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FOURTH EDITION

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Efron

CONTACT LENS COMPLICATIONS



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Contact Lens Complications

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Fourth Edition

Nathan Efron
AC BScOptom PhD (Melbourne) DSc (Manchester)
FAAO (Dip CCLRT) FCCLSA FACO
Emeritus Professor
School of Optometry and Vision Science
Queensland University of Technology
Brisbane, Australia

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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PREFACE

I recently wrote an editorial entitled 'Contact lenses continue to evolve' (Clin Exp Optom 2017;100:409–10). Perhaps that says it all. As with any area of health care, our understanding of conditions we are dealing with advances; investigative techniques become more sophisticated; and new modes of treatment are developed. In the field of contact lenses, this translates to new and improved lenses and lens care systems and more advanced ophthalmic instrumentation. These developments need to be matched by an updated and easily accessible source of current information, and I am proud to present this to you as the fourth edition of *Contact Lens Complications*.

When the first edition of this book was published in 1999, silicone hydrogel contact lenses were just entering the market. Corneal topography, anterior segment optical coherence topomography and laser-scanning confocal microscopy were in the early stage of development and not readily available for clinical application. Conditions such as 'lid wiper epitheliopathy' and 'lid-parallel conjunctival folds', were yet to be described. The Tear Film and Ocular Surface Society had yet to convene its acclaimed and highly influential Dry Eye (I and II), Contact Lens Discomfort and Meibomian Gland Dysfunction workshops. Contemplating these developments makes it easy to appreciate why constant revisions of a pivotal textbook in a rapidly advancing field are essential.

My aim in writing this fourth edition of *Contact Lens Complications* has been to assemble a comprehensive, evidence-based account of this topic, drawing extensively from the current literature and moderated from my personal experience as a clinician and researcher spanning over 40 years. This book covers all forms of ocular responses to contact lens wear, ranging from the most subtle of innocuous and largely harmless tissue reactions – such as endothelial blebs – to the most severe of reactions, such as microbial keratitis.

My basic approach to this topic is simple and remains unchanged from the first three editions of this work; that is, ocular complications of contact lens wear are dealt with in a systematic 'tissue by tissue' approach. The alternative approach would have been to adopt a more theoretical approach, for example, by arranging material according to causation (aetiology), such as metabolic, hypoxic, mechanical, allergic, infectious etc. However, I have always believed that a 'tissue by tissue' approach is intuitive to contact lens practitioners, because this is the way we think. We first identify the particular tissue in distress, based on presenting signs and symptoms, and then try and understand what is going wrong.

Consistent with this 'tissue by tissue' approach, subject matter in the book is divided into eight sections, seven of which relate to the primary anterior ocular tissues that can affect, or be affected by, contact lenses. The other section (Part 1) relates to anterior eye examination and grading systems. Within each section, various identifiable tissue pathologies or conditions are discussed by way of a systematic consideration of signs, symptoms, pathology, aetiology, management, prognosis and differential diagnosis.

This systematic approach is reflected in the large 'quick-find index' on pages ix to xxvii, which is designed to assist practitioners in (a) gaining a quick overview of a specific complication in a broader context and (b) locating information on a particular complication in the main text. I am sure students will find this index to be an invaluable study guide and pre-examination refresher!

I am proud to once again to be presenting my grading scales, which cover 16 of the most important contact lens complications; these are presented in Appendix A of this book, together with a comprehensive account of how they can be used (see Chapter 2). In addition, all 16 grading scales have been converted to user-friendly movie morph sequences, which are also available with this fourth edition. These grading morphs, and a self-help grading tutor, offer the possibility of computer-based grading. Details on how to download the morph and tutor programmes are given in Chapter 3. Also presented in Appendix B is a system for classifying the various appearances of the tear film during contact lens wear.

From a personal perspective, this book essentially represents a distillation of my lifetime pursuit of developing a better understanding of the ocular response to contact lens wear. In a sense, this means that if you purchase this book, you are purchasing a little piece of me! I hope you gain as much enjoyment, knowledge and inspiration out of this book as I gained from writing it.

Emeritus Professor Nathan Efron AC

ACKNOWLEDGEMENTS

Although I am the sole author of this book, I am not the sole illustrator. I am very fortunate to have been given open access to a number of extensive and outstanding slide libraries of contact lens complications, and in this regard, I would like to thank Bausch & Lomb, the British Contact Lens Association, the International Association of Contact Lens Educators and the Brien Holden Vision Institute. I applaud the clinical excellence and skills of the many practitioners who took the photographs that belong to these magnificent collections; each of these clinicians is acknowledged by name in the respective figure legends. A special word of thanks to Brian Tompkins, who gave me access to his personal digital image collection.

