Contact lens wear and its complications
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CHAPTER VI

GENERAL DISCUSSION
This thesis focused mainly on the epidemiology and the pathogenesis of microbial keratitis in cosmetic CL wearers. These issues are described in chapter 2 to 4, and will be discussed consecutively.

Three questions formed the background to the study presented in chapter 2: what were the incidence rates for CL-associated microbial keratitis, its related morbidity and costs in the Netherlands.

**Epidemiology**

Until now, the most conclusive data on the incidences of this disorder were provided by the New England study (1). A remarkable similarity of the incidence rates for the two soft CLs groups in the USA to those found in our study were noticed (table 2, chapter 1). In light of our larger sample of wearers of RGP lenses (46.6% of the total CL users in the Netherlands versus 10% in the USA), our incidence rate (1.1 per 10,000 RGP wearers) may be a more reliable estimate. It is noteworthy that this incidence figure is exactly the same as the incidence of ulcerative keratitis observed in the general community in Minnesota from 1980 to 1988 (2). This finding implies that the risk of developing ulcerative keratitis in daily-wear RGP users is similar to that of the general population, suggesting that RGP wear does not impose a significant risk to the individual wearing them.

In the past decades, both professional and popular journals expressed the concerns of CL-associated microbial keratitis, especially in regard to extended-wear soft CL users who had the greatest risk of developing this disease (3-7). The current incidence study shows that despite of many efforts, and the awareness among physicians and the public concerning the risk of extended-wear, the actual risk of keratitis in this group was virtually the same as nine years ago (1). On the basis of our results, we estimate that 368 cases of CL-induced corneal ulcers will occur in the Netherlands per year, of which 48 (13%) are associated with extended-wear. Since only 1.7% of the total CL wearers use extended-wear (table 1, chapter 1), this wearing modality carries an unacceptable high risk.

To date, there have been no population-based studies to determine the morbidity and costs associated with CL-induced microbial keratitis. In chapter 2, a long-term follow-up (more than nine months) study showed that 5 of the total 92 (approximately 5%) case patients with CL-associated microbial keratitis ended with a severely decreased visual acuity, including one patient with only light perception due to *Acanthamoeba* infection. The mean age of the case patients was 32 years.

Our study also reveals that *P. aeruginosa* accounted for the most culture-positive cases, and for the poor final visual acuity as observed by others (4,5,8). The next most common isolate was *Serratia marcescens*, which
is also an opportunistic pathogen such as *P. aeruginosa*. The severity of the morbidity due to *Serratia* keratitis was significant but less than those caused by *P. aeruginosa* and *Acanthamoeba*. Since this potentially preventable blinding disease occurs in young myopic patients with otherwise healthy eyes, the CL practitioner should be cognizant of the risk-benefit ratio associated with CL use.

In the cost-of-illness study, the minimal health care costs were estimated to be US$ 2,809 per case patient (chapter 2). This expense is an underestimate because costs such as reduced quality of life and reduced productivity at work (due to keratitis and decreased vision) are not included (9). The results of the cost-of-illness study may serve as a point of reference for cost-effectiveness analyses. A cost-effectiveness study of a new intervention investigates changes in health care costs and effects compared to the current therapy. At this moment, excimer laser is considered as an alternative for cosmetic CLs to correct refractive errors.

**Excimer laser photorefractive keratectomy**

The goal of excimer laser photorefractive keratectomy (PRK) is to decrease the patient’s dependency on spectacles and CLs by improving uncorrected visual acuity. Although PRK may offer a great potential for the treatment of myopia, hyperopia, and astigmatism, its application for myopia is technically and clinically most advanced. Many clinical reports indicate that PRK can effectively decrease low and moderate myopia (10-12). Since the introduction of PRK in 1986, approximately 1 million eyes have been treated with this procedure worldwide (13). Several studies show that PRK does not cause damage to the corneal endothelium or even demonstrate improvements in the polymegathism and pleomorphism (possible due to cessation of contact lens wear) after this procedure (13-15). However, PRK is associated with various limits and complications. In some patients, especially those with high myopia, an unpredictable healing response of the corneal tissue to excimer laser ablation occurs. This may result in complications such as regression, overcorrection and corneal haze.

