contemporary information including modifiable and nonmodifiable risk factors with new lens wearing modalities.[56,62,70–72] Although the magnitude of increased risk varies between studies, modifiable risk factors which are reported consistently include EW, occasional overnight lens use, poor hygiene, omission of handwashing before handling lenses, swimming (perhaps qualified more recently by the lack of goggle use or lens disinfection following swimming), poor general health, and smoking. Nonmodifiable risk factors consistently reported include younger age, males, and socioeconomic class.

Frequent Replacement Lenses and Daily Disposable Lenses. In the late 1980s, the frequent replacement modality was developed and introduced as an improvement that would reduce the complications of lens wear and potentially reduce the risk of infections in soft contact lens wearers. In fact, although poor compliance is a risk factor for microbial keratitis in daily wear of soft lenses, it has not been shown to modulate the risk for microbial keratitis in overnight soft lens use (Table 3). Early case–control studies showed an unexpected increased risk for microbial keratitis with frequent replacement lens wear.[65,66] However, neither study was able to show a significant difference in risk between frequent replacement and conventional lenses when used on the same wear schedule. A re-analysis of the latter article,[64] identified a significantly increased risk of microbial keratitis of 3.2× (95% confidence interval 1.2–14.4) with disposable compared to conventional use after controlling for the degree of overnight lens use. However, the authors hypothesized that this increased risk was because of a classification error with respect to overnight use among their subjects. A UK study demonstrated significantly increased risks with daily use of frequent replacement lenses (odds ratio 3.5×, 95% confidence interval 1.6–7.7) and EW frequent replacement lenses (odds ratio 4.8×, 95% confidence interval 1.5–14.9) when compared with conventional lens use. Risks were adjusted for the degree of overnight wear, demographic variables, lens use, and hygiene variables[67] (Fig. 2). Other population based studies demonstrated a decreased risk with frequent replacement lens use in Sweden[35,63] or no differences in microbial keratitis rates between frequent replacement and conventional daily wear.[73] It should be pointed out that the latter study lacked sufficient statistical power to detect relative risks of less than three times, and was designed to test differences between modalities for more common complications. What was not addressed in these early studies is the impact of planned replacement or disposability of the same lens type on risk, nor the impact of differences between early adopters of new technologies, such as their beliefs and behaviors, compared with wearers who successfully wear existing technologies.

A recent review has argued that the early excess risk associated with use of frequent replacement contact lenses is no longer evident in contemporary studies where these lenses are widely used in the community.[74] Conceivably, the risk of microbial keratitis measured with new products may be complicated by the characteristics of the small number of people wearing the latest technology. It might be reasonable to expect that the early adopters of new technology are unique, possibly due to different demographics, socioeconomic status, compliance behaviors, risk-taking behaviors and lifestyles, or those who may have been fitted with frequent replacement contact lenses after poor success with conventional hydrogel contact lenses. This factor should be considered in interpretation of epidemiological studies of contact lens related microbial keratitis involving new technologies which focus on the first group of wearers to adopt new products.

The use of daily disposable lenses avoids the need for attention to ongoing lens hygiene and eliminates the use of a contact lens storage case. Poor contact lens hygiene is a well-established risk factor for corneal infections in daily contact lens use.[20,27,57,67] Microbial contamination of the contact lens storage case has been implicated as the likely source of causative organisms in microbial keratitis.[75–77] Appropriate use of daily disposable contact lenses would therefore be expected to reduce the risk of contact lens related microbial keratitis[78] and appropriately designed case–control and large cohort studies are required to evaluate the risk attributable to this mode of wear.

Encouraging results for daily disposable contact lens use have been reported in small populations who were carefully selected and monitored[79–81] or were followed up for short periods.[82] However, case reports of ulcerative keratitis in daily disposable wearers have been published, including those where wearers are reportedly fully compliant.[83–87]

