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# How Could Contact Lens Wearers Be at Risk of *Acanthamoeba* Infection? A Review

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#### **ABSTRACT**

Contact lens wear is highly influential on the incidence of ulcerative keratitis worldwide, particularly in developed countries. The association between Acanthamoeba keratitis and contact lens wear is firmly established; it may account for up to 95% of the reported cases. Before the popularisation of soft contact lens wear, Acanthamoeba keratitis was extremely rare. In 2000 it was estimated that the number of contact lens wearers worldwide was about 80 million, out of whom 33 million were in the United States and 90% of them wore hydrogel soft lenses. Contact lens-related problems depend on many factors, such as lens material, wearing modality, lens hygiene, type of lens-caring solution, the degree of compliance of the lens user with lens wear and care procedures, lens overwear, sleeping in lenses, rate of changing lenses, and lens case hygiene. This paper is a thorough review of the literature aiming to highlight the role of one of the main risk factors of infectious keratitis, contact lens wear, and also to show the responsibility of lens users in aggravating this risk.

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KEY WORDS: Acanthamoeba; keratitis; contact lenses; contact lens wearer; lens overwear.

### **RESUMEN**

La utilización de lentes de contacto es un factor que influye sumamente en la incidencia de la queratitis ulcerosa, en particular en los países desarrollados. La asociación entre queratitis por Acanthamoeba y el uso de lentes de contacto está firmemente establecida; podría representar aproximadamente hasta un 95% de los casos registrados. Antes de la popularización del uso de lentes de contacto, la queratitis por Acanthamoeba era muy poco frecuente. En el año 2000 se estimó que, a nivel mundial, había unos 80 millones de usuarios de lentes de contacto, de los cuales 33 millones residían en los Estados Unidos y, de ellos, el 90% utilizaban lentes de contacto blandas de hidrogel. Los problemas derivados del uso de lentes de contacto dependen de otros muchos factores, como el material del que está hecha la lente, la modalidad de uso, las medidas de higiene empleadas, el tipo de solución utilizada para la limpieza y el mantenimiento de la lente, el grado de cumplimiento terapéutico del usuario de las lentes respecto a su utilización y a su limpieza/mantenimiento, el uso de las lentes durante periodos excesivamente prolongados, el dormir con las lentes de contacto puestas, la frecuencia con la que el usuario se cambia de lentes y la limpieza de la funda de las lentes de contacto. Este artículo presenta una revisión minuciosa de la literatura, con el objetivo de resaltar el papel de uno de los principales factores de riesgo de desarrollo de queratitis infeccionsa, como es el uso de lentes de contacto,

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y con el fin de poner de relieve que el propio usuario de las lentes es, en ocasiones, el responsable de agravar este riesgo.

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PALABRAS CLAVE: Acanthamoeba; queratitis; lentes de contacto; usuario de lentes de contacto; uso excesivo de las lentes de contacto.

### Introduction

Acanthamoeba is a ubiquitous pathogen that can be found worldwide with different incidence rates, showing the ability to survive in very harsh environmental circumstances.1 Acanthamoeba keratitis is a potentially blinding corneal infection<sup>2</sup> that may aggressively affect both eyes<sup>3,4</sup> with the possibility to recur after penetrating keratoplasty.4 Contact lens wear remains the main risk factor in transmitting Acanthamoeba trophozoites and cysts to the cornea.5,6 A 7-year 1997-2003 survey<sup>7</sup> showed an increase in the number of hospitalised patients due to contact lens-related corneal ulcers, which correlated with the increase in the number of lens wearers. Acanthamoeba has a great affinity for the attachment to the corneal epithelium<sup>8</sup> and to contact lenses.<sup>9</sup> The tendency for Acanthamoeba to adhere to surfaces is a key first step in the pathogenesis of Acanthamoeba keratitis, particularly in contact lens wearers. Contact lenses affect corneal epithelium integrity in two different ways: directly, through the associated fitting-related abrasions<sup>10</sup> and indirectly, by altering the normal physiological and metabolic cellular activities.<sup>11</sup> These later changes render the epithelial cells in a hypoxic status that eventually alters their integrity. Corneal oxygenation is significantly reduced during contact lens overwear, particularly for those who sleep in their lenses overnight.<sup>12</sup> However, patient's compliance and some basic hygienic standards can effectively minimise the risk of Acanthamoeba keratitis. 13