It was an honour and a privilege to work with the renowned medical ophthalmic artist Terry Tarrant, who painted the grading scales that appear in Appendix A. Production of the grading scales was originally sponsored by a company called Hydron UK, which was taken over some time ago by CooperVision. I wish to acknowledge Joe Tanner, who provided great support for the grading scale project when it commenced in the mid-1990s.

I am grateful for the assistance of Dr Philip Morgan and Gordon Addison, from the University of Manchester, UK, who assisted in the production of the grading morphs and grading tutor computer programmes. Specifically, Gordon created the morph movie sequences and Phil created the interactive program in which the morphs are embedded. I am sure that the fruits of the labour of these two gentlemen will be enjoyed by all who use these programmes. I also thank Dr. J.P. Guillon for giving me permission to publish his tear film classification system, which appears in Appendix B.

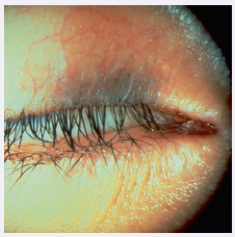
I am most grateful to my publishing team at Elsevier – Russell Gabbedy, who initiated work on this edition, and Kayla Wolfe, who took over mid-production – and to their outstanding team for their wonderful editorial and technical support.

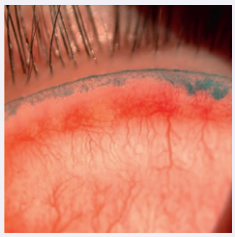
My wife, Suzanne, has provided tremendous personal support throughout the writing of this book (and all my other books). Suzanne is an accomplished contact lens practitioner in her own right and has also provided material assistance by supplying some of the images used in the book, acting as a 'listening board' for ideas, sourcing references from the literature and helping with proofreading of the manuscript. I am forever grateful.

And finally, I thank you, the reader, for showing faith in me by buying and/or using this book. I truly hope that my devotion and dedication to the subject has translated into an offering that will be of real clinical value, in the first instance to yourself and ultimately to your patients, who deserve only the very best clinical care.

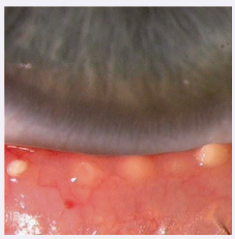
Emeritus Professor Nathan Efron AC

EYELIDS

Condition	Signs	Symptoms	Pathology
Blinking abnormalities 	• Complete blink – 80% • Incomplete blink – 17% • Twitch blink – 2% • Forced blink – 1% p. 45	• Dry eye if incomplete blink p. 47	• Lens drying and deposits • Epithelial desiccation • Post-lens tear stagnation • Hypoxia and hypercapnia • 3 & 9 o'clock staining • Poor lens fitting p. 47

Lid wiper epitheliopathy (LWE) 	• Use lissamine green
	• Grade severity
	  ◦ Linear extent
	  ◦ Severity
	• Six categories of staining
	p. 56
		• Dryness
		• Discomfort
		• Signs do not always relate to symptoms
		p. 56
			• Compromised epithelial cell membranes
			• Discomfort
			• ↓ Lid sensitivity
			• ↑ Langerhans cell density
			p. 59

Ptosis 	• ↓ Palpebral aperture size
	  ◦ No lens: 10.10 mm
	  ◦ Soft lens: 10.24 mm
	  ◦ Rigid lens: 9.76 mm
	• ↑ Gap between upper skin fold and upper lid margin
	• Mainly in rigid, but also soft, lens wearers
	p. 69
		• Complaints of poor cosmesis when excessive
		p. 70
			• Trauma during insertion and removal because of:
			  ◦ Forced lid squeezing
			  ◦ Lateral lid stretching
			• Rigid lens displacement of tarsus
			• Blepharospasm
			• Papillary conjunctivitis
			p. 71

Meibomian gland dysfunction (MGD) 	• Cloudy, creamy, yellow expression • Inspissated discharge • Poorly wetting lenses • Tear meniscus frothing • No secretion if blocked • Distended or distorted meibomian glands p. 80	• Smeary vision • Greasy lenses • Dry eye • Lens intolerance p. 85	• MGD is a form of posterior blepharitis • Blocked meibomian orifice • Increased keratinization of duct walls p. 85

External hordeolum (Stye) 	• Discrete inflamed swelling of anterior lid margin
	• Occurs singly or as multiple small abscesses
	p. 92
		• Discomfort and tenderness
		• Soft lens touches stye, causing discomfort and ↑ lens movement
		  ◦ Rigid lens buffets lid margin
		p. 92
			• Inflammation of:
			  ◦ Tissue lining lash follicle
			  ◦ Associated gland of Zeis or Moll
			p. 92

