CLEAR Complications Report

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KEYWORDS

Infection, inflammation, metabolic, mechanical, toxic, hypersensitivity, papillary conjunctivitis

ABBREVIATIONS

ADDE	Aqueous deficient dry eye
CIE	Corneal infiltrative events
CLADE	Contact lens-associated dry eye
CLD	Contact lens discomfort
CLIDE	Contact lens-induced dry eye
CLPC	Contact lens-Induced papillary conjunctivitis
CLPU	Contact lens-related peripheral ulcers
DED	Dry eye disease
EDE	Evaporative dry eye
ECP	Eye care practitioner
IVCM	*In vivo* confocal microscopy
LSCD	Limbal stem cell deficiency
LWE	Lid-wiper epitheliopathy
MGD	Meibomian gland dysfunction
MK	Microbial keratitis
PHMB	Polyhexamethylene biguanide
PMMA	Polymethylmethacrylate
SICS	Solution-induced corneal staining
SiHy	Silicone hydrogel
TBUT	Tear film break-up time
TFOS DEWS II	Tear Film and Ocular Surface Dry Eye Workshop II

Abstract

Contact lens-related complications are common, affecting around one third of wearers, although most are mild and easily managed. Contact lenses have well-defined anatomical and physiological effects on the ocular surface and can result in other consequences due to the presence of a biologically active material. A contact lens interacts with the tear film, ocular surface, skin, endogenous and environmental microorganisms, components of care solutions and other antigens which may result in disease specific to contact lens wear, such as metabolic or hypersensitivity disorders. Contact lens wear may also modify the epidemiology or pathophysiology of recognised conditions, such as papillary conjunctivitis or microbial keratitis. Wearers may also present with intercurrent disease, meaning concomitant or pre-existing conditions unrelated to contact lens wear, such as allergic eye disease or blepharitis, which may complicate the diagnosis and management of contact lens-related disease.

Complications can be grouped into corneal infection (microbial keratitis), corneal inflammation (sterile keratitis), metabolic conditions (epithelial: microcysts, vacuoles, bullae, tight lens syndrome, epithelial oedema; stromal: superficial and deep neovascularisation, stromal oedema [striae/folds], endothelial: blebs, polymegethism/ pleomorphism), mechanical (corneal abrasion, corneal erosion, lens binding, warpage/refractive error changes; superior epithelial arcuate lesion, mucin balls, conjunctival epithelial flaps, ptosis, discomfort), toxic and allergic disorders (papillary conjunctivitis, solution-induced corneal staining, incomplete neutralisation of peroxide, Limbal Stem Cell Deficiency), tear resurfacing disorders/dry eye (contact lens-induced dry eye, Meibomian gland dysfunction, lid wiper epitheliopathy, lid parallel conjunctival folds, inferior closure stain, 3 and 9 o'clock stain, dellen, dimple veil) or contact lens discomfort. This report summarises the best available evidence for the classification, epidemiology, pathophysiology, management and prevention of contact lens-related complications in addition to presenting strategies for optimising contact lens wear.

1 Introduction

Contact lens-related complications are common, with one third of wearers surveyed in the USA reporting having experienced a red or painful eye requiring emergency eye care [1]. A similar proportion of wearers derived from eyecare practices reported experiencing a complication arising from lens wear [2]. Forty three percent of asymptomatic wearers present with clinically observed ocular surface signs, which may predispose them to contact lens-related complications [3]. Complications may result in a reduction in wear time, discontinuation from contact lens wear or a need for emergency eye care. Severe complications may result in vision loss and in significant cost and morbidity [4].

Contact lens-related complications differ from other ocular surface conditions in several ways. Contact lenses can have well-defined anatomical and physiological effects on the ocular surface and can result in other consequences due to the presence of a biologically active material [5]. A contact lens interacts with the tear film, ocular surface, skin, endogenous and environmental microorganisms, components of care solutions and other antigens which may result in disease specific to contact lens wear, such as metabolic or hypersensitivity disorders. For the same reasons, contact lens wear may also modify the epidemiology or pathophysiology of recognised conditions, such as contact lens induced papillary conjunctivitis (CLPC) or microbial keratitis (MK). Wearers may also present with intercurrent disease, meaning concomitant or pre-existing conditions unrelated to contact lens wear, such as allergic eye disease or blepharitis, which may complicate the diagnosis and management of contact lens -related disease.

This report summarises the best available evidence for the classification, epidemiology, pathophysiology, management and prevention of contact lens-related complications in addition to presenting strategies for optimising contact lens wear.

1.1 Scope of the report

This report will consider only contact lens-related complications per the definition below and where possible recent evidence will be prioritised. The effects of contact lens wear on the anatomy and physiology of the eye and medical and speciality indications for contact lens wear are outside of the scope of the report and are covered elsewhere.

1.2 Definition of a contact lens complication

A contact lens complication is considered to be an event caused by contact lens wear, which is generally symptomatic, causing the wearer to seek care, or requiring intervention, such as an interruption to contact lens wear or pharmacological intervention .

1.3 Classification of complications

Several approaches have been proposed in order to classify contact lens -related complications, including classification based on anatomical location, presumed aetiology and severity of the condition. Each approach may be suitable for different applications.

1.4 Anatomical location

Contact lens complications have been classified according to anatomical location [6, 7], which is a useful approach in systematically evaluating the physiological effect of contact lenses on each of the ocular structures. This can be helpful from a teaching perspective. However, this approach does not inform the pathogenesis and may not be helpful in managing or preventing the complication.

1.5 Presumed aetiology

Categorisation by presumed aetiology can be helpful for treatment as well as management and prevention of adverse events. For example, to assist in managing sterile corneal infiltrates, an approach based on presumed aetiology has been described, where corneal infiltrates were classified as traumatic, viral,

allergic, preserved solution-related, contact lens fitting-related, due to coated lenses, toxic vapours or idiopathic [8]. This method has also been used in a broader range of complications, classified as patient-, contact lens - or care-related events, in an attempt to support their management [9].

A similar approach was used in a series of epidemiological studies where complications were classified as either 'ulcerative' (microbial keratitis) or 'non-ulcerative'. The latter group were categorised into six divisions based on presumed aetiology: sterile keratitis, toxic and hypersensitivity, metabolic, mechanical, tear resurfacing and other contact lens related events [5, 10, 11]. Most recently, this classification has been modified to include four categories, based on microbial challenge, hypoxia, mechanical and toxicity challenges to the ocular surface due to contact lens wear [12].

One of the difficulties with an aetiological classification approach is where more than one mechanism may be involved in the pathophysiology of the condition. For example, the presentation of CLPC is thought to be primarily due to a mechanical stimulus in silicone hydrogel (SiHy) lenses and is localised to the region corresponding to the lens edge. Conversely with hydrogel contact lenses, protein deposition and subsequent denaturation, the stimulus is likely to be antigenic and the response inflammatory, manifesting as a generalised palpebral response [13].

While it is clear that MK and sterile infiltrates have different underlying pathophysiology, there is an argument to suggest that there is significant overlap in their clinical signs and that they form a "continuum" of conditions that includes microbial and sterile events [14]. Challenges with this approach include that a binary approach (sterile or microbial) is required to determine management strategy, and a range of clinical presentations are described by one descriptor, such as "generalized or localized conjunctival redness", which limits the diagnostic value of this analysis. This is an inherent problem of retrospective datasets, where diagnostic criteria are not pre-defined and prospectively collected.

1.6 Severity

Several models of classification of sterile keratitis (or corneal infiltrative events, CIE) have been proposed based on disease severity and impact. Corneal infiltrates may be described as severe or non-severe events based on their signs and symptoms [15], however a contrary view suggested that these different categories of sterile inflammatory events were not distinguishable clinically [16].

In summary, while multiple classification systems have been proposed, each with their respective advantages and disadvantages, for the purposes of this report an approach based on likely aetiology has been used. This supports a pragmatic approach to management and prevention. Corneal infection (microbial or ulcerative keratitis) is differentiated from the less serious non-ulcerative events. The “non-ulcerative” are further categorised into six sub-groups: sterile keratitis, toxic/hypersensitivity, metabolic, mechanical, tear resurfacing and other contact lens related events (Table 1).

Table 1: Classification of contact lens-related disorders (adapted from Stapleton et al, 1992[11])

Classification Contact Lens-Related Disorders					
Classification	**Disorder**	**Symptoms**	**Probable origins**	**Corneal signs**	**Conjunctival signs**
Infection	Microbial keratitis	Rapid onset and progression of pain, redness, and discharge	Breach of ocular surface defence due to tear stagnation or microtrauma [17]; infection, inflammation and necrosis of corneal tissue	Epithelial ulcer with underlying stromal infiltrate; *Pseudomonas aeruginosa* common and associated with fulminating course; adherent mucous; gross corneal oedema	Ciliary injection
Inflammation	Sterile keratitis	Discomfort, redness, and discharge	Inflammatory response in absence of infecting organism; factors include delayed hypersensitivity to thiomersal [18], tight lenses [19] and hypersensitivity to bacteria [8] or bacterial toxins [20]; in overnight-wear soft CLs, poor tear exchange causes build-up of trapped cellular/metabolic debris	Like those of marginal keratitis; small peripheral self-limiting subepithelial infiltrates, with/without overlying epithelial defect	Hyperaemia
Metabolic *Epithelial*	Microcysts	None	Impaired metabolic activity; thought to be cellular debris; seen in 85% to 100% of users of overnight-wear soft low Dk [21, 22]; Spike occurs following high Dk refitting [23]	Reverse illumination irregular 15-50um discrete bodies. As reach surface of cornea, exhibit negative staining	None
	Vacuoles	None	Most common in low Dk overnight wear; non reversed illumination suggests fluid filled [24]	Round intraepithelial 20-50µm bodies with distinct margins; seen in conjunction with microcysts	None

	Bullae *Mechanical	Pain and epiphora when coalesce	Hypoxia with possible mechanical component, non-reversed illumination suggest fluid filled [24].	Oval, greater than 40µm bodies that tend to coalesce	None
	Tight lens syndrome	Overwear, starting in morning after over-night anoxia; vision usually affected	Lens tightening precipitated by osmolarity changes causing altered lens parameters	Stromal oedema and epithelial staining	Ciliary injection and limbal indentation
	Epithelial oedema	Blurred vision after wear or adaptation to rigid corneal lens [25]	Hypoxia causing central corneal clouding[26]; osmotic changes due to hypotonic reflex tearing [25].	Dull corneal reflex from central epithelial oedema; diffuse oedema with reflex tearing	None
Stromal	Superficial and deep neovascularisation	None unless lipid keratopathy results from deep vessels, where vision may be lost	Hypoxia causing stromal softening and release of vasogenic mediators	Superficial/deep stromal vessels; lipid keratopathy associated with deep vessels	If active, associated limbal hyperaemia
	Stroma/ oedema (striae/folds)	Blurred vision in some cases	Osmolarity changes causing increased corneal-swelling pressure [27]	Striae occur when 5-6% and folds when 10% oedema [28]	None
Endothelial	Endothelial blebs	None	Hypoxic stress [29]	Black zones in mosaic, occur on CL insertion, transient [30]	None
	Polymegethism/ pleomorphism	None	Chronic hypoxia [22]	Increased size and irregularity of endothelial cells	None
Mechanical	Corneal abrasion	Sudden onset of pain and epiphora;	Trauma caused during CL insertion or removal; foreign	Linear or sharply circumscribed epithelial defect	Hyperaemia

		resolves in hours	bodies trapped behind CL; deposits on CL; poor CL fitting		
	Corneal erosion	Pain, redness, light sensitivity, blurred vision, and tearing	Mechanical injury; overnight wear [31]; Gram negative bacterial CL contamination [32]	Circumscribed epithelial defect; mild stromal oedema	Hyperaemia
	Lens binding	Pain, redness, light sensitivity, blurred vision, and tearing	More frequent with rigid corneal lenses, orthoK and high modulus soft CL overnight wear [31, 33, 34].	Indentation ring or corneal erosion may be present	Indentation ring
	Warpage/Refractive error/ *metabolic	Subtle to marked visual effects	PMMA and low Dk rigid corneal lenses can result in warpage; low Dk overnight wear is associated with small increase in myopia, while no change [35] or slight decrease found in high Dk [36]	Corneal topographical changes	None
	Superior epithelial arcuate lesion	Asymptomatic mostly, irritation, photophobia	Steep corneas [37]; poor CL wetting, tight fitting CLs [38]	Full thickness corneal epithelial lesion, diffuse infiltrates	Sectorial hyperaemia
	Mucin balls	None	Likely associated with lack of tear exchange; Common with high Dk overnight wear, steep corneas [39]	Spherical translucent balls of mucin 20-200um, between lens and cornea; leave depression when removed	None
	Conjunctival epithelial flaps	None	Lens edge and material shear forces on bulbar conjunctiva; increases with wear time [40]	None	Goblet and epithelial cells detached from underlying conjunctiva, often superior and inferior

	Ptosis	Cosmetic	Rigid:upper lid stretching, rubbing the lens while blinking, lid edema or blepharospasm [41]; Soft: inflammation or CL insertion and removal [42]	None	None
	Discomfort *Inflammation	Lens awareness, gritty, scratchy	Multifactorial including: CL material, deposits, wettability, bioburden, CL movement, lens care solutions, inflammatory and other tear film components [43]	Often none	Hyperaemia
Toxic and allergic disorders	CL-related papillary conjunctivitis *Mechanical/ Hypersensitivity	Increased discharge and greasing of CLs; itching on CL removal in early stages; later severe irritation; resolves within days of CL disuse	Multifactorial: immunologic response to proteins deposited on CLs acting as an antigen [44]; mechanical effect of CL edge[18, 45]	None	Upper tarsal hyperaemia; mucous and fine papillary response; 'giant' (compound) papillae in advanced disease
	Solution-induced corneal staining	Stinging on insertion, dryness, redness at the end of wearing time, itching, mucous discharge	Solution toxicity &/or hypersensitivity; response to exposure to compounds adsorbed onto or absorbed by the CL	Diffuse or midperipheral annular corneal punctate staining; can be associated with low grade inflammation [46]	Conjunctival hyperaemia
	Incomplete neutralisation of peroxide	Burning and stinging	Failure to neutralise low pH	Punctate keratitis	Conjunctival injection

	Limbal Stem Cell Deficiency (LSCD) *Mechanical	Pain, decreased vision, foreign body sensation, CL intolerance and photophobia [47]	Preservatives or enzymes may act as haptens causing a local delayed hyper-sensitivity response [48]; interactions between preservatives, lenses, and adsorbed surface mucoproteins may also contribute [49, 50]. Mechanical irritation and inflammation of limbus as a result of CL friction [51]	Progressive epitheliopathy with translucent epithelium, Vortex keratopathy, Loss of palisades of Vogt.[52] Extending centripetally into cornea in a whorl shape. In late stages, superficial and deep vascularisation, scarring, conjunctivalisation, and calcification [52]	Chronic conjunctival redness
Tear resurfacing disorders/Dry Eye	Contact lens induced dry eye (CLIDE) *Inflammation	Foreign body sensation, dryness, eye strain, blurred vision and discomfort [53-56]; asymptomatic on CL removal	Partitioning of tear film leading to tear film thinning and instability [57]	Reduced tear break up time, reduced tear meniscus height, corneal staining	Hyperaemia in severe cases
	Meibomian gland dysfunction *Mechanical	Symptoms of ocular irritation and intermittent blurred vision; may reduce comfortable wear time	Changes to morphological features of Meibomian glands, altered expressibility of glands, quality of meibum. Reduced tear break up time and lipid layer thickness. Mechanical trauma [58] and/or desquamated epithelial cell accumulation at gland orifices [59]	Often none	Structural gland changes, altered expressibility, meibum quality, morphological changes to the lid margin occur

	Lid Wiper Epitheliopathy (LWE) *Mechanical		A sign of mechanical friction due to poor lubrication between lid margin and anterior CL [60]		Exhibits lissamine green/fluorescein staining of lid margin
	Lid parallel conjunctival folds (LIPCOF)*Mechanical	Dry eye symptoms, discomfort	Generalised sign of dry ocular surface exacerbated by CL wear [58, 59, 61]	None	Appear nasal and temporal to inferior limbus
	Inferior closure stain	Inferior redness and discomfort	Incomplete blinking	Inferior/interpalpebral punctate stain	Inferior limbal hyperaemia
	3 and 9 o'clock stain (dellen in severe cases)	Interpalpebral redness; discomfort is rare	Drying of corneal surface adjacent to rigid CL edge	Punctate keratopathy in 3 and 9 o'clock positions with or without vascularized superficial stromal scars	Interpalpebral hyperaemia
	Dimple veil	None or blurred vision	Static air bubbles under lens	Fluorescein pooling in epithelial depression	None
Contact Lens Discomfort	Contact lens discomfort	Reduced comfort while wearing CLs. Reduced comfortable wear time	Origin not fully understood but aetiologies may include mechanical friction, inflammation, dry eye, MGD	Often none, sometimes reduced TBUT, signs of LIPCOF, LWE, MGD	Often none, occasionally mild hyperaemia

*Denotes secondary aetiology; CL: contact lens; Dk: Oxygen permeability; PMMA: Polymethylmethacrylate

2 Contact Lens-related corneal infection

Corneal infection or MK is a rare but potentially severe complication of contact lens wear, which is associated with signficant morbidity including visual loss, societal cost and patient symptoms.

2.1 Frequency

Contact lens-related corneal infection accounts for around 35-65% of new cases of hospital presenting MK in urban tertiary centres [62-66]. In working age adults, contact lenses and trauma are the two main risk factors for corneal infection [66], accounting for 2/3 of all urban cases.