Regression is more common in patients who undergo higher dioptric (D) or smaller (5-mm) diameter treatments and those who have had earlier regression after treatment of the first eye (16). Because of regression or undercorrection, 29% of the low myopia (to -5 D) and 52% of the high myopia (>-5 D to -10 D) have been re-treated 12 months after refractive surgery (17).

Overcorrection is seen more often in higher-order corrections, occurring in 4.9% of extreme myopes (>10 D) and 1.5% of low myopes at 12 months after PRK (17). Furthermore overcorrection is positively associated
with the use of topical nonsteroidal anti-inflammatory drugs and bandage CLs(17).

Corneal haze (opacity) may reduce the best-corrected visual acuity and result in glare when viewing bright light sources under conditions of low ambient illumination (16). The intensity of the haze is graded from 0 to 5 (not detectable to severe opacity), and many agree that grade 1 is not of clinical importance. The frequency and severity of corneal opacity is related to increasing preoperative myopia. One year postoperative corneal haze at grade 2 is found in 20% of patients at -12.0 preoperative diopters and the haze still improves between 12 and 24 months (18).

Loss of best-corrected visual acuity is another important issue. This is caused by irregular epithelial thickening, corneal opacity, residual stromal central islands or decentration of ablation zones (18,19). The risk of loss of the best-corrected vision increases with increasing preoperative myopia. For myopes at -8.00 D preoperatively, there is a 10% risk of a 2-line loss of best-corrected vision at the end of one year (18). After correction for the retinal image magnification, the loss in the mean best-corrected low-contrast visual acuity (1½ lines) is notably greater than the loss in the mean best-corrected high-contrast visual acuity (half a line) in myopes with an average of -5.08 D, one year following PRK (20). These findings may explain why some ‘successful’ refractive surgery patients with a high-contrast Snellen visual acuity of 20/20, complain about impaired vision under dim illumination. The low-contrast visual acuity with a dilated pupil (20) or with a glare source (21) seems to be a sensitive measure of visual performance after PRK, and an important component in the evaluation of visual effect after refractive surgery.

Pain following PRK is considerable and requires one or variable combinations of the following regimens: topical anaesthetics, nonsteroidal anti-inflammatory drugs, corticosteroids, sedatives and soft bandage CLs. Although soft CLs are effective in decreasing pain after PRK, their use can be complicated by infectious keratitis (22). Up to now, 13 patients with microbial keratitis after PRK have been reported (19,22-24). All but one case patient had worn therapeutic disposable soft CLs after surgery (24). The absence of a protective epithelium, the administration of corticosteroid eye drops, and the presence of an extended wear soft CL, increase the risk to develop an infection. As yet the true incidence of microbial keratitis after PRK is not known.

In summary, the greater the preoperative myopia, the greater the problems with predictability, regression, overcorrection and corneal haze. Also, the re-treatment rate and most importantly, the loss of the best-corrected visual acuity increase with increasing myopia. Since PRK is a cosmetic surgery, the risk for loss of best-corrected acuity in the high myopia group is unacceptable. The safety and efficacy are certainly better for lesser
degrees of myopia, and many patients are happy about the reduction or elimination of their myopia. However, most of the visual gains after PRK can also be achieved by CL corrections. Although there is still a low risk of loss of the best-corrected vision, this elective surgery can be a good alternative for CL correction in low myopes, especially in those with CL intolerance. Long-term effects of PRK are not known yet.