## CONTACT LENS-RELATED PROBLEMS Contact Lens-Induced Trauma

*Direct Traumatic Effect of Lenses.* The corneal epithelium, with its tight junctions, creates an important barrier against *Acanthamoeba* invasion to the underlying corneal structures. Corneal epithelial cells are more resistant to the cytopathic effect of *Acanthamoeba* trophozoites than keratocytes. <sup>14</sup> Contact lens wear cause minor corneal abrasions, which is the key initial step for *Acanthamoeba* infection. Martinez et al. <sup>10</sup> suggested that corneal trauma was the crucial factor for *Acanthamoeba* infection, rather than immunosuppression. The adherence of the *Acanthamoeba* protozoon to an intact corneal epithelium without trauma did not lead, in animal models,

to the development of keratitis. Corneal abrasion was absolutely essential for the induction of Acanthamoeba keratitis in hamsters infected with contaminated contact lenses.<sup>15</sup>

Corneal epithelial defects make it possible for the Acanthamoeba protozoon to attach to the epithelium and to subsequently invade the rest of the underlying stromal layers. Corneal injury exposes protein sites known as mannose glycoproteins on the surface of injured corneas. The adhesion of the Acanthamoeba to the corneal epithelial cells is the result of mutual interaction between corresponding mannose-binding glycoproteins on the adjacent surface membranes.<sup>8,16,17</sup> Sugar inhibition assays16,18 revealed how Acanthamoeba can selectively bind with high affinity to mannose saccharides and not to non-mannosylated neoglycoproteins, such as galactose, fucose, galactosamine or lactose. The corneal surface mannose receptors stimulate Acanthamoeba to secrete pathogenic proteases16 which, in turn, induce epithelium apoptosis19 and facilitate amoeba invasion to the underlying stroma. Alizadeh et al.<sup>20</sup> showed that contact lens wear exacerbated Acanthamoeba keratitis through the secretion of mannose-induced protease 133. In addition, the attachment of Acanthamoeba to corneal epithelial cells helps the phagocytosis and digestion of bacteria<sup>21</sup> that provide an important nutrition source for Acanthamoeba. However, Sharma et al.22 found no difference between the adherence ability of Acanthamoeba to corneal epithelial cells of normal non-lens wearers and that of asymptomatic contact lens wearers.

Indirect Traumatic Effect of Lenses. Contact lens wear is usually associated with corneal epithelial hypoxia and hypercapnia, particularly when sleeping in lenses or when using lenses having low oxygen transmissibility.11 Carbon dioxide accumulation alters the normal metabolic pathways, which leads to a series of micro-structural changes affecting all corneal layers, such as epithelial microcysts, depletion of epithelial glycogen storage, lactic acid accumulation, corneal acidosis, epithelial oedema,11 decreased mitotic rate, increased central corneal thinning,<sup>23</sup> corneal hypoesthesia,<sup>24</sup> compromised junctional integrity, increased epithelial cells permeability,<sup>25</sup> increased cellular epithelial fragility, epithelial punctation, microscopic abrasion, sloughing of the epithelium and, eventually, corneal ulceration. In addition, changes in tear film thickness and stability<sup>26</sup> and alteration of the normal profile of conjunctival commensals<sup>27</sup> have been recognised. All these changes collectively breach the natural extra ocular protective mechanisms, rendering the cornea an easy target to a wide array of pathogens, including the Acanthamoeba.

### Attachment of Acanthamoeba to Contact Lenses

Contact lenses serve as a vehicle for the harbouring, transmission and delivery of microorganisms to the eye. Acanthamoeba has a high affinity for contact lens surfaces, a property that plays an important role in the pathogenesis of Acanthamoeba keratitis and creates an actual threat to contact lens wearers.<sup>28</sup> The adherence of Acanthamoeba trophozoites and cysts to contact lenses can be detected and quantified using different methods and techniques. 9,29-31 The ability of Acanthamoeba to attach to contact lenses is influenced by several factors:

Contact Lens Material, Ionicity, and Water Content. The manufacturing material affects contact lens ability as a mechanical host allowing attachment and transfer of Acanthamoeba trophozoites or cysts onto the corneal surface. The incidence of Acanthamoeba is much lower with rigid lenses, as compared with the soft type. The lower incidence of Acanthamoeba keratitis found in the Netherlands<sup>32</sup> was attributed to the greater proportion of Dutch contact lens wearers that used rigid gas-permeable lenses. Rigid gas-permeable lenses were recommended to hospital staff members wearing lenses, with the aim of minimising the risk of infectious keratitis, due to the easy removal of the attached Acanthamoeba trophozoites and cysts from the surface of this type of contact lenses.<sup>33</sup> Kilvington et al.34 showed that cyst attachment occurred only for soft lenses, but not for gas-permeable ones. However, a significant adherence of trophozoites was detected in the case of rigid gas-permeable lenses, as compared with soft contact ones35, with greater affinity for the silicone acrylate material of rigid lenses than for the fluoropolymer material of those same lenses.36

The greater affinity of Acanthamoeba trophozoites for silicone hydrogel lenses, as compared with conventional hydrogel lenses (P<0.001) was attributed to the attachment characteristics of the polymer of silicon type.<sup>37,38</sup> The attachment of Acanthamoeba trophozoites to different soft contact lens materials, such as polymacon, etafilcon A, lidofilcon A, and bufilcon A varied significantly, with the greatest adherence being observed for lidofilcon A and the least for the etafilcon A lenses.<sup>29</sup> Adherence of cysts and trophozoites was found to be higher for the non-ionic than for the ionic disposable lenses.<sup>28</sup> Simmons et al.<sup>39</sup> suggested that the attachment of Acanthamoeba was highly dependant on the ionic nature and the water content of soft contact lenses. Collectively, these reasons could explain why Acanthamoeba adherence is higher for disposable and extended-wear soft lenses than for the conventional soft daily and rigid lenses.

Duration of Exposure and Protozoon Concentration. Both cysts and trophozoites showed an immediate adherence to contact lenses, which was observed to happen within 10 seconds after exposure.36 Acanthamoeba adherence to lens surface increased significantly for longer exposure durations and for higher concentrations of inoculum.<sup>29,40</sup> The higher water content of disposable soft contact lenses allows longer time of lens wear and, in turn, gives enough time of exposure for the lenses to be loaded with Acanthamoeba. This could add to the reasons why disposable soft contact lenses wearers are at greater risk of suffering from Acanthamoeba keratitis than those wearers of other types of contact lenses. However, Sharma et al.<sup>22</sup> found no difference in Acanthamoeba adherence to different contact lenses with increasing exposure time.

Acanthamoeba-Life Stage. Acanthamoeba trophozoite shows a greater tendency to adhere to contact lenses, as compared with the cystic form.<sup>29,36,40-42</sup> In contrast to the cystic form, Sharma et al.<sup>36</sup> noticed more adherence of trophozoites to rigid gas-permeable lenses than to soft ones. Similarly, Kelly et al.29 observed more preference of trophozoites to adhere to rigid gas-permeable lenses and polymethylmethacrylate (PMMA) contact lenses compared with the cystic form, which showed non specific similar rates of adherence to a variety of lenses, such as rigid gas-permeable, PMMA, daily and disposable soft lenses.

Lens Surface Deposits. Attachment of trophozoites and cysts to contact lenses is highly influenced by the presence of protein deposits on the lens surface. Protein deposits on contact lens surface increase the adhesion of other bacterial microbes like Pseudomonas aeruginosa, on which Acanthamoeba feeds.43 Protein and lipid deposition on lens surface is mediated by the chemical structure of the lens material and its water content. The high water content and the ionic material of some disposable soft lenses allow for more deposition of proteins, a fact that could explain the greater affinity of the Acanthamoeba protozoon for worn lenses than for unworn ones.39 Jones et al.44 reported significant deposition of low levels of lysozyme and high levels of lipid on silicone hydrogel contact lens materials, as compared with ionic contact lens materials. The adhesion of Acanthamoeba in unwashed worn versus unwashed unworn contact lenses showed a significantly lower adherence of Acanthamoeba to new lenses. 40,41 The serine protease subtilisin A enzyme used for protein removal from contact lenses has been found to have no cysticidal action even after 24 hours of exposure.<sup>45</sup> However, it could lower the number of protozoa attached to lens surface through protein removal.