The annualised incidence of corneal infection varies with contact lens type and wear modality, and ranges from 1-2 per 10,000 wearers for daily use of soft and rigid corneal contact lenses to 20 per 10,000 for overnight wear with SiHy or hydrogel lenses [67]. The risk of corneal infection increases with a greater number of days wear per week and with any overnight use, indicating a dose response effect [68]. In overnight wear, there is greater risk in the first six months of wear, indicating possible adaptation with time and/or persistence of survivors in this lens wear modality [67]. Daily disposable contact lens wear is associated with a lower risk of severe disease and vision loss [67]. The incidence of contact lens-related MK has remained stable over time [69], however there have been no prospective studies of corneal infection since the mid-2000s, consequently no reliable incidence estimates with contemporary contact lenses, orthokeratology (See CLEAR Orthokeratology Report[70]) and soft myopia control contact lenses.

2.2 Pathophysiology, risk factors, presenting signs, differential diagnosis, management, outcomes

The majority of contact lens-related infections are due to bacteria (around 80-95%) [63, 71], with the remainder caused by other pathogens including *Acanthamoeba* and filamentary fungi (such as *Fusarium* spp.). The most common bacterial pathogen in most centres is *Pseudomonas aeruginosa* (Figure 1). The proportions

of causative organisms vary depending on the climate; for example in Australia, *Pseudomonas aeruginosa* is more common in tropical regions, compared to the temperate regions, where *Staphylococcus aureus* and *Serratia* spp are more commonly recovered [72]. In addition, in daily disposable contact lens wear, keratitis is more likely to be caused by endogenous bacteria, such as *Staphylococcus* spp. compared to reusable soft lens wearers, in which environmental bacteria, such as *Pseudomonas aeruginosa* predominate [73]. Contact lens storage cases harbour environmental bacteria [74] and are thought to be the source of the pathogen in many reusable wearers with MK.

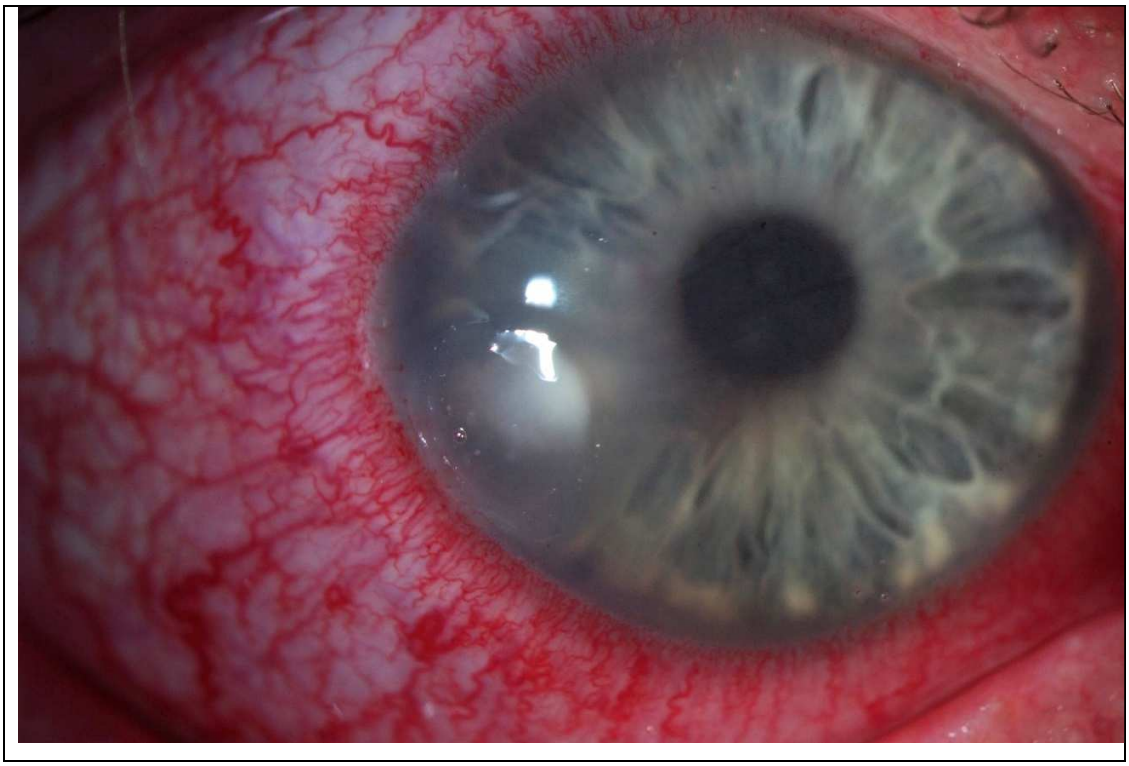

Figure 1: *Pseudomonas aeruginosa* keratitis in a soft contact lens wearer. Image courtesy of Mr Stephen Tuft, Moorfields Eye Hospital. Image reproduced from Carnt et al., 2017 [75].

Established risk factors, presenting signs, differential diagnosis, management and outcomes for different causative organisms are described in Table 2.

Table 2. Risk factors, presenting signs, differential diagnosis, management, and outcomes for each type of causative organism in contact lens-related microbial keratitis

	Causative agent		
	Bacteria	**Acanthamoeba**	**Fungi**
Risk factors			
Modifiable	Poor hand and lens case hygiene [67], overnight wear [67], smoking [67], showering in lenses [76]	Water exposure [77], poor hand and lens hygiene[77, 78], certain lens disinfecting solutions[77, 79]	Certain lens disinfecting solutions [80, 81], non-scheduled lens replacement[80]
Non-modifiable	Male sex [68], young age [68] high SES [67]	Caucasian race [77], low SES [77]	Male sex [80], high income [80], Malay race [80]
Pathognomic signs & symptoms	Irregular focal anterior-mid stromal lesion/s with overlying staining/ulcer	Early: Epithelial disruption, often in branched pattern, peri-neural infiltrates Late: scleritis, ring infiltrate	Focal deep stromal lesion, fluffy edge, slough-like surface commonly with satellite infiltrates
Common signs	Generalised conjunctival hyperaemia, pain and photophobia, bystander effects: anterior chamber reaction and lid oedema		
Differential Diagnosis	Fungal keratitis, sterile keratitis, marginal keratitis, peripheral ulcerative keratitis	Herpes Simplex/Zoster keratitis, foreign body, healing abrasion	Bacterial keratitis, marginal keratitis
Diagnostic tests (in addition to clinical judgement)	Corneal scrape for culture* and smear, PCR	Corneal epithelial biopsy, scrape and smear, PCR, *in vivo* confocal microscopy	Corneal scrape and smear, *in vivo* confocal microscopy
Management (typical)	Intensive broad-spectrum topical antibiotics, typically fluoroquinolone (15 min loading dose for first 6 hours), hrly night and day, reduce frequency according to repithelialisation then qid; optional	Biguanide (PHMB or chlorhexidine) monotherapy or with diamidine (brolene, hexamidine), hrly night and day 2-5 days; then qid; concurrent topical or oral corticosteroids if scleritis/ring infiltrate; Concurrent topical antibiotic if superinfection	Topical antifungal (eg natamycin), hrly for an extended period; highly invasive, so surgical intervention common

	concurrent topical corticosteroids after 2 days*		
Outcomes	14% lose ≥ 2 lines VA [66]	43% lose ≥ 2 lines VA; 26% keratoplasty [77]	48% lose ≥ 2 lines VA; 17% keratoplasty [82]

*Corneal scrape is positive in only around 50% of clinically diagnosed cases [83] SES: socioeconomic status; PCR: polymerase chain reaction; PHMB: polyhexamethylene biguanide
Hrly=hourly, min=minutes, qid=four times per day

2.3 Prevention

Contact lenses, like all medical devices, carry a certain degree of inherent risk. An evidence-based approach to decrease frequency and severity of contact lens-related infection includes attention to those risk factors associated with a greater impact on disease load as follows:

- Avoidance of overnight wear [62, 67, 68, 84]
- Attention to hand, lens and case hygiene. As these behaviours are common, a sense of diminished risk can result. Frequent and repeated compliance education is required. Novel reminder cues may be helpful, for example, a recent study has shown that a simple “no water” graphic on contact lens paraphernalia can reduce water exposure behaviours and environmental contact lens case contamination [85]
- Daily disposable lenses, while not decreasing the absolute risk of contact lens infection, do result in less severe disease and fewer cases of vision loss compared with frequent replacement soft contact lenses [67, 73]
- Daily wear rigid corneal lens use is associated with a lower rate of disease compared with soft contact lenses [62, 67]
- Early presentation to an eye care practitioner (ECP) is associated with reduced risk of severe disease [86]

3 Contact lens-related corneal inflammation

For ECPs, the most important differential diagnosis for a contact lens wearer presenting with a painful red eye should focus on determining whether they have sight-threatening MK or a non-infectious or sterile keratitis, referred to as a corneal infiltrative event (CIE). Although accurately classifying ocular signs is important, understanding the incidence and risk factors for MK and CIEs helps the clinician with defining differential diagnoses. More importantly, knowledge of risk factors helps the clinician recommend contact lenses that will minimise risk of CIEs for patients who have non-modifiable risk factors that increase their risk.

3.1 Signs associated with CIEs

Sweeney and colleagues developed a classification system for CIEs in the early 2000s that has been used in most of the larger studies of soft contact lens-related adverse events (see Section 2.3) [15]. CIEs may or may not be accompanied by symptoms, but when they are symptomatic, the wearer typically presents with discomfort ranging from none to moderate pain, and a red and watery eye. Asymptomatic CIEs are almost exclusively reported in randomized clinical trials and present infrequently in population-based studies [87-90]. Tables 3, 4a and 4b outline the incidence and risk factors for symptomatic CIEs.

Table 3: Incidence of CIEs in large observational contact lens studies

Study Design & Name (citation)	Population Features	Years of Wear	CIE Incidence %/year (95% CI)
Soft Contact Lenses			
ReCSS Retrospective Cohort Study of Pediatric Soft Contact Lens Wear [91]	N= 962, 782 patients in USA clinical practices and 181 subjects in 2 multi-national randomised controlled trials fit while 8 through 12 years old	2,713	0.74%/yr (0.48 – 1.14%)
TEMPO Prospective Registry of Daily Disposable Wearers [92]	N = 1,171 registered patients newly fit with Daily Disposable soft contact lenses in 37 US clinical practices	960.3	Etafilcon A: 0.0% /yr (0 – 0.6%) Narafilcon B: 0.4%/yr (0.1 – 1.5%)
CLAY Study Retrospective Chart Review [93]	N = 3,549 patients wearing marketed soft contact lenses aged 8-32 years 2,110 adults, 1,054 minors 6 US optometry school clinics	4,663	All ages: 4.0%/yr (3.48– 4.61%) 8-12 yrs: 0.97%/yr (0.31 – 2.35%) 13-17 yrs 3.35%/yr (2.48 – 4.43%) 18–25 yrs 5.71%/yr (4.65 – 7.0%) > 26 yrs: 3.40%/yr (2.57 – 4.53%)
FDA Mandated Prospective Post-Market Surveillance Registry [94]	N= 6,245 registered patients newly fit with lotrafilcon A for 30 night overnight wear in 31 US clinical practices	5,561	Annual incidence: 2.54%/yr (2.18 – 2.97%)
UK Hospital Prospective Case Control Study [95]	N= 181 hospital presenting patients, hospital, and community controls	N/A	Daily Disposable Hydrogel: 0.14%/yr Daily Wear Hydrogel: 0.20%/yr Daily Wear SiHy 0.56%/yr
Rigid Lenses for Orthokeratology			
Observational FDA Mandated Retrospective Post-Market Surveillance [96]	N = 1317 Orthokeratology patients 640 adults, 677 minors 86 US clinical practices	2,599	Adults: 0.17%/yr (0.02 - 0.62 %) Minors: 0.42%/yr: (0.15 - 0.91%)

Table 4a. Modifiable risk factors for CIs from recent soft contact lens studies

Risk factor **Study Citation**	***Overnight Wear***	***Reusable lens use***	***MPS disinfection***	***Silicone Hydrogels***	***Lens case age***	***Rinse with Tap water***	***Smoking***
Referent	***Daily Wear***	***Daily Disposable***	***Hydrogen Peroxide***	***Hydrogel***	***N/A***	***No Tap Water Rinse***	***No***
CLRS Case Control [97]	aOR = 5.5 Upper 95% CI: 21.5	aOR = 9.5 Upper 95% CI: 92.2	aOR = 17.3 Upper 95% CI: 107.7	--	> 6 months aOR = 7.7 Upper 95% CI: 31.6	aOR = 2.85 Upper 95% CI: 8.2	--
CIEs in University Students [98]	If using PHMB OR = 10.0 (2.0 – 51.2)	--	Polyquad, DW OR = 18.4 (1.9 - 173.9) PHMB, overnight wear OR = 10.0 (2.0 - 51.2)	NS	NS	--	--
SiHy Daily Wear [90]	--	--	NS	--	--	--	NS
Private Practice Case Control [99]	OR = 4.0 (2.3 – 6.8)	DW Only OR = 12.5 (1.5 – 100.6)	NS	DW Only OR = 2.0 (1.1 – 3.8)	--	--	NS
CLAY Retrospective Chart Review [93]	aOR = 3.25 (1.4 - 7.5)	*2 weekly aOR = 3.0 (1.2 – 7.5) *Monthly aOR = 3.4 (1.4 – 8.6) *Other intervals aOR = 5.1	aOR = 2.85 (1.3 – 6.3)	aOR = 1.85 (1.3 - 2.7)	--	--	--

		(1.8 – 14.2)					
SiHy Continuous Wear [100]	--	--	--	--	--	--	HR+ 4.1 (1.7 – 9.9)
Retrospective Chart Review [101]	--	NS	NS	IRR = 1.3 (1.01 - 1.7)	--	--	--
Prospective Case Control [10]	OR = 1.3 (1.0-1.7)	Dailies (CIBA Vision) OR = 2.2 (1.5-3.2)	--	SiH OR = 1.9 (1.5 – 2.6)		--	--

Abbreviations; CLRS: Contact lens risk survey, CIEs: Corneal infiltrative events, Conj: Conjunctiva, OR: Odds ratio, aOR: Adjusted odds ratio IRR: Incidence ratio, CI: Confidence interval, SiHy: Silicone hydrogel, CLAY: Contact lens assessment in youth; PHMB: polyhexamethylene biguanide.

*Univariate model only, -- Data not captured in study or unable to test due to homogeneity in sample, NS Not Significant, + Hazard Ratio

Table 4b: Non-modifiable risk factors for CIEs from recent soft contact lens studies

Risk Factor **Study Citation**	**Age**	**Bacterial Bioburden**	**Previous Red Eye**	**High Rx >5.0D**	**Recent Use of Eyedrops**	**Recent Cold or Flu**	**New to Lens Wear**
Referent	***N/A***	***No Burden***	***No Previous Red Eye***	***< 5.0D***	***No Recent Drop Use***	***No Recent Cold or Flu***	***> 1 Year of Lens Wear***
CLRS Case Control [97]	NS	Lid Margin OR = 8.1 Bulbar Conj. OR = 16.7 Contact Lens OR = 35.3 Lens Case	aOR = 4.2 Upper 95% CI 13.5	--	aOR = 7.7 Upper 95% CI 24.8	aOR = 3.4 Upper 95% CI 9.7	--

		OR = 3.6					
CIEs in University Students [98]	20% lower/yr from 18 to 36	--	--	--	--	--	--
SiHy Daily Wear Prospective [90]	NS	Lid Bioburden OR = 4.3 (1.1 – 16.7)	--	--	--	--	--
Case Control [99]	5% less per year after 18 years	--	--	Mean Rx *OR = 1.09 (1.02 – 1.16)	--	--	--
CLAY Retrospective Chart Review [93]	Non-Linear Highest risk: 15 to 25 yrs	--	--	NS	--	--	Approximately 1/3 risk in 1st year of wear
SiHy 30 Night Wear Prospective [100]	NS	Lens Bioburden at 4 Mos HR^{+} = 8.7 (2.9 – 26.0) at 12 Mos HR^{+} = 4.8 (2.3 – 9.9)	--	--	--	--	--
Retrospective Chart Review [101]	* < 25 yr IRR = 1.35 (1.1 – 1.7)	--	--	IRR = 1.5 (1.2 – 1.9)	--	--	IRR = 0.07 (0.01 – 0.46)

Prospective Case Control [10]	----	--	--	--	--	--	>3 yr OR = 2.4 (1.7-3.4)

Abbreviations; CLRS: Contact lens risk survey, CIEs: Corneal infiltrative events, Conj: Conjunctiva, OR: Odds ratio, aOR: Adjusted odds ratio, IRR: Incidence rate ratio, CI: Confidence interval, SiHy: Silicone hydrogel, CLAY: Contact lens assessment in youth.

*Univariate model only, -- Data not captured in study or unable to test due to homogeneity in sample, NS Not Significant, + Hazard Ratio, Mos: months, yr: year, IRR: Incidence rate ratio, Rx: prescription

The number of infiltrates, their size, location and presence of overlying staining help determine the differential diagnoses for the sub-categories of CIEs. In patients with CIEs, signs and symptoms typically begin to resolve as soon as lens wear is temporarily ceased. An important differential between CIEs and MK is that the discomfort/pain is not relieved by contact lens removal in MK, but the pain progressively increases [75].

Contact lens peripheral ulcers (CLPU) occur in the periphery or mid-periphery of the cornea, have overlying fluorescein staining and are typically <1mm in diameter with regular edges (Figure 2). CLPU events will resolve to a small scar over time. Although they are not infectious, management of CLPUs usually involves coverage by a combination antibiotic-steroid combination in countries where ECPs have access to prescribing them.

Infiltrates seen with contact lens acute red eye (CLARE) can be diffuse, or multiple focal, much smaller and often do not have overlying staining. They are accompanied by eye redness, watering and pain on waking and are highly associated with overnight wear of lenses. These will resolve with cessation of lens wear, although coverage with antibiotic-steroid is sometimes used to manage the condition.