Risk factors of CL-associated microbial keratitis

Why have the introduction of disposable extended-wear CLs, the improvement in CL materials and care products not led to a drop in the incidence rate for CL-associated microbial keratitis in extended-wear users? Multiple factors contribute to the excessively high incidence rate in this lens group. These include insufficient gas transmissibility capacity of the currently available extended-wear soft CLs (25), imperfect compliance with lens-care regimen (26-28), trivializing of CL use (7), deficient consumer education (7), decrease of host local immunological defence mechanisms (chapter 3), and lens deposit formation (chapter 4). Using an animal model, “critical oxygen transmissibility levels” for extended-wear lenses have been determined in which no detectable damage of the corneal epithelium and no significant increase of \( P. \ aeruginosa \) binding to the cornea were found (25). It appeared that CL-induced corneal changes may be prevented with Dk/L values that equal or exceed \( 50 \times 10^9 \) and \( 80 \times 10^9 (\text{cm/second}) \) (ml \( O_2/\text{ml mmHg} \)) for hydrogel and RGP lenses, respectively. At this moment, the Dk/L units of all extended-wear soft CLs currently available for consumers, are lower than this “critical oxygen transmissibility value”, indicating that (if these experimental data are applicable to human corneas) this wearing paradigm is inevitably associated with an enhanced risk of microbial keratitis. The fact that bacteria can irreversibly attach to both new and worn CLs (like other biomaterials), may further contribute to the risk of keratitis (29-31). A case-control study has indicated that most of the risk associated with overnight wear is assumed to occur with as little as 1 to 3 nights of extended-wear (32). Based on the results of above-mentioned studies, disposable soft CLs can not be expected to reduce the risk of keratitis by simply replacing the lens frequently if these lenses are continuously worn for at least 7 days. Indeed, our incidence study confirms that disposable lenses do not have additional value in the safety of CL use, because the highest risk of keratitis occurs in the disposable extended-wear group. A recent case-control study demonstrated that the use of disposable soft CLs itself are associated with an excess risk of microbial keratitis (33). The properties of some disposable soft CL, such as manufacturing defects (34) and rapid tear protein deposition (35) may
cause mechanical and immunological corneal compromise, thereby increasing the risk of infectious keratitis in wearers of this lens group. As shown in the consumer surveys, an increasing number (in the Netherlands, virtually all) of extended-wear users are wearing disposable lenses (table 1, chapter 1). It is possible that this group of lens users may wear their lenses overnight more frequently than the recommended wearing period to save on the purchasing costs (36). They might do so because disposable CLs are relatively more expensive than the conventional lenses. Also, the advices with regard to the lens-care hygiene for disposable lenses, ranging from no disinfection or cleaning at all to daily cleaning vary between practitioners and are often confusing (37). The knowledge that the lenses will be thrown away after 2 weeks wear, may greatly reduce the lens hygiene habits of the disposable CL users (38).

The advertising and promotion of extended-wear soft CLs overstressed the convenience and carefree aspect of using these lenses (7, 38). The trivializing of CLs misleads the public. CL wearers should realize that sleeping with lenses is a risky practice because all currently-marketed extended-wear soft CLs induce overnight corneal hypoxia that predispose to infection, especially *P. aeruginosa* keratitis.

Most discussions have focused on the effect of CLs on the oxygen availability to the cornea. It is now known that during a nocturnal eye closure, a marked exudation of polymorphonuclear neutrophils (PMN) cells occurs onto the ocular surface (39). These PMN cells play a vital role in preventing bacterial invasion of the cornea during the night while tear flow virtually ceases (40). Furthermore, the PMN cells are thought to clear cellular debris from the ocular surface and subsequently to prevent the release of cytotoxic enzymes from the desquamated epithelial cells (39). It is possible that sleeping with CLs impedes the migration of these cells and markedly disturbs their function during the night, leading to a compromised cornea (40). If this hypothesis is correct, the increase of oxygen permeability of CLs alone, is not sufficient to reduce the risk of CL-associated microbial keratitis. The presence of a CL which acts as a mechanical barrier will still impair the host’s defence mechanisms making the cornea vulnerable to infection. The above-mentioned hypothesis is of course extremely speculative and should be tested.