TABLE 3.
Unadjusted odds ratio by lens type for microbial keratitis

Source	Lens type	Test lens		Referent (daily wear soft)		OR	Confidence intervals	Comment
		Cases	Controls	Cases	Controls			
Stapleton et al., 1993[27]	PMMA	2	71	28	309	0.31	0.07–1.34	Hospital-based contemporaneous controls
Poggio et al., 1989[29]	PMMA	4	NS	48	NS	0.50	0.15–1.65	Community-based contemporaneous controls. 4178 households surveyed
Seal et al., 1999[30]	RGP	1	24,980	25	14100	**0.02**	0.00–0.17	Estimate for controls based on National Opinion Polls extrapolated to the population of the West of Scotland Health Board areas
Stapleton et al., 1993[27]	RGP	2	92	28	309	0.24	0.06–1.03	Hospital-based contemporaneous controls
Morgan et al., 2005[62]	RGP	2	38	19	142	0.39	0.09–1.76	Hospital-based contemporaneous controls
Macrae et al., 1991[32]	RGP	1	1471	1	1923	1.31	0.08–20.92	Compilation of premarket studies
Nilsson and Montan, 1994[63]	RGP	1.21	10,000	0.51	10,000	2.37	0.09–62.57	Estimate based on the ratio of incidence values presented, not raw data
Schein et al., 1994[64]	RGP	4	37	11	110	1.08	0.32–3.60	Contemporaneous practice based controls
Cheng et al., 1999[31]	RGP	17	961	63	1072	**0.30**	0.17–0.52	Community based controls
Poggio et al., 1989[29]	RGP	5	NS	48	NS	1.00	0.34–2.89	Population based contemporaneous controls
Buehler et al., 1992[65]	RGP	4	43	14	129	0.86	0.27–2.74	Practice-based controls—5 controls derived per case from the practice where the case originated
Matthews et al., 1992[66]	RGP/PMMA	1	79	2	140	0.89	0.08–9.93	Hospital-based contemporaneous controls
Morgan et al., 2005[62]	Daily disposable soft	8	64	19	142	0.93	0.39–2.25	Hospital-based contemporaneous controls
Radford et al., 1998[67]	Daily wear soft (frequent replacement)	23	86	34	426	**3.35**	1.88–5.97	Hospital-based contemporaneous controls
Matthews et al., 1992[66]	Daily wear soft (frequent replacement)	1	13	2	140	5.38	0.46–63.46	Hospital-based contemporaneous controls
Morgan et al., 2005[62]	Daily wear silicone hydrogel	0	4	19	142	0.03	Infinite–infinite	Hospital-based contemporaneous controls
Stapleton et al., 1993[27]	Extended wear soft	28	35	28	309	**8.83**	4.70–16.57	Hospital-based contemporaneous controls
Lam et al., 2002[33]	Extended wear soft	25	19	20	100	**6.58**	3.06–14.15	Mixed community based, LASIK screening and hospital based controls
Morgan et al., 2005[62]	Extended wear soft	4	9	19	142	3.32	0.93–11.84	Hospital-based contemporaneous controls
Schein et al., 1989[57]	Extended wear soft	52	136	34	325	**3.65**	2.27–5.89	Practice and hospital-based contemporaneous controls
Macrae et al., 1991[32]	Extended wear soft	1	549	1	1923	**3.50**	0.22–56.09	Compliation of premarket studies
Nilsson and Montan, 1994[63]	Extended wear soft	3.12	10,000	0.51	10,000	6.12	0.32–118.12	Estimate based on the ratio of incidence values presented, not raw data
Schein et al., 1994[64]	Extended wear soft	5	18	11	110	2.78	0.86–8.94	Practice based contemporaneous controls
Cheng et al., 1999[31]	Extended wear soft	12	36	63	1072	**5.67**	2.81–11.43	Community based controls
Poggio et al., 1989[29]	Extended wear soft	80	NS	48	NS	**5.15**	3.47–7.65	Community based controls
Buehler et al., 1992[65]	Extended wear soft	5	25	14	129	1.84	0.61–5.58	Practice based controls—5 controls derived per case from the practice where the case originated
Matthews et al., 1992[66]	Extended wear soft	1	19	2	140	3.68	0.32–42.60	Hospital-based contemporaneous controls
Nilsson and Montan, 1994[63]	Extended wear soft (frequent replacement)	4.17	10,000	0.16	10,000	26.06	0.18–3841.79	Estimate based on the ratio of incidence values presented, not raw data
Radford et al., 1998[67]	Extended wear soft (frequent replacement)	24	26	34	426	**11.57**	6.00–22.28	Hospital-based contemporaneous controls
Matthews et al., 1992[66]	Extended wear soft (frequent replacement)	5	22	2	140	**15.91**	2.91–87.12	Hospital-based contemporaneous controls
Buehler et al., 1992[65]	Frequent replacement (daily and extended wear)	19	13	14	129	**13.47**	5.50–32.97	Practice based controls—5 controls derived per case from the practice where the case originated
Morgan et al., 2005[62]	Extended wear silicone hydrogel (up to 30-nights EW)	3	31	19	142	0.72	0.20–2.60	Hospital-based contemporaneous controls
Macrae et al., 1991[32]	Extended wear RGP	1	418	1	1923	4.60	0.29–73.70	Compliation of premarket studies

Bold type indicates a significantly different relative risk compared to the referent.
NS, not specified.

Recent studies have not confirmed a statistically significant reduction in either the absolute incidence or relative risk of microbial keratitis with daily disposable lenses.[34,54,56,62] Interim analysis of the unpublished latter study has suggested that daily disposable lenses may reduce the risk of more severe disease.[54] Conceivably, eliminating the contact lens storage case may reduce the likelihood of lens contamination by Gram-negative bacteria, which have been shown to be associated with more severe disease.[6]

TABLE 4.
Risk factors for microbial (bacterial) keratitis in soft contact lens wearers

DW
Male gender[20,29]
Infrequent lens disinfection[20]
Chlorine disinfection[27]
Heat disinfection[27]
No disinfection[27]
Infrequent disinfection[20]
Diabetes[57]
No surfactant or rub and rinse step[68]
Case cleaning (reduction)[67]
Compliance with hygiene regimen[33]
Smoking[62]
Gender[62]
EW
Younger age group (12–19 years)
Longer duration of extended wear[20,31,33,55]
Lower socioeconomic class[20]
Smoking[31,62]
Overnight use of DW lenses[20,33]
Topical steroid therapy[69]
Warm climate[69]
Gender[62]

Acanthamoeba Keratitis. The frequency of *Acanthamoeba* keratitis appears to vary dramatically with region and with trends in contact lens wear and care practices. Predisposing factors have included corneal trauma associated with vegetation, contact with wind blown foreign bodies or insects, or contact with hot tub water.[88,89] Overwhelmingly the major risk factor has been contact lens wear, with 85% of cases reported to the Centers for Disease Control associated with contact lens wear during the 1980s.[90] More recent studies have confirmed this strong association between contact lens wear and *Acanthamoeba* keratitis.[91–94]