Infiltrative keratitis presents as single or multiple anterior focal infiltrates that sometimes show overlying fluorescein staining (Figure 2). It presents with mild to moderate irritation, some redness and occasional discharge. Management of infiltrative keratitis depends on the degree of redness, discomfort and presence of overlying staining. It is managed similarly, with prophylactic coverage with antibiotics or combination agents.

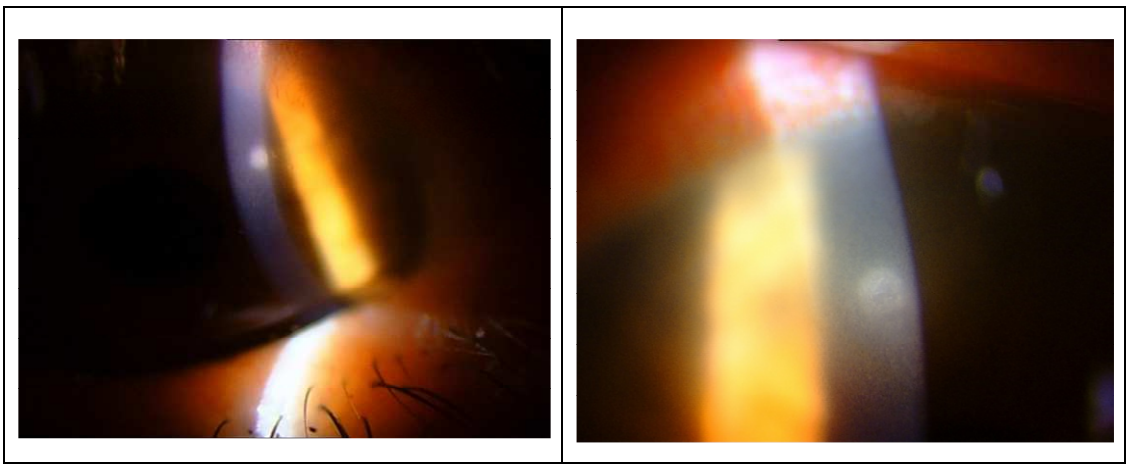

Figure 2: Left: Contact lens peripheral ulcers (CLPU). Right: Infiltrative Keratitis; Images courtesy of Centre for Research and Education (CORE).

The differential diagnosis of CIEs is equivocal [14]. Using data from the Manchester Keratitis Study, the authors propose that the various classification schemes at the time were most likely describing an infiltrative response that is actually a continuum of disease rather than distinct conditions. Most importantly for the practicing clinician, they also concluded that if a contact lens wearing patient presents with an increasingly uncomfortable red eye with an infiltrate that contact lens wear should be ceased and intensive antimicrobial treatment commenced immediately.

3.2 Incidence of CIEs

The incidence of CIEs varies widely depending on the proportion of the study population with risk factors for CIEs, the contact lens wearing schedule (daily versus overnight wear), contact lens replacement schedule (daily disposable versus reusable), contact lens material (hydrogel versus SiHy), history of prior CIEs and the age of the wearer (Table 3 and Figure 3). It is clear that studies that included large proportions of wearers using daily disposable soft contact lens have rates that are approximately ten times lower than with reusable contact lenses, with incidence ranging from 0.0% to 0.4%/yr depending on daily disposable contact

lens material [92, 95].The incidence of CIEs in overnight wear reusable soft contact lens studies ranges between 2.5 to 7.0% per year in observational cohort studies [69] and these rates have been fairly robust over time [102].

3.3 Risk Factors for CIEs

CIE incidence varies depending on the presence of risk factors in the population that is being studied (Figure 3). The most consistent risk factors, divided into those that are modifiable by different choice of wear schedule, lens replacement schedule, frequency of case replacement, disinfection system, compliance with lens care or lens material and other factors are not modifiable, such as the age of the wearer, sex, their refractive error, or general or eye health history (Tables 4a and 4b; note that some studies did not analyse all of the factors listed).

Among the modifiable risk factors, overnight wear increases risk significantly [10, 93, 97-99]. In these studies the increased risk ranged from 2.5 to 10 times higher depending on the subgroup being studied. Use of reusable contact lenses was consistently identified, with increased risk from 3.0 to 12.5 times the risk compared to daily disposable use [93, 97, 99], however one study showed differences in risk between types of daily disposable contact lenses [10]. Compared to use of hydrogen peroxide disinfection, the use of multi-purpose systems were associated with additional risk [93, 97, 98] and SiHy contact lens wear showed increased risk in a number of studies [10, 93, 99].

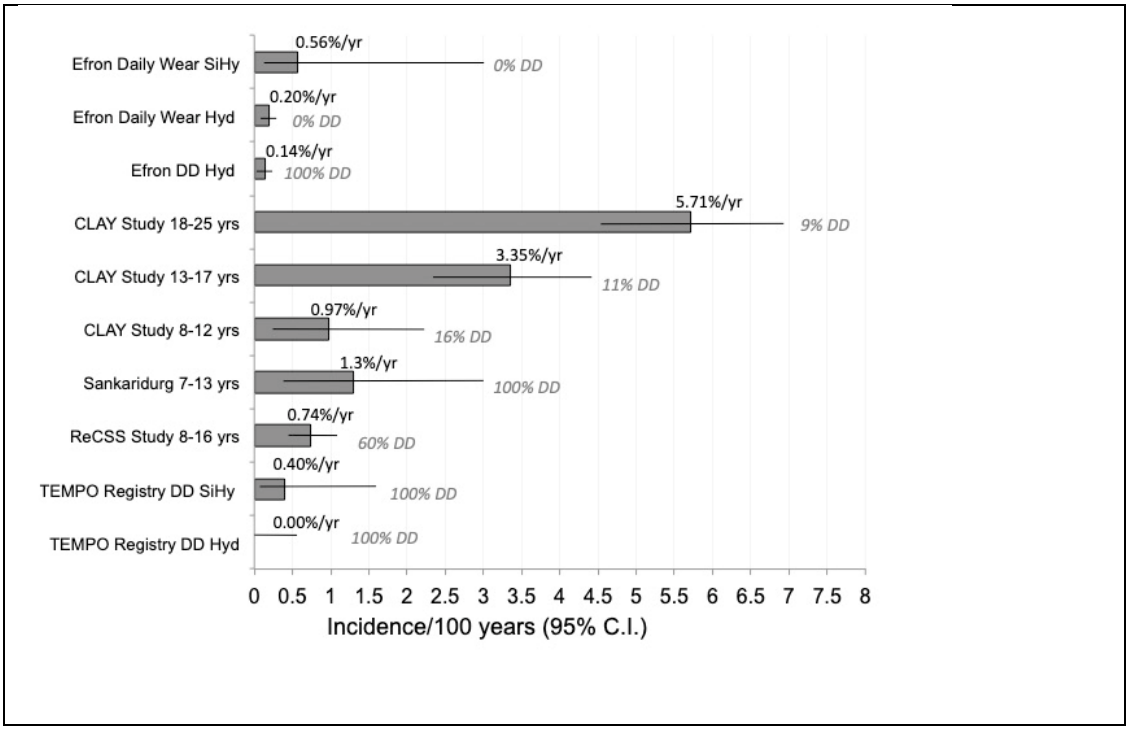

Figure 3: Incidence of CIE per 100 wearers per year. Error bars show 95% confidence intervals. (Modified from Chalmers et al., 2021, [91])

Non-modifiable risk factors that put a wearer at increased risk are shown in Table 4b. Older teens and young adults carry increased risk of CIEs [93, 98, 99, 101] and the presence of bacterial bioburden on the eyes, contact lenses and contact lens cases also add to risk [90, 97, 100].

3.4 Prevention and advice to wearers

The clinician should consider the risk factors for each contact lens wearer to arrive at the best contact lens option for that patient. In general, use of daily disposable contact lenses and avoiding overnight wear bring lower risk for CIEs, as does use of hydrogen peroxide disinfection for wearers of reusable contact lenses. For example, a 23 year old with a history of previous CIEs or with blepharitis should be encouraged to wear daily disposable contact lenses in order to mitigate the added risk that their age and history contribute. Similarly, patients with high refractive errors or a history of a previous red eye should be steered toward daily

disposable contact lenses as the safest choice for them. All daily disposable contact lenses wearers should be advised at all follow-up visits to never sleep in their contact lenses and to discard contact lenses every day.

4 Metabolic Complications

Contact lens wear results in metabolic stress to the cornea, which is influenced by both the oxygen transmissibility of the contact lens as well as the degree to which tear exchange is impeded by the contact lens (See CLEAR Material Impact Report [103].

Although the development of recent lens materials has led to a decrease in the frequency and severity of disorders resulting from hypoxia, these complications still exist because high Dk lenses are not universally prescribed [104], oxygen transmissibility is limited by lens thickness in specific designs and lens powers [105, 106], and individual responses to hypoxia vary. Moreover, closed eye wear by intention (e.g. orthokeratology) or by neglect (non-compliance) further limits oxygen to the eye. Metabolic complications from hypoxia manifest as distinct clinical entities (Table 5).

Table 5: Contact lens complications attributed to hypoxia

Condition	Presenting signs	Temporal pattern	Lens type
Limbal redness	Dilation of limbal blood vessels	Short-term, reversible	Hydrogel [107-112], Scleral [113]
Epithelial staining	Diffuse, punctate, coalesced staining with sodium fluorescein	Short-term, reversible	Hydrogel [114, 115], PMMA [114], rigid corneal [114]
Epithelial oedema	Circumscribed oedema	Short-term, reversible	PMMA [116], Hybrid [117]
Epithelial vacuoles	Round, distinct borders, unreversed illumination	Long-term, reversible but recalcitrant	Hydrogel [24]
Epithelial bullae	Oval, blurred borders, unreversed illumination	Long-term, reversible	Hydrogel [24], Scleral [118]
Epithelial microcysts	Small, irregular shaped vesicles, reversed illumination	Long-term, reversible but recalcitrant	Hydrogel [24, 119], rigid corneal [120, 121]
Corneal warpage	Change in corneal contour with topography or keratometry	Short-term, variable resolution	Hydrogel [122, 123], PMMA[122-124], rigid corneal [122-124], Scleral [125]
Changes in refractive error	Variable refraction, myopic shift with low Dk materials	Short-term, variable resolution	PMMA [124], Hydrogel[35, 36, 126], SiHy [36]
Vascularisation	Extension of blood vessels into the previously avascular cornea	Long-term, ghost vessels remain	Hydrogel [107, 111, 127] Scleral [128]

Stromal oedema	Striae 5-6% oedema Folds 10% oedema	Short-term, reversible	Hydrogel [27, 28]
Endothelial blebs	Circumscribed black zones, separation of cells	Short-term, reversible	Hydrogel [30, 129], rigid corneal [130], Scleral [131], SiHy[129]
Endothelial polymegethism and pleomorphism	Variation in endothelial cell size or shape	Long-term, not completely reversible	PMMA [132], [133]Hydrogel [134] Rigid corneal [135]
Corneal exhaustion syndrome	Corneal oedema accompanied by decreased tolerance to contact lens wear	Long-term, reversible but recalcitrant	PMMA [136], Hydrogel [136]

PMMA: Polymethylmethacrylate; SiHy: silicone hydrogel

4.1 Limbal redness

Reducing oxygen to the cornea promotes limbal blood flow and the manifestation of circumlimbal flush. Limbal redness is routinely observed with reusable and daily disposable hydrogel contact lenses, though it has been largely eliminated with SiHy contact lenses in both daily and overnight wear [88, 107, 109, 111, 112]. Limbal redness varies inversely with oxygen transmissibility of the soft contact lens material [110]. Similarly, limbal redness has been reported as a strong indicator of hypoxic stress in other modalities, including scleral lens wear [137].

4.2 Epithelial staining

Corneal staining in contact lens wear has been proposed as a potential response to epithelial hypoxia and has been reported with polymethylmethacrylate (PMMA), rigid corneal, and conventional hydrogel contact lens wear [114]. Consistent with earlier reports in high Dk contact lenses [138-140] epithelial staining is also associated with contemporary SiHy contact lenses [115].

4.3 Epithelial oedema

Epithelial oedema is a complication associated primarily with PMMA corneal lens wear. However, it has also been reported with contemporary hybrid contact lenses [117]. Historically, central corneal clouding was described as a visual disturbance characterised by glare and haloes surrounding lights [116]. This phenomenon was attributed to a disruption in the corneal epithelium that produced stromal light scattering [26]. Hypotonic reflex tearing is also believed to inhibit the fluid barrier and osmotically induce epithelial oedema [25]. As such, oedema may present with adaptation to rigid lenses or as a response to foreign body tearing. The clinical presentation varies depending on the underlying stimuli. For example, oedema from central corneal clouding manifests as a circular zone reflecting the diameter of the rigid corneal lenses while oedema in response to excessive lacrimation is diffuse.

While overall corneal thickness increases with hypoxia, ocular coherence tomography has established that epithelial thickness does not increase [141]. In fact, long term epithelial oedema is associated with thinning [22]. Epithelial thinning is partially attributed to hypoxia when conventional hydrogel lenses are worn for overnight wear, but a mechanical aetiology is likely for thinning associated with rigid corneal lenses and first generation SiHy lenses with a high modulus [142]. Epithelial thinning is more prevalent with conventional hydrogels as compared to SiHy contact lenses [143].

4.4 Epithelial vacuoles

Epithelial vacuoles are suggestive of long-term hypoxia and may be differentiated from structures such as epithelial bullae or microcysts, based upon size, colour, and shape. Epithelial vacuoles are small (5-30µm in diameter) spherical bodies within the corneal epithelium [24]. They display distinct borders and unreversed illumination (same appearance as the background) with biomicroscopy, suggesting that their contents are fluid filled and characterised by a lower refractive index than the surrounding epithelium [23]. They are commonly observed in conventional hydrogel lenses and overnight wear regimens. Management includes decreasing lens wearing time and/or refitting into higher Dk materials.

4.5 Epithelial bullae

Epithelial bullae are larger (40µm or larger), oval clustered bodies in the corneal epithelium. Their margins are less distinct than the margins of epithelial vacuoles [144]. They also display unreversed illumination, implying that their contents are liquid or gas [23, 24]. Epithelial bullae are associated with contact lens-induced metabolic stress. Like vacuoles, they are associated with hydrogel contact lenses and overnight wear. While not typically associated with rigid corneal contact lenses, they have been reported with contact lens bearing in small diameter scleral lenses [118]. Although patients are generally asymptomatic, epithelial bullae should be considered a sign of hypoxic stress/oedema and should be managed accordingly.

4.6 Microcysts or Microcystic epitheliopathy

Epithelial microcysts are ‘pinpoint’, irregular-shaped vesicles in the corneal epithelium presumed to be composed of cellular debris and epithelial cells [23]. They usually form after four or more weeks of overnight wear with hydrogel contact lenses [145]. They may be distinguished from epithelial vacuoles and bullae by retro-illumination with a biomicroscope at high magnification. Microcysts display reversed illumination, appearing darker than their surrounding background. Patients are generally asymptomatic.

As with other signs of chronic metabolic stress, they are prevalent with conventional hydrogels [119], particularly when worn for overnight wear [24]. Similarly, they are reported in older rigid corneal lenses [121] and also observed with orthokeratology lenses [120]. Some investigators have noted a transient response where microcysts first increase and then decrease when wearers are refitted from low Dk/t to high Dk/t materials [145]. This seemingly paradoxical response suggests that microcysts are a sign of altered corneal metabolism rather than solely attributed to hypoxia.

4.7 Corneal warpage and changes in refractive error

A change in corneal shape induced by contact lenses, as reflected by variable keratometry and refraction, was first reported with PMMA contact lenses [124] and later observed with low Dk rigid corneal lenses [146]. Mechanical molding and contact lens-induced corneal oedema have been suggested as causes of contact lens-related ‘myopic creep’ since the 1970s [126]. Corneal warpage was often associated with ‘spectacle blur’ whereby a patient manifested reduced visual acuity upon contact lens removal. The reduced vision was attributed to corneal irregularity and associated hypoxia.

More subtle changes detectable only with computer-assisted topographic analysis have also been observed in asymptomatic rigid corneal and hydrogel contact lens wearers [122, 123]. Given that contact lens-induced corneal warpage has also

been reported with SiHy contact lenses, hypoxia may not be the only predisposing cause [147].

Contact lens management is dictated by the underlying cause; while some patients may benefit from being refitted into higher Dk materials, other factors such as contact lens modulus or fitting should be considered. Corneal warpage affects biometry measurements required for optimal laser refractive and cataract surgery and therefore a period without lens wear before measurements are taken is usually recommended.

4.8 Vascularisation

Contact lens-related vascularisation has been attributed to various mechanisms, including mechanical injury and hypoxia. Hypoxia stimulates an interaction between inflammatory cells and angiogenic growth factors (e.g. vascular endothelial growth factor) which, in turn, induce new blood vessel growth [148].

Contact lens-related vascularisation is usually superficial and peripheral. It does not immediately threaten vision, but its presence suggests tissue compromise. It is uncommon with well fitted rigid corneal lenses, but frequently associated with conventional hydrogel contact lenses [127], particularly in conjunction with overnight wear [107, 111] or high minus refractive error [149]. It is rarely observed with SiHy contact lenses [107]. Although vascularisation has been reported with scleral lenses [128], its prevalence with contemporary products is unknown. The first line of treatment is to eliminate hypoxia by refitting contact lenses or reducing wear time [150] and with treatment, new vessels regress to barely visible ‘ghost vessels’.

Deep stromal vascularisation is rare but predisposes the wearer to vision loss [151, 152] and secondary complications such as graft failure should a patient undergo keratoplasty [153]. Corticosteroids and other anti-inflammatory medications comprise the foundation of pharmacological treatment, although anti-vascular endothelial growth factor agents are an emerging therapy for advanced disease [148, 154].