**Mechanical Ways Used in Contact Lens Care.** While shaking showed no significant effect on adherence, a post-incubation wash using phosphate buffered saline decreased the number of adherent cysts and trophozoites.<sup>28</sup>

Several studies suggested that a good wash significantly decreased the adherence of trophozoites and cysts to the contact lens surface, 40,42 though one study46 suggested that washing had no effect on either *Acanthamoeba* stage. Rinsing contact lenses in saline using the flow method was significantly more effective than the immersion technique in removing adherent *Acanthamoeba* trophozoites from rigid gas-permeable lenses.41 Wiping, rinsing, and rubbing of contact lenses and lens cases with multipurpose disinfecting solutions dislodged adherent cysts and trophozoites and reduced the associated microbiological load.47 Recent studies, showed that multipurpose contact lens solutions that employed a manual rub regime were more effective in removing adherent loosely-bound deposits48 and different pathogenic microbes49 from soft hydrogel lenses than rinsing or soaking alone.

Associated Bacterial Organisms. The contamination of lens care systems with bacteria is an essential association in the development of Acanthamoeba keratitis. The bacterial microorganisms that adhere to the surfaces of contact lenses provide a good medium that facilitates attachment, feeding, survival, and growth of Acanthamoeba. Acanthamoeba can easily attach and grow on a lens surface previously loaded with bacterial microorganisms. Gorlin et al.<sup>50</sup> found that about 50% of the eyes infected with Acanthamoeba had positive cultures for bacteria. Other study<sup>51</sup> showed that 85% of contact lens

systems infected with *Acanthamoeba* were contaminated with bacterial strains, mainly with the aerobic gram-negative bacilli *P. aeruginosa* and *Xanthomonas maltophilia*.

Other bacterial microorganisms, such as Flavobacterium breve, P. paucimobilis, P. fluorescens, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Enterobacter agglomerans, Flavobacterium indolgenes, Salmonella enterica, Corynebacterium xerosis, Serratia marcescens and Klebsiella pneumoniae were isolated in patients with Acanthamoeba keratitis. 20,52-56 Alizadeh et al. 20 showed that Acanthamoeba could secrete increased amounts of pathogenic mannose-induced protease 133 upon exposure to C. xerosis.

Acanthamoeba trophozoites and cysts could retain viable bacteria with human pathogenic potential. <sup>57</sup> Intra-Acanthamoeba detection, survival, growth, and multiplication of salmonellae <sup>56</sup> and P. aeruginosa <sup>58,59</sup> were reported, with the possibility of reisolating <sup>58</sup> P. aeruginosa from Acanthamoeba cysts. P. aeruginosa could significantly enhance Acanthamoeba trophozoite attachment to hydrogel contact lenses, <sup>60</sup> but not to silicone ones. <sup>37</sup> The combination of P. aeruginosa and Acanthamoeba was assumed to be selectively exclusive, causing potentially devastating ocular infections in contact lens wearers, <sup>33,61</sup> Sodium salicylate reduced trophozoite attachment to hydrogel lenses when inoculated with P. aeruginosa. This effect was attributed to the inhibition of bacterial biofilm-formation, interference with the biofilm-amoebal attachment, or modification of the lens surface. <sup>60</sup>

Contact Lens Disinfecting Solutions. The use of ineffective contact lens disinfecting solutions is strongly linked to the threat of Acanthamoeba infection in contact lens wearers. A 10-year survey (1994-2004)62 showed that Acanthamoeba was isolated in contact lenses and contact lens disinfecting solutions in all cases of Acanthamoeba keratitis. The one-step 3% hydrogen peroxide and multipurpose solutions were found to be ineffective in killing Acanthamoeba cysts and trophozoites, as well as bacteria and fungi. However, in addition to the broad antimicrobial activity of multipurpose solutions, they were found to be capable of reducing the adherence capability of Acanthamoeba to contact lenses. 63 Opti-Free express multipurpose solution significantly reduced the adherence of trophozoites and cysts when used to clean, rinse, and soak soft contact lenses.<sup>64</sup> Complete Easy Rub multipurpose solution was effective in removing bacteria, fungi and Acanthamoeba from silicone hydrogel lenses.<sup>49</sup>