The incidence of *Acanthamoeba* keratitis in noncontact lens wearers has been estimated using a 2-year prospective surveillance study to be 1 per 1,000,000 individuals per year in the United Kingdom, with regional variations noted.[94] Among lens wearers, incidence estimates of 0.5 to 3 per 100,000 soft contact lens wearers have been estimated from cohort and surveillance studies from the United Kingdom, Holland, and Hong Kong.[31,33,92,94,95] Higher estimates were obtained from a cohort study carried out in the West of Scotland of 14.9 per 100,000 soft contact lens wearers (confidence intervals 11.2–18.6).[30]

Early case–control studies[90,96] identified potential risk factors in contact lens wearers. These have included the use of homemade saline, infrequent use of a disinfection system, male gender, the use of hybrid (gas permeable lenses with a hydrogel skirt) contact lenses, and the wear of lenses while swimming. More recent case–control studies which included disposable lenses, demonstrated that failure to disinfect soft lenses, the use of chlorine release systems, and "hard" water in the home system were the major factors accounting for the increase in *Acanthamoeba* keratitis observed in the United Kingdom.[93,97] Both of these risk factors were more common among disposable lens users, although there was no excess risk associated with disposable lenses per se.[97]

The true incidence of *Acanthamoeba* keratitis may yet prove to be higher than previously thought. The use of in vivo confocal microscopy[98] in cases of microbial keratitis has lead to an increased

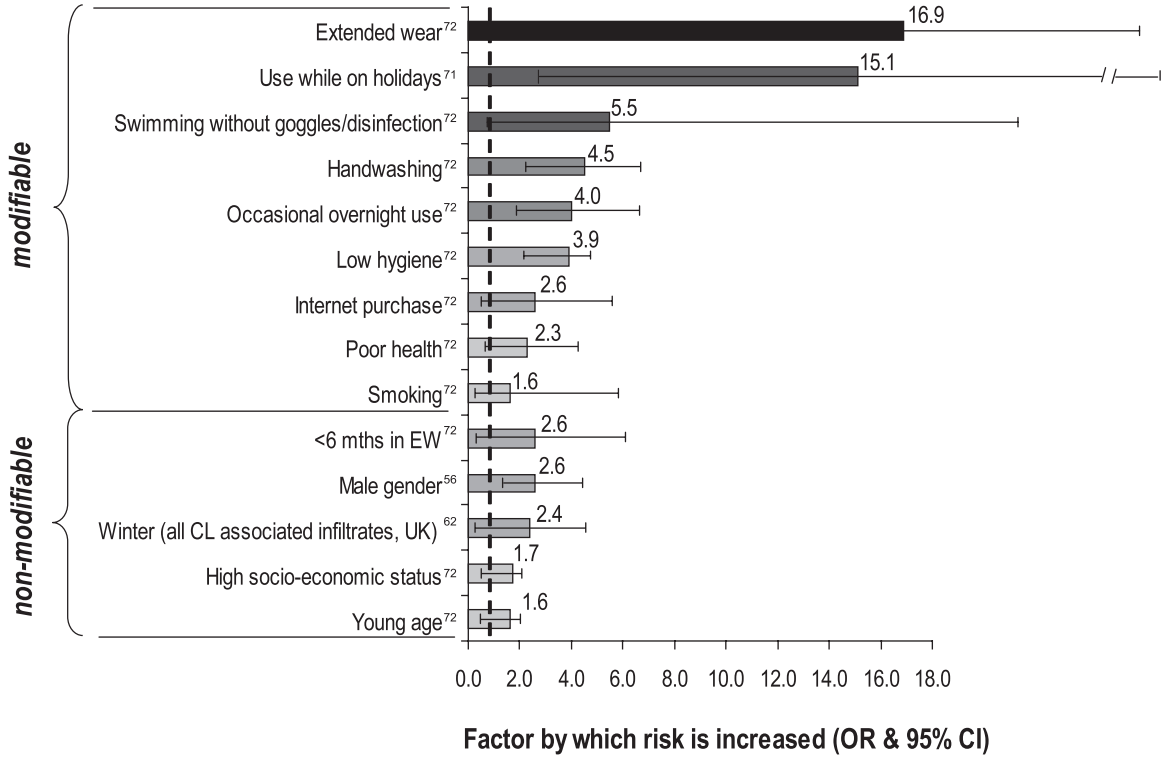

FIGURE 1.
Risk factor data for microbial keratitis for contemporary contact lens types. Reproduced with permission from the BCLA Dallos Award, Keay and Stapleton, 2006.[70]