4.9 Stromal oedema

Stromal oedema, another indicator of hypoxic stress in contact lens wear, is commonly expressed as the percentage increase in stromal thickness. Striae can be produced experimentally by depriving the cornea of oxygen [27]. Striae form when stromal oedema is approximately 5 to 6%; the number of striae increases with the magnitude of the hypoxia. Stromal folds develop when the oedema is 10% [28].

4.10 Endothelial blebs

Endothelial blebs have been described as circumscribed black zones obscuring the endothelial mosaic and visible with specular microscopy. Appearing within minutes of contact lens application and disappearing shortly after removal or adaptation [30], they are associated with the accumulation of carbon dioxide and the resultant acidic shift in the posterior stroma [29]. Although transient and reversible, endothelial blebs are viewed as an indicator of hypoxic stress. While the response is less frequently observed with high Dk contact lens materials [155], endothelial blebs have been observed in varying degrees in older hydrogels [30], rigid corneal contact lenses [130], scleral lenses [131], and contemporary hydrogel and SiHy contact lenses [129].

4.11 Endothelial polymegethism

Contact lens wear is associated with variation in endothelial cell size (polymegethism) and shape (pleomorphism). This condition was first reported in PMMA contact lens wear [132], and later observed in rigid corneal [135] and hydrogel contact lenses [134]. This condition is absent from high Dk contact lens materials such as silicone elastomer [156] and SiHy contact lenses [157]. Notably, changes in endothelial morphology were absent in children wearing high Dk orthokeratology contact lenses for two years [158]. The association of this condition with low Dk contact lens materials supports the understanding that this condition is associated with hypoxia and concomitant stromal acidosis [22]. Opinions vary with regards to the potential impact of this phenomenon on cell

function [134, 159], but a review of the literature suggests that these morphological changes do not significantly predispose wearers to other disease [160]

4.12 Corneal exhaustion syndrome

Corneal exhaustion syndrome is a condition characterised by blurred vision, corneal oedema, and reduced tolerance to contact lens wear [136]. This condition is observed with PMMA and hydrogel contact lenses. Corneal exhaustion syndrome is attributed to chronic hypoxia and acidosis. It is managed by discontinuing wear or refitting into higher Dk contact lens materials.

4.13 Management and advice to wearers

The development of high Dk rigid corneal and SiHy contact lens materials has substantially reduced hypoxia-induced complications. Some disorders have been eliminated while the frequency and severity of others have lessened. Many remaining conditions can be managed by decreasing contact lens wearing time, avoiding overnight wear, or changing to lenses with a different design. The synergy between clinical signs and underlying pathophysiology should direct appropriate clinical interventions and future study.

Table 6: Contact lens complications attributed to mechanical effects

Condition	Presenting signs	Lens type	Management
Corneal and conjunctival abrasions	Epithelial defect observed with sodium fluorescein	Rigid corneal > soft CLs Damaged CLs, foreign body trapped behind CLs [161]	Discontinue CL wear temporarily, ocular lubricants and/or prophylactic antibiotic depending on severity. Consider lens/cornea fitting relationship
CL binding	Decreased CL movement and possible epithelial defect post-CL removal, observed with sodium fluorescein	More common during overnight wear, in high modulus materials including rigid corneal [162, 163], SiHy [31, 33], silicone elastomer lens [34]	Replace or refit CLs; educate patient on lens handling, particularly recognising condition, and CL removal strategies
Corneal warpage	Change in corneal contour	rigid corneal [123], conventional hydrogel [123], SiHy [147], scleral [125]	Refit: modify fitting relationship for rigid corneal CLs or, refit to soft CLs or, change material modulus
Superior epithelial arcuate lesions	Superior arcuate epithelial defect observed with sodium fluorescein	SiHy > conventional hydrogel [164, 165]	Refit into lower modulus material
Mucin balls	Spherical, translucent bodies between the back surface of the CL and the corneal epithelium	SiHy hydrogel > conventional hydrogel [166-168]	Refit into lower modulus material
Contacts lens-induced papillary conjunctivitis	Enlarged papillae on the tarsal conjunctiva	SiHy > conventional hydrogel [169] Overnight wear > daily wear	Reduce CL wearing time, increase replacement frequency, change CL material, pharmacological treatment

Conjunctival epithelial flaps	Goblet and epithelial cells detachment from the underlying conjunctiva	SiHy > conv	Decrease wearing time or refit; reduce material modulus
3 and 9 o'clock staining	3 and 9 o'clock staining with sodium fluorescein	Rigid corneal CL	Modify the CL design or refit into soft or scleral lenses [170]
Vascularized limbal keratitis	Hyperplasia, inflammatory response, vascularisation, and erosion adjacent to the limbus at 3 and 9 o'clock	Rigid corneal CL [171, 172]	Modify the CL design or refit into soft or scleral lenses
Contact lens-induced stem cell deficiency	Late staining pattern on the conjunctivalised epithelium	Soft CLs [51, 173]	Discontinue CL wear, dry eye treatment, anti-inflammatory medications, surgery
Ptosis	Descent of the upper eyelid	Rigid corneal CLs > soft contact CLs [174]	Discontinue CL wear, lid surgery, scleral lenses

SiHy: silicone hydrogel; CL: contact lens

5. Mechanical lens-induced complications (Table 6)

5.1 Corneal/conjunctival abrasion

Corneal and conjunctival abrasions can result from a deposited or damaged contact lens. Occasionally an abrasion is precipitated by external debris that becomes trapped between the cornea and the contact lens. The injury is typically superficial and managed by discontinuing contact lens wear, instilling ocular lubricants, and cleaning or replacing the lens as needed. Prophylactic antibiotics may be indicated if severe [175]. More common is the appearance of abrasive damage in rigid corneal lens wearers, often visualised as foreign body tracks and thought to be the consequence of environmental debris entrapment behind the contact lens while the contact lens moves during blinks.

5.2 Lens binding

While contact lens binding has been reported with a broad spectrum of materials and wearing schedules, most reports focus on rigid corneal lenses, orthokeratology use (See Section 13) and high modulus soft contact lenses with overnight wear [31, 33, 34]. Contact lens binding may be accompanied by an indentation ring or corneal erosion, notable because erosions are linked to MK [32]. Management includes refitting into lower modulus soft contact lenses or modifying the rigid corneal lens design. Although rigid corneal lens binding has been associated with large diameter, flat-fitting, and low edge lift contact lenses, no consensus exists regarding optimal fitting strategies to prevent this condition [162]. Rigid corneal lens wearers may also benefit from proactive contact lens replacement [176]. Further, instillation of lubricants and contact lens manipulation with the eyelids prior to removal may avert a corneal erosion [163].

5.3 Corneal warpage

Corneal warpage is characterised by changes in corneal contour and refractive error. In a study of soft and rigid corneal lens wearers, contact lens resting position induced changes in corneal topography [123]. For example, a superiorly positioned

contact lens induced inferior steepening suggestive of mild keratoconus [123]. Upon cessation of wear, corneal topography returned to normal in most wearers with rigid corneal lenses necessitating a longer rehabilitation period [123]. Corneal flattening has been also been reported with SiHy contact lenses [147] as well as with short term scleral lens wear in keratoconic patients, irrespective of patient history of corneal cross-linking [125]. Warpage associated with hypoxia is described in Section 5.7.

5.4 Superior epithelial arcuate lesion

A superior epithelial arcuate lesion (SEAL) is a full-thickness break in the superior peripheral corneal epithelium, sometimes associated with mild symptoms such as foreign body sensation or contact lens awareness. This condition has been described as a misalignment between the contact lens and superior ocular surface. First reported in 1987 [177] and thought to be associated with peripheral contact lens design and an infrequent complication of conventional hydrogel contact lens wear, this finding is more commonly associated with the higher modulus materials that are representative of first-generation SiHy contact lenses [164, 165]. Proposed etiologies of superior epithelial arcuate lesion include mechanical stimulation [178] and desiccation [179]. The lower prevalence of the condition with later-generation SiHy contact lenses lends support to the mechanical hypothesis [180]. Management includes discontinuation of wear until resolution and refitting into a lower modulus material [164, 165].

5.5 Mucin balls

Mucin balls (See CLEAR Maintenance Report [181]) are spherical, translucent bodies of debris of varying size that form between the back surface of the contact lens and the corneal epithelium and result in corneal surface depressions [166]. Mucin balls were initially reported with first-generation SiHy contact lenses [167, 168] but have also been observed in conjunction with conventional hydrogels [39]. Mucin ball formation has been attributed to the elastic properties of SiHy contact lenses [182]. Patients with steeper corneal curvature appear to be predisposed to

their formation, implying that their formation is related to the contact lens fitting. The clinical significance of mucin balls is unknown. Although it has been suggested that a mucin rich tear film inhibits upregulation of the immune system [183], a subsequent study did not support this hypothesis [184].

5.6 Contact lens-induced papllary conjunctivitis (CLPC)

CLPC is thought to be immunologic in origin with the deposited contact lens serving as the antigen (see Section 7.1). However, its association with high modulus contact lens materials such as first-generation SiHy contact lenses [164, 169, 185] or local stimuli such as sutures suggests that mechanical stimuli may also play a role [186]. The presence of elevated neutrophil chemotactic factors in the tears of symptomatic contact lens wearers also supports the mechanical hypothesis [187].

5.7 Conjunctival epithelial flaps

Conjunctival epithelial flaps are characterised by goblet and epithelial cells that are detached from the underlying conjunctiva. Although observed with other contact lens materials, this entity is commonly associated with first-generation SiHy lenses during overnight wear [40, 188]. This condition is believed to be a product of the interaction between the bulbar conjunctiva, contact lens material, and edge contour and worsened by increased wearing time. Conjunctival epithelial flaps are frequently observed in the superior or inferior quadrants of the bulbar conjunctiva, suggesting that they are mechanical in nature and that the lens edge plays a role in their formation [40]. Although patients are generally asymptomatic, management includes decreasing contact lens wearing time or refitting with lower modulus materials or contact lenses with different edge designs.

5.8 3 and 9 o'clock staining

This condition is characterised by epithelial punctate staining in the 3- or 9- o'clock regions of the peripheral cornea in association with a rigid corneal lens and is a sequelae to a gap created under the eyelid between the contact lens and the

cornea that results in insufficient tear film formation. Reduced blink frequency, incomplete blinking, the interaction of lids with the edge of a rigid lens and disruption of the lid/ocular surface relationship [189] cause tear evaporation, local thinning of the post-lens tear film and lens edge adherence to the cornea, which manifest as 3 and 9 o'clock corneal and conjunctival staining [170, 189]. Corneal dellen is a less common contact lens complication and is reported in ocular diseases and after ocular surgery. The mechanism of dellen formation in rigid corneal lens wear is similar to 3 and 9 o'clock staining. It occurs due to a persistent 3 and 9 o'clock staining caused by the inability of lids to conform to the shape of the cornea [190]. It leads to a localized tear film instability, corneal depression and thinning [191].

Modification of the contact lens to corneal fitting relationship includes edge lift, edge shape and thickness, back surface geometry, contact lens diameter, back optic zone radius, contact lens centration, and movement may help to manage the condition; other strategies include modification of the contact lens material surface properties, patient blinking behavior and tear supplement use [170].

5.9 Vascularised limbal keratitis

Vascularised limbal keratitis is also attributed to insufficient tear film at the corneal limbus in conjunction with the mechanical stimulus of rigid corneal contact lenses. It is characterised by elevated lesions with poorly defined borders adjacent to the limbus and located on the horizontal axis at 3 and 9 o'clock. Four progressive stages including hyperplasia, inflammatory response, vascularisation and erosion have been described [171]. Management includes modifying the contact lens diameter or peripheral curve system and decreasing contact lens wear time. Refitting the patient into soft or scleral lenses that cover the limbus is also an alternative [172]. Pharmacological management (antibiotic/steroid combination) and artificial tears are adjunctive therapy.

5.10 Contact lens-induced limbal stem cell deficiency

Limbal stem cell deficiency (LSCD; see section 7.2) is initially characterised by superior punctate staining, subsequently coalescing to a whorl-like pattern [192] with a late staining appearance attributed to the increased permeability of compromised epithelial cells [193].

5.11 Ptosis

Contact lens-related ptosis results from dehiscence of the levator aponeurosis or disinsertion from its natural position. Rigid lens wearers (OR, 17.4x) and soft contact lens wearers (OR, 8.1x) have an increased risk of ptosis as compared to non-wearers [174]. Ptosis is associated with prolonged contact lens wear as defined by wearing schedule [194] and years of wear [41, 42]. Various mechanisms have been proposed, including the antagonistic action of the orbicularis and levator muscle, stretching the upper lid on contact lens removal, rubbing the contact lens while blinking, and irritation leading to lid oedema or blepharospasm [41]. The mechanism for ptosis with soft contact lens wear is less clearly understood, although it has been suggested that inflammation or contact lens application and removal may play a role [42].

5.12 Prevention and advice to wearers

Complications associated with SiHy contact lenses such as superior epithelial arcuate lesion, mucin balls, CLPC, and conjunctival flaps are well documented in the literature with first-generation SiHys, but less frequently observed with second- and third-generation materials [169, 180], attributed to the lower modulus and improved biocompatibility of the more recent products. While newer rigid corneal lens materials have a higher oxygen permeability than their predecessors and incorporate innovative surface treatments, mechanical complications persist.

6 Toxic and hypersensitivity complications

Contact lens care solutions are highly complex mixtures of preservatives (biocides), surfactants, and other agents designed to disinfect, clean, and wet the contact lenses [195] (CLEAR Maintenance Report [181]). The interactions of these solutions with contact lenses depends on polymeric make up i.e. material water content, charge, relative hydrophobicity, surface treatment and surface porosity [195, 196]. Through these interactions, contact lenses take up and release biocides and other components in the eye [197]. Components of the tear film may bind to the surface of contact lenses, denature and present an antigenic stimulus to the ocular surface. Such interactions may cause allergic and toxic reactions, which are characterised by conjunctival hyperaemia, papillary conjunctivitis, pannus, corneal epithelial staining and infiltrates [175]. Certain conditions may also occur because of wearer error, such as omission of the neutralizing step after use of hydrogen-peroxide based solutions resulting in toxic keratopathy [198]. Other interactions between the contact lens, cornea, care products or in-eye preparations may lead to complications such as LSCD and solution induced corneal staining (SICS).

6.1 Contact lens-induced papillary conjunctivitis (CLPC)

CLPC is an inflammatory condition of the upper tarsal conjunctiva and a disease unique to contact lens wearers. It was first described as Giant Papillary Conjunctivitis in 1974 [199] and despite comprehensive research on its pathophysiology [200-202] and treatment [203-205], the condition remains a major cause of contact lens wear discontinuation [206]. While recent innovations in contact lens materials and modalities have helped to eliminate certain adverse events, particularly those related to hypoxia [207], CLPC persists and accounts for 15-33% of acute complications presenting to emergency rooms [208, 209].

Risk factors and pathophysiology

CLPC is more commonly associated with soft contact lens , especially SiHy contact lenses [207, 210, 211], overnight wear [211, 212] and in neophyte wearers [213].

The incidence of the disease varies between 0.4% to 21.3% [87, 207, 211, 213, 214]. There is a dose-dependent effect, whereby the risk increases as the duration of contact lens wear increases [206]. Similarly, the risk of the disease may increase with the use of contact lens care solutions that provide a toxic or immunological stimulus to the ocular surface [87]. CLPC usually follows the same seasonal trends as the local peaks in environmental allergens [211], but is not associated with bacterial bioburden, sex or race [206]. CLPC has also been reported in patients with rigid corneal lenses [215] and ocular prostheses [216] while a similar tarsal conjunctival appearance is seen with vernal or atopic keratoconjunctivitis, an extruded scleral buckle, filtering blebs, band keratopathy and limbal dermoid [217].

Both Type I (i.e. immediate reactions involving Immunoglobulin E) and Type IV hypersensitivity reaction (i.e. delayed reactions involving T lymphocytes) have been implicated in CLPC [200-202]. However, the role of mechanical trauma caused by contact lens movement or the contact lens edge, which stimulates release of neutrophil chemotactic factors, triggering a local pro-inflammatory reaction is also plausible [187, 218]. Regardless of the mechanism, CLPC is strongly associated with contact lens deposits [169, 214, 219, 220], although the immunological trigger is unknown. High modulus SiHy contact lenses may contribute to the mechanical aspects of the disease due to increased mechanical or frictional irritation of the upper palpebral conjunctiva [206, 221]. Moreover, these contact lenses have increased propensity to lipid deposits [222], which may or may not be implicated. Cytokines and chemokines are present in the tear film of patients with CLPC, including but not limited to interleukin–6 (IL-6), eotaxin–2 and tissue inhibitor of matrix metalloproteinase–2. Tear immunoglobulin levels (IgE, IgG and IgM) may also increase [202, 223].

Clinical signs and symptoms

The term CLPC describes hypertrophied papillae in the upper tarsal conjunctiva associated with contact lens wear. Under slit lamp examination, hypertrophic papillae often appear in a cobblestone pattern [201]. Histopathological assessment of the conjunctival epithelium in papillary conjunctivitis due to an ocular prosthesis has revealed irregular thickening, proliferation, atrophy and fibrosis in the sub-

epithelial region, the severity of which increases with increasing exposure [216]. In the early stage of CLPC, the conjunctiva is hyperaemic and papillae are relatively small (about 0.3 mm in diameter). As the disease progresses, hyperaemia increases and the tarsal conjunctiva thickens. Subsequently papillae increase in size, often reaching 1 mm or larger in diameter, resulting in the characteristic appearance [186]. Increased tear levels of eotaxin (a chemokine that selectively recruits eosinophils into inflammatory sites) likely plays a role in papilla formation [224, 225]. Generally, papillae first appear towards the upper margin of the tarsal plate in soft lens wearers [226] and towards eyelid margin in rigid contact lens wearers [227].