Consumer education is an important issue with regard to the safe use of CLs. A recent multicentre survey in the UK shows that a dramatic fall in the incidence of *Acanthamoeba* keratitis (93% of these patients are CL wearers) is partly associated with an intensive media attention to this corneal infection and increased education of CL wearers (41). Since the knowledge accumulates, CL wearers should be informed with update
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data (42,43). At present, the minimal information that the CL practitioner has to give to the cosmetic CL wearers are:
1. Extended-wear should be avoided.
2. RGP is the first choice of lens.
3. Clean and disinfect lenses, including disposable lenses daily.
4. Scrub lens-case daily and replace it frequently.
5. Nonsterile and homemade solutions should not be used.
6. In case of pain or redness of the eye, lens wear should promptly be discontinued and evaluation by a CL practitioner should be sought as soon as possible.

In view of the complexity of the risk factors for CL-associated microbial keratitis, complicated by the myriad of lens-care systems, a seller of an outlet or a mail-order service can not guarantee an adequate consumer education, but only discount on volume sale. In short, dispense of CLs should be reserved to well-trained professionals such as CL practitioners, optometrists and ophthalmologists. In our opinion CLs should be considered as medical devices, and as a consequence this should allow the implementation of appropriate legal regulations for the distribution of CLs and the training required to fit CLs.

Pathogenesis of P. aeruginosa-induced keratitis

P. aeruginosa is an opportunistic pathogen, and often causes fulminating and destructive corneal infection among CL wearers (5,44). Risk factors such as bacterial contamination of lens-care systems (26,27), poor patient compliance (28), bacterial adherence to CLs or lens deposition (45-46) do not fully explain the pathogenesis of infection since P. aeruginosa can not attach well to intact corneal epithelium (47). The minimal condition for the development of this disorder is the adherence of microorganisms to compromised corneal epithelial cells. Factors that inhibit the binding of bacteria to host tissues decrease the risk of infection. The ocular surface like some of the other mucosal sites, is exposed to tremendous microbial challenges. The mucosal compartment cannot kill and dispose of all microorganisms present on the mucosal surface. The prevention of bacterial epithelial attachment referred as immune exclusion, is the most important host defence against bacterial invasion of mucosal sites (48,49). The ocular surface possesses several defence mechanisms to prevent colonization of pathogens. These include the epithelial barrier (intact corneal epithelium), mucus secretion (tear mucins) that form a barrier and act as a carrier for elimination via flow mechanism (bacteria swept away by tear flow), and specific (anti-bacteria s-IgA) and innate (lysozyme and lactoferrin) secretory factors (50,51). The role of specific
antibodies in immune exclusion is to prevent bacterial adherence to epithelium by the formation of antibody-bacterium complexes (52). Antibody-mediated antiadherence has been found in almost all mucosal sites: oral (52), bronchial (48), intestinal (53), urinary (54), and genital mucosa (55).

An experimental study shows that ocular mucin or human tears inhibits the binding of \textit{P. aeruginosa} to the cornea (56). A recent study reveals that specific antipseudomonal s-IgA in tears can be elicited by topical ocular immunization with heat-killed \textit{P. aeruginosa}, and the elevated s-IgA significantly protects against experimentally induced bacterial keratitis in the mouse (57). These investigations suggest that specific s-IgA may play a role in the pathogenesis of \textit{P. aeruginosa}-induced keratitis. The study presented in chapter 3 may be used as an initial step towards testing this hypothesis. This study shows two interesting findings. First, 9\% to 23\% of the CL wearers and non-CL users tested, lack detectable IgA antibodies against \textit{P. aeruginosa} in their tears (non-responders). Second, a significant lower anti-\textit{P. aeruginosa} response was observed in extended-wear CL users. We speculate that CL users with decreased anti-\textit{P. aeruginosa} responses and especially the non-responders are susceptible to \textit{P. aeruginosa} keratitis when their cornea is compromised and contamination with this bacterium occurs.

