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Thirty years of 'quiet eye' with etafilcon A contact lenses

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ABSTRACT

Frequent replacement contact lenses made from the etafilcon A hydrogel lens material were introduced onto the market over 30 years ago, and etafilcon A remains the most widely used hydrogel lens material today. Although the prescribing of silicone hydrogel lenses is increasing, millions of lens wearers globally have been wearing hydrogel lenses for many years and exhibit a physiologically-stable 'quiet eye', with a low profile of adverse events. Hydrogel lenses are demonstrated to maintain a low inflammatory response and infection risk profile during daily wear, which in the case of etafilcon A, may be related to its low modulus, and the naturally-protective, anti-microbial, non-denatured lysozyme absorbed into the lens from the tear fluid. Although improved corneal physiology from decreased hypoxia with silicone hydrogel lenses is well accepted, equivalent levels of corneal oxygenation are maintained during daily wear of low to medium powered hydrogel lenses, which do not impede the daily corneal de-swelling process, and do not induce clinically significant changes in ocular health. Therefore, hydrogel lenses remain an important alternative for daily wear in modern contact lens practice.

1. Introduction

The first conventional (non-frequent replacement) hydrogel lenses manufactured from HEMA (poly-hydroxyethyl methacrylate) (SofLens, Bausch & Lomb) were sold in the USA in 1971 and were replaced when the lenses were deemed to be unsatisfactory (e.g. uncomfortable, damaged or heavily coated with visible deposits), which was typically more than a year after the lenses were dispensed [1]. The concept and practice of contact lens disposability were introduced by Michael Bay, in Denmark, around 1982 [2]. Johnson and Johnson bought the rights to this concept and went on to manufacture and market the first globally-available frequent replacement and daily disposable modalities, manufactured from etafilcon A material, in 1987 (ACUVUE, Johnson & Johnson Vision Care) and 1995 (1 DAY ACUVUE, Johnson & Johnson Vision Care), respectively [3].

During the 1990s, continuous wear was considered the 'Holy Grail' for contact lenses but an unacceptable rate of corneal infection deterred practitioners from this modality [4]. Silicone-hydrogels were "designed to offer the high levels of oxygen transmissibility required to avoid the hypoxic effects of overnight wear" [5], hypothesized to be the mechanism of microbial keratitis. However, when fear of infection and adverse responses remained significant inhibitory factors for practitioners [4], manufacturers turned to promoting silicone-hydrogels for daily wear use. It is noteworthy that the first peer-reviewed paper of daily wear usage of these materials came seven years after the first publication on their use in extended wear [6,7].

Important factors considered by practitioners for contact lens wear success are safety, comfort, and vision. With the growing number of options in lens material choice, there are different schools of thought when it comes to considering the use of hydrogel materials. For some practitioners, a hydrogel lens is the lens of first choice, especially in a daily disposable replacement schedule. For others, oxygen

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transmissibility considerations may overshadow all other desirable material characteristics, suggesting that hydrogel lenses are being considered as an inferior choice. Other practitioners may prioritize hydrogel lenses in specific situations/population – for example, to enhance comfort relating to lens design or generally lower material modulus (stiffness) [8].

Hydrogel lenses still play an important role in the armamentarium of the contact lens fitter. Their low adverse event rates (see Section 7) have contributed to their long and successful history, which when coupled with the introduction of more frequent replacement schedules, has resulted in 'quiet eyes' (i.e. eyes that are physiologically stable and show minimal signs of inflammation) in the vast majority of those wearing such lenses.

This paper reviews the properties of hydrogel lenses, especially etafilcon A, which was introduced into the market 30-plus years ago. Consideration will also be given as to why hydrogel contact lenses are still a desired, viable and relevant option for daily wear in contact lens practice today. Evidence-based guidance for the continued use and fitting of hydrogel lenses for daily wear will be provided.

2. Contact lens material classification

Hydrogel materials are classified by the International Organisation for Standardisation [9] into one of five groups. Four of these groups describe conventional hydrogel materials, which are categorized into Groups I – IV, depending upon their water content and ionicity. A fifth group –Group V – describes silicone hydrogel materials. These groupings have also been adopted by the USA Food and Drug Administration (FDA) [10] (Table 1).

Very few lenses today are manufactured from FDA group III materials. Examples of commonly fitted lenses from the remaining three groups are: Group I – polymacon (HEMA); Group II – omafilcon A, nelfilcon A and nesofilcon A; and Group IV – etafilcon A, ocufilcon B, ocufilcon D and methafilcon A. Table 2 provides a list of commonly available commercial lenses and their main composition.

The oxygen permeability of conventional hydrogels is directly related to the amount of water in the material [11]. The most basic hydrogel contact lens material is polymacon (HEMA), which has limited oxygen transmission due to its low water content (38 %). In an attempt to increase oxygen transmission, manufacturers added more hydrophilic monomers such as methacrylic acid (MA) and N-vinyl pyrrolidone (NVP). Both of these monomers provide increased oxygen transmission compared to polymacon, but their incorporation results in different material characteristics, as evidenced by examination of Table 2. Addition of MA creates a high water content ionic lens polymer (etafilcon A, Group IV), while addition of NVP produces a neutral material of even higher water content (nesofilcon A, Group II), resulting in these polymers being placed in differing FDA categories.

It is widely held that the increased thickness for higher negatively powered hydrogel lenses leads to major reductions in peripheral lens oxygen transmission [12]. However, manufacturers minimise thickness by adopting lens design strategies such as controlling optic zone size and potentially asphericity of lenses to constrain thickness across all powers. Most commercially available, stock, spherical, minus-power, daily disposable lenses have a maximum thickness of around 0.25 mm, regardless of power. Because of this, the minimum oxygen transmissibility of any lens brand will tend to be constant across a wide range of powers [13].

3. Tear film wetting of the hydrogel lens surface

3.1. Tear film wetting

Technically, wettability is the capacity of a liquid to spread (or cover) the surface of a solid. This is measured in vitro by assessment of contact angles [14], which occur at the junction of the solid-liquid interface. However, given that wettability is an in vitro assessment, there are questions about its relevance to the in vivo scenario as it relates to a contact lens on the eye and its interaction with the tear film [15]. For instance, to date it has been difficult to replicate an in vitro solution that mimics the tear film, with its biologically and biochemically diverse composition. As such, measures of tear film breakup, or coverage, are performed in vivo clinically, with the use of a slit-lamp, or though more sophisticated devices such as various types of interferometry.

Differences in soft lens materials might have an impact on their interaction with the tear film. Likewise, differences in tear film composition associated with a variety of factors (normal biological differences, contact lens induced, and ocular surface disease) may also be a factor in the interaction of the contact lens with the tear film [16]. One potential polymer composition that has an impact on tear film wetting is when considering the incorporation of silicone (or siloxanes) into soft lens materials to improve their oxygen permeability. Silicone itself is inherently hydrophobic, and is naturally unwettable. Thus, without a surface modification, one would predict that a soft contact lens incorporating siloxane moieties would tend to be associated with poor tear film wetting [17].