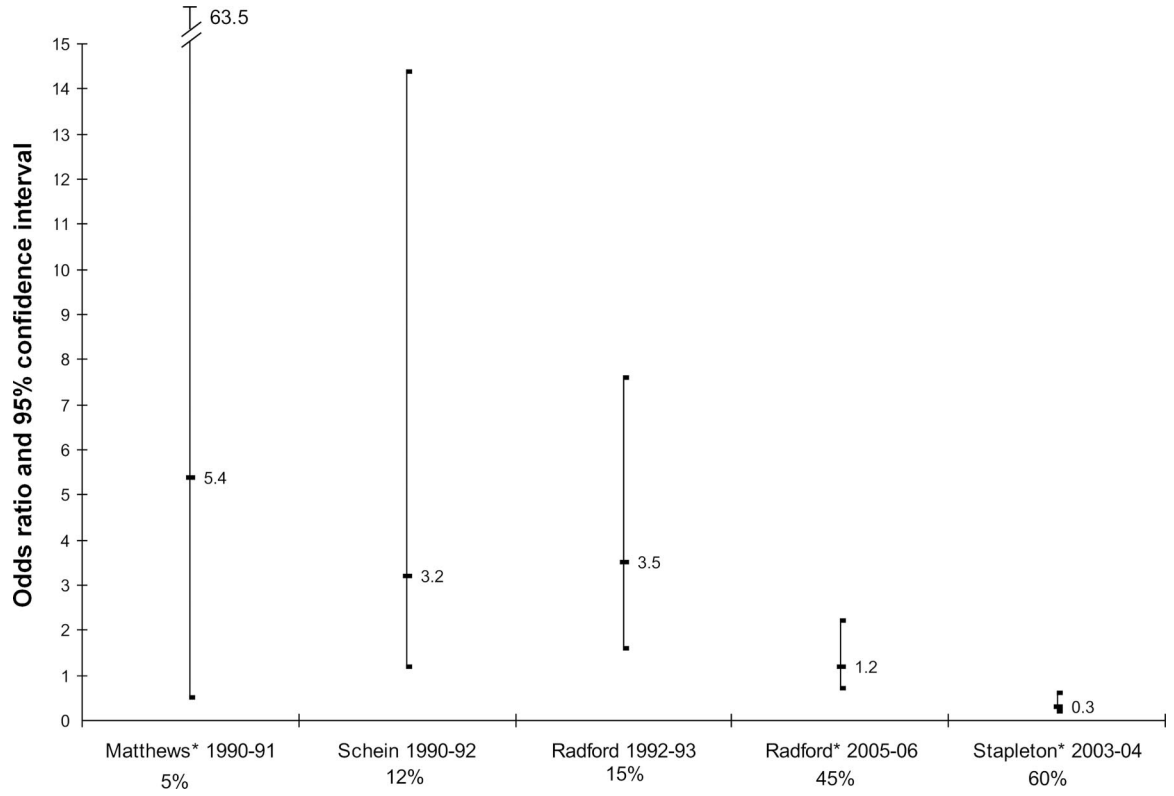

FIGURE 2.

Odds ratios and 95% confidence intervals for the risk of frequent replacement contact lenses worn on a daily wear schedule. All odds ratios are calculated in comparison to conventional soft contact lenses also worn on a daily wear schedule. The studies are listed on the x axis with year of data collection and the % use of frequent replacement contact lenses in the population at the time of the study. Figure reproduced with permission from Eye Contact Lens, 33, 2007; in press.[74] * = univariate analysis.

detection rate of *Acanthamoeba* keratitis, particularly in mild culture negative cases.[99] The use of confocal microscopy in future epidemiological studies may result in a revised estimate.

New Issues in Contact Lens Related Microbial Keratitis. Recently there have been a number of reports describing fungal keratitis associated with soft contact lens wear, particularly in *Fusarium* species. Alfonso et al. (2006) reported a doubling in incidence from 2004 to 2005 at the Bascom Palmer Eye Institute (FL)[100] following closely on a report of an outbreak of *Fusarium* keratitis in 66 contact lens wearers in Singapore.[8] The Singapore analysis comprised a national case series, and the numbers of wearers in the community was estimated from a 1998 wearing survey with the numbers extrapolated to recent census data. The national annual incidence was estimated to be 2.35 cases per 10,000 contact lens wearers (95% confidence interval, 0.62–7.22) per year. An epidemiological study identified 164 confirmed cases in the United States between June 2005 and June 2006[9] and a case–control study design was used. Forty-five cases identified before the widespread publicity about the disease in April 2006 were compared with 78 neighborhood-matched contemporaneous contact lens wearing controls. Univariate analysis established a higher risk associated with the use of ReNu with MoistureLoc only (OR 13.3×, 95% CI 3.1–119.5) and a higher risk associated with reuse of solution in the storage case (OR 3.2×, 95%CI 1.2–9.4). Multivariable analysis identified the use of ReNu with MoistureLoc only. Species of causative organisms were consistent with local environmental sources. Although poor hygiene showed an association with disease in univariate analysis, multiple other factors including possibly the effects of a novel disinfectant (Alexidine) and surfactants (Poloxomer 407) in this particular solution on environmental isolates of *Fusarium* may be relevant.

Resurgence in the popularity of orthokeratology (OK) contact lens fitting, particularly in countries where myopia is reaching epidemic proportions has been noted recently.[101] Concerns have been raised about the risk of microbial keratitis and vision loss associated with overnight OK wear, particularly given the target demographic of children and adolescents.[102] Watt and Swarbrick (2005)[103] have provided an analysis of the first 50 cases of microbial keratitis, although others have subsequently been reported. Their findings showed that 60% of the affected OK patients were 15 years of age or younger. Of interest is that 30% of these cases during overnight OK were caused by *Acanthamoeba* when compared with 5% of infections reported in regular contact lens wearers. The incidence or relative risk of OK when compared with other lens wear modalities has not yet been determined because reliable estimates of patients fitted with OK lenses are not easily obtained. The relatively severe cases reported in the literature likely represent an underestimation of the true number of cases of microbial keratitis associated with OK. It has been suggested that the fitting relationship of OK lenses is more likely to compromise the corneal epithelium.[104] The refractive change in OK appears to be because of the central corneal epithelial thinning (Swarbrick, 2006 for review),[105] which may compromise the epithelial barrier. Ad-

herence of *P. aeruginosa* to the corneal epithelium is increased after 24 h of closed eye wear of reverse-geometry lenses in an animal model.[106] These findings suggest that OK wear may alter the susceptibility of the cornea to infection, however there are no data currently available on the risk of microbial keratitis in OK contact lens wear. Clearly, appropriately designed prospective population studies are necessary to provide robust estimates of the incidence of and risk factors for microbial keratitis during OK.