Dart (58,59) emphasized that some CL wearers with microbial keratitis have good lens hygiene and uncontaminated lens-care systems. He hypothesized that some CL wearers may be uniquely susceptible to infection by ‘background’ levels of contamination with \textit{P. aeruginosa} or other bacteria that do not affect normal people not wearing CLs. The findings in chapter 3 suggest that these uniquely susceptible individuals might represent the non-responders in whom the local specific anti-\textit{P. aeruginosa} immune response is decreased, resulting in insufficient immune exclusion. \textit{P. aeruginosa} is ubiquitous in our environment. This microorganism may be introduced directly in eye in small quantities, binds to damaged epithelial cells and causes infection without contamination of lens-care systems. As mentioned in chapter 3, a case-control study is needed to obtain more vigorous evidence of the role of slgA in tears in the development of bacterial keratitis. If such proof is clearly demonstrated, it may provide the rationale to implement preventive measures other than improving lens hygiene. Recently, cystic fibrosis patients (\textit{P. aeruginosa} is the leading cause of bronchopulmonary infections in these patients) were immunised with \textit{P. aeruginosa} O-polysaccharide-toxin A vaccine. This vaccine was safe and evoked a significant titre of functional antibodies, which were long-lived (60). The rapid development in vaccine technology may result in the application of simple procedures (e.g. oral vaccination) to enhance the local ocular
immune response against those microbes which are involved in CL-associated keratitis (61). Using an animal model, oral immunization with Acanthamoeba antigens induces significant anti-Acanthamoeba IgA titers in tears and is associated with a strong protection against infection to the challenge with Acanthamoeba-laden CLs (62). Immunization after corneal infections have been established, does not produce any ocular protection. These findings further support the concept of the important role of IgA in immune exclusion and may form the basis to investigate whether oral immunization with P. aeruginosa antigens may mitigate keratitis in animals.

Lens deposits

Lens deposit formation has been implicated in the etiology of P. aeruginosa-induced keratitis in CL users. The main theory is that mucin-coated CLs increase P. aeruginosa adhesion because sialic acid (a moiety of glycoprotein of tear mucins) may be a receptor for this bacterium. As mentioned in the introduction, this theory is controversial since many studies are contradictory. An alternative hypothesis is that the lens deposits may cause mechanical trauma to the corneal epithelium to which P. aeruginosa can attach.

The introduction of disposable nonreusable extended-wear CLs in 1987, aimed to reduce deposit-induced complications (such as microbial keratitis and giant papillary conjunctivitis) since the protein buildup would be negligible during the short wearing period (2 weeks) of these lenses. In theory, the absence of CL-care solutions and paraphernalia which eliminates the potential sites for bacterial contamination, would further contribute to the safety of the disposable lenses. Unfortunately, several case-control studies yielded an excessive risk of ulcerative keratitis in disposable extended-wear users (32,37,63). After controlling the lens types, the exorbitant risk was principally related to the wearing pattern and not to the replacement schedule. However, as stated-above, disposable CLs themselves (because of defects in these lenses and rapid tear protein deposition) may be partly responsible for the increased risk of microbial keratitis (33). An unexpected finding in the reusable CL users was that the levels of lens-care hygiene had only marginal (59,64) or even no protective effects (32), suggesting that good lens hygiene may slightly lower the risk of microbial keratitis. The poor association between lens hygiene and keratitis is an indirect evidence that lens deposits (presumably that the amount of lens deposits correlate with the frequency of lens care) may not be a key factor in the pathogenesis of keratitis.

The results of the study described in chapter 4 shows that apart from a detection of an unidentified tear protein on lenses, the maximal deposit
formation on CLs was already achieved within 2 day’s wear. Thus, if lens deposits play any role in the etiology of bacterial keratitis, disposable CLs should be discarded at the end of the day’s wear, and not after 1-2 weeks as instructed by the manufacturer. Meanwhile, this mysterious 30 kD protein has been identified as the dimer of tear lysozyme which does not exist in normal tear fluid but is the unique product of lysozyme interaction with hydrophilic soft CLs (65). Whether this denatured form of lysozyme on CLs plays a role in microbial keratitis, remains to be studied.