With the above background in mind, it is important to consider the weight of evidence as it relates to hydrogel and silicone hydrogel materials and their associated tear film wetting characteristics. Pre-lens tear film break-up on soft lens materials may be driven by the increase in tear evaporation that occurs during lens wear [18–21]. However, what is not fully understood, or accepted, is whether true differences in tear film wetting occur across soft contact lens materials. While small differences in tear film wetting may be noted, they do not typically support clinically meaningful differences in lens performance [22]. These small differences are highly dependent on the measurement method, as there is no universally adopted standard in this regard for measuring tear film wetting, or thinning, in vivo [23].

3.2. Comfort

Studies show that up to 50 % of soft contact lens wearers suffer from discomfort and dryness at least occasionally [24–27]. The precise mechanisms that determine contact lens comfort (or discomfort) are unclear, but may be related to factors such as lens surface lubricity and wettability, lens design, lens material modulus [28,29] and lens-induced, sub-clinical inflammation [30–32].

The use of silicone hydrogels does not appear to show differences in the rates of dryness and discomfort as compared to the frequencies found from earlier studies with hydrogel materials [8,29,33,34]. Lazon de la Jara et al. [35] found no difference in comfort between those wearing hydrogel versus silicone hydrogel lenses. There have been

Table 1
Contact lens material grouping.

Polymers	Low water content (≤50 %)	High water content (≥51 %)
Hydrogel non-ionic (neutral charge)	Group I	Group II
Hydrogel ionic (negative charge)	Group III	Group IV
Silicone hydrogel	Group V	

Table 2
Common contemporary examples of FDA hydrogel lens materials.

FDA group	USAN	Proprietary Name	Manufacturer	Water Content (%)	Calculated Dk*	Principal Monomers
I	polymacon	Optima 38; SofLens 38	Bausch + Lomb	38	7.5	HEMA
II	omafilcon A	Proclear; Proclear 1 Day MiSight 1 day	CooperVision	60	18.1	HEMA; PC
	nelfilcon A	DAILIES AquaComfort Plus	Alcon	69	25.8	PVA
	nesofilcon A	Biotrue ONEday	Bausch + Lomb	78	36.9	HEMA; NVP
IV	etafilcon A	1-Day Acuvue Moist; Acuvue 2	Johnson & Johnson Vision	58	16.7	HEMA; MA
	ocufilcon B	BioMedics 1Day	CooperVision	52	13.2	HEMA; MA
	ocufilcon D	BioMedics 55	CooperVision	55	14.8	HEMA; MA
	methafilcon A	Frequency 55	CooperVision	55	14.8	HEMA; MA

* Dk (oxygen transmissibility [11]). HEMA (poly-2-hydroxyethyl methacrylate); MA (methacrylic acid); NVP (N-vinyl pyrrolidone); PC (2-methacryloxyethyl phosphorylcholine); PVA (polyvinylalcohol); USAN (United States Adopted Name).

suggestions in the literature that some patients have allergic responses associated with silicone hydrogel lens wear, but this idea has been largely refuted [36–38].

4. Hydrogel contact lens material interaction with tear film components

Contact lens material interaction with protein and lipid components of the tear film differs markedly between materials, as described in wide-ranging reviews on this topic. Relevant material factors that impact deposition include material polymeric composition, water content, pore size, surface roughness, and material hydrophobicity and surface charge [16,39–45].

Hydrogel materials tend to deposit protein to a greater extent than lipid, with the reverse true for silicone hydrogels [16]. However, within this broad concept, many subtleties exist between materials and the various proteins and lipids of the tear film. For the purposes of this targeted review, this paper will mainly concentrate on tear film interaction on hydrogel materials.

4.1. Tear film protein interactions with hydrogel materials

Proteins are a major component of the human tear film and perform a variety of important tasks, which include protecting the ocular surface from microorganisms, cell membrane transport/metabolism and regulating immune responses [46]. Most of these proteins are relatively small, with approximately 80 % of the proteins being <100 kDa [47]. Protein uptake into lens materials will depend upon a number of factors, including the pore size of the lens material, the size of the protein, and their respective surface charges. Contact lens materials have pore sizes that vary between 4 and 1700 Å, with higher water content materials tending to have larger pore sizes than low water content hydrogels [48]. Thus, protein uptake occurs more readily in higher water content materials than lower water content materials if other factors remain the same. With respect to protein size, smaller proteins more readily penetrate contact lens materials than their larger counterparts [49,50]. With respect to surface charges between tear proteins and lens materials, their interaction also depends on their ionicity between each other. Tear film proteins range in charge from isoelectric points (IEPs) of pI = 1 to pI = 11.

Tear film proteins that have received the greatest attention in research into contact lens deposition include lysozyme (size 14.3 kDa, IEP pI = 11.4), lactoferrin (80 kDa, IEP pI = 8.7) and albumin (66 kDa, IEP pI = 5.2). The average pH of the tear film is approximately 7.4, which results in lysozyme and lactoferrin being positively charged and albumin being negatively charged at this pH. Lysozyme is relatively small and more positively charged compared with lactoferrin and albumin [46]. These considerations are highly relevant with regards to their degree of deposition, as discussed below.

4.1.1. Lysozyme and its interaction with contact lens materials

Lysozyme is an antimicrobial enzyme and part of the innate immune system causing lysis of bacterial cell walls. There are over 100 peer-reviewed papers discussing its measurement and relevance, as summarised in a recent review [43]. Given its small size of 14.3 kDa, lysozyme is able to penetrate hydrogel lens materials and be incorporated into the bulk of the lens material [48,51–54]. Lysozyme uptake is significantly higher in Group IV materials than Group II materials [43].

4.1.1.1. Speed and quantity of deposition. Many studies have determined the amount of lysozyme deposited on hydrogel lenses (see Luensmann and Jones [41] and Omali et al. [43] for reviews). Lysozyme is detectable on etafilcon A materials within seconds of in-eye wear [55,56] or exposure to an in vitro assay [50,57,58]. In addition, uptake of lysozyme to etafilcon A is substantially more rapid than that seen in five other contemporary hydrogel materials (polymacon, omafilcon A, nelfilcon A, nesofilcon A and ocufilcon B) [50]. Etafilcon A attracts the highest amount (approximately 1300 µg/lens) [41,50] while all other HEMA-based lenses deposit typically less than 100 µg/lens lysozyme. Silicone hydrogel materials attract less protein than HEMA-based hydrogel materials, with < 10 µg/lens for non-ionic and < 40 µg/lens for charged silicone hydrogels [41].