Sterile/"Aseptic" Corneal Infiltrates

From a clinical decision-making perspective, it is important to differentiate between corneal infiltrates that result from a disease because of replicating microorganisms when compared with conditions resulting from noninfectious inflammation from a range of causes. The cornea has a limited range of responses to insult and corneal infiltrates can range from mild, asymptomatic, self limiting disease to frank microbial keratitis with the potential for visual loss or significant morbidity, which requires prompt and appropriate treatment. Debate in the literature has focused on whether symptomatic infiltrates are best considered as a continuum of suppurative keratitis,[27,37–39] which may be graded for severity according to preestablished clinical guidelines or scoring system or which may grouped according to possible etiology[5] to facilitate management. A classification scheme should be valid if it is based on basic scientific and clinical research and if it is applied prospectively by clinicians familiar with the system. Retrospective application of a scheme is problematic as complete data are not always available. Notwithstanding these discussions, as a minimum, a distinction between infective keratitis and sterile keratitis must be made to ensure treatment is received to manage a corneal infection.

Epidemiology of Sterile Infiltrates in Contact Lens Wear. Clinical criteria have been used to distinguish presumed microbial and sterile infiltrates,[107] and this is supported by epidemiological data.[27] As previously discussed, however, the disease definition and study design have major impact on reported disease frequency.

More frequent observation of inflammatory infiltrates in conjunction with hydrogel contact lens wear was first reported by Josephson in 1979.[1] As soft contact lenses became more popular, infiltrates were observed more frequently and interest in their incidence, risk factors, and pathogenesis grew (Robboy et al., 2003 for review).[108] Because sterile infiltrates may be asymptomatic,[1] they may not lead to patients consulting their practitioner. In a Casualty setting, where only acute symptomatic episodes would present, sterile infiltrates accounted for only 8.4% of contact lens wearers presenting to the Emergency Department.[109] Josephson reported that 4% of their soft contact lens wearers presented with sterile infiltrates over a 2-year period to their practice.[1]

The clinical picture of sterile infiltrates can vary tremendously for a small single peripheral asymptomatic focal infiltrate to a much more severe symptomatic inflammatory reaction, involving widespread focal and diffuse infiltrates. Depending on whether symptomatic or asymptomatic infiltrates are included, estimates of the frequency of infiltrates will vary. The incidence of symptomatic sterile infiltrates has ranged from 0.5 to 3.3% per year in hydrogel lens use, with higher rates associated with overnight lens use.[73,110–113] Clinical trials have quoted an incidence figure of sterile (symptomatic and asymptomatic) infiltrates in EW disposable hydrogel wearers of 10%[114] in Australia per year and as high as 44% in India.[115] In a series of hospital presenting acute corneal infiltrates, estimates of incidence was derived for nonsevere keratitis from contact lens fitting survey data extrapolated to the calculated hospital catchment population.[34] For daily and EW hydrogel use, estimates were 0.14 and 0.48 per 100 wearers per year, respectively.[34] It is likely however that this approach underestimates the total incidence because a proportion of such self-limiting conditions would be expected to be managed through eyecare practitioners, pharmacies, or general medical practitioners rather than a local casualty department. Clearly incidence rates are affected by disease definition, population under review, and environmental factors. Some studies are contralateral producing rates by "eye years," whereas in others, lenses are worn in both eyes. The schedule for evaluation of subjects in a study will also influence the rate of detection of asymptomatic events. The differences in study design and the infiltrate rates are summarized in Table 5.

Effect of Lens Type and Modality. Among contemporary lens types, in a prospective clinical trial of daily disposable hydrogel wearers carried out in India, symptomatic infiltrates were reported in 4 per 100 eyes per year and asymptomatic infiltrates in 20.5 per 100 eyes per year,[116] compared with symptomatic infiltrates in a UK hospital casualty population with an estimated incidence of 9.1 (95% confidence interval 5.5–15.1) per 10,000 wearers per year. High infiltrate rates in India may be associated with environmental conditions, also higher habitual levels of bacterial colonization of contact lenses have been reported in India compared with Australia.[119]

Two studies report 12 month-randomized clinical trials of a single silicone hydrogel lens worn on an EW basis. The rate of sterile infiltrates in silicone hydrogel wearers is 4.7 per 100 eyes in a study carried out in Sweden[117] and 5 per 100 wearers in a US based study.[120] In a nonrandomized open label observational study of 317 wearers, the cumulative incidence of corneal infiltrates in silicone hydrogel EW in a nonrandomized observational study was 5.7 per 100 in year 1 and rising to 10.3 per 100 at the end of the third year of wear.[121] The annualized rates of infiltrates (criteria not defined) in a 212-patient study involving the wear of a silicone hydrogel lens in one eye and an hydrogel lens in the contralateral eye were slightly lower at 1.1 per 100 and 0.5 per 100, respectively and differences between the two modalities were not significant.[118] A similar rate of nonsevere symptomatic infiltrates in EW silicone hydrogel use was reported in a hospital casualty population, although this study would have been unlikely to have captured mild cases of disease.[34] A recent large scale postmarket surveillance study involving continuous wear of a single silicone hydrogel lens type reported symptomatic infiltrates in 2.6 per 100 per year in 6245 participants.[39]