### PROBLEMS CAUSED BY CONTACT LENS WEARERS Contact Lens Overwear

Corneal overwear-related problems could develop in the long term for any type of contact lenses, including those designed for extended wear. The overwear problems were influenced by the rate of oxygen transmission and permeability through the lens material, lens thickness, lens type, wearing modalities, replacement schedule, repeated wear of disposable lenses, and overnight sleep in lenses. A lower incidence of microbial keratitis was reported for silicone hydrogel lenses with high oxygen permeability than for other soft lenses having low oxygen permeability used with an extended

wear scheme. 65,66 However, occasional pathophysiological problems, such as diffuse corneal infiltration,67 development of mucin balls, superior epithelial arcuate lesions, contact lens papillary conjunctivitis, corneal erosions, 11,68 corneal dryness and discomfort,69 central corneal thinning,70 and thickened conjunctival epithelium due to increased metaplasia<sup>71</sup> were reported with the overwear of silicone hydrogel lenses with high oxygen permeability. A significantly higher risk of bacterial keratitis and a greater incidence of complications, such as limbal neovascularisation and corneal oedema, were reported in wearers whose daily wear time was higher than 12 hours.72

### Overnight Sleep in Different Types of Contact Lenses

The cornea gets its oxygen supply directly from the air when the eye is opened and from the surrounding blood vessels when it is closed. The new versions of rigid and soft contact lenses were designed to allow oxygen delivery to the cornea at an almost similar level under either opened or closed-eye conditions.<sup>73</sup> However, corneal hypoxia, subepithelial infiltrations, immune ring formation,12 changes in corneal curvature, central corneal thinning,<sup>70</sup> alteration in the number of polymorphonuclear leukocytes, and variations in the level of different inflammatory mediators in the tear film<sup>74</sup> were reported upon wearing contact lenses for multiple sleep cycles. The results of various surveys<sup>75-78</sup> suggested that the overnight wear of contact lenses was the main cause of microbial keratitis, with a greater concern for the immunocompromised patients, where the risk of unusual infections was very high.79

The overnight wear-related corneal changes and the risk of ulcerative keratitis was found to be significantly dependant on the lens type. Overnight wear of rigid gas-permeable contact lenses was associated with higher levels of corneal hypoxia and epithelial oedema, as compared with soft lenses.25 However, Graham et al.80 stated that the severity of corneal swelling with rigid gas-permeable lenses was not a reliable predictor of ocular complications. No significant difference was recognised in the bacterial binding ability to the corneal epithelium between the overnight wear of either conventional or hyper-oxygen transmissible rigid contact lenses.81 However, central corneal epithelial thinning with visual impairment<sup>82</sup> and the increased risk of bacterial<sup>83,84</sup> and Acanthamoeba keratitis<sup>84-89</sup> were reported with the overnight wear of orthokeratology contact lenses.

The overnight wear of extended wear lenses increased the risk of ulcerative keratitis,90 with the possibility of conjunctival cytologic changes.71,75,76 Schein et al.76 mainly attributed the high risk of microbial keratitis among the users of extended wear lenses to the overnight wear, rather than to lens hygiene or lens type. However, Brennan<sup>91</sup> contradicted the common perception of optometrists in Western societies, who state that the use of extended wear lenses could increase the risk of microbial keratitis and the loss of vision. Brennan correlated the safety of the overnight wear to the high oxygen transmissibility of silicone hydrogel contact lenses. Other surveys<sup>92,93</sup> denied the occurrence of clinically serious events of microbial keratitis with daily disposable contact lenses.

Corneal hypoxic changes, such as epithelial oedema and microcysts were not recognised among the overnight wearers of extended wear lenses, with no significant difference in limbal redness between them and the non-lens users.94 Kenyon et al.95 suggested that neither the level of overnight corneal swelling nor the period between removals could influence the incidence or the severity of corneal problems of extended wear lenses.