Aetiology	Treatment	Prognosis	Differential Diagnosis

• Tear break-up induces blinking
• Other unknown factors are involved
• Oral contraceptives reduce blink rate
	• Blink training
	• Alter lens fit
	  ◦ Less post-lens debris with rigid lenses
	  ◦ Inter-palpebral rigid lens
		• Training can improve blinking
		• Altering lens design can improve blinking
			• Interruption to neural input
			• Interruption to muscular systems
			• Local eyelid pathology

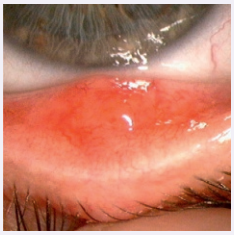
p. 47	p. 50	p. 50	p. 51
• Friction between lid wiper and lens surface • Inflammation • ↓ Lid margin sensitivity • ↑ Microvascular network	• Alleviate 'dry eye' • Lubricant eye drops • Fit lens of high surface lubricity • Corticosteroids	• Good if dry eye can be solved	• Line of Marx • Lid imbrication • Blepharitis • Demodicosis • Iatrogenic staining
p. 60	p. 63	p. 65	p. 65

• Lid oedema
• Levator aponeurosis:
  ◦ Disinsertion
  ◦ Dehiscence
  ◦ Thinning
  ◦ Lengthening
	• Cease lens wear 1–3 months
	• Cure papillary conjunctivitis
	• Refit with soft lenses
	• Lid surgery
	• Scleral lens ptosis crutch
	• Spectacle prop
	• Surgical tape
		• If caused by oedema: good
		• If aponeurogenic: poor
		• Surgery can yield good results
			• Embedded lens
			• Ectropion
			• Entropion
			• Lagophthalmos

p. 71	p. 72	p. 73	p. 74

• Increased turnover of ductal epidermis
• Abnormal meibomian oils
  ◦ More keratin proteins
• Absence of lid rubbing
	• Warm compresses
	• Heating devices
	• Lid scrubs/hygiene
	• Mechanical expression
	• Antibiotics
	• Tears/lipid supplements
	• Essential fatty acids
	• Sex hormones
		• Excellent if good control can be achieved	• External hordeolum
			  ◦ Lid margin swelling
			• Internal hordeolum
			  ◦ Tenderness
			• Chalazion
			  ◦ Chronic form of meibomian gland dysfunction

p. 86	p. 86	p. 89	p. 89
• Typically acute staphylococcal infection • Often occurs in patients with staphylococcal anterior blepharitis	• Remove eyelash • Apply hot compress • May spontaneously discharge anteriorly • Cease lens wear during acute phase	• Self-limiting • Typical time course: 7 days	• External hordeolum • Internal hordeolum • Chalazion
p. 92	p. 92	p. 92	p. 92

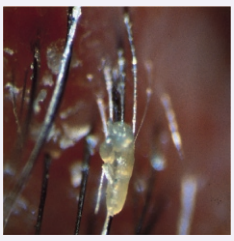
Condition	Signs	Symptoms	Pathology
Internal hordeolum (meibomian cyst) 	• Enlarged swelling deep within tarsal plate • Lid swelling and distortion of lid margin • Overlying skin red p. 89	• Moderate discomfort • Mechanical effect of contact lenses: ◦ Soft lens presses cyst, causing discomfort and ↑ lens movement p. 89	• Acute inflammation of meibomian gland p. 89

Staphylococcal anterior blepharitis

	• Redness
	• Telangiectasis
	• Scaling of lid margins
	• Lashes stuck together
	• Lash collarette
	• Madarosis
	• Poliosis
	• Tylosis
	p. 92
		• Burning
		• Itching
		• Mild photophobia
		• Foreign body sensation
		• Dry eye
		  ◦ Worse in morning
		• Lens intolerance
		p. 92
			• Staphylococcal endotoxin-induced complications include:
			  ◦ Low-grade conjunctivitis
			  ◦ Toxic punctate epitheliopathy
			p. 92

Seborrhoeic anterior blepharitis

	• Redness
	• Telangiectasis
	• Scaling of lid margins
	• Lashes stuck together
	• Madarosis
	• Poliosis
	p. 93
		• Burning and itching
		• Mild photophobia
		• Foreign body sensation
		• Dry eye (morning)
		• Lens intolerance
		p. 93
			• Staphylococcal endotoxin-induced complications include:
			  ◦ Low-grade conjunctivitis
			  ◦ Toxic punctate epitheliopathy
			p. 93