The disease appears in two distinct forms: local and generalised [13, 45]. In the localised form of the disease, which is more common among SiHy contact lens wearers, papillae are confined to one or two areas of tarsal conjunctiva near the lid margin. In the generalised form, enlarged papillae are present across the entire palpebral conjunctiva [228]. Local CLPC has been suggested to be initiated by mechanical stimuli, relating to contact lens edge design and thickness, that facilitate release of chemotactic factors attracting leucocytes [187]. Similarly, generalised CLPC has been attributed to an immunological response towards contact lens deposits from denatured tear film proteins, which act as an antigenic stimulus [229].

Increased concentrations of leukotrienes (a type of inflammatory mediator) in the tear film in contact lens wearers [230] are thought to cause symptoms such as itching, burning sensation, photophobia, lacrimation, foreign body sensation, sticky mucoid discharge or redness [201]. There can be delayed tear clearance and a shorter tear film break up time leading to increased inflammatory mediators in the tear film [225]. Elevated mucus secretion in CLPC is associated with an increased surface area and thickening of the conjunctival epithelium leading to a functional increase in the total number of goblet and non-goblet cells [231].

Differential diagnoses

Patients with CLPC may present with signs and symptoms similar to those in vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis, seasonal allergic conjunctivitis and superior limbic keratoconjunctivitis. The use of contact lens differentiates CLPC from those conditions [232]. Histopathology has shown an extensive degranulation of mast cells which release more inflammatory components such as eosinophils in VKC, that may underpin the more severe itching and inflammation than in CLPC [233]. Additionally, unlike other severe allergic conjunctivitis conditions, CLPC usually does not have corneal involvement [216].

Management of CLPC

Because of increased contact lens dropouts [206], contemporary management of CLPC is focused on prevention rather than treatment. This practice relies on the use of more frequently replaced contact lenses (such as daily disposables) [234] or temporary cessation of contact lens wear [175]. Following contact lens wear cessation, tear levels of cytokines and chemokines return to normal [235] and symptoms improve [236]. Daily disposable contact lens wear appears to result in lower levels of tear inflammatory mediators than reusable contact lens use [237], which may help in disease prevention. Rub and rinse regimens with all types of multipurpose solutions, hydrogen peroxide-based lens care systems, enzymatic cleaners [87] and changes in contact lens parameters (e.g. reduced edge thickness) [164] may help to reduce CLPC.

Pharmacologically, CLPC can be managed by inhibiting local inflammatory events by using topical mast cell stabilisers (e.g. 2% to 4% Cromolyn sodium)[203-205], anti-histamines (e.g.Ketotifen furmarate 0.25%) or combination antihistimine/mast cell stabilier (e.g. Olopatadine 0.1%) [238], non-steroidal anti-inflammatory agents [239], steroids (e.g. 0.1% fluorometholone alcohol) [218, 240] or immunomodulatory ointments or drops (e.g. Tacrolimus 0.03%) [236]. Steroids may also improve tear function [238], but may transiently increase intraocular

pressure. Innovative therapeutic approaches for allergic conditions are under investigationwhich include anti-histamine releasing contact lenses [241].

6.2 Limbal stem cell deficiency (LSCD)

Limbal stem cells are a subset of epithelial cells in the basal layer of the limbal epithelium, which divide rapidly to replace lost cells during corneal wound healing [242]. Any depletion in density and function of limbal stem cells is called LSCD [243]. An estimated 2.4% to 5.0% of contact lens wearers develop signs of LSCD [47, 173], and many other contact lens wearers do not show any signs and symptoms [244-246]. The condition tends to be bilateral, often in a sub-clinical stage in the less affected eye [173] [247]. It is more common in females [192, 245] and invariably occurs in soft contact lens wearers [51, 173, 245]. Presenting symptoms include eye irritation, photophobia, and decreased visual acuity [173].

The disease presents with corneal vascularisation, peripheral pannus, stromal scarring, persistent epithelial defects with patchy fluorescein uptake (Figure 4) [192, 244], and corneal and limbal epithelial thinning [246]. The disease can sometimes mimic sterile keratitis [248]. *In vivo* confocal microscopy [249] and impression cytology [247] can help to diagnose the disease. Impression cytology alone, however, may not detect subclinical LSCD [247].

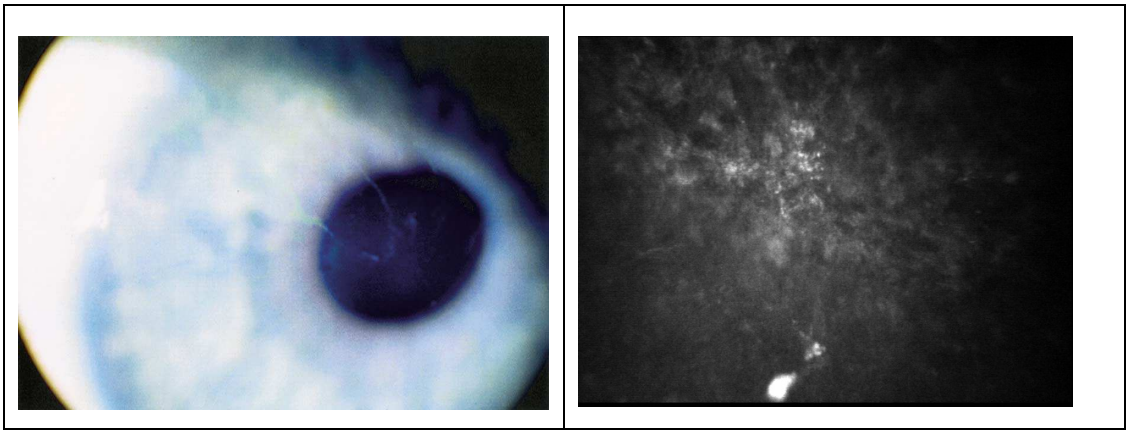

Figure 4: Limbal stem cell deficiency (LSCD) shown as a corneal pannus extending from the limbus at 11 o'clock to the pupil centre, accompanied by infiltrates in a

daily soft contact lens wearer. The IVCM image shows sub-epithelial inflammatory signs at the tip of the pannus. Image reproduced from Stapleton et al. [250].

Contact lens wear may lead to LSCD by two mechanisms: 1) mechanical stress and hypoxia, and 2) toxicity due to contact lens care solutions. It is hypothesised that mechanical pressure due to overnight contact lens wear tends to stress limbal stem cells, causing their depletion [192, 251]. Therefore, the risk increases as the duration and length of wear increases [192]. Similarly, preservatives in contact lens solutions, such as thimerosal, may cause LSCD [251, 252].

Previously, several authors described LSCD arising due to contact lens wear under different names, such as contact lens -induced keratopathy [253], chronic contact lens -associated epitheliopathy [251], advancing wave-like epitheliopathy [254], hurricane keratopathy [255], and contact lens -induced superior limbic keratoconjunctivitis [256]. However, an improved understanding of the disease pathophysiology has now made it possible to categorise all those conditions as contact lens -induced LSCD if they exhibit a gradual loss of stem cell function due to contact lens wear [51].

Cessation of contact lens wear reverses mild forms of LSCD by allowing adult stem cells to repopulate [192]. Preservative-free eye drops and the management of concurrent ocular surface disorders helps to maintain the limbal stem cell niche [51, 245]. Schornack reported reversing the mild form of the disease using scleral lenses [248]. Severe LSCD requires surgical interventions to restore the renewal process of corneal epithelium [257, 258] although topical autologous serum has been proposed [244].

6.3 Solution-induced corneal staining (SICS)

SICS is an asymptomatic condition associated with the use of reusable hydrogel and SiHy contact lenses and certain care regimens [259]. First reported in 1997 ([260], SICS shows transient and reversible [261] [262] corneal staining after contact lens wear. It occurs frequently with a combination of polyhexamethylene

biguanide (PHMB) based care systems and group II lenses [262] [263, 264]. Polyquad and Aldox-containing solutions are known to cause less staining than polyhexanide [196, 265]. The staining may appear as early as 15 minutes [261] of lens wear, peaks at one hour [266] and may remain up to four hours [262]. The reported incidence rate is between 10.6% to 37% where the rate varies with contact lens material and care solution combination [267-270].

Clinically, SICS can appear either as superficial diffuse punctate dots across the entire cornea or a characteristic annular ring pattern [268], primarily in the peripheral region of the inferior cornea [270] (Figure 5). The dots can be observed under appropriate magnification [271], and higher levels of micro-punctate corneal staining reduce comfort ([196, 267].

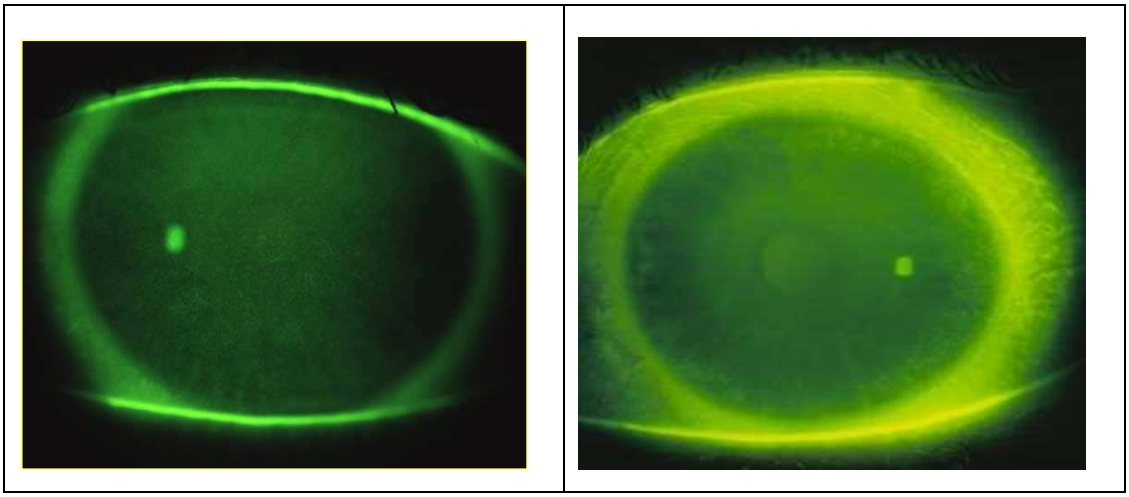

Figure 5: Solution-induced corneal staining (SICS) can appear either as superficial diffuse punctate dots across entire cornea (A) or as a characteristic annular ring on the peripheral cornea (B). © Brien Holden Vision Institute 2020. Reproduced with permission. Please contact the Brien Holden Vision Institute via www.brienholdenvision.org for further information.

Originally SICS was thought to be a corneal response to toxic effects of contact lens care solutions [270, 272-275], causing increased epithelial cell shedding and fluorescein uptake [276]. However, there are arguments which claim the condition is benign and non-pathological [277-279] and may be due to enhanced binding of

fluorescein with components of contact lens care solutions to corneal cells [278], occurring preferentially with high water content contact lenses [262]. The condition has been termed 'Preservative-Associated Transient Hyper-fluorescence' (PATH) [277]. While there is limited evidence of corneal histological changes after using products that are associated with SICS [278, 280], there has been report of an association with CIEs [268]. Regardless of the pathophysiological processes, increased lens deposits exacerbate the condition [281].

Generally, the corneal staining in SICS is of low grade and reversible [262]. Non-PHMB based care solutions [265, 270, 282], hydrogen peroxide-based disinfection system [263, 268], and the inclusion of a rub and rinse step during contact lens cleaning can help to remove biocides and alleviate staining [283]. Preapplication of carboxy- methylcellulose based lubricant can reduce polyhexanide-induced staining [284].

6.4 Prevention and advice to wearers

Mild forms of allergic, mechanical and toxic reactions of contact lenses and care systems are reversible with cessation of contact lens wear [192]. Including rub and rinse step for all types of care products [283], switching to hydrogen peroxide-based care regimen [263, 268], changing material, changing contact lens type (e.g. switching to daily disposable contact lenses), and changing the care system can also minimise such complications [265, 270, 282].

7 Contact lens-induced dry eye

7.1 Introduction

Contact lens-induced dry eye (CLIDE) is used to refer to symptomatic contact lens wearers who become asymptomatic after contact lens removal [285]. CLADE conversely refers to pre-existing dry eye among contact lens wearers who are symptomatic regardless of contact lens wear [43].

Similarly, the TFOS Dry Eye Workshop II (TFOS DEWS II) defines DED as “a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles” [286]. The global prevalence of DED ranges between 5 and 50% [287], being more common among contact lens wearers than non- contact lens wearers. Thus, contact lens wear has been listed as a modifiable risk factor for DED [287] and it has been reported to be one of the main causes of lens discontinuation and drop out worldwide [288].

7.2 Prevalence

The prevalence of CLIDE among contact lens wearers ranges between 15% to 55% [53, 55, 56, 289-295]. The rate, however, varies between studies depending on the study population, contact lens material, diagnostic criteria (e.g. self-assessment or symptomology questionnaire), and clinical tests or a combination thereof [53, 55, 292, 294].

7.3 Risk factors

Similar to DED, CLIDE is also a multifactorial condition. The risk factors for CLIDE include: contact lens-related factors (e.g. material, water content, contact lens design, wear modality, replacement schedule and the duration of contact lens wear), environmental factors and patient-related factors (e.g. gender and ethnicity and concurrent ocular surface conditions)) [292, 296, 297].

Soft contact lens wearers have a higher incidence of CLIDE than rigid corneal lens wearers [54, 292]. Similarly, CLIDE occurs more frequently in hydrogel compared with SiHy contact lenses [298, 299], conventional SiHy compared with disposable SiHy [300] and in toric compared with spherical contact lenses [294]. High water content contact lenses have also been proposed as a potential risk factor for CLIDE [53, 292, 301], probably as a consequence of contact lens dehydration and local thinning of the tear film [301]. Additionally, poor wettability has also been strongly linked to dry eye symptoms [302] (See CLEAR Maintenance Report

[181]). There appears to be a dose dependent effect with increased wear time associated with CLIDE [303]. Environmental factors have been suggested to increase the risk of CLIDE, including an increase in temperature coupled with reduced humidity [302, 304] and prolonged use of video display terminals [305]. Females are more likely to experience CLIDE than males [292]. Racial differences in CLIDE have also been reported, where Asian contact lens wearers have more severe dryness compared to non-Asians [306].

Specific ocular surface manifestations during contact lens wear have been proposed to contribute to CLIDE. Those include 3 and 9 o'clock staining [170, 189], corneal dellen in rigid corneal lens wearers [191] (Section 6.8) and inferior closure staining in soft contact lens wearers [307].

Inferior closure staining occurs due to incomplete blinking during contact lens wear. It is more common with high water content soft contact lenses, which result in dryness of inferior cornea leading to epithelial desiccation [307].

7.4 Pathophysiology

The core mechanism of CLIDE involves partitioning of the tear film into pre- and post- contact lens films. It leads to tear film thinning and a decrease in overall tear volume and its stability [292, 308, 309].

CLIDE may also occur due to increased instability of the tear film. This includes sequelae of events that start with incomplete blinks, reduced blink frequency, increased evaporation of the post-contact lens tear film and decreased contact lens and ocular surface wettability [292, 310]. Evaporation of the post- contact lens tear film increases ocular surface temperature and friction between the contact lens and the ocular surface [311], which subsequently may contribute to increased tear osmolarity and ocular surface inflammation [312]. The inflammatory cascade may involve several events such as upregulation of Langerhans cells in the lid wiper region [313], upregulation of nerve growth factor in the tear film [314], and the secretion of pro-inflammatory cytokines and metalloproteases [315].

CLIDE may also be associated with increased meibomian gland drop out [316, 317], plugged gland orifices [318] or altered meibomian gland function (MGD) [319] (see Section 9). It may contribute to changes in lipid layer thickness and integrity [320], tear instability and decreased lens wettability due to a buildup of lipid deposits on the contact lens surface [321]. Contact lens wear also reduces goblet cell density and the amount of mucin secreted on the ocular surface, resulting in protein deposition on the contact lens and increased tear film instability [322-324].

7.5 Presenting symptoms and signs

CLIDE symptoms are variable and increase with prolonged contact lens wear [53, 289, 325, 326]. Symptoms may include, but are not limited to, reduction in vision quality, foreign body sensation, dryness, eye strain, blurred vision and discomfort [53-56]. Similarly, reduced tear breakup time, decreased tear meniscus height [327], corneal epithelial staining [322], increased blink rate [189] and tear hyperosmolarity and ocular surface inflammation may occur, depending on the severity of the condition [312, 328].

7.6 Differential diagnosis

Differential diagnosis in CLIDE includes CLADE, contact lens discomfort, MGD and other ocular surface conditions such as demodex, blepharitis, CLPC and allergy [309]. A specific diagnostic approach for CLIDE does not exist [329], probably due to varying sensitivity and specificity of several tools used in DED assessment [330]. Therefore, the diagnostic methodology presented in TFOS DEWS II [331] can be adapted to diagnose CLIDE. It is based on initial triaging questions for DED, ocular history, risk factor assessment and presenting symptoms and signs that are combined with clinical findings [331]. The assessment of symptomatic and asymptomatic wearers may be complicated as signs and symptoms are necessarily linked in DED and they vary between individuals [332-335].

Table 7: Diagnostic tests that can be used to assess CLIDE

CLIDE	Diagnostic tests Diagnostic Outcomes	
Clinical history	- General medical history - Ophthalmic history - Risk factor identification	Potential risk factors include: lens material, water content, surface properties of the lens, ocular surface conditions and environmental factors [292, 297, 304].
Subjective assessment	**Symptoms assessment based on validated symptomology questionnaires:** -CLDEQ-8 - OSDI	Positive result: CLDEQ-5 ≥ 6 [336] or OSDI ≥ 13 [337].
Objective clinical assessment	**Ocular surface evaluation using slit lamp without vital stains** - Corneal assessment - Conjunctival assessment for hyperaemia and lid parallel conjunctival folds (LIPCOF)	-Corneal thinning and desiccation due to localized tear film instability in prolong contact lens wear [170]. -Increased hyperaemia [312], LIPCOF are likely to occur during contact lens wear [338].
	Evaluation of the tear film **A. Tear film composition** - Osmolarity testing - Tear film ferning testing **B. Tear film volume** - Tear meniscus height using slit lamp (Meniscometry), anterior segment ocular coherence tomography or interferometry **C. Tear production and secretion** using Schirmer test or phenol red thread test **D. Tear film stability** -TBUT -Non-invasive tear film break-up time (NIBUT) using interferometry e.g. Tearscope, topography-based imaging systems **E. Tear film stability from the surface of contact lens/contact lens surface wettability**	-Osmolarity: 308 mOsm/L (cut off value) in either eye or an interocular difference >8 in normal and early stages of DED [339]. -Tear film ferning: the pattern is fragmented or absent in severe DE [340]. -Reduced total volume of upper and lower tear meniscus [341]. -Neither tear production nor turnover rate are significantly altered during contact lens wear [342]. -Reduced TBUT value < 10s and in NIBUT as low as 2.7 s for automated algorithms and up to 10 s for subjective observation techniques [296]. -A relative decrease in pre-lens NIBUT [329] Abnormal lipid layer thickness and quality that increased with increased lens wear [319, 321].

	Using *in vivo* pre-lens non-invasive TBUT **F. Assessment of lipid layer thickness** (Tearscope, Interferometry, specular reflection)	
	Ocular surface evaluation using slit-lamp and vital stains (fluorescein and Lissamine green)	Positive corneal and conjunctival staining is not frequent but can be observed in severe prolonged DE or CLIDE [343].
	Assessment of eye lids **A. Lid wiper region** Assessment of the superior lid wiper region using sodium fluorescein and lissamine green, or lissamine green only.	Positive Lid-wiper epitheliopathy (LWE) of 2 mm in length and/or 25% sagittal width (excluding Marx's line) is a frequent finding in soft lens wearers [344].
	B. Meibomian glands assessment - Meibomian gland expression - Meibomian gland imaging (infrared Meibography, Spectral domain, OCT, and confocal microscopy	Increased Meibomian gland morphological changes and drop-out [316, 317, 319].
	C. Assessment of blink rate and completeness	Increased blink rate was observed in patients with CLIDE [290, 345].
Laboratory assessment	**Quantitative assessment of inflammatory biomarkers** e.g. matrix metalloproteinase (MMP-9), cytokines and chemokines	Contact lens wear may alter inflammatory biomarkers in tears [346].
	Assessment of mucin function and goblet cell density Impression cytology	Deficiency and alternation in goblet cells and changes in mucin structure have been reported in symptomatic contact lens wearers [322, 324]

Abbreviations; CLDEQ-8: Contact Lens Dry Eye Questionnaire, OSDI: Ocular Surface Disease Index, LIPCOF: lid parallel conjunctival folds, TBUT: Tear film break-up time, LWE: Lid-wiper epitheliopathy, MMP-9: Matrix metalloproteinase. DE: Dry eye

*TBUT with fluorescein and staining of the ocular surface should be avoided prior to osmolarity

7.7 Management

The management of CLIDE includes treating pre-existing ocular surface diseases that may contribute to tear film dysfunction. Then a tailored treatment aimed to restore the homeostasis of the ocular surface and normal tear function can be

instituted [331]. Therapeutic approaches proposed for DED in non- contact lens wearers can be used to manage CLIDE, specifically to target the specific subtype of DED i.e. EDE or ADDE with consideration of the presence of symptoms and clinical signs [331, 339]. A recent concept in CLIDE management suggested by the Japanese Dry Eye Society in their report on Tear Film Oriented Therapy [347, 348] focused on targeting either the tear film or the contact lens or both [296].

Treatments targeting the tear film

Treatment modalities are categorized according to noted deficiencies in each layer of the tear film: aqueous, lipid and mucin layers [342].

Treatments targeting the contact lens

These may include switching to SiHy contact lenses [298, 349], using contact lenses with higher wettability [302] or applying wetting agents such as polyvinylpyrrolidone, polyvinyl alcohol or surface-bound hyaluronic acid [350-352] (CLEAR Maintenance Report [181]). Similarly, switching to daily disposable contact lenses can be helpful [353]. Scleral lenses may improve symptoms of dryness and protect the ocular surface in patients with pre-existing DED and CLADE [354].

7.8 Prevention and advice to wearers

Contact lens wearers with dryness symptoms should be informed about CLIDE, the management options and the prognosis. They should also be aware of possible risk factors as discussed above**.**

8 Meibomian gland dysfunction in contact lens wear

The 2011 TFOS International Workshop on meibomian gland dysfunction (MGD) defined the condition as follows: "… a chronic, diffuse abonormality the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/ quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease". [355]. Early signs of MGD may precede dry eye disease (DED),

specifically the evaporative subtype [355]. Increased signs of MGD are likely to lead to contact lens dropout [356] and signs of MGD are a predictor of worsening symptoms [357].

8.1 Prevalence of MGD amongst contact lens wearers

A meta-analysis on the four studies available at the time reported a statistically similar prevalence of 37% in contact lens wearers and 32% in non-lens wearers [358]; however the authors note that, of the included studies, there were limitations in sample size, design and analysis. More recently, Young et al (2012) found that the primary reason for contact lens discomfort for 14% of symptomatic contact lens wearers in their study was MGD [343]. It is possible that the overall prevalence of MGD in this cohort may be higher as the remaining 86% may have had signs of MGD concurrent to other noted causes of contact lens discomfort, but MGD was not their main cause for contact lens discomfort.

8.2 Does contact lens wear increase the risk of MGD?

The earliest report of contact lens wear and MGD was published in 1980 [59]. However, there have been no longitudinal studies that have assessed the structure of meibomian glands in neophytes before and after lens wear. All studies relate to comparisons of symptomatic contact lens wearers with either asymptomatic lens wearers, lapsed lens wearers or non-lens wearers and are divided as to whether the glands stucture and function is affected by lens wear (Table 8).

Table 8: Summary of human clinical in vivo studies that have examined whether soft contact lens wear affects meibomian gland structure and/or output, categorised according to the method of assessment and clinical feature of interest.

Meibography (gland atrophy)		Sample size (n)	Duration of CL wear
Arita et al., 2009 [316]	Yes (correlated with duration of CL wear)	258 (121 CL wearers, 137 non-lens wearers)	≥1 year
Alghamdi et al., 2016 [319]	Yes (not correlated with duration of CL wear)	100 (20 individuals in	5 groups: 1. Short CL experience 2 ± 1 year

		each CL experience group)	2. Moderate CL experience 5 ± 1 year 3. Long CL experience 10 ± 2 year 4. Previous CL wearers for ≥2 years who stopped lens wear at least 6 months prior to the study 5. Control (Non-CL wearers)
Machalinska et al., 2015 [318]	No	72 (41 CL wearers, 31 non-CL wearers	≥1 year
Pucker et al., 2015 [356]	Inconclusive	140 (70 CL wearers, 70 non-lens wearers)	≥5 years
Siddireddy et al., 2018 [320]	Yes	30 CL wearers	≥6 months
Pucker et al., 2019 [359]	No	74 (37 CL wearers, 37 CL dropouts)	CL wearers: 10.9 ± 6.5 years CL dropouts: 7.8 ± 6.7 years
Ucakhan and Arslanturk-Eren, 2019 [360]	No[a]	142 (87 CL wearers, 55 non-lens wearers)	Three groups: 1. <3 years 2. 3-7 years 3. >7years
In vivo confocal microscopy			
Villani et al., 2011 [361]	Yes (basal epithelial cell density, glandular orifice diameter, secretion reflectivity, inhomogeneity of peri glandular interstices)[b]	40 (20 CL wearers, 20 non-CL wearers)	≥1 year
Siddireddy et al., 2018 [320]	Yes (reflectivity)	30 CL wearers	≥6 months
Meibum expressibility			
Villani et al., 2011 [361]	Yes	40 (20 CL wearers, 20 non-CL wearers)	≥1 year
Machalinska et al., 2015 [318]	No	72 (41 CL wearers, 31 non-CL wearers	≥1 year

Pucker et al., 2015 [356]	No	140 (70 CL wearers, 70 non-lens wearers)	≥5 years
Alghamdi et al., 2016 [319]	Yes	100 (20 individuals in each CL experience group)	5 groups: 1. Short CL experience 2 ± 1 year 2. Moderate CL experience 5 ± 1 year 3. Long CL experience 10 ± 2 year 4. Previous CL wearers for ≥2 years who stopped lens wear at least 6 months prior to the study 5. Control (Non-CL wearers)
Cox et al., 2016 [362]	Yes	203 CL wearers	9 month study CL wearers required at least 5 days a week and at least 8 hours a day lens wear in the month before the baseline visit
Siddireddy et al., 2018 [320]	Yes	30 CL wearers	≥6 months
Pucker et al., 2019 [359]	Yes	74 (37 CL wearers, 37 CL dropouts)	CL wearers: 10.9 ± 6.5 years CL dropouts: 7.8 ± 6.7 years
Meibum quality			
Pucker et al., 2015 [356]	No	140 (70 CL wearers, 70 non-lens wearers)	≥5 years
Machalinska et al., 2015 [318]	Yes	72 (41 CL wearers, 31 non-CL wearers	≥1 year
Siddireddy et al., 2018 [320]	Yes	30 CL wearers	≥6 months
Lipid layer thickness			
Young et al., 2012 [343]	No	274 CL wearers (226 with CL-related dryness, 48 asymptomatic CL wearers)	N/A Average wearing time per day 12.8 and 13 hours for dry and not dry groups respectively
Siddireddy et al., 2018 [320]	No	30 CL wearers	≥6 months

[a] Although the authors of the paper report statistical significance, the findings are not considered clinically significant.

[b] The authors also reported a difference in acinar unit diameters however subsequent histological examinations [363] indicate that the dermatological feature, rete ridges, were incorrectly identified as meibomian gland acini.

CL Contact lens

In vivo confocal microscopy (IVCM) has also been used to image meibomian glands to assess their morphology and meibum quality. IVCM images of the eyelid has shown circular and oval structures with a hyporeflective interior and hyperreflective border, intially assumed to be meibomian gland acini but more recently shown to be rete ridges [363]. Retes ridges are invaginations of the epidermis into the underlying dermis between papillae at the dermal-epidermal junction. While changes in these structures have been associated with both contact lens wear and ocular symptoms [320, 361, 364], the interpretation of any IVCM data related to meibomian glands should be treated with caution, given the likely potential for confusion of meibomian glands with rete ridges, in addition to the limtation of the IVCM's 670nm laser to penetrate to the depth of the meibomian glands themselves [365]. Two studies [320, 361] also explored the reflectivity of the "meibomian gland secretions" using IVCM, reporting that contact lens wearers had significantly increased gland secretion reflectivity compared to non-lens wearers. Changes in secretion reflectivity are thought to indicate alterations in meibum quality, where clear meibum within an acinar unit appears as a fairly dark region of the image and thickened, inspissated meibum appears as white regions of the image [320], however, given our understanding of rete ridges in IVCM, this data should also be treated with caution.

Optical coherence tomography (OCT) has also been used to image meibomian glands. Imaging using OCT allows three-dimensional evaluation of the meibomian glands compared with two-dimensional evaluation using meibography or IVCM. One study found a 50% discrepancy in the assessment of meibomian gland dropout with infrared meibography compared with a images acquired using a customized OCT [366]. However, to date, no peer reviewed publications have

evaluted meibomian gland characteristics amongst contact lens wearers using OCT.

Even though changes detected using meibography may be inconclusive, many studies are in agreement that contact lens wearers have altered meibum expressibility and quality (Table 5). Ong and Larke (1990) reported that meibum collected from contact lens wearers had a melting point 3°C higher than non-lens wearers [58]

Gland loss and changes in meibum expression or quality impact lipid layer thickness (LLT) [367]. However, there are very few studies that examine the tear film lipid layer in contact lens wearers presenting with MGD. Young et al found the mean LLT of a group of symptomatic contact lens wearers whose primary cause of lens discomfort was MGD was not significantly different to the other dry eye diagnosis groups [343]. Siddireddy et al found no significant difference in mean LLT between symptomatic and asymptomatic contact lens wearers [320]. Although symptomatic contact lens wearers had significantly more capping of meibomian glands and greater tear evaporation rates compared to the asymptomatic contact lens wearers, there were no associations between LLT and MGD features [320].

In addition to structural gland changes and alterations in meibum, morphological changes to the lid margin associated with MGD have been consistently reported in contact lens wearers. These include increased vascularity, roundness, irregularity, plugging of gland orifices and displacement of the mucocutaneous junction [59, 318, 319, 362]. Although the mucocutaneous junction seems to be able to recover to its almost “normal” position after the cessation of wear, other changes such as gland expressibility and dropout persist after discontinuation of wear [319]

8.3 Presenting signs and symptoms

Asymptomatic MGD is more prevalent than symptomatic MGD [368], therefore relying upon symptoms alone is not reliable in the diagnosis of MGD. Key clinical

signs of MGD include meibomian gland loss, altered meibomian gland secretion and changes at the lid margin [369]. Symptoms, when present, include irritation, dryness, soreness, foreign body sensation, burning, watering, itching and reduced or fluctuating vision. The TFOS International Workshop on MGD proposed a four-stage disease severity scale where each stage takes into account the expressibility and quality of meibum secreted, presenting symptoms, ocular surface damage and other clinical presentations [370].

8.4 Differential diagnoses

When examining a contact lens wearer for MGD, it is imperative to consider concurrent ocular surface disease which may also impact their contact lens comfort. MGD commonly co-exists with other ocular surface conditions, including anterior blepharitis, ocular allergy, phlyctenular disease, trichiasis, hordeolum, Demodex infestation, and chalazia. This is acknowledged by the TFOS International Workshop on MGD, where this stage of MGD is referred to as “Plus” disease [370].

DED is characterised by two non-mutually exclusive categories: aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE). The majority of DED is evaporative in nature, resulting from lid-related changes (including MGD) or ocular surface-related causes (e.g. contact lens wear) [371]. ADDE, caused by conditions affecting lacrimal gland function, may co-exist with MGD. Assessing tear volume non-invasively by meniscometry is recommended over the Schirmer test which should be reserved for confirming severe aqueous deficiency [331].

8.5 Management

MGD can exist with and without contact lens wear. The TFOS International Workshop on MGD and the TFOS DEWS II report provide extensive summaries of the management and therapies indicated for MGD and DED [331, 370]. Approaches for management may occur at a local, ocular level (e.g. lid hygiene, lid warming treatments, ocular lubricants or topical azithromycin) or a systemic level (e.g. dietary amendments to increase omega-3 fatty acid intake, oral

tetracycline derivatives). MGD may be secondary to other systemic disorders (e.g. skin conditions such as acne rosacea, atopic dermatitis or cicatrizing ocular conditions) and these conditions need to be managed accordingly. Strategies for managing MGD should be staged according to disease severity. There are few studies specific to contact lenses, however improvements in meibomian gland capping, secretion volume and gland expressibility have been reported in symptomatic contact lens wearers after treatment with microblepharon exfoliation [372]. One study has shown topical azithromycin ophthalmic solution (1%) in contact lens-associated dry eye (CLADE) to be well tolerated and significantly improved comfortable wear time, however MGD-specific assessments or outcomes were not reported [373].

8.6 Prevention and advice to wearers

It is evident that a significant proportion of contact lens wearers exhibit signs of altered meibum expressibility and suboptimal meibum quality and that these changes persist in those who have discontinued from wear. These changes lead to contact lens discomfort and can result in dropout. Given the high proportion of contact lens wearers who cease wearing contact lenses due to discomfort, it is important that ECPs take a *proactive* approach of managing early clinical signs of MGD (before symptoms emerge) rather than a *reactive* approach. Compliance with at-home therapies such as lid hygiene or warm compresses is poor [374]. Patient education and clear communication by the ECP plays a key role in improving compliance with any treatment regimen. The treatment plan for each patient should be staged according to the severity of the disease. Regular and complete blinking exercises may be recommended to enhance tear film stability [375] and regular after-care visits should afford proper management of the condition and to improve ocular comfort during contact lens wear [376] (CLEAR Evidence-based Practice Report [377].

9 Contact lens discomfort (CLD)

9.1 Introduction

Contact lens discomfort (CLD) has been defined as “a condition characterized by episodic of persistent adverse ocular sensations related to contact lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear” [378].

9.2 Frequency

CLD is one of the leading causes for discontinuation of contact lens wear [379]. Using standardised questionnaires, 31% to 58% of lens wearers are classified as symptomatic [379]. Using standardised questionnaires, 31% to 58% of lens wearers are classified as symptomatic [380-390], and this figure reaches 88% if reports of any discomfort during wear are included [391]. Prevalence also varies by region, with more wearers in North America classified as having CLD compared to the UK (53% vs. 44%) [380]. Risk factors for CLD can generally be categorised as contact lens-related, patient-related or associated with contact lens hygiene or replacement. Findings related to contemporary contact lens types are discussed, along with current management strategies for CLD.

9.3 Risk factors

Contact lens-related risk factors

Contact lens-related factors pertain to material, fitting, design and surface characteristics and the care solution. Initially, it was proposed that refitting habitual hydrogel contact lens wearers with SiHy lenses was effective for improving comfort [392, 393]. However, these studies comparing newly fitted SiHy contact lenses and habitual hydrogel contact lenses were not well-controlled, some were contralateral, and likely led to biased responses [394]. Greater discomfort has been reported with higher water content [387] or higher modulus contact lens materials [395]. Although two retrospective studies showed no difference in comfort between SiHy

and hydrogel contact lens materials [389, 396], higher dryness symptoms were reported amongst hydrogel contact lens wearers in a UK study [380]. Conversely, when comparing normal and adverse environmental conditions, a greater reduction in comfort was observed when a SiHy was worn compared to a hydrogel contact lens [386]. Comfort also varies between different SiHy contact lenses [397, 398], which suggests that other factors, such as the contact lens surface, design, material modulus and the care solution likely affect comfort [399]. However, contralateral eye studies comparing low modulus hydrogel to higher modulus SiHy contact lenses showed no differences in comfort [400, 401].

Greater front surface contact lens deposits and poor wettability wettability [402] and the presence of substantial contact lens bioburden have also been associated with discomfort [403]. The profile of lipid [404] and mucin [405] deposits on worn contact lenses differs between symptomatic and asymptomatic subjects. The role of contact lens osmolality is uncertain given increased osmolality of worn contact lenses was negatively associated with comfort in one study [406], whereas osmolarity was positively correlated with comfort in another [407].

Tighter fitting [395, 408] and steeper base curve contact lenses [395] offer better comfort, whereas greater post-blink movement [402, 409] and smaller diameter contact lenses reduce comfort [410]. Inferior contact lens decentration has also been associated with symptoms of dryness [402], but movement on blink in upgaze is not associated with comfort [411]. Therefore, well centred and less mobile contact lenses appear to promote lens comfort.

Contact lens design also has an impact on comfort. More discomfort and dryness are reported with toric [380] and multifocal contact lens designs [412], which could implicate variations in contact lens thickness. Greater discomfort was associated with lower contact lens power in experienced contact lens wearers up to 6 hours post-insertion [409]. A less rounded edge shape, which clinically manifests as conjunctival indentation [413], has also been negatively associated with comfort in SiHy contact lens materials [406]. Conversely, SiHy contact lenses with a rounded

edge away from the ocular surface produced less staining compared to a knife-edge in close apposition to the ocular surface, but was associated with worse comfort [413]. Mechanically-induced conjunctival staining in the circumlimbal region is material dependent, as two contact lenses with the same knife edge design produced less staining in a low rigidity hydrogel material versus a medium rigidity SiHy material [413].

To optimise contact lens-related comfort, the contact lens surface must be smooth and wettable with minimal deposits and contact lenses are well centred and not too mobile. Where possible, consideration should also be given to reducing the impact of contact lens design features on CLD, such as contact lens type, thickness and edge shape.

Patient-related risk factors

Patient-related factors associated with CLD can be broadly classified into demographics, the eyelids including the meibomian glands, the tear film, ocular surface characteristics and the environment.

Increasing age has been associated with better lens comfort upon insertion [402, 414] and better end of day comfort [414] in experienced lens wearers. This may be due to self-selection, whereby older wearers who experience symptoms have discontinued contact lens wear [415]. However, this is contrary to other reports that found symptomatic patients were older [61] and had a longer history of lens wear [381].

Differences in comfort scores based on ethnicity have been reported in short-term wear studies. On average, comfort scores for Caucasians were 5 units lower on a 100 point scale compared to Latinos [409], while decreased comfort has also been associated with Asian ethnicity [402], which may be attributed to previously reported differences in the ocular response to contact lens wear in Asians compared to Caucasians [416-418]. Symptoms are mor common in females [61, 387]. However, another study of habitual wearers evaluating the effect of different

lipid supplements showed ocular comfort was not influenced by age, ethnicity or sex [419].

The lid-wiper (CLEAR Anatomy Report [420]) describes the portion of the marginal conjunctiva of the eyelid, which acts as a wiping surface to spread the tear film over the ocular surface or the surface of the contact lens, and staining observed in this region is termed lid-wiper epitheliopathy (LWE) [60]. Greater upper LWE (average length and width) has been associated with more discomfort in symptomatic populations [320, 421] and greater symptoms have also been reported with increased severity of LWE width alone amongst habitual contact lens wearers [422]. However, other studies of habitual wearers and populations including symptomatic, asymptomatic, rigid corneal lens wearers and non- contact lens wearers have failed to find associations between LWE and comfort [407, 423, 424]. Although increased microvascular density in the lid wiper region was associated with a reduction in comfort in neophytes fitted with a SiHy contact lens after 6 hours of wear [425], generalised lid margin vascularity was not associated with comfort in experienced contact lens wearers [362]. In symptomatic wearers, tarsal conjunctival papillae are more circular and more regular when imaged using *in vivo* confocal microscopy compared to asymptomatics [426]. The presence of Demodex mites on the eyelid margins has been associated with symptomatic wear [388], and in individuals who had abandoned contact lens wear due to discomfort [427].

Although no difference was found in meibomian gland atrophy between dropouts from lens wear (aged 18 to 45 years), sex and age-matched successful contact lens wearers had less upper eyelid tortuosity, but greater tortuosity in the lower eyelid [359]. Upper and lower meibomian gland plugging and worse meibum quality were observed in the dropout group [359] and worse secretion quality associated with discomfort has also been confirmed in existing symptomatic contact lens wearers [320] and amongst habitual contact lens wearers [362]. Furthermore, the presence of foam at the meibomian gland orifice is associated with discomfort [320].

Clinical characteristics and components of the tear film contributing to CLD have also been widely explored. Reduced tear film stability in terms of shorter non-invasive [384, 428] and invasive tear film breakup time (TBUT) [381, 429], higher tear film evaporation rate and thinner lipid layer thickness [388] have been associated with discomfort in symptomatic contact lens wearers. Furthermore, reduced non-invasive pre-contact lens thinning time has been associated with symptoms [387], and dropouts from contact lens wear displayed shorter invasive TBUT 3 months after discontinuation compared to matched controls [430]. Conversely, other studies have shown no association between non-invasive TBUT, tear volume (phenol red thread test) and comfort in subjects fitted with SiHy contact lenses [407], or when comparing dropouts to successful contact lens wearers [431]. Tear film osmolality findings are also inconclusive, given no associations with comfort were identified in short-term or dispensing studies [406, 407], but increased tear film osmolality [387], and a greater difference between inferior and superior tear osmolality [432] were associated with symptoms amongst habitual contact lens wearers. With regards to tear film osmolality, these findings seem to suggest that long term studies of habitual wearers where tear film changes have had the opportunity to equilibrate may be more meaningful than short-term studies or studies evaluating previous contact lens wear dropouts.

Inflammatory mediators in the tear film including leukotriene B4 [433, 434], prolactin-induced protein [433, 434], prolactin-induced protein [435], cytokines [436] and interleukin 17A [432] have been associated with decreased comfort during contact lens wear, although other studies have reported no association between tear cytokines [437], arachidonic acid mediators and histamine concentrations [438] and comfort. The ratio of certain tear film components such as wax esters to triacylglycerols is different between symptomatic and asymptomatic lens wearers [428]. Recently, substance P, a molecule involved in the transmission of pain has been shown to be higher in symptomatic contact lens wearers [439]. This finding is of particular interest, given reports of alterations to corneal and conjunctival sensitivity to mechanical and cold stimuli amongst dropouts from contact lens wear, compared to healthy matched controls [430], and

in symptomatic versus asymptomatic habitual contact lens wearers [429], respectively. Increased tortuosity of nerve fibres in the central cornea is associated with higher ocular symptoms [440]. Conversely, other studies have found no differences in mechanical or thermal corneal sensitivity thresholds between symptomatic, asymptomatic hydrogel contact lens wearers and non-contact lens wearers [441], and no associations between alterations in the corneal sub-basal nerve plexus and CLD in habitual SiHy and hydrogel contact lens wearers [442], although differences in methodology make comparisons between these studies challenging.

Other patient-related characteristics associated with decreased contact lens comfort include greater limbal injection [387], inferior corneal staining [402] and lid parallel conjunctival folds in the lower quadrant of the bulbar conjunctiva parallel to the lower lid margin [61]. However, no associations were found between comfort and corneal and conjunctival staining when all quadrants were considered [406]. Symptomatic contact lens wearers also display greater diurnal variation in comfort compared to asymptomatic wearers [382], although the time of contact lens insertion has less impact on comfort than duration of contact lens wear on eye [443].

Lens hygiene and replacement frequency-related risk factors

Some studies have shown particular combinations of contact lenses and contact lens care products to offer superior comfort [408, 444]. Other studies comparing multipurpose versus peroxide-based systems have reported conflicting results, including no difference in overall comfort [444, 445], more favourable initial comfort on insertion with the peroxide solution [444], and less symptoms with a multipurpose solutions versus a peroxide system [446]. Although several studies report no difference in comfort between various multipurpose solutions [393, 445, 447], those that are PHMB-based have frequently been associated with decreased comfort [448, 449] and higher levels of gritty or scratchiness symptoms compared to polyquaternium-based systems [450]. Short-term studies reporting on the comfort of contact lenses pre-soaked in solution [451, 452] would have greater relevance if comfort was reported for longer than 2 hours of wear.

Reports of better comfort with daily disposable versus daily wear contact lenses ([444, 453] seem to imply that removal of lens care products and/or contact lens surface considerations such as deposition would be beneficial. However, when contact lenses were worn contralaterally, no difference in comfort was found between contact lenses replaced on a monthly or daily disposable basis [454]. Other studies reporting on the effect of daily disposable lenses on contact lens wear comfort have been limited to refit studies with no cross-over [455], or bilateral comparisons of various daily disposable lens types only [411]. Given the neural cross talk between the two eyes and the understanding that contralateral eye study designs are insensitive to detecting small differences in comfort [456], well-designed, bilateral cross-over studies are better able to provide quality evidence in studies of contact lens discomfort.

Studies evaluating the effect on comfort of replacing with a new contact lens five hours into wear have shown no benefit on end of day comfort [457, 458]. Not requiring an adaptation period (10 hours wear from the first day) to new contact lens wearers had no impact on comfort after two weeks compared to gradually increasing wear time by two hours each day [459].

The evidence seems to suggest that switching lens care products for patients experiencing CLD, possibly avoiding PHMB-based solutions or changing to a daily disposablemodality are effective strategies to improve contact lens comfort.

Environmental risk factors

The most uncomfortable environments for habitual hydrogel contact lens wearers include sitting under an air conditioning or heating vent, spending time in a low humidity or dry air environment and being in dusty, smoky and windy conditions [460]. Interestingly, these contact lens wearers naturally limited their exposure to harsh conditions where they could predict and avoid wear. Short-term (90 minutes) simulated exposure to an adverse in-flight air cabin environment significantly affected tear film and ocular surface characteristics, but had no effect on symptoms [386]. However, pre-empting and decreasing exposure to adverse environmental conditions, where possible, is advisable to reduce CLD.

9.4 Management

Numerous management options for CLD are available. The mainstay of treatment options are rewetting drops including saline [461, 462], hypo-osmotic saline [463], aqueous-based [362, 462, 464-466], lipid-based [362, 419, 465, 467, 468] and povidone[453] eye drops. Increasingly, eye drops with anti-inflammatory properties including Manuka honey [464] and lifitigrast 5% [469] instilled twice daily (before and after lens wear) and 2% rebamipide [470] instilled four times daily with contact lenses *in situ*, are being utilised. All of these eye drops are generally effective for improving comfort, with some treatments shown to be better and/or longer lasting compared to others or to a placebo control. Lid hygiene such as warm compresses and lid scrubs [380], commercial eyelid wipes [453], warming masks [471] and microblepharon exfoliation of the eyelids [472], as well as a liposomal spray when applied to the upper eyelids [428] have also shown varying degrees of success for improving symptoms of CLD. Furthermore, oral supplementation with fish oil also improved comfort [468].

Where symptoms cannot be controlled with conventional treatments, refitting with alternate contact lens modalities such as scleral lenses may improve comfort [473]. Orthokeratology also improved end of day comfort in SiHy lens wearers refitted to this modality [474].

Given that discomfort is commonly cited as a reason for contact lens wear discontinuation [379], appropriate management of CLD is imperative to reduce dropout from wear. The range of treatment options for CLD available is broad, and the particular strategy employed should be tailored to meet the individual wearer's needs based on careful clinical assessment of the contact lens fitting parameters, tear film, eyelids and ocular surface.

9.5 Prevention and advice to wearers

Based on the risk factors described above, to optimise comfort, contact lenses should be well-centred, not too mobile and have edge profiles in close apposition with the bulbar conjunctiva to minimise mechanical interaction with the eyelids.

Avoiding PHMB-based lens care products or changing to daily disposables may also be beneficial. Careful evaluation of wearers is important to enable targeted management strategies to be implemented when wearers begin to experience a reduction in comfortable wear time. ECPs should closely monitor contact lens wearers and actively manage those who report discomfort, to maximise the likelihood of continuing in successful lens wear.

10 Complications with specialty contact lenses

10.1 Scleral

Scleral lenses may be used for visual or therapeutic indications (CLEAR Sclerals Report [475], CLEAR Medical Uses Report [476]). Visual indications include the management of high refractive errors, primary corneal ectasias and post-transplant or refractive surgery. Complications associated with scleral lenses include hypoxia, visual disturbances, discomfort, MK and CLARE. In diseased eyes, there may also be exacerbation of the primary disease.

Inflammatory Complications

10.1.1.1 Microbial Keratitis (MK)

A number of studies have reported MK following the use of scleral lenses. These include keratitis of bacterial origin [477-480] including one report of polymicrobial keratitis [481] and *Acanthamoeba* keratitis [482, 483]. In most of these studies the scleral lenses were used to manage ocular surface disease rather than for the correction of low refractive errors. Poor compliance with lens hygiene has been identified as a potential risk factor [479, 480]. There are limited epidemiological studies of MK associated with scleral lens wear, and reports are mainly confined to retrospective reviews of clinic populations where lenses were predominantly used for primary corneal ectasias. MK has been reported in six out of 374 eyes and one out of the 188 eyes fitted with scleral lenses [484, 485].

10.1.1.2 Infiltrative Keratitis

Non-infectious infiltrative keratitis is an uncommon complication of scleral lenses wear with only two reported cases reported [486, 487].

Physiological Complications

Corneal swelling as a sequela to contact lens-induced hypoxia was a major complication of scleral lenses made from PMMA [116] (CLEAR Material Impact Report [103]). The use of high Dk materials has minimised corneal hypoxia [488]. Despite the use of high Dk materials, mathematical modelling [489-491] and one clinical study [492] suggest that a thinner post-contact lens tear reservoir at insertion should be achieved to minimise corneal swelling, although there are limited long term clinical studies to support this. Significantly greater endothelial bleb response is associated with a thicker post-contact lens tear film after 25 minutes of scleral lens wear [131]. However, short term wear studies in healthy subjects demonstrated corneal oedema following high Dk scleral lens wear ranging between 1.6 – 3.9% which is within the range of normal overnight physiological corneal swelling [106, 489, 493-495]. A recent study showed that closed eye corneal swelling in normal eyes was higher with a high (716±16µm) compared with low (160±7µm) post-contact lens tear film thickness and suggested that modelling studies overestimated the impact of post-contact lens tear thickness on corneal swelling [496] Recently, a 12 month prospective study reported less than 2% increase in corneal thickness in both compromised corneas and healthy corneas following contemporary scleral lens wear [497].

Mechanical Complications

10.1.3.1 Corneal bullae

Corneal bullae as a consequence of epithelial mechanical damage were observed following short term scleral lens wear in six of 14 habitual contact lens wearers who were fitted with small diameter scleral lenses for six hours wear [118]. Localised hypoxia and mechanical damage to the epithelium under the scleral lens edge was suggested as the likely aetiology. Similarly, two case series reported transient epithelial bullae and macrocysts [498, 499]. However, unlike those reported by Nixon et al,. [118] all subjects in this case series who developed bullae had ocular surface compromise. The authors of both these studies suspected that

negative pressure created by the fitting relationship of the scleral lenses caused the bullae, which resolved following contact lens removal.

10.1.3.2 Corneal staining

Nixon et al., reported increased corneal staining in over 90% of normal contact lens wearers following refitting with small diameter scleral contact lenses [118]. In prospective studies, increased corneal staining was noted after 3 – 12 months of scleral lens wear [497, 500]. Conversely, analysis of scleral lens wearers with at least six months wear experience, provided by 292 scleral lens ECPs, showed a 20% decrease in the number of eyes with corneal staining following scleral lens wear [501].

10.1.3.3 Corneal Sensitivity

Long term scleral lens wear increased the corneal sensitivity and tear production in wearers with irregular corneas [502]. However, the same study did not note changes in corneal sensitivity in wearers using scleral lenses for the management of ocular surface disorders.

10.1.3.4 Conjunctival Complications

Increased conjunctival redness has been noted in two studies ranging from 20 – 50% of eyes following scleral lens wear [500, 501]. Increased bulbar redness, limbal redness and conjunctival staining were also noted in a 12 month prospective study where scleral lenses were fitted for the management of ametropia and for irregular corneas [497]. Other complications arising due to poor scleral alignment include conjunctival blanching that can lead to rebound hyperemia [137], conjunctival prolapse, defined as the migration of conjunctival tissue under the scleral lens due to the negative pressure beneath the contact lens [137, 497, 503, 504], CLPC [504] and conjunctival cysts [505].

10.1.3.5 Intraocular Pressure

It has been hypothesised that tight-fitting scleral lenses could elevate intraocular pressure [506]. Short-term studies in normal eyes reported some variations in the intraocular pressure following scleral lens wear [507-509]. However, long term

studies in experienced and neophyte scleral lens wearers did not find a significant impact on intraocular pressure [510-512].

10.1.3.6 Mid-day fogging

Mid-day fogging is the most common visual complication of scleral lens wear and has been noted in 16 – 85% of wearers [501, 503, 513-516]. Fogging likely occurs due to accumulation of debris in the tear reservoir beneath the scleral lenses or poor wetting of the contact lens back surface. Some studies have observed a significant relationship between increased corneal clearance with midday fogging [513, 515], however this has not been consistently reported [517]. Higher levels of inflammatory mediators [518] and immune cells [515] in the post-contact lens tear film of scleral lens wearers with mid-day fogging suggest an inflammatory aspect to this condition.

10.1.3.7 Lens discontinuation

Discontinuations may arise due to handling difficulties [485, 497, 519], pain and discomfort [520], poor or inadequate improvement in vision [519] and exacerbation of existing disease.

Summary

Scleral lens use has increased in recent years and such contact lenses are frequently used an alternative to surgical intervention for managing ocular surface disorders, indeed they may be the only option suitable for visual or therapeutic outcomes. Complication rates vary between those using scleral lenses for medical compared with refractive indications and the risk:benefit needs to be considered on a case by case basis.

Serious complications such as MK are relatively rare with retrospective case studies reporting incidence ranging from 0.5 to 1.6%. Mid-day fogging, the most frequently noted visual complication of scleral lens wear can be minimised by optimising post-contact lens tear film thickness and quality and improving back surface contact lens wetting, using alcohol-based cleaners or in-contact lens lubricants containing wetting agents. Hypoxic changes following scleral lens wear

are generally minimal and clinically insignificant due to the use of high Dk lens materials. Mechanical effects of scleral lens wear such as microcyts and bullae are transient in nature and often resolve completely following cessation of lens wear. Unilateral lens wear may be challenging due to the sensation of thickness and mass of the lens or the change in appearance of the contact lens-wearing eye. Discontinuations are primarily driven by a poor visual result, intractable mid-day fogging, inablity to obtain an adequate fitting and in rare cases worsening of the exisiting disease. Scleral lenses are generally a safe and effective option for the management of ocular surface disorders and corneal irregularity.

10.2 Orthokeratology Contact lenses

Orthokeratology is the use of rigid corneal lenses to mold corneal shape to correct myopia, hyperopia, presbyopia and astigmatism [521, 522] and used as an off-label indication to slow the progression of myopia in children [523]. One orthokeratology lens has received CE approval for myopia control and is now an on-label option for slowing the progression of myopia in children available in certain territories [524].

Infectious and inflammatory Complications

10.2.1.1 Microbial Keratitis (MK)

While estimates of the incidence of MK in orthokeratology lens use are limited, several case reports during orthokeratology lens wear have been published [525-530]. In a review of hospital records, 6 of 15 cases of bacterial or *Acanthamoeba* keratitis were due to orthokeratology lenses, with the remainder in soft contact lens wear [531]. In reviews of cases of *Acanthamoeba* keratitis, 13 (Chicago, USA) to 67% (Beijing, China) of all cases were from patients wearing orthokeratology lenses [532, 533].

In a historical review of 123 records of orthokeratology associated MK cases [534], 86% of cases were located in East Asia, aged 9 to 15 years with 38% due to *Pseudomonas aeruginosa* and 33% *Acanthamoeba* spp.. A more recent review [535] of orthokeratology associated MK cases involving 173 eyes of 166 subjects and reported that 10% of eyes were left with corneal scarring requiring surgical

treatment. The incidence of MK associated with orthokeratology was estimated [536] to be 13.9 per 10,000 wearers per year in children and 7.7 in 10,000 per year for all age groups, with the conclusion that this rate was similar to that seen with overnight wear of soft contact lenses.

10.2.1.2 Infiltrative Keratitis

Non-infectious corneal infiltrates were noted as a complication in one retrospective hospital record review study [537].

[redacted]Metabolic Complications

Corneal neovascularisation in less than 5% of orthokeratology wearers has been reported [531]. Corneal oedema as response to hypoxia appeared suppressed in orthokeratology lens wearers [538].

[redacted]Mechanical Complications

10.2.3.1 Corneal erosions/abrasions

Two incidences of erosions were reported in a cohort of 66 participants with complete recovery following a non-contact lens wearing period [539]. A review of a hospital records reported one instance in 21 orthokeratology wearers [531].

10.2.3.2 Corneal staining

Corneal staining is reported infrequently and generally at very mild/minimal levels [539, 540]. Minimal levels of staining during 56 study visits in a 126 participant study over a 6-month period [541] and 8 of 66 study participants [539] has been reported. The level and frequency of mild staining (less than grade 1) was unchanged when orthokeratology lenses were fenestrated [542]. Mild corneal staining was also reported in one hospital records review in orthokeratology lens wearers [537]. Frequently the corneal staining is observed centrally and is considered transient in nature, diminishing after initial adaptation to orthokeratology lens wear [543, 544].

10.2.3.3 Corneal sensitivity

Corneal sensitivity is reported as having reduced during orthokeratology lens wear [545], which recovered after ceasing wear [546] (CLEAR Material Impact Report [103]). However in one study, this reduction was noted only by the 1 month wearing period and then returned to baseline levels after 3 months of orthokeratology lens wear [547], conceivably as a consequence of changes in nerve morphology from orthokeratology lens wear [546], which may not reverse following a period of no lens wear [548].

10.2.3.4 Corneal epithelial pigmented arcs

Pigmented arcs in the corneal epithelium increased in frequency and and intensity with the length of wear, reaching 84 to 90% of wearers by 12 months [542, 549]. The consequence of these pigmented arcs was not clear.

10.2.3.5 Lens binding

In the absence of clinical signs, contact lens binding was reported by up to 39% of orthokeratology study participants [540]. In a study comparing the impact of fenestrated lenses, 40% of fenestrated orthokeratology lens showed binding compared with 67% without fenestration after 1 month of wear [542]. Binding frequency was unchanged over a 9 month wear period.

10.2.3.6 Residual astigmatism

Persistent residual astigmatism following orthokeratology lens discontinuation has been reported in unsuccessful wearers, most likely due to poor orthokeratology lens fitting [550].

[redacted]Conjunctival Complications

A reduction in the frequency of conjunctival staining with orthokeratology lens use has been reported [541]. Another study reported it as a reason for two wearers to present to a hospital for care [531]. Conjunctival follicles have been reported in around 10% of orthokeratology lens wearers [531].

Dry eye and other related symptomatic complications

Signs and symptoms consistent with allergic conjunctivitis have been reported as a consequence of orthokeratology lens wear in hospital record reviews [531, 537, 551]. Dry eye and MGD were noted in 24% and 14% of orthokeratology lens wearers respectively [531].

Summary

Except for MK, the majority of the complications were reported as mild or very mild. This may be unexpected as the mode of action of orthokeratology lenses is to physically change the corneal profile through forced epithelial migration. The resulting epithelial thinning and the fact this process takes place during orthokeratology lens wear overnight, conceivably greater morbidity may be expected. A number of studies have also stated that there were no complications arising from orthokeratology lens wear [552], although there are limited appropriately powered studies to determine rates of less common complications.

The majority of complications were similar to those seen with rigid corneal lens use, however corneal epithelial pigmented arcs [542, 549], dimple veil [540, 542] and contact lens binding [540, 542] appear to be more commonly reported with this modality.

Whereas symptoms of dryness have been reported as a key reason for contact lens wear discontinuation with soft contact lenses, this was not the case with orthokeratology and contact lens use was rarely associated with MGD, though signs consistent with allergic conjunctivitis had been occasionally reported [531, 537, 551].

Prevention and advice to wearers

The majority of complications reported appear to arise from the fitting relationship between the orthokeratology lens and the cornea and could all be managed by changing the orthokeratology lens, although fitting changes may impact the refractive efficacy. Dimple veil staining and contact lens binding can be reduced by orthokeratology lens fenestration [540, 542]. It would also appear that some

complications are self-limiting as the purpose of orthokeratology lens wear changes from the initial molding of the cornea to its use as a crutch or a maintainer of corneal shape.

As with other modalities, attention to orthokeratology lens and storage case hygiene, the avoidance of water contact with the orthokeratology contact lenses and seeking care early are important recommendations in limiting the frequency of severe MK.

10.3 Diagnosis and management

The first priority in managing an acute complication is to rule out MK or if infection presents to manage it urgently. Other conditions are self-limiting on removal of the contact lens and a decision can be made about managing the condition while continuing with wear in some form. Table 9 describes a decision-making approach to symptomatic complications, starting with the presence or absence of a red eye, discomfort or pain, vision loss and unilateral or bilateral disease.

Where there is a complication related to a red eye or discomfort during wear where the diagnosis is unclear and symptoms non-specific, the management approach may be similarly non-specific [175]; improve lens hygiene and disinfection frequency; reduce contact lens replacement frequency or consider daily disposable contact lenses; in reusable lens use, consider case hygiene and replacement frequency; optimise the contact lens fitting; consider a non-preserved care system; avoid topical preserved therapy; consider tachyphylaxis; manage lid or ocular surface disease and manage intercurrent disease.

Relevant intercurrent diseases for consideration include corneal degenerations or dystrophies, disease associated with primary corneal ectasias, pre-existing dry eye or MGD, blepharitis, allergic disease, viral keratoconjunctivitis, toxic keratopathy, marginal keratitis, exposure keratitis, HSV disease, cicatrising disease or Demodex.[175]

Table 9: Features of and factors associated with contact lens complications

Presenting feature or condition	Microbial keratitis	Corneal infiltrates	Metabolic	Mechanical	CLPC	Toxic and hypersensitivity	Tear resurfacing disorders	Intercurrent disease
Red eye	Yes	Yes	Yes	Usually	No	Yes	Sometimes	Sometimes
Discomfort or pain & pattern	Yes, progressive on CL removal	Sometimes, reduces on CL removal Some asymptomatic	Sometimes, reduces on CL removal	Usually, reduces on CL removal	Reduced CWT	Yes, reduces on CL removal Toxic – acute on insertion	Sometimes, reduces on CL removal	Present without CL, may be exacerbated by wear
Vision loss	Depending on location	Depending on location	Uncommon	Depending on location	No	No except LSCD	May be intermittent	Sometimes
Other symptoms	Photophobia, discharge	Not usually	Photophobia		Itching, mucous discharge		Dryness	Usually
Unilateral	Yes	Usually	No	Yes	May be asymmetric	Toxic - usually	No	Rarely
Duration and onset	Acute	Acute, may be recurrent	Acute or chronic	Acute	Chronic, but reduced CWT prompts care	Toxic – acute Hypersensitivity chronic	Chronic	Usually chronic
Wear modality	Overnight wear> DW; soft CL>corneal lens	Overnight wear> DW; soft CL>corneal lens Reusable soft CL>DD	Overnight wear> DW; soft CL>corneal lens	corneal lens>soft CL Orthok Scleral	Overnight wear > DW; soft CL>corneal lens	DW Reusable soft CL	corneal lens – 3 & 9 stain & Dellen soft CL – other	Often dose dependent exacerbation
Non-compliance	Likely	Likely	Not necessarily	Not necessarily	Unlikely	Not necessarily, check care solution	Unlikely	Not necessarily
Corneal signs	Epithelial defect, underlying	Diffuse or focal corneal infiltrates	Staining Microcysts Vacuoles	Depends on location	None	Diffuse or annular staining	3 & 9 stain Dellen	Possible: Staining,

	corneal infiltrate	Staining +/-	Striae/folds Vascularisation Oedema	Staining, arcuate, linear, erosion Dimple veil CLbinding		Pannus Conjunctivalisation Vascularisation Infiltrates	Inferior corneal stain	Infiltrates, Thinning, Ulceration, Vascularisation, Pannus
Conjunctival signs	Generalised bulbar redness	Localised bulbar redness	Bulbar redness	Redness & staining depending of location	Papillae Tarsal redness Mucous discharge	Bulbar and tarsal redness Small papillae	Lissamine green staining of exposed area LIPCOF	Possible: Papillae, Follicles, Chalazia, Hordeolum, Cicatrisation
Lid margin signs	Lid oedema	None	None	None	Thickening	None	MGD LWE Telangiectasia Demodex collarettes	Possible: MGD, telangiectasia, LWE, altered lid apposition to globe, blepharitis
Tear film signs	Purulent or mucopurulent discharge	Watery eye	None	None	Mucous/stringy discharge	Watery eye	Foam Hyperosmolarity Short BUT Low volume	Foam Hyperosmolarity Short BUT Low volume
Other	Anterior chamber response	Old corneal scar in recurrent cases	None	Ptosis	Ptosis	None	Other risk factors may be present	Scarring

CLPC: Contact lens papillary conjunctivitis, CL: Contact lens, CWT:Comfortable lens wear time, LSCD: Limbal stem cell deficiency, DW: Daily Wear, DD: daily disposable; LIPCOF: Lid-parallel conjuctival folds, MGD: Meibomian gland dysfunction, LWE: Lid-wiper epitheliopathy, BUT: Break up time,

11 Future Research

11.1 Complications with Myopia Control Treatments in Children

With increased prescribing of myopia control contact lenses for children, it will be incumbent on the eye care community to establish systems for vigilant oversight of both soft and corneal lens options in order to track the the safety of those treatments.Currently about half (52.1%) of all contact lenses fitted for myopia control in children were rigid lenses; this compares with 12.0% for non-myopia control fits with rigid lenses [553]. Post-market oversight systems include studies that are mandated by regulatory bodies, such as those described in the U.S. Food and Drug Administration Guidance for any device that is indicated for paediatric use [554] or large condition-specific registries that are established by academic or professional bodies [555, 556].

Adverse events in young contact lens wearers have typically been reported along with efficacy results in prospective myopia-control studies. For soft myopia-control contact lenses, peer-reviewed results from ten prospective and retrospective studies (enrolled between 30 and 1,054 subjects and reported on adverse events have covered more than 3,600 years of wear in children and young teens reported no cases of MK or other sight-threatening complications, although no single study was of sufficient size to estimate the rate of MK [92, 93, 557-566]. A recent retrospective chart review of lens wear by children aged 8 to 12 years old who were fitted with soft contact lenses in practices and clinical trials estimated a MK incidence of 7.4 cases per 10,000 years of wear (95% C.I. 1.7-29.8) after observing records for 963 young soft contact lens wearers for 2,713 years of wear [91].

Fortunately, most of the newly introduced myopia control contact lenses will be prescribed as daily disposable contact lenses, a replacement schedule known to help reduce the risk for inflammatory complications in adults [92, 93, 97, 99]. Going forward, clinicians and parents must balance between the very low risk, but high impact of potential vision loss due to MK in children and teens and the benefits of myopia control treatment and freedom from spectacle wear. The body of evidence

on adverse events associated with myopia control treatments will grow over the next decade to add more certainty to the understanding of safety with these treatments.

11.2 Microbiome and immune response

It is thought the ocular microbiome protects the ocular surface from disease by preventing the profilferation of pathogenic microorganisms. Studies have indicated differences in microbiome between contact lens and non-contact lens wearers [567] and between contact lens types [568]. In addition, the ocular surace microbiome diversity is greater in children compared to adults, suggesting a 'tunability" with time [569, 570].

While the implications for changes to the microbiome with contact lens wear and aging are unclear, it is reasonable to hypothesise that presence of the contact lens and common low grade inflammatory events may affect the long term adaptation of the microbiome. One recent study using IVCM analysis of dendritic-like cells in the cornea, found a positive correlation between a lower ratio of central to peripheral cells and age in young adults [571], which could indicate a more naïve and less robust ocular surface immune status in youth.

11.3 Role of genetics in contact lens success

Several studies have shown that differences in immune and ocular surface defence genes, [572-575] as well as tear proteins,[575, 576] are associated with susceptibility to and the severity of corneal infection in some contact lens wearers. As laboratory techniques improve in sensitivity and decrease in cost, these findings may facilitate the development of risk profiles that include '-omics' (gene to metabolome) as well as behavioural factors to better advise and manage refractive choices for individuals.

11.4 Non-prescribed contact lenses

In South East Asia particularly, use of coloured, decorative or cosmetic contact lenses (defined as having the primary purpose to change the appearance of the

eye) is widespead, with a recent estimate of over a third of contact lens wearers in Singapore using this type of lens [577]. Cosmetic contact lens infections comprise 12.5% of all contact lens infections in a multicentre study in France [578], but 41% of infections in a recent multicentre study in South Korea [208]. The incidence of cosmetic contact lens-related infection has not been estimated and there are limited studies where risk factors have been identified [578], partly because of the difficulty in identifying an appropriate unaffected cosmetic contact lens wearing control group. A study in France however, has identified that cosmetic wearers are at a 1.4x higher risk of infection compared with those wearing contact lenses for refractive reasons [579].

Typically, wearers are young females, new to contact lens wear who may be influenced by social media and purchase inferior quality products marketed as cosmetic rather than medical devices and without contact lens wear and care education [580, 581]. Supply route, quality control, licensing and regulation of the sale of such contact lenses, provide significant challenges in managing this population of vulnerable wearers as the penetrance of this type of contact lens use increases, particularly in Asia [577].

12 Summary and conclusions

Contact lenses provide optical, sporting, vocational, cosmetic and increasingly myopia control benefits to millions of wearers worldwide. Severe complications of contact lens wear are rare and a progressively painful red eye requires urgent management for possible microbial keratitis. The majority of complications are self-limiting on contact lens removal and are associated with limited morbidity. Prompt management of minor complications can assist with preventing contact lens wear drop out and managing wearer comfort, vision and safety expectations.

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Figure legends

Figure 1

Pseudomonas aeruginosa keratitis in a soft contact lens wearer. Image courtesy of Mr Stephen Tuft, Moorfields Eye Hospital. Image reproduced from Carnt et al. 2017 [75].

Figure 2

Right: Contact lens peripheral ulcers (CLPU). Left: Infiltrative Keratitis; Images courtesy of Centre for Research and Education (CORE).

Figure 3

Incidence of CIE per 100 wearers per year. Error bars show 95% confidence intervals. Image modified from Chalmers et al., 2020 [91]

Figure 4

Limbal stem cell deficiency (LSCD) shown as a corneal pannus extending from the limbus at 11 o'clock to the pupil centre, accompanied by infiltrates in a daily soft contact lens wearer. The IVCM image shows sub-epithelial inflammatory signs at the tip of the pannus. Image reproduced from Stapleton et al., 2003 [250].

Figure 5

Solution-induced corneal staining (SICS) can appear either as superficial diffuse punctate dots across entire cornea (A) or as a characteristic annular ring on the peripheral cornea (B).

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