### Non-Compliant Contact Lens Users

The compliance of contact lens wearers with the recommended lens care hygiene procedures is crucial to reduce the risk of serious infections. D'Aversa et al.% reviewed the medical records of 12 patients and found that substandard lens-care methods were used in 13 out of 14 (92.9%) eyes infected with Acanthamoeba. The use of tap water for the care of contact lenses was widely accepted as the main risk factor in Acanthamoeba infection. 5,85,97-102

In the United Kingdom, 91% of the soft contact lens wearers and 94% of the rigid lens wearers avoided the disease by the complete avoidance of water and the use of powerful lens disinfecting solutions.5 In the USA, the withdrawal of salt tablets from the market was responsible for the decrease in the incidence of Acanthamoeba keratitis in the mid 80s.98 A recent study<sup>103</sup> showed that the Chicago-area tap water contained a highly virulent Acanthamoeba strain that was contributing to the increased incidence rate of Acanthamoeba keratitis in this area. Swimming, diving, showering or washing the face while wearing contact lenses was reported to cause Acanthamoeba keratitis. 97,104-108 The 50-fold increase in the risk of Acanthamoeba keratitis among disposable contact lens users was largely attributable to repeated wear of lenses, lack of disinfection, and use of saline and chlorine-based solutions.75

The compliance of contact lens users with the recommended care procedures is ineffective if these solutions do not manage to kill Acanthamoeba. 6,105,109 To avoid the persistent use of non-sterile solutions by non-compliant lens wearers, Moore<sup>13</sup> recommended heat disinfection of lenses—between 70 and 80°C for 10 minutes—and the use of 3% hydrogen peroxide for 2-3 hours, 0.001% thimerosal with edetate for 4 hours, 0.005% benzalkonium chloride with edetate for 4 hours, 0.001% chlorhexidine for 4 hours or 0.004% chlorhexidine for 1 hour. Better compliance of contact lens wearers was achieved with the introduction of multipurpose solutions. The multipurpose solutions replaced the need for an additional rinsing solution, offering a single solution for the cleaning, disinfection and contact lens storage.<sup>110</sup> The multipurpose solutions provided potent antimicrobial protection with less toxic and less allergenic effects. 48,49,75

The non-compliance of contact lens users could occur in the case of deliberate reuse of daily disposable contact lenses, when wearing expired lenses without replacement or if using cheap contact lenses purchased from unlicensed vendors.111 Old contact lenses could colonise more microorganisms due to the increased lens surface tear and wearrelated scratches<sup>40</sup> or to the accumulated deposits.<sup>43-45</sup> The relationship between repeated use of daily disposable lenses and risk of *Acanthamoeba*<sup>112,113</sup> and microbial keratitis<sup>93,114</sup> is well established.

Daily disposable lenses were designed for single use only, where a new sterile set should be opened every morning and discarded in the evening. This wear modality aimed to provide a great hygienic advantage, by avoiding the necessity and the cost of disinfecting solutions and storage cases. For hygienic purposes, daily disposable lenses were recommended for those lens wearers having jobs entailing a great potential risk of infection, such as hospital staff members.<sup>33</sup> Dart et al.<sup>115</sup> reported that vision loss was less likely to occur for daily disposable than for reusable soft lens wearers, though no significant reduction in the risk of microbial keratitis was found for users of daily disposable and silicone hydrogel lenses. However, the assumed lens wearers' compliance could sometimes divert the attention of professionals from considering Acanthamoeba infection in daily disposable contact lens wearers. A delay of 17 days before starting the anti-Acanthamoeba treatment was reported.116

Radford et al.<sup>75</sup> stated that the low care philosophy of daily disposable lens use has resulted in an absolute absence of care, and emphasised the importance of warning patients against the increased risk of infection upon reuse of daily disposable contact lenses. The non-compliance of contact lens users has been attributed to the convenience of using multipurpose or one-step solutions instead of using two-step hydrogen peroxide solutions. Financial savings achieved by reusing daily disposable contact lenses is another factor.<sup>117</sup>

### **CONCLUSION**

Contact lens wear is the main cause of ulcerative keratitis, which could get seriously complicated with corneal scarring and lead to permanent vision loss. The association between *Acanthamoeba* keratitis and contact lens wear is firmly established. Contact lenses have a great impact on corneal epithelium integrity. This, added to the greater affinity of *Acanthamoeba* to adhere to either corneal or lens surfaces, increase the risk of keratitis in contact lens wearers. Lens hygiene, lens care solutions, wearing modalities and the compliance of lens users are important factors in the lens-keratitis relationship. Every lens wearer should be aware of what the main risk factors are and, when given the routine instructions regarding lens fitting and care, they should also be provided with a thorough explanation of how contact lens misuse can seriously affect vision.

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