Cases involving unusually severe presentations of sterile infiltrates have been described,[122] although other investigators have suggested that inflammatory conditions associated with silicone hydrogel lens wear are typically less severe than previously encountered with hydrogel lens wear.[123]

Estimates of relative risks for the different lens types and modality of wear have been evaluated for sterile peripheral infiltrates in hospital studies.[27, 62, 66, 109, 127] Although an increased risk for the development of sterile infiltrates in daily and EW soft lens use has been demonstrated when compared with gas permeable lenses, the magnitude of increased risk and associated risk factors differ from those associated with microbial keratitis. Compared with hard gas

TABLE 5.
Summary of studies estimating the annualized incidence of sterile infiltrates in hydrogel contact lens wear, stratified by study design.

Study	Study design and disease definition	Lens types	Location	Years	Incidence per 100 (95% CI)
Randomized controlled trials					
US FDA Summary of Safety and Efficacy Data 2001[111]	12 month, controlled, contralateral, randomized, non-blinded (n = 820) >grade 2 and higher infiltrate	Balafilcon A (30N, mthly replacement) Etafilcon A (6N EW, 2 wkly replacement)	Multisite: 35 investigational sites (USA)	1999–2000	2.9 (1.7–4.1)[a] 1.3 (0.8–2.1)[a]
US FDA Summary of Safety and Efficacy Data 2005[113]	Prospective, randomized contralateral evaluation of two contact lens types (n = 1046), All serious and significant corneal inflammatory adverse events	Senofilcon A <30 N wear hydrogel 6N, wkly replacement	Multisite: 33 investigational sites (USA)	N/A	**5.8 (4.4–7.2)**[a] **2.3 (1.4–3.2)**[a]
US FDA Summary of Safety and Efficacy Data 2001[112]	Prospective, randomized, controlled, open label clinical trial.Infiltrates with overlying staining or infiltrates (>grade 2)	Lotrafilcon A 30 N hydrogel 6 N, wkly replacement	Multi-site: 20 investigational sites (USA)	N/A	3.3 (1.3–5.3) 5.5 (1.8–9.2)
Sankaridurg et al., 2003[116]	Prospective, randomized, controlled, open label clinical trial All serious and significant adverse events.	Daily disposable (DD) Spectacle lens wear (control)	India	1996–1997	5 (2–8)[a] 0 (no events in spectacle group)
Nilsson SEG 2001[117]	12-month evaluation of response to 30 night (n = 353) and 6 night (n = 151) extended wear silicone hydrogel lenses. All corneal infiltrates	Balafilcon A 7 day Balafilcon A 30 day	Multi-site, 23 practices in Sweden	2000	2.3 (0.7–3.9) 4.6 (1.3–7.9)
Brennan et al., 2002[118]	Prospective, randomized contralateral evaluation of two contact lens types (n = 212). All corneal infiltrates	Balafilcon A 30N EW Etafilcon A 6N EW	Global Multi-centre (Australia, Canada, UK, and Switzerland)	N/A	6.7 (3.2–10.2)[a] 3.6 (1.0–6.2)[a]
Solomon et al., 1996[41]	Prospective, randomized, 4 parallel groups, 3 year longitudinal study. All complications	DD (n = 68) Conventional (n = 126) FR (1–3 months) (n = 32) FR (2 wks) (n = 112)	Multisite (USA)	1991–1994	**2.0 (0.1–3.9)** **6.6 (4.1–9.1)** 6.5 (1.5–11.6) 5.2 (2.8–7.7)
Nonrandomized clinical trials					
Schein et al., 2005[39]	Prospective, open label, 12 month study of 30-night extended wear silicone hydrogel lenses (183 events in 5561 patient years experience) All corneal infiltrates	Lotrafilcon A <30 N wear	USA	2002–2003	3.3 (2.8–3.7)
Szczotka-Flynn et al., 2007[121]	Nonrandomized, prospective, open label, 3 year longitudinal study (27 events) (n = 317) First occurrence of any infiltrative event	Lotrafilcon A <30 N wear (n = 317)	USA	N/A	Year 1 5.7 (3.0–8.4) Year 2 8.5 (5.2–11.9) Year 3 10.3 (6.6–13.9)
Sankaridurg et al., 1999[115]	Nonrandomized, prospective, open label. First 13 months of longitudinal study (n = 330, 122 events) All infiltrative events	Disposable hydrogel 6 N wear	India	1993–1996	44.4 (38.5–50.3) Excluding asymptomatic infiltrates: 36.0 (30.3–41.7)
Other methods					
Morgan et al., 2005[34]	Prospective, 12 month, hospital population study and indirect estimation of denominator (76 cases) Hospital presenting infiltrative events with clinical severity ≤8 'nonsevere' keratitis	EW SH EW hydrogel DW SH DW hydrogel DD hydrogel	Manchester, United Kingdom	2003–2004	1.0 (0.6–1.6) 0.5 (0.1–1.7) 0.6 (0.1–3.1) 0.14 (0.1–0.2) 0.09 (0.06–0.2)
Poggio et al.,1993[73]	Retrospective records review from private optometric practices to compare prevalence of infiltrates conventional (n = 1055) to disposable (n = 905) hydrogel lenses	Disposable hydrogel EW Conventional hydrogel Conventional hydrogel EW	USA	1987–1989	Prevalence: 1.2 (0.4–0.9) 0.5 (0–1.0) 0.6 (0–1.5)
Cutter et al., 1996[110]	Cross-sectional, masked, multi-centre study evaluating prevalence of focal infiltrates with overlying staining amongst patients presenting for soft lens related visit	All soft lenses types	USA	1989	Prevalence: 1.6 (1.1–2.2)

Bold type indicates a significant difference in incidence between test and control.
FR = frequent replacement.
[a]Incidence is calculated per eye exposed to the lens/lens wear modality.