The high affinity between etafilcon A and lysozyme is driven by the specific electrostatic interaction that occurs between the negatively charged etafilcon A and the positively charged lysozyme, coupled with the relatively large pore size of etafilcon A and the low molecular weight of lysozyme. Etafilcon A has a higher affinity for lysozyme compared to other Group IV materials, such as ocufilcon B – which has a similar water content, pore size, and composition (HEMA + MA) as etafilcon A – probably because the latter comprises a higher percentage of MA than the other materials, as suggested by Tighe and co-workers [59].

4.1.1.2. Conformational state. While protein deposition alone is unrelated to contact lens comfort and performance [22], one report has linked contact lens comfort with denaturation of lysozyme, whereby higher amounts of denaturation are linked to lower comfort [60]. A recent in vitro study has demonstrated that a reduction in metabolic activity and an increase in the release of inflammatory cytokines occurred after human corneal epithelial cells were exposed to denatured lysozyme [61]. Several studies have shown that FDA Group IV materials (including etafilcon A) have the greatest ability to conserve protein configuration and keep denatured lysozyme to low levels [62–65]. This could partially explain the generally high levels of comfort achieved with etafilcon A lenses [60].

4.1.2. Lactoferrin deposition

Lactoferrin bound to contact lenses has an antibacterial effect [66] and thus a higher deposition of lactoferrin in, or on, contact lenses may be beneficial. Lactoferrin is detectable on clinically worn etafilcon A

lenses after as little as one minute of wear [56] and progressively increases over time [67]. An in vitro analysis of lactoferrin deposition over a 28-day period demonstrated that more lactoferrin was deposited on etafilcon A than omafilcon A, with a significant difference ($p = 0.03$) found between materials after 28 days (etafilcon A: 11.3 ± 1.9 μg lactoferrin/lens vs. omafilcon A: 6.8 ± 2.0 μg lactoferrin/lens).

4.1.3. Albumin deposition

Albumin deposition on contact lenses is unwanted because it has been shown to increase binding of both gram positive and gram negative bacterial strains for both hydrogel and silicone hydrogel lenses [66,68]. Albumin-coated etafilcon A lenses show significantly lower bacterial binding (*S. aureus*) than albumin-coated balafilcon A and lotrafilcon B lenses [66]. This study also looked at the effect of bacterial adhesion on albumin deposition between lysozyme coated vs. uncoated lenses [66]. There were no differences in albumin adsorption between uncoated and lysozyme-coated polymacon, nelfilcon A, omafilcon A, and ocufilcon. However, non-coated nesofilcon A lenses deposited the highest amount of albumin compared to other non-coated lenses. Lysozyme-coated etafilcon A lenses exhibited lower levels of deposited albumin than uncoated etafilcon A lenses.

The above result suggests that the integration of lysozyme into etafilcon A should provide an additional benefit: lowering the deposition of albumin, which may contribute to its low incidence of bacterial infection or adverse events rate in daily wear, since bacterial adhesion to contact lenses is considered to be a key initiator of adverse events [69].

4.2. Tear film lipid interactions with hydrogel materials

The clinical implications of lipid deposits on contact lenses are unclear. Anecdotally, excess lipid deposition is thought to be responsible for slight visual degradation (so-called ‘smeary vision’). On the other hand, selective adsorption of some lipids at certain levels could improve comfort in contact lens wearers [70].

Lipid deposition on contact lenses was first reported in the 1980s, with reports of lens calculi (which are largely lipid in origin) being common on high water content hydrogels [71–73]. Early work suggested that the presence of relatively hydrophobic monomers such as NVP resulted in increased amounts of lipid deposition [59,74,75]. Lipid deposition on a clinically-worn NVP-based hydrogel (alphafilcon A) progressively increased over a four-week period and was shown to markedly differ between wearers [75]. In comparison, etafilcon A deposited very low levels of lipid across a four-week period and there was very little difference between subjects [64]. More recent work investigating the deposition of lipids on hydrogel materials has confirmed that etafilcon A exhibits very low levels of lipid deposition over a 2–4 week period in both in vitro and *ex vivo* studies [68,76–80]. Kinetic studies show that lipid accumulation is progressive over time with hydrophobic materials, with no plateau in hydrophobic substrates [81], but is very low and relatively flat with etafilcon A [75,76,79].

The introduction of frequent replacement and disposable hydrogel lenses largely eradicated deposit-related clinical problems. Examination of lens materials replaced daily also supports the fact that lipid accumulation is very low with hydrogel compared with silicone hydrogel materials [81]. Silicone hydrogels are more prone to lipid deposits than hydrogels due to their incorporation of hydrophobic silicone components, whose hydrophobicity drives increased lipid deposition [16,39,45,68,79].

4.3. Summary of tear film deposition on hydrogel materials

Hydrogel materials rapidly interact with tear film proteins and lipids once inserted onto the ocular surface. Protein deposition on contact lenses is substantially impacted by the lens material and its ionicity, water content, the individual protein structure and its surface charge. It is largely driven by electrostatic forces, with MA facilitating rapid and substantial uptake of positively charged lysozyme.

Table 2 demonstrates that etafilcon A is different in its chemical composition to other commonly fitted hydrogel materials, in that it has a high water content and is negatively charged through the presence of MA. This unique composition results in a material that rapidly takes up significantly higher amounts of lysozyme and keeps it in an active state. Etafilcon A also takes up higher amounts of lactoferrin and resists the deposition of albumin and lipids compared to other hydrogel lenses. The interaction of etafilcon A with these major tear film proteins may be beneficial in keeping bacterial adhesion low and minimising inflammatory reactions (see Section 7.2).

5. Corneal oxygenation during hydrogel lens wear

It is often forgotten that the original ‘gas permeable’ contact lenses were not the rigid lenses afforded this terminology today but the first hydrogels, [82] which emerged in the late 1960s and received FDA approval in 1972 [83]. As such, any review of hydrogel lens development runs in parallel with an understanding of material oxygen performance, the delivery of oxygen to the cornea and the overall clinical significance of these parameters.

5.1. Lens oxygen permeability and transmissibility

Debate raged in the mid-1980s about the precise techniques which should be employed for measuring the oxygen permeability of hydrogels and the different corrections required to overcome errors inherent with the relatively inexpensive polarographic method [84–86]. In that era, the only tool which manufacturers could deploy to alter the oxygen permeability (termed ‘Dk’ in the contact lens literature as this property is the product of the material diffusivity [D] and solubility [k]) of their hydrogel materials was to vary their water content by modifying the chemical composition of their polymers.