**Therapeutic application of CLs**

CLs are the last treatment modality prior to surgical intervention in keratoconus patients whose vision is inadequately corrected with eyeglasses. In chapter 4, promising results of the therapeutic application of aspherical (sphero-elliptical) CLs with high oxygen permeability in these patients are reported. The main findings were: increased visual acuity compared with low oxygen permeable spherical CLs fit priorly, and minimal CL-induced corneal epithelial damage with these aspherical lenses. The success of the treatment with these lenses is based upon the improvement in both CL materials and design. The high oxygen permeability of these aspherical CLs provide better corneal oxygenation, reducing corneal hypoxia and edema. On extended-wear basis, these lenses did not show significant change in the morphology of the corneal endothelium (66). Because of the new lens geometry (in contrast to spherical CLs), these lenses align well with the conic cornea, eliminating excessive bearing at the apex and thereby preventing corneal scarring due to mechanical trauma. The better alignment of the posterior surface of the aspherical CLs with the keratoconic corneas was demonstrated by the even distribution of the fluorescein pattern. During the study period, no sphero-elliptical lenses had been lost compared to frequent loss of spherical CLs fitted previously. The good lens fit improved the tear exchange, and in combination with the high oxygen permeable materials resulted in better corneal physiology and visual acuity. Since the deviant corneal topography in the keratoconic cornea is comparable to that of a scarred cornea, this aspherical lens type has also been applied to this patient group (67). Both corneal disorders cause irregular astigmatism which are insufficiently corrected by spectacles. In contrast to spherical CLs, the aspherical lens designs provided a better lens-to-scarred cornea fitting, and in combination with a high oxygen permeability, resulting in significant improvement of visual function and reduction of lens-related complications.

CL fitting in keratoconus patients is time-consuming because of the wide
A computer-assisted fitting technique (chapter 5) was used to shorten the fitting procedure. Two central and 4 peripheral keratometer readings served as input data to a computer, which calculated the base curve radius of the best trial lens. A high correlation was found between the final selected base curve radius and the calculated base curve radius, implicating the effectiveness and the time saving benefit of this computer-aided fitting system.

Concluding remarks

To provide the best CL care, particularly to patients whose fitting is difficult and time-consuming such as in keratoconus patients, the optimal collaboration between ophthalmologists and the CL practitioners is essential. Also, they and the CL manufacturers have to work in concert to find better and safer lens polymers, and lens designs to minimize the CL-induced complications, especially microbial keratitis. Despite the continuous technical improvement in CL materials, there are no extended-wear soft CLs currently available with Dk/L values above the “critical oxygen transmissibility level” which can prevent overnight corneal hypoxia. Because of the convenience of extended-wear, some individuals will still prefer this wearing modality. It is now a challenge for the polymer chemistry to invent hydrogel lenses with higher Dk/L values that meet the metabolic requirements of the cornea during overnight lens wear, possibly reducing the risk of the development of infectious keratitis. This significant public health concern cannot be only solved by introducing ultra-oxygen transmissible CL materials, but appropriate consumer education and good patient compliance with the lens-care regimens are also mandatory. The fact that extended-wear soft CLs carry an unacceptable high risk of developing severe corneal infection, this wearing pattern should not be prescribed for cosmetic use without appropriate warning, adequate instructions and strict supervision. Theoretically, daily disposable daily-wear (not reusable, 1 day) lenses should decrease the incidence of many complications, including microbial keratitis and giant papillary conjunctivitis, since the need for lens hygiene compliance, the risk of overnight hypoxia, lens deposit accumulation and bacterial contamination from CL paraphernalia would all be eliminated. However, ulcerative keratitis in a person wearing daily disposable CLs has been reported recently (68). It is hoped that this is an incidental case. The lessons learned from the weekly disposable extended-wear in the past is, that the possible value of these ‘1 day’ lenses have to be confirmed by epidemiologically rigorous prospective studies.
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