TABLE 6.
Unadjusted odds ratio by lens type for sterile keratitis from hospital studies, using daily wear soft lenses as a referent

Source	Lens type	Test lens		Referent (daily wear soft)		OR	Confidence intervals	Comment
		Cases	Controls	Cases	Controls			
Bates et al., 1989[109]	PMMA	4	110	50	448	**0.33**	0.12–0.92	Hospital-based contemporaneous controls
Stapleton et al., 1993[27]	PMMA	13	71	101	309	0.56	0.30–1.05	Hospital-based contemporaneous controls
Bates et al., 1989[109]	RGP	9	126	50	448	0.64	0.31–1.34	Hospital-based contemporaneous controls
Matthews et al., 1992[66]	RGP/PMMA	6	74	11	131	0.97	0.34–2.72	Hospital-based contemporaneous controls
Stapleton et al., 1993[27]	RGP	13	71	101	309	**0.33**	0.17–0.66	Hospital-based contemporaneous controls
Morgan et al., 2005[62]	Daily disposable soft	15	64	42	142	0.79	0.41–1.53	Hospital-based contemporaneous controls
Matthews et al., 1992[66]	Daily wear soft (frequent replacement)	3	11	11	131	3.25	0.79–13.40	Hospital-based contemporaneous controls
Morgan et al., 2005[62]	Daily wear silicone hydrogel	1	4	42	142	0.85	0.09–7.77	Hospital-based contemporaneous controls
Bates et al., 1989[109]	Extended wear soft	14	84	50	448	1.49	0.79–2.82	Hospital-based contemporaneous controls
Stapleton et al., 1993[27]	Extended wear soft	23	35	101	309	**2.01**	1.13–3.56	Hospital-based contemporaneous controls
Morgan et al., 2005[62]	Extended wear soft	2	9	42	142	0.75	0.16–3.61	Hospital-based contemporaneous controls
Matthews et al., 1992[66]	Extended wear soft (frequent replacement)	7	20	11	131	**4.17**	1.45–12.01	Hospital-based contemporaneous controls
Morgan et al., 2005[62]	Extended wear silicone hydrogel	15	31	42	142	1.64	0.81–3.31	Hospital-based contemporaneous controls

Bold type indicates a significantly different relative risk compared to the referent.

permeable lenses, daily use of soft lenses carries a 2.3× (95% confidence interval 1.3–4.3) increased risk and overnight use carries a 4.6× (95% confidence interval 2.2–9.9)[27] increased risk. The relative risk for sterile keratitis and nonsevere keratitis for EW hydrogel lenses has been consistently estimated as 2 to 3× higher than for daily use of hydrogel lenses.[27,34] Using hospital-based contemporaneous controls, the relative risk of nonsevere keratitis in EW silicone hydrogel lens use was 2.2× (95% confidence interval 0.4–11.4) higher than in EW soft lens use, although this was not statistically different.[62] Similarly, the relative risk in daily wear silicone hydrogel lens use was 0.85× (95% CI 0.09–7.8) that of daily wear hydrogel use.[62] While the increased risk of overnight lens use compared with daily lens use is well supported (Tables 5–7), the impact of silicone hydrogel lenses is less clear. The data in EW are suggestive of higher infiltrate rates in silicone hydrogel compared with hydrogel lenses, although some single stud-

TABLE 7.
Risk factors for sterile infiltrates in contact lens wearers

Daily wear hydrogel
Omitted disinfection[27]
Infrequent disinfection[27]
Use of nonaerosol saline[27]
Bacterial contamination of the storage case[109]
Extended wear hydrogel
Smoking[110]
Lower socioeconomic class[27]
Bacterial contamination of contact lenses[115,124]
Bacterial contamination of the storage case[109]
Daily disposable hydrogel
Bacterial contamination of the storage case[109]
Daily wear silicone hydrogel
Toxic corneal staining[125]
Bacterial contamination of the storage case[109]
Extended wear silicone hydrogel
History of prior lens related corneal inflammation[120,121]
Initial period of adaptation[120]
Limbal redness[121]
Corneal staining[121]
Younger age (≤25 years)[120,126]
Older (50< years) age[126]
Smoking[120]
High ametropia[126]
Shorter duration of continuous wear[126]
Bacterial contamination of the storage case[109]

ies do not reach significance in these estimates and there is potential for confounding because of the duration of continuous wear in silicone hydrogel lens use. A summary of relative risk by lens type using daily wear soft lens use as the referent is shown in Table 6.

Risk Factors for Disease. Recent randomized and nonrandomized prospective clinical trials have established risk factors for corneal infiltrates in silicone hydrogel wear (Table 7). Of note is that the risk of corneal infiltrates appears to be higher in the early period of silicone hydrogel continuous lens wear[127] and in those wearing lenses for a shorter continuous period (<21 days).[126] Both high limbal redness and corneal staining appear to be predictive of development of a subsequent corneal infiltrate in a multivariable analysis.[121] In a pooled analysis of silicone hydrogel daily wear clinical trials, limbal redness was not associated with the subsequent development of a corneal infiltrate, however, eyes which demonstrated toxic staining related to the lens type/care solution combination had a higher risk in univariate analysis (OR 3.1×, 95% CI 1.4–6.8) than eyes without staining and the rate of such infiltrates significantly increased with degree of staining observed.[125] These reports suggest that in addition to consideration of well-established risk factors, careful observation of wearers during the initial period of wear is extremely important in managing such complications. A summary of risk factors associated with sterile infiltrates is shown in Table 7.

As discussed, sterile infiltrates are a broad category that encompasses all corneal infiltrates not presumed to be associated with replicating organisms in the tissue. Such inflammatory events can be analyzed as a group as described above or separated into different categories. Although the difficulty in differentiating between clinical entities has been described,[128] specific conditions with clearly different causes and manifestations within the spectrum of sterile corneal infiltrates have been recognized and described. The epidemiology of two of these groups, contact lens induced acute red eye (CLARE)[129] and contact lens peripheral ulcer (CLPU)[5] are described below.

Contact Lens Acute Red Eye. CLARE is an inflammatory reaction characterized by severe conjunctival and limbal hyperemia, corneal infiltration, and pain. By definition, it occurs during EW only and usually has an early morning acute onset.[5] In a study of continuously worn hydrogel lenses, 34% of patients developed contact lens acute red eye over a 12-month period.[130] In studies of disposable EW use, an incidence of CLARE of 12% has been reported in India[115] and 1.4% in Australia.[131] When subjects were fitted with silicone hydrogel lenses, 0.8% of eyes were reported to develop a CLARE reaction in a study of 504 patients followed for a year in Sweden.[117] Risk factors include high water contact lenses,[129] tight fitting contact lenses,[129] and a recent episode of upper respiratory tract infection.[132] More recently, an association between microbial contamination of contact lenses worn overnight, particularly Gram-negative bacterial contamination, and CLARE has been reported.[124] When exposed to inadvertently contaminated contact lenses, one-third of patients developed an acute inflammatory reaction during a single overnight wear period.[133] In addition, *Haemophilus influenzae* have been cultured from the conjunctivae and contact lenses of wearers diagnosed with CLARE.[131] Other Gram-negative bacteria such as *Haemophilus parainfluenzae* and certain Gram-positive bacteria such as *Streptococcus pneumoniae* have also been implicated.[134] Animal models synonymous with human CLARE, showing an inflammatory response in the absence of microbial infection have been established in the presence of colonization of the contact lens by high numbers of Gram-negative bacteria.[135,136]

Contact Lens Peripheral Ulcer. A CLPU is an acute inflammatory response characterized by small circular full-thickness epithelial lesions in the peripheral cornea, associated with stromal infiltration.[137] Differentiation from infectious ulcers is based on a clinical criteria.[5,27,107] Histopathological studies of biopsies taken from these lesions have shown no invasion of the stromal tissue by microorganisms.[138] Like CLARE, CLPU is primarily associated with overnight wear and the incidence in disposable EW varies from 1.6 to 2.9% in Australia[130] to 13%[115] per year in India. The annualized rate in wearers of silicone hydrogel lenses appears similar to Australian rates at 1.1% of eyes in Sweden,[117] 0.3% of subjects in a large multinational study,[139] 1.2% of subjects in Spain,[140] and 1% of wearers in the United States.[120] An association between microbial contamination of contact lenses and CLPU has been demonstrated,[136] although, more specifically, colonization of the contact lenses and/or the lids and conjunctiva by low numbers of the Gram-positive bacterium *Staphylococcus aureus*[53,141] and the Gram-negative bacteria *Pseudomonas* spp.[132] Epithelial trauma was shown to be a significant factor for the production of CLPU in contact lens wearing rabbits[141] and although unproven, may prove to be a significant factor in humans.

CONCLUSIONS

Contact lenses clearly have optical, occupational, sporting, and cosmetic advantages for millions of wearers; however, certain risks have been associated with their use. Given the large population currently wearing contact lenses worldwide, even rare reactions can affect large numbers of wearers. This becomes an issue for the delivery of primary eye care and for practitioners involved in the fitting of lenses and in the management of lens related disease. Differences in risk for different types of contact lenses and wearing patterns have been demonstrated for both rare and common lens related complications. This article has reviewed the epidemiology of both microbial keratitis and sterile keratitis for contemporary contact lens types.

Understanding the epidemiology of lens related disease, particularly with the introduction of new lens types and modalities, is crucial for practitioners to enable an informed choice of lens modality, wear schedule and hygiene regimes to be made. Emerging risk data have indicated that careful observation is important during the early period of lens wear and that early adopters of new technologies may show different patterns of risk. Epidemiological data also provides information on the etiology of lens related complications, which is required to enable safer lens wear modalities to be developed.

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Fiona Stapleton
School of Optometry and Vision Science
University of New South Wales
Level 3, Rupert Myers Building
North Wing, Gate 14, Barker St.
Sydney, NSW 2052, Australia
e-mail: f.stapleton@unsw.edu.au