A good example of this is the etafilcon A material itself, where the addition of small quantities of MA to the standard base hydrophilic polymer of HEMA causes an increase in equilibrium water content, at room temperature, from 38 % to 58 % and an associated increase in Dk from seven units to about 20 units [11]. Indeed, the relationship between water content (W) and Dk was established by Morgan and Efron [11] to be entirely predictable using this formula:

$$Dk = 1.67e^{0.0397W}$$

At that time, the general use of Dk (and the more clinically-relevant parameter of oxygen transmissibility, which incorporated lens thickness, Dk/t) was uncontroversial [87]. This is because the models developed at that time indicated that a change of Dk/t from 10 to 20 units in open eye conditions provided approximately double the amount of oxygen at the corneal surface. Describing contact lens oxygen performance with laboratory-derived measures such as Dk was considered quite appropriate.

5.2. Corneal flux and oxygen consumption

The introduction of silicone hydrogels at the turn of the century forced a re-think on how oxygen performance should be described. Most notably, Brennan presented models which predicted the relationship between Dk/t and both oxygen flux [88] (the amount of oxygen reaching the front surface of the cornea) (Fig. 1) and corneal oxygen consumption [89].

Such relationships were often described as a ‘law of diminishing returns’, to emphasise the notion that there was an upper limit to the amount of oxygen which can be transported by a contact lens (related, ultimately, to the partial pressure of oxygen in the atmosphere). The

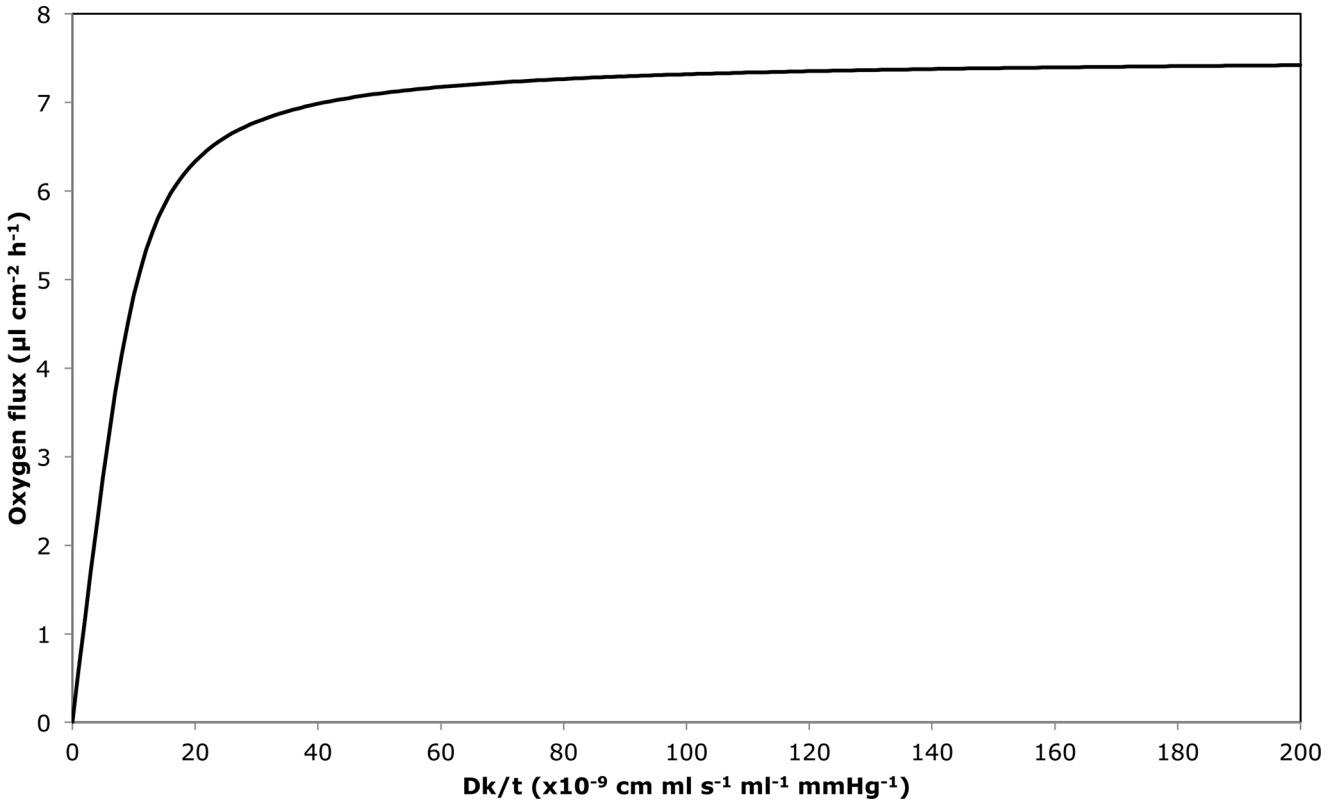

Fig. 1. Relation between corneal oxygen flux and contact lens oxygen transmissibility, demonstrating the 'law of diminishing returns'.

model demonstrates, for example, that doubling Dk/t from five to 10 units is associated with a 75 % increase in oxygen flux, whereas the same proportionate change from 40 to 80 units is associated with only a 4% improvement [88]. Brennan calculated that, in the open eye, there is no difference in central corneal oxygen consumption – determined to be 44.8 nL/cm/sec – above a Dk/t of approximately 20×10^{-9} (cm/sec)(mLO_2/mL/mm Hg); thus, there is no difference between etafilcon A and lotrafilcon A (the silicone hydrogel material with the highest Dk/t) [89].

5.3. Determining the critical oxygen transmissibility for maintaining normal anterior eye physiology

Numerous workers have attempted to define the contact lens Dk/t values required for various definitions of normal ocular surface physiology. The best known work is that of Holden and Mertz [90], who reported that the Dk/t requirement for the absence of corneal swelling during open eye wear was 24.1 units. It is generally overlooked that the permeability measures reported by Holden-Mertz were neither edge-corrected [86] nor boundary layer corrected [91] and an equivalent, properly-corrected, value is 21.8 [11].

Other researchers have found broadly similar values, with Morgan et al. [92] suggesting a value of 19.8 units to avoid swelling in the central cornea and 32.6 units in the corneal periphery. Since the central oxygen transmissibility of a thin, medium water content hydrogel (say -3.00D etafilcon A which has a Dk/t of 27 units) exceeds the thresholds to avoid central corneal swelling, the central cornea is fully oxygenated under such conditions. Indeed, calculations from the models from both Brennan [88,89] and Chhabra et al. [93] predict that the cornea will consume essentially the same amount of oxygen during wear of thin, minus power contact lenses as it would under open eye conditions. Oxygen transmissibility thresholds for this form of lens wear have varied from 56 to 300 units [94–96], which is the equivalent to 87%–98% of the oxygen flux to the anterior cornea in the non-lens wearing, closed eye state [97].