Mites

	• Presence of mites
	• Erythema of lid margins
	• Lid hyperplasia
	• Madarosis
	• Conjunctival redness
	• Lash collarette
	• Follicular distension
	• Meibomian blockage
	• Lashes easily removed
	p. 94
		• Burning
		• Itching
		• Crusting
		• Lid margin swelling
		• Loss of lashes
		• Lens intolerance
		p. 96
			• *Demodex folliculorum*
			  ◦ Resides in space between follicle wall and lash
			  ◦ Eats epithelial lining of lash follicle
			• *Demodex brevis*
			  ◦ Resides in gland of Zeis
			  ◦ Reproduces in oily environment
			p. 94

Lice

	• Presence of lice and nits
	• Erythema of lid margins
	• Conjunctival redness
	• Madarosis
	• Brown deposit at base of lashes
	  ◦ Blood from host
	  ◦ Faeces from lice
	• Blue spots on lid margins
	  ◦ Secreted by lice
	p. 97
		• Burning
		• Itching
		• Crusting
		• Swelling of lid margins
		• Lens intolerance
		p. 97
			• Lice suck blood and serum from lid margin via stylus
			• Secondary inflammation along lid margins
			p. 97

Aetiology	Treatment	Prognosis	Differential Diagnosis
• Typically acute staphylococcal infection • Often occurs in patients with staphylococcal anterior blepharitis	• Incision and curettage • Apply hot compress • Topical antibiotics after surgery • Cease lens wear during acute phase	• Self-limiting • Typical time course: 7 days	• External hordeolum • Internal hordeolum • Chalazion
p. 89	p. 89	p. 89	p. 89
• Staphylococcal infection of eyelash follicle	• Antibiotic ointments • Promote lid hygiene • Steroids • Artificial tears • May need to suspend lens wear during acute treatment phase	• Variable: expect periods of remission and exacerbation	• Need to differentiate from seborrhoeic anterior blepharitis ◦ See later
p. 92	p. 94	p. 94	p. 94
• Disorder of glands of Zeis or Moll	• Promote lid hygiene • Artificial tears	• Variable: expect periods of remission and exacerbation	• Need to differentiate from staphylococcal anterior blepharitis ◦ See earlier
p. 93	p. 94	p. 94	p. 94

• *Demodex folliculorum*
• *Demodex brevis*
	• Topical anaesthetic and application of toxic substances
	• Vigorous lid scrubbing
	• Viscous ointment overnight
	• Heavy metal ointments
	• Pilocarpine gel
	• Avoid use of facial oils
		• Good – if patient complies with treatment	• Lice
			  ◦ See later
			• Blepharitis
			  ◦ See earlier

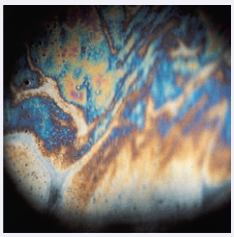
p. 94	p. 98	p. 96	p. 96

• *Phthirus pubis*, also known as:
  ◦ Pubic louse
  ◦ Sucking louse
  ◦ Crab louse
	• Mechanical removal
	• Cryotherapy (freezing)
	• Argon laser
	• Anti-cholinesterase agents
	• Vigorous lid scrubbing
	• Sexually transmitted?
	• Heat clothes, bedding etc.
	• Soak combs, brushes etc.
	• Isolate material for 2 weeks
		• Good – if patient complies with treatment	• Mites
			  ◦ See earlier
			• Blepharitis
			  ◦ See earlier

p. 97	p. 99	p. 99	p. 99

TEAR FILM

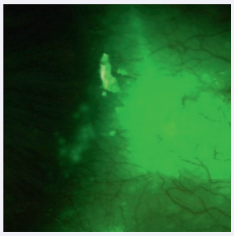
Condition	Signs	Symptoms	Pathology

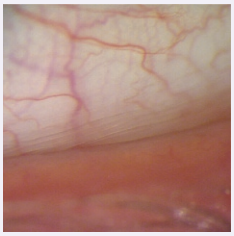
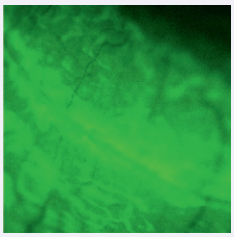
Dry eye 	• Abnormalities in:
	  ◦ Lipid layer
	  ◦ Tear volume
	  ◦ Tear structure
	  ◦ Tear film stability
	  ◦ Post-lens tear film
	• Epithelial staining
	• LWE and LIPCOF
	p. 107
		• Primarily 'dryness'
		