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Risk factors for contact lens associated microbial keratitis☆

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Abstract

Although the risk of developing contact lens associated microbial keratitis is small, the potential consequences of this condition, such as vision loss, are serious. This paper presents an analysis of the risk factors that have been identified for contact lens induced microbial keratitis, which include extended wear, hypoxia, non-compliance, blepharitis, diabetes mellitus, epithelial trauma, steroid use, therapeutic lens use, tobacco use, and possibly travel to warm climates. By remaining mindful of these risk factors, practitioners can take action and offer advice to patients so as to optimize the safety of contact lens wear.

Keywords: Contact lens; Microbial keratitis; Risk; Safety

1. Introduction

The number of patients who suffer severe or permanent compromise of the cornea—restricted to central corneal vascularization or microbial infection and their sequelae—is really quite small [1–7]. The most severe complication of contact lens wear—and a leading cause of vision loss [8] through secondary vascularization, scarring, and thinning of the cornea—is direct microbial keratitis (Fig. 1). Potential infectious microbes include fungi, viruses, and protozoa; however, most corneal infections are associated with bacteria. Fortunately, microbial infection is probably the least commonly encountered complication of contact lens wear.

2. Ocular defence mechanisms

The blinking action of the lid and the flow of tears over the anterior segment of the eye mechanically remove microorganisms. Tears are relatively cool and nutrient poor, and contain various antibacterial substances, such as lysozyme, betalysin, lactoferin, and mucus (which envelopes microorganisms). Tears also contain secretory IgA, as well as the alternative pathway of complement factors, which can trap and coat microorganisms, suppress adhesion, and alter binding of microbes to ocular surface antigens—all of which can enhance lysis and phagocytosis.

The corneal epithelium poses a formidable mechanical barrier to most microbes. Only *Corynebacterium diphtheriae*, *Listeria* sp., *Neisseria gonorrhoeae*, and *Hemophilus aegyptius* (Koch-Weeks bacillus) are believed able to invade the intact corneal epithelium [9,10].

It is felt that the normal ocular microbial flora of the conjunctiva and ocular adnexa exist in a stable balance between proliferation and control by the various indigenous antibacterial factors discussed above. *Staphylococci* and diptheroids predominated in ocular cultures from 10,271 individuals aged 1–90 years [11]. The normal bacteria are thought to protect the tissues from colonization by organisms of greater virulence and pathogenic potential.

3. Risk factors

The ocular defence mechanisms described above are constantly being challenged by a variety of specific risk factors that are believed to encourage the infectious process during contact lens use.

3.1. Extended wear

'Extended wear' implies that contact lens wear is 'extended' through one or multiple sleep cycles before cleaning and 'disinfection'. This concept should be distinguished from 'continuous' wear, which implies that contact lenses are never removed for routine cleaning. Non-compliant patients (as opposed to clinicians) probably introduced cosmetic extended wear. Anecdotal reports of rare patients 'safely' napping or sleeping with PMMA con-

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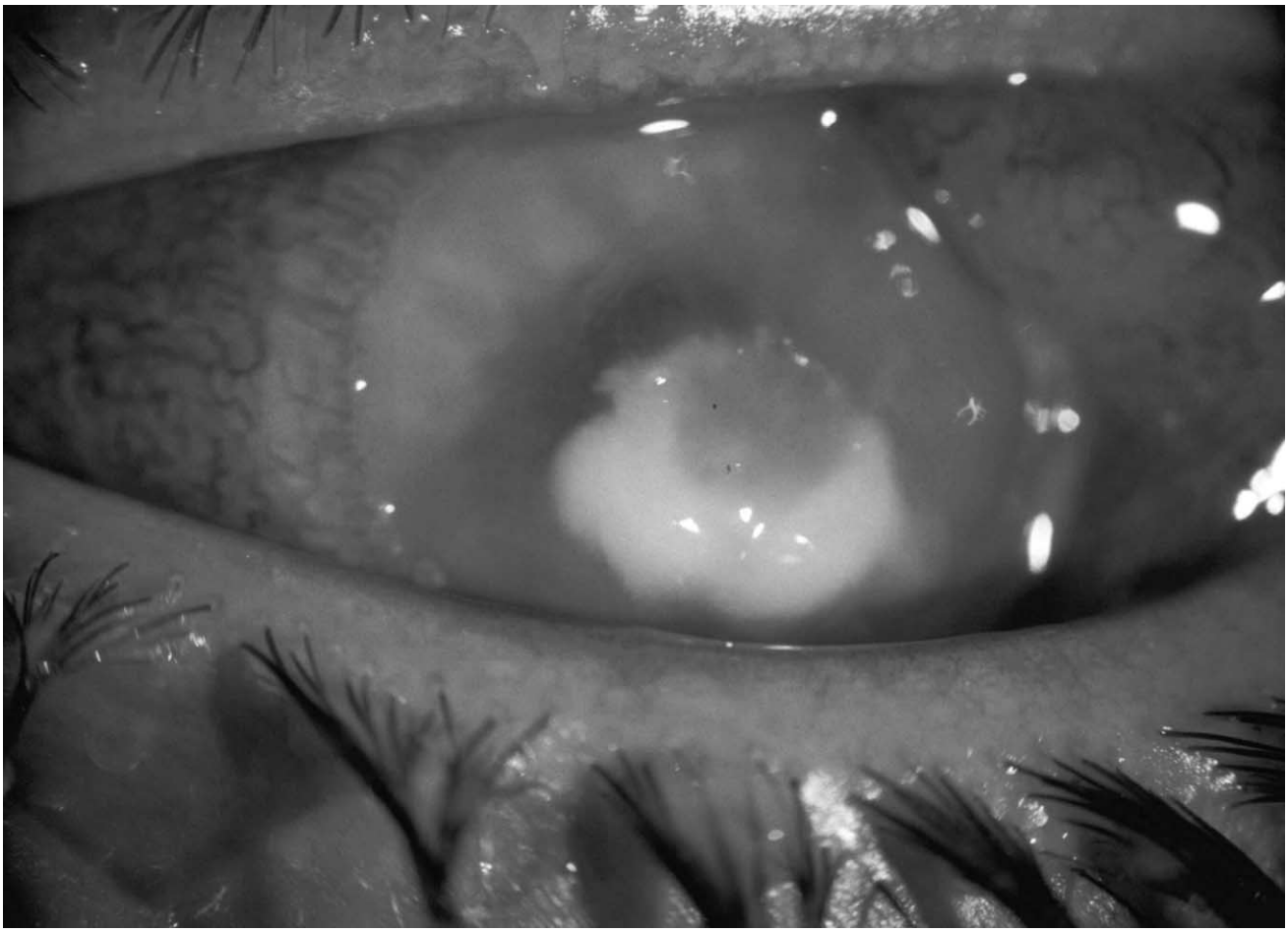

Fig. 1. This advanced corneal ulcer displays the 'soupy' appearance typical of Gram-negative bacterial keratitis; the lesion was culture positive for *Pseudomonas aeruginosa*.

tact lenses still on the eye, perhaps 'parked' on the sclera, were common 30 and 40 years ago.

Soon after hydrogel contact lenses were introduced, these devices were prescribed as continuous wear bandages to treat diseases of the ocular surface. Complications were common but disasters few. Dohlman et al. [12] found that 11 of 278 bandage hydrogel contact lens patients developed corneal infiltrates. Four patients suffered definite microbial infections, resulting in permanent damage to the eyes. These authors concluded, however, that the advantages of therapeutic continuous contact lens wear in the treatment of eye disease far outweighed the risks.

The 'Permalens' was developed in about 1970 by DeCarle, working in the UK. This was perhaps the first hydrogel contact lens design intended for extended wear, and was originally fitted using a very small diameter and steep back central curvature, compared to other hydrogel contact lenses of the day. In June 1979, the United States Food and Drug Administration (FDA) approved the use of two extended wear hydrogel contact lens designs—Permalens and Hydrocurve—initially to be prescribed only for aphakia [13].

Early clinical reports of the USA experience suggested that extended wear was successful and safe [14–16]; complications occurred, but the risks appeared similar to those encountered with daily wear. The benefit of patient convenience led to much satisfaction among both phakic and aphakic patients, perhaps justifying the anticipated limited risk.

Another clinical trial in the UK also concluded that continual wear (only for 20 weeks) of Sauflon 85 hydrogel contact lenses was innocuous (for only 20 subjects). Although several indices of corneal integrity were monitored, only a decrease in corneal sensitivity and perhaps central stromal thickness, and an increase in contact lens soilage, were noted [17,18].

The report of Cooper and Constable [19] from Perth, Australia was perhaps the first warning of a problem. Zantos and Holden [20], also in Australia, originally intended to enroll 100 patients to wear a variety of contact lenses for continuous wear for up to 2 years. They observed multiple complications, however, including corneal oedema, neovascularization, microcysts, 12 instances of acute red eye reactions, and several infections. Three patients developed small marginal ulcers and one presented with multiple small central

epithelial lesions which later coalesced into a large central ulcer. Every patient who attempted continuous wear experienced some difficulty resulting in an interruption of wear, and the study was terminated after the first 35 patients.

As extended wear proliferated throughout North America in the early 1980s, the original glowing reports faded and the reality predicted by the Australian observations became clear. Several reports in the early 1980s provided evidence that extended wear was associated with a higher rate of corneal infection in both aphakic and phakic patients. Mondino et al. [21] for example, studied 40 patients who presented with corneal infections associated with contact lens wear. Eleven of these patients wore lenses solely for daily wear, and all were found to be noncompliant with appropriate care (e.g. eight patients reported occasionally sleeping with their lenses on their eyes!). Twenty-nine patients used FDA extended wear approved hydrogel contact lenses for extended wear (for three days to 30 months). Twelve were found to be compliant with the then current care guidelines, and of the noncompliant 17, the most common defect in compliance was microbial contamination of care systems. This study highlights the conclusion that must be reached from the literature reviewed above: specific risk factors for corneal infection during contact lens wear include (a) extended wear, and (b) noncompliance with contact lens care procedures and hygiene. As perhaps 70 million people worldwide now wear contact lenses, often, for extended wear, it is not surprising that many believe that contact lens-related microbial keratitis has the potential of becoming an important public health concern.

3.2. Hypoxia

Oxygen tension (expressed in units of Torr or mmHg) is found by multiplying the percentage of oxygen in the air by the barometric pressure (the presence of water vapor introduces only slight errors into this calculation). As oxygen accounts for about 21% of the atmosphere and sea level pressure is given as 760 mmHg, normal sea-level oxygen tension is about 155 mmHg. Polse and Mandell [22] proposed that there was an anterior corneal 'critical oxygen tension' (COT), below which corneal metabolism would be compromised. By use of a goggle through which gases of specified oxygen concentrations were passed, and observation of subsequent corneal swelling, these authors suggested that the COT was 11–19 mmHg. The COT criterion of Polse and Mandell [22] represents about 2% of the oxygen tension at sea level. Later human goggle studies, with better controls and additional subjects, showed that the COT to prevent corneal oedema should be more like 40–70 mmHg (5–10% O_2) [23,24].

Holden and Mertz [24] used contact lenses of known oxygen transmissibilities (Dk/t) (on a limited number of subjects) to determine the 'critical Dk/t.' They suggested that human corneal swelling could be precluded by use of contact lenses with Dk/t values of 24×10^{-9} (cm/s) $\times$ (ml O_2/ml mmHg) for daily wear conditions or 87×10^{-9} (cm/s) $\times$ (ml O_2/ml mmHg) for extended wear. Either of these situations presumably permits an oxygen tension of 40–70 mmHg or more under contact lenses. Few hydrogel contact lenses available through the 1980s even met their daily wear criteria and only recently [25] have contact lenses been developed which come close to the Holden–Mertz extended wear critical Dk/t value. It is also valuable to note that both human corneal oxygen utilization [26] and oxygenation of the palpebral conjunctiva [27,28] vary substantially from individual to individual, limiting the usefulness of such criteria for specific patients.

It has been proposed that hypoxia at the corneal surface results in metabolic compromise of the epithelium, which renders the epithelium less resistant to microbial infection [29]. Although hypoxia causes numerous metabolic problems for the cornea—resulting in multiple changes in the epithelium, stroma, and endothelium—the link between these problems and microbial keratitis has yet to be established. However, it is also clear, that all extended wear hydrogel contact lenses, used on a wearing schedule ranging from four to 28 nights in a row, cause ocular complications. No severe infections were encountered in one study, but superficial punctate epithelial staining, epithelial microcysts, red eye reactions and other changes occurred at similar rates across several wearing schedules [30].

3.3. Non-compliance

Another identified risk factor is that of noncompliance with contact lens care techniques [31]. Mondino et al. [21] provided a definition of compliance with contact lens wear. A compliant patient washes hands before any contact lens manipulations, appropriately uses an FDA-approved care system in a manner in agreement with both the published guidelines of the manufacturer and good hygiene, adheres to the recommended wear schedule (for either daily or extended wear), and is found to have no microbial contamination of solutions and cases.

Wilson et al. [32] established the link between poor contact lens care and hygiene and corneal infection by demonstrating the same serotype of *Pseudomonas* in corneal ulcers and the care systems of their patients. Garwood [33] presented data suggesting that corneal infection incidence increases more than 10-fold when cleaning and disinfection techniques are not employed with daily wear use of hydrogel contact lenses.

Both Collins and Carney [34] and Chun and Weissman [35] studied compliance and found that 40 to 70% of contact lens users were noncompliant by history. Claydon et al. [36] failed in their attempt to enhance compliance by subjecting patients to a more thorough initial instruction protocol concerning contact lens wear and care procedures, which emphasizes the importance of developing other strategies to enhance patient compliance.

Several authors have studied microbial contamination of contact lens solutions and cases. Pitts and Krachmer [37] cultured the cases and conjunctivae of 29 patients and found that 10 (34%) had contaminated cases despite use of heat disinfection. Donzis et al. [38] cultured all elements of the care systems of 100 asymptomatic contact lens users, including 38 rigid contact lens users and 62 hydrogel contact lens users (50 daily wear and 12 extended wear). More than 50% of these patients had microbial contamination in some element of their care system; the microbes found by culture included potential pathogenic bacteria such as Gram-negative *Pseudomonas* and *Serratia*, Gram-positive *Staphylococcus* and *Bacillus*, as well as two cultures positive for the protozoan *Acanthamoeba*.

Campbell and Caroline [39] suggested that even patients who use care regimens compliantly may not be able to avoid microbial contamination of their care systems. They suggest that care systems that are effective during manufacturer studies may later become ineffective in the home environment because the bacteria encountered are more resistant through development of bacterial biofilm. Thirty-nine of 45 patients studied used their disinfection techniques correctly, yet 29% of their patients using heat disinfection, 50% using peroxide disinfection, and 75% of those using chemical disinfection, provided cases from which bacteria were recovered.

Microbes adhere to contact lens surfaces, most likely by formation of biofilms. The contact lens may then act as a vector, transferring pathogenic agents from the contaminated case and/or solutions directly to the ocular surface. As *Pseudomonas* appears to be responsible for 50–70% of culture-positive corneal infections in contact lens wearers (see below), the ability of several subtypes of this particular microorganism to attach to corneas as well as to all form of contact lenses (new and worn, rigid and hydrogel, high and low water content, ionic and nonionic) has been studied. However, the exact role of bacterial adherence in the pathogenesis of corneal infection has yet to be clearly described [40]. It seems unlikely that bacteria trapped in a biofilm on a contact lens surface could infect an eye, but their progeny might do so.

The source of these microbes is still unclear. Schein et al. [41] specifically point out that the relative paucity of corneal infections involving enteric bacteria (such as *E. coli*, Proteus, and Klebsiella) argues against faecal contamination. Bacteria cultured from 'healthy' (non-contact lens-wearing) eyes are those commonly found also on the skin and in the upper respiratory tract (i.e. *Staphylococci* and diptheroids), and these have indeed been associated with some contact lens associated corneal infections. Wet areas in the bathroom and kitchen, moreover, such as taps and sinks, are often contaminated with Gram-negative bacteria (specifically *Pseudomonas*). Wilcox et al. [42] presented data which suggests that Gram-negative bacteria indeed are derived from the domestic water supply while other bacteria most likely have the lid margins as their source. *Acanthamoebae* are ubiquitous.

3.4. Blepharitis

Patients presenting for initial or continued contact lens care who show signs of blepharitis or dacryocystis are believed to be at greater risk of infection because there is a known source of pathogenic microbes in close proximity to the ocular surface.

Signs of acute blepharitis include inflammation of the lid margins, flaky debris on the eyelashes, and yellow or frothy exudates. Chronic blepharitis is often associated with meibomian gland dysfunction and blockage, telangiectatic and dilated blood vessels, and perhaps small irregularities (notches), in the lid margin. The bulbar conjunctiva may be either white or inflamed, and the cornea may be clear or may exhibit superficial staining, especially inferiorly. Some patients suffer from recurrent styes and chalazia, or hordeoli.

The tear film is often compromised in blepharitis. Debris is noted in the tear fluid and tear film breakup time is abnormally short. This is partially due to interference with the normal production of sebum from the meibomian glands and the rain of bacterial toxins and metabolic waste products falling into the palpebral aperture. Mechanical irregularities in the apposition of the diseased lid margins to the globe may further compromise the tears.

Patients commonly present to ophthalmic practices with small, marginal limbal 'sterile ulcers' or phlyctenules. Although corneal phlyctenules and peripheral infiltrates may initially be sterile, it is presumed that any epithelial defect increases the risk of a secondary direct infection, especially when bandaged by a contact lens and considering the proximity of available microbes.

Staphylococcus sp. are known to be important agents in blepharitis, but many other microbes may be involved, including other bacteria and even arthropods such as lice or Demodex folliculorum.

Patients who suffer from acne rosacea are particularly at risk for blepharitis (usually associated with *S. aureus*), corneal neovascularization, and corneal ulceration/infection even when no contact lenses are worn.

3.5. Diabetes mellitus

Diabetes mellitus has been suggested as a risk factor for corneal infection, specifically when contact lenses are used for extended wear [3]. Eichenbaum et al. [43] studied 100 aphakic patients who wore hydrogel contact lenses on an extended wear basis, and all three patients who were diabetic developed infections. A fourth patient, who concomitantly had cancer of the colon, also developed a corneal infection. None of 135 control patients wearing spectacles (eight diabetics) developed corneal infections. Spoor et al. [44] found that their data supported this conclusion.

Diabetic patients have systemic metabolic abnormalities that theoretically place them at greater risk for microbial

infections. O'Leary and Millodot [45] determined that both contact lens wear and diabetes specifically result in abnormal fragility of the corneal epithelial layer. However, O'Donnell et al. [46] were unable to find any evidence of significant ocular compromise in a prospective, randomized, masked, controlled experiment which followed the progress of 40 diabetic contact lens wearers versus 40 non-diabetic contact lens wearers for 12 months.

Other forms of immunosuppression may also increase the risk of acquiring corneal infection during contact lens wear or potentiate the severity of the disease should it occur.

3.6. Epithelial trauma

Epithelial trauma while wearing, removing, or inserting a contact lens possibly plays a role in subsequent corneal infection. As noted above, the intact corneal epithelium presents a substantial barrier to infection. Before a microbe can establish an infection, it must adhere to its target. Experimental bacterial inoculation of linear abrasions has been effective in first increasing adherence of *P. aeruginosa* to the corneal tissues and then producing corneal ulceration [47–49]. Stern et al. [50] showed that *Pseudomonas* adheres better to injured or exposed basal epithelial cells than to an intact epithelial surface or even to exposed bare corneal stroma.

Adams et al. [51] found that five of six patients presenting with corneal infections associated with extended wear of hydrogel contact lenses reported recent manipulations of their contact lenses. These authors speculated that this might have led to epithelial defects that predisposed these patients to the infectious process. Mondino et al. [21] however, could not support this particular hypothesis with data from their patient group.

Minor epithelial erosions are commonly seen in all contact lens practice [52]. What is not clear, however, is why such lesions appear to be relatively innocuous when contact lenses are used on a daily wear basis, and if, or how, the role of such lesions changes during extended wear. Some believe that treatment of minor epithelial staining with prophylactic topical antibiotics represents cautious practice, whereas others feel that this practice risks encouraging resistance among local bacteria and hence eventual 'superinfection', and that the toxicity of some antibiotics may actually prolong the healing process.

Direct damage may not be necessary to initiate the infectious process in the cornea during contact lens wear. An electron microscopy study of primate corneal epithelia after use of excessively thick hydrogels for daily or extended wear showed epithelial thinning (loss of superficial cells and flattening of the remaining ones), oedema, and degenerative cytoplasmic changes [53]. Imayasu et al. [29] reported that contact lens-induced hypoxia increases the binding of *Pseudomonas* to corneal epithelial cells.

3.7. Steroid use

Topical corticosteroid use is generally recognized as an exacerbating factor with corneal microbial infection [12,54], particularly herpes, *Pseudomonas* sp., and fungi. Steroids suppress immunologic defence mechanisms and inflammatory reactions (as well as increasing the risks of glaucoma and cataract formation), and by doing so may also mask the severity of an infection. Chalupa et al. [55] identified inappropriate steroid therapy as a major factor contributing to the severity of corneal infection after contact lens wear.

3.8. Therapeutic/bandage contact lens use

Therapeutic contact lenses are occasionally employed to protect the corneal surface, facilitate healing, and relieve pain in patients suffering from filamentary keratitis, bullous keratopathy, persistent non-healing epithelial defects (including those found following refractive surgery procedures), exposed sutures (e.g. after keratoplasty), neurotrophic or exposure keratitis, keratitis sicca and ocular pemphigoid. All of these situations involve disruption of the epithelial surface barrier. Many patients suffering from these conditions are elderly, some are diabetics, and often they are using topical corticosteroids. The combination of known risk factors is believed to place these patients at particular risk, and it is not surprising that infection is a major concern in this group [12,56].

As an example of the above concerns, six corneal ulcers (both bacterial and fungal by culture) developed in 38 eyes treated with therapeutic hydrogel contact lenses for severe epithelial diseases including Stevens–Johnson and Sjögren syndromes, ocular pemphigoid, neurotrophic keratitis, herpes simplex keratitis, and ocular burns [57]. Several factors were felt to contribute to these infections, including concurrent dry eye, use of antibiotics and steroids, and microbial contamination of a bottle of sodium chloride drops in one case.

3.9. Tobacco use

In studies of corneal infection associated with contact lens wear by the Contact Lens Institute [3,4], a number of potential risk factors were investigated, including age, sex, and race of patients, the age of the contact lens and type of fit (initial or replacement), length of time since last professional evaluation, and identification of providing professional. The only factor that appeared to have some statistical relation to corneal infection was smoking, which was statistically significant for extended wear use of contact lenses and almost significant for daily wear as well. Data from Cutter et al. [58] supported this observation with regard to the occurrence of non-infectious corneal infiltrates in association with hydrogel contact lens wear. The mechanism by which tobacco

use renders the cornea of contact lens wearers to be more susceptible to infection remains unclear.

3.10. Other potential risk factors

Some clinical reports have suggested additional risk factors for the development of microbial keratitis among contact lens wearers, such as travel to regions of warm weather [19,20,59], but these have not been scientifically verified.

4. Conclusions

Corneal infection is a rare but potentially serious complication of contact lens wear. Certainly, contact lens wear—especially extended wear—has become an important known risk factor in corneal infection. Accumulated evidence over three decades has enabled the identification of key risk factors in the development of lens-induced infection. Although the precise magnitude of all the risk factors can not be quantified precisely, practitioners can use the 'risk profile' presented here to formulate contraindications for lens wear and to offer appropriate guidance. Patients can then evaluate this evidence and make an informed choice concerning the safety or otherwise of various modalities of contact lens wear versus other possible vision correction options that they may be contemplating.

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