While the oxygen needs of the central cornea are satisfied during open-eye wear of thin, medium water content hydrogels, some degree of hypoxia will be experienced by the peripheral cornea or where lenses are thicker, say for vision correction in plus powers. The extent of hypoxia

depends on the specific material and lens power characteristics, whereas silicone hydrogels will almost always exceed the required levels [98]. As such, it is pertinent to consider the potential clinical ramifications of the oxygen deficit found when hydrogel lenses with high powers are worn.

5.4. Microbial keratitis and corneal infiltrative events are unrelated to oxygen deprivation

That microbial keratitis is not reduced with silicone hydrogel lenses and the rate of corneal infiltrative events (CIEs) is higher in reusable silicone hydrogel lens wear compared to hydrogel lens wear [99–103] suggests that corneal oxygenation is not a key determinant for such adverse events. Some authors have speculated that materials with a higher modulus of elasticity (which is typically greater in silicone-containing materials) may also be implicated in the aetiology of CIEs, due to the greater mechanical impact of such lenses on the corneal surface [104,105].

Reasons for the decreased risk of CIEs with conventional hydrogel lenses are unclear but are unlikely to be due to the oxygen performance of these lenses and may relate to differences in deposition profiles [106], mechanical properties (see Section 7.3) and solution interactions (see Section 7.4) for these two major classifications of materials.

5.4.1. Corneal swelling

In daily wear, some modest corneal swelling may be measured during the use of hydrogel lenses [90,92]. Whilst this is clearly not desirable under the 'first, do no harm' maxim, no studies have

demonstrated a relationship between low levels of corneal swelling and longer-term corneal pathologies.

For daily wear in low to moderate degrees of myopia, there is no evidence to support the need to fit silicone hydrogel lenses, over lower Dk hydrogels, due to concerns around corneal swelling. For example, Moezzi et al. [107] reported no clinically significant differences in corneal swelling when habitual, reusable, silicone hydrogel, daily wear subjects were refitted into etafilcon A, multifocal daily disposable lenses and followed for four weeks. Also, Moezzi et al. [108] demonstrated no difference in topographical corneal swelling between Acuvue Define lenses and Acuvue Define lenses with Lacreon, versus no lens wear. Further long-term research would be required to validate these'no difference' observations.

The human cornea swells about 3% overnight [109]. Compared to two hours after waking, the normal non-lens wearing cornea thins throughout the day with the cornea being thinnest in the evening [110,111]. Several studies have demonstrated no impediment to this normal corneal deswelling process using the etafilcon A hydrogel material [92,108,112,113]. Szczotka-Flynn et al. [113] measured central corneal thickness before and after daily wear in 36 participants wearing etafilcon A (Dk ~17), lotrafilcon B (Dk ~ 110) and comfilcon A (Dk ~128) lenses between -1.00D and -6.00D in power. They documented about 0.3 % deswelling with the etafilcon A lens, which showed no clinically significant difference (within a 1.5 % non-inferiority margin) compared to the other two silicone hydrogel lens types.

5.4.2. Corneal vascularisation

Corneal vascularisation is a potential concern because vessel growth which impinges on the pupil area may be sight-threatening. Although this was an important clinical issue in the early days of thick hydrogel lenses [114], there have been very few reported cases of corneal vascularisation with current-generation hydrogel or silicone hydrogel lenses used for cosmetic daily wear.

5.4.3. Limbal hyperaemia

Although small, statistically significant differences in limbal redness can be detected in well-controlled studies, consideration needs to be given to the magnitude of difference or change that can be considered to be clinically important. Efron et al. [115] demonstrated that a difference or change in limbal redness of ≥ 0.7 grading scale units can be considered as being clinically important. Pult et al. [116] reported that a difference in limbal redness of less than 0.5 grade scale units cannot be reliably detected clinically.

Several studies have examined short-term differences in limbal hyperaemia between those wearing hydrogel versus silicone hydrogel lenses. Maldonado-Codina et al. [117] reported increased limbal redness over a four week period in daily wear use of etafilcon A lenses compared to galyfilcon A and lotrafilcon A lenses in neophytes in a masked study. The difference was about 0.5 grading units, which is at the boundary of what can be considered clinically important [115,116].

Other studies have not found the degree of limbal redness with hydrogels to be clinically significant. Szczotka-Flynn et al. [113] assessed differences in limbal hyperaemia and endothelial bleb formation between etafilcon A and two silicone hydrogel lens types (lotrafilcon B and comfilcon A) over a seven day period. The difference in limbal redness fell within 0.10 (compared to lotrafilcon B) and 0.18 (compared to comfilcon A) grade units. Diec et al [118] reported a statistically significant difference of 0.2 units comparing etafilcon A with two silicone hydrogel lenses (narafilcon A and senofilcon A) in a randomized 3 month study involving 120 subjects.

Moezzi et al. [107] made objective measurements of bulbar and limbal conjunctival hyperaemia among presbyopes who switched from silicone-hydrogel lenses to daily disposable hydrogels. These authors reported no clinically significant differences in these measures among subjects followed for four weeks.

Although the studies discussed above suggest little cosmetic difference in limbal redness between hydrogel and silicone hydrogel lenses, the slightly greater hyperaemia with hydrogel lenses can assume physiological significance since this is a potential precursor of neovascularisation. Such occurrences are rare with cosmetic wear of any form of hydrogel lens, and discontinuation or refitting of lenses would be seldom required; nevertheless, all lens wearers displaying excess limbal hyperaemia should be monitored during routine aftercare examination.

6. Bacterial adhesion to hydrogel lenses

Microbial adhesion to contact lenses is believed to be an important initial step in many adverse events that can occur during contact lens wear. This may result in the production of corneal infection, microbial keratitis or CIEs [119]. With microbial keratitis, it is thought that microbes attached to the lenses become detached and then penetrate the corneal surface and replicate within the tissue [120]. It has also been hypothesized that non-adherent microbes trapped behind a soft lens with poor tear exchange can cause infection. With CIEs, there is an immune reaction to the adherent microbes that results in conjunctival redness, infiltration of corneal tissue by white blood cells, and often pain [121].

Many types of microbes can be implicated in contact lens-associated keratitis, such as bacteria, amoeba and fungi. To cover all of these microbes is considered to be beyond the scope of this review; therefore, only bacterial adhesion to hydrogel lenses will be considered by way of example, as epidemiological studies show that bacteria are the prime culprit in contact lens-associated keratitis [122].

Bacteria adherent to contact lenses are considered to be the initiators of some of these adverse events. Different types of bacteria are associated with these adverse events. Contact lens-induced microbial keratitis is most commonly caused by *Pseudomonas aeruginosa* [119]. Contact lens-induced acute red eye is commonly caused by adhered Gram-negative bacteria such as *P. aeruginosa, Serratia marcescens, Haemophilus influenzae,* as well as by the Gram-positive bacterium *Streptococcus pneumoniae* [123–127]. Contact lens-induced peripheral ulcers are driven by the Gram-positive bacterium *Staphylococcus aureus* adhering to contact lenses or lids [128]. Infiltrative keratitis can be driven by Gram-negative bacteria adherent to lenses [121].

Epidemiology studies have demonstrated that there is increased risk (>1.8x) of developing CIEs when reusable silicone hydrogel contact lenses are worn on a daily wear basis compared to hydrogel lenses [99–103]. Etafilcon A-based lenses have been one of the most commonly prescribed hydrogel lenses worldwide [113]. Furthermore, in daily disposable wear, there is an increased risk of developing microbial keratitis with certain HEMA-based polymers compared to etafilcon A lenses [129].

Examining the published literature for adhesion of microbes to contact lenses presents several issues. The most serious issue is the lack of consistency between study designs, especially with regard to the medium in which microbes had been grown, the growth phase which the microbes had reached, the suspension medium in which cells had been suspended prior to incubating with lenses, the incubation time, the incubation density of microbial cells with lenses, whether the incubation was static, with shaking or (rarely) using flow cells, the microbial type (although *P. aeruginosa* was the most commonly studied, many different strains have been used), and finally the enumeration method to determine the number of cells adhered to lenses. All of these differences have been shown to affect the numbers of microbes adhering to lenses. It appears from reviewing the relevant literature that microbes tend not to be recovered from etafilcon A lenses in greater numbers than from other lens types [130].

7. Adverse events with daily wear hydrogel lenses compared to other modalities

The frequency of hypoxic complications (such as corneal neovascularisation and endothelial polymegethism) and hypoxic signs (such as limbal hyperaemia) have reduced with the introduction of silicone hydrogel materials [131], which is why such lenses are required for successful extended wear. However, there is no evidence to support refitting patients into higher oxygen transmissible soft lenses to decrease the risk of adverse events during *daily* wear. In fact, the use of silicone hydrogel lenses on a reusable basis has unexpectedly *increased* the incidence of some types of inflammatory and mechanical adverse events [99]. Daily disposable lenses have been found to significantly reduce the incidence of CIEs [99,132]. Since the incidence of CIEs with daily disposable lenses is so low and daily disposable lenses made in silicone hydrogel materials are more recent additions to the market, modern studies have not been able to demonstrate any differences between silicone hydrogel and hydrogel daily disposable lenses [132].

7.1. Microbial keratitis

Prior to the introduction of silicone hydrogel contact lenses, corneal hypoxia was thought to be an important contributory factor to adverse events, even in bacterially driven complications, including microbial keratitis [133,134]. However, there has been no reduction in the incidence of microbial keratitis among contact lens wearers with any of the higher oxygen transmissible materials, regardless of replacement schedules [135].

Fortunately, the incidence of microbial keratitis during any lens wear remains low at about 4 per 10,000 lens users per year [136], the same rate that was identified by Poggio et al. [137] in 1989 in the US with non-disposable conventional hydrogel lenses, although there have not been any large studies addressing this issue in the past decade. In fact, rates of microbial keratitis with daily wear hydrogel lenses reported in other countries have been low – 2.7/10,000 in the United Kingdom [138]; 2.2/10,000 in Sweden [139]; and 1.9–2.0/10,000 in strict daily hydrogel lens wear (absolutely no occasional overnight use) in Australia [136]. Brennan and Coles [106] have advanced the concept that anti-microbial protein components adhere well to hydrogel lenses, and Efron [30] has suggested that this low microbial keratitis rate is due to the protective effect of the ubiquitous sub-clinical inflammation present in all forms of lens wear, which primes the immuno-protective mechanisms in the anterior eye to ward off any noxious insult.

Despite industry innovation, neither programmed replacement [140], daily disposable or silicone hydrogel lenses [136] have reduced the risk of microbial keratitis, although studies assessing the impact of hydrogel daily disposable lenses indicate they lessen the severity of the disease [136,141,142]. Interestingly, among the hydrogel-based daily disposable lenses, there are brand differences pertaining to risk of microbial keratitis. As outlined in Table 3, daily disposable lenses manufactured in etafilcon A material have shown the lowest risk of microbial keratitis compared to other daily disposable lenses, as reported in several multicenter case-control studies [129,143]. On the other hand, Carnt et al. [148] have reported that the wearing of reusable group IV lenses carries an increased risk of acanthamoeba keratitis of 6.71 (confidence interval 1.31–34.29, $p = 0.022$). The incidence of microbial keratitis with silicone hydrogel daily disposable lenses has yet to be determined.

Given the reports of increased risk of microbial keratitis and CIEs as seen in Table 3 with the first generation of daily disposable contact lenses other than those made from etafilcon A, it is surprising that there is a paucity of studies examining the microbial adhesion to etafilcon A compared other daily disposable materials such as hilafilcon B (SofLens; Bausch and Lomb, Rochester, NY) or nelfilcon A (Dailies; Alcon, Fort Worth, TX). Of the studies examining this, most have found that there are similar recoveries of bacteria from etafilcon A lenses compared to other disposable lens materials such as such as hilafilcon B (SofLens; Bausch and Lomb, Rochester, NY) or nelfilcon A (Dailies; Alcon, Fort Worth, TX) (see Section 6). However, further studies are warranted in order to draw any firm conclusions regarding microbial adhesion and differences in adverse events.

7.2. Corneal infiltrative events

Similarly, inflammatory events have not diminished, but rather the overall incidence of CIEs is higher during reusable daily and extended wear with silicone hydrogel lenses [99,103]. As seen in Table 3, silicone hydrogel materials approximately doubled the risk of CIEs, independent of the mode of use or during daily wear [99,100]. Hydrogel lenses may therefore be preferred over silicone-based lenses in people who have experienced previous inflammatory events, as CIEs are known to recur in certain predisposed individuals [144].

Although true silicone allergy is not plausible [36], immune cells may interact more with antigens on the surface of silicone hydrogel lenses than hydrogel lenses. Indeed, the incidence of CIEs with non-silicone hydrogel lenses remains very low, and specifically for daily disposable hydrogel lens use, ranges from 0 to 2.5% [118,132,145,146].

7.3. Mechanical events

There are fewer corneal erosions and mechanical events with lower modulus hydrogels compared to silicone hydrogels [102,149]. In fact, the combination of erosions and gram-negative bacterial contamination is greatest with reusable silicone hydrogel materials [149], which may explain why microbial keratitis rates continue to be static with the newer lens types. Among daily disposable lenses, mechanical complications overall have been reported to be lowest with the etafilcon A material [149].

7.4. Solution interactions

Since the introduction of silicone hydrogel lenses at the turn of the century, numerous papers [152–158] have highlighted significant corneal staining associated with the wearing of such lenses with certain lens care solutions [159].

On the other hand, studies evaluating corneal staining in response to hydrogel lens wear suggests a generally lower level of response to those same solutions. Andrasko and Ryen [152] reported very low levels of corneal staining (with the exception of a single solution that was subsequently withdrawn from the market) in subjects wearing etafilcon A lenses maintained with a large range of lens care solutions, compared with the staining responses observed with silicone hydrogel and two other Group II hydrogel lenses.

Garofalo et al. [155] assessed corneal staining in patients wearing etafilcon A, alphafilcon A, and lotrafilcon A lenses exposed to four different multipurpose solutions. Lenses made in etafilcon A had the lowest levels of staining, which remained low regardless of time of wear or solutions used. With current day solutions, corneal staining is typically low overall and fewer differences are found among lens types. Kitamata-Wong et al. [160] studied only etafilcon A lenses exposed to a range of modern lens care solutions; in four of five solutions assessed, the average extent of staining was around grade 1. Similarly, Bernstein et al. [161] studied etafilcon A, galyfilcon A, and senofilcon A with four solutions and all combinations produced mean corneal staining < grade 1.

7.5. Clinical implications

Taken together, the low adverse event rate during daily wear with hydrogel lenses, and especially the 12.5 times lower rate of CIEs with daily disposable hydrogels [99], supports their ongoing use in clinical

Table 3
Soft lens material impact on risk and incidence of soft lens complications in daily wear.

Author, Year	Study Type	Study Size (N)	Results	P-Value *Other Findings*
Microbial keratitis				
Stapleton F, Edwards K and Keay L, et al 2012 [147] (Moderate & Severe Keratitis) *Data Source 2003 – 2004*	Multi-Center Case Control	Cases = 90 Controls = 1090	Relative Risk All Keratitis: Reusable Hyd (ref) OR 1.0 Reusable SH OR 2.62 95 % CI [0.97 – 7.1] DD Hyd OR 3.48 95 % CI [0.5 – 4.8] Moderate + Severe Keratitis: Reusable Hyd (ref) OR 1.0 Reusable SH OR 2.18 95 % CI [0.97 – 7.1] DD Hyd OR 3.48 95 % CI [0.5 – 4.8]	All Lens Comparisons N.S. *Significant Storage Case & Compliance Factors*
Stapleton F, Nadivulath, Keay L, et al. 2017 [129] *Data Source 2003 – 2004*	Multi-Center, Case Control of daily disposable wearers	Analyzed Set Cases = 67 Controls = 374	Relative Risk All Keratitis: etafilcon A (ref) OR 1.0 nelfilcon A OR 4.0 95 % CI [3.6 – 4.4] hilafilcon B OR 2.1 95 % CI [1.5 – 2.8] Others OR 2.5 95 % CI [2.3 – 2.8] Moderate + Severe Keratitis: etafilcon A (ref) OR 1.0 nelfilcon A OR 4.8 95 % CI [2.5 – 9.4] hilafilcon B OR 2.6 95 % CI [2.1 – 3.3] Others OR 2.8 95 % CI [1.7 – 4.6]	**All comparisons vs. etafilcon A P < 0.0001**
Dart JK, Radford CF, Minassian D, et al. 2008 [143] *Data from 2003 – 5*	Prospective Case Control		Relative Risk: Reusable Hyd (ref) RR 1.0 Reusable SH RR 0.9 95 % CI [1.7 – 4.6] DD materials: DD etafilcon A RR 0.7 95 % CI [0.4 – 1.3] nelfilcon A RR 3.2 95 % CI [1.9 – 5.6] hilafilcon B RR 2.5 95 % CI [1.0 – 6.0] Other RR 2.1 95 % CI [1.2 – 3.7]	Generic Comparison N. S. **nelfilcon A p < 0.001** **hilafilcon A p = 0.043**
Morgan PB, Efron N, Hill EA et al. 2005 [101] *Data from 2003 – 4*	Prospective Cross-sectional Study	Severe Keratitis: N = 38 Controls: N = 297	Incidence: Reusable Hyd 6.4 % 95 % CI [4.1 %–9.9 %] Reusable SH 0% 95 % CI [0 %–210.0 %] DD Hyd 4.9 % 95 % CI [2.5 %–9.6 %] Relative Risk: Reusable Hyd (ref) OR 1.0 Reusable SH OR NA (annual incidence 0) DD Hyd OR 0.8 95 % CI [0.3 – 1.8]	All Lens Comparisons N.S. or indeterminate due to no events
Carnt N, Hoffman JJ, Verma J et al. 2018 [148] *Data from 2011 – 17*	Prospective Case-control and retrospective Incidence Study	Severe Keratitis: N = 63 Controls: N = 213	Acanthamoeba Keratitis Incidence: 2000 – 3 8 – 10 cases p.a. 2014-6 36 – 65 cases p.a. Increased Risk of AK: Group I + II + III lenses RR2.39 95 %CI [0.44 – 12.98] Group IV lenses RR6.71 95 %CI [1.31 – 34.29] Group VB + VC lenses RR2.30 95 %CI [0.84 – 6.32] Referent (Group VA lenses) RR1.0	Group I + II + III P = 0.313 Group IV P = 0.022 Group VB + VC P = 0.107
Corneal infiltrative events (CIEs)				
Diec J, Tilia D, Thomas V. 2018 [145] *Data collection dates not provided*	Retrospective analysis of 5 prospective trials	N = 201 (174 unique participants)	Incidence: DD Hyd (omafilcon A, nelfilcon A) = 2.5 % DD SH (delefilcon A, somofilcon A, narafilcon A) = 6.7 %	p = 0.32 power 30 %

(*continued on next page*)

Table 3 (*continued*)

Author, Year	Study Type	Study Size (N)	Results	P-Value *Other Findings*
Chalmers RL, Hickson-Curran SB, Keay L, et al. 2015 [132] *Data from 2011 – 12*	Prospective Safety Registry	N = 1,171	Incidence: DD etafilcon A = 0.0 % 95 % CI [0.0 %– 0.6 %] DD narafilcon B 0.4 % 95 % CI [0.1 %–1.5 %]	N.S.
Chalmers RL, Keay L, McNally JJ, et al. 2012 [99] *Data from 2006 – 9*	Retrospective Case Control	Cases: N = 201 Controls: N = 603	Relative Risk: Hyd materials (ref) OR 1.0 SH materials OR 2.0 95 % CI [1.1 – 3.8]	**p < 0.05**
Chalmers RL, Wagner H, Mitchell GL, et al 2011 [100] *Data from 2006 – 9*	Retrospective Case Control	Cases: N = 187 Controls: N = 3,362	Reusable Hyd (ref) OR 1.0 Reusable SH OR 1.9 95 % CI [1.3 – 2.7]	**p < 0.05**
Radford CF, Minassian D, Dart JKG et al. 2009 [102] *Data from 2003 – 5*	Prospective Case Control	Cases 877 Controls: Hospital = 1069 Population = 639	Relative Risk: Generic Categories: Reusable Hyd (ref) OR 1.0 Reusable SH OR 2.0 95 % CI [1.2 – 3.3] DD materials: DD etafilcon A OR 0.5 95 % CI [0.3 – 2.0] nelfilcon A OR 2.7 95 % CI [1.7 – 4.1] hilafilcon B OR 0.8 95 % CI [0.3 – 2.2]	**SH vs Hyd p = 0.005** **etafilcon A reduced risk p = 0.039** **nelfilcon A increased risk p < 0.001**
Morgan PB, Efron N, Hill EA et al. 2005 [101] *Data from 2003 – 4*	Prospective Cross-sectional Study	Non-Severe Keratitis (CIEs): N = 80 Controls: N = 297	Incidence: Reusable Hyd 14.1 % 95 % CI [10.4 %–19.0 %] Reusable SH 55.9 % 95 % CI [9.9 %–309 %] DD Hyd 9.1 % 95 % CI [5.5 %–15.1 %] Relative Risk: Reusable Hyd (ref) OR 1.0 Reusable SH OR 4.0 95 % CI [0.6 – 28.7] DD Hyd OR 0.7 95 % CI [0.4 – 1.2]	All Lens Comparisons N.S.
Corneal erosions and mechanical disorders				
Willcox MD, Naduvilath TJ, Vaddavalli PK, et al. 2010 [149] Data from 1996 – 2000	Randomized Prospective Clinical Trials	DD Hyd = 278 Reusable Hyd = 1,183 Reusable SH = 1,641	Incidence *(% eyes per visit)* DD etafilcon A 0% [0.0 %-0.0 %] Reusable Hyd 0.01 % [0.0 %-0.4 %] Reusable SH 0.02 % [0.0 %-0.13 %] Risk of co-occurrence of corneal erosion and gram-negative bacteria on CL DD etafilcon A 0/10,000 Reusable Hyd 1.6/10,000 95 % CI [0.2 – 10.6] Reusable SH 5.2/10,000 95 % CI [1.6 – 16.4]	No statistical comparisons computed
Radford CF, Minassian D, Dart JKG et al. 2009 [102] *Data from 2003 – 5*	Prospective Case Control		Reusable Hyd (ref) OR 1.0 **Reusable SH OR 1.8** 95 % **CI [1.1 – 2.8]** DD materials: etafilcon A OR 1.1 95 % CI [0.7 – 1.6] **nelfilcon A OR 2.2** 95 % **CI [1.5 – 3.2]** hilafilcon B OR 1.6 95 % CI [0.8 – 3.1]	**SH vs Hyd p = 0.015** **nelfilcon A p < 0.001**
Overall symptomatic complications				
Wagner H, Chalmers RL, Mitchell GL et al 2011 [150] *Data from 2006 – 9*	Retrospective Case Control	Cases = 426 Controls = 3,123	Reusable SH (ref) OR 1.0 Reusable Hyd OR 0.7 95 % CI [0.6 – 0.9]	**P = 0.001**
Forister JF, Forister EF, Yeung KK et al. 2009 [151] *Data from 2006 – 7*	Prospective Cross-section in Tertiary Clinic	N = 572	Incidence complications/eye: SH 0.79 +/- 0.76 Hyd 0.90 +/- 0.87	P = 0.23

DD = daily disposable, Hyd = non-silicone hydrogel, SH = silicone hydrogel.
OR = Odds Ratio, RR = Relative Risk, **Bold** = statistically significant comparison.

practice to maintain a "quieter eye" relative to the occurrence of adverse responses associated with silicone hydrogels. Similarly, daily disposable hydrogels are known to be successful in refitting "problem patients". Hickson-Curran et al. [162] studied problematic reusable contact lens wearers, a high proportion of whom were silicone hydrogel lens wearers; after refitting with hydrogel daily disposables, their wearing time, dryness and corneal staining improved. From an inflammatory, infectious and mechanical adverse event perspective, daily disposable hydrogel lenses will continue to be a mainstay in contact lens practice because of their proven safety profile.

7.6. Impact of corneal oxygenation on adverse events

Overall, conventional hydrogel lenses such as etafilcon A generally have lower levels of oxygen transmissibility compared to silicone hydrogel lenses; however, at the central cornea under daily wear conditions, they deliver the same levels of corneal oxygenation. Thus, for daily lens wear, there is little difference between hydrogel and silicone hydrogel lenses in respect of hypoxic corneal adverse event rates, and most importantly, infection rates. Eyecare practitioners considering their material of choice for daily wear – assuming all other parameters such as vision and comfort are equivalent – need to decide whether to select (a) a silicone hydrogel, which delivers oxygenation similar to the no-lens wear situation, but which may be associated with an increased risk of corneal inflammatory events when worn on a reusable basis, or (b) a conventional hydrogel, which may deliver a quieter eye with a lower risk of adverse events, but will not afford the same oxygen benefits as required in extended wear.

8. Conclusions

Contact lens practitioners can remain assured that contact lenses manufactured in conventional low modulus hydrogel materials can continue to provide good comfort, wettability, low lipid deposition (such as with etafilcon A) and a lower rate of inflammatory and mechanical adverse events compared to their silicone hydrogel counterparts. Although protein deposition is higher, in particular non-denatured lysozyme, in a frequently replaced lens modality this may be counterintuitively beneficial. Large studies have confirmed very low inflammatory event rates with daily disposable lenses manufactured in etafilcon A [102,132], which has the highest lysozyme deposition profile.

It is apparent from this review that there are many gaps in the literature. For example, almost all studies examining differences between hydrogel and silicone hydrogel lenses have been short-term (typically less than three months); it would be interesting to know if such differences, or the absence of any difference, was still apparent after many years. More needs to be learned about the benefits of lysozyme absorption into etafilcon A lenses and its role in lowering albumin and consequent bacterial adhesion. Further epidemiological studies are required to establish the incidence of microbial keratitis with daily disposable silicone hydrogel lenses, since the most recent studies [101,136] were conducted prior to the widespread use of this lens type.

There are circumstances where practitioners have returned or maintained patients in lenses made in hydrogel materials over silicone hydrogel materials to achieve a low inflammatory and risk profile [163,164]; this clinical approach is generally consistent with the literature presented herein. Although improved corneal physiology from decreased hypoxia with silicone hydrogel lenses is understood, the literature also supports that, for low to moderate degrees of myopia, daily wear hydrogel lenses do not impede the daily corneal de-swelling process, and within an acceptable non-inferiority margin, do not induce limbal redness or endothelial blebs compared to modern silicone hydrogel lenses [113]. Therefore, hydrogel lenses remain an important alternative in modern contact lens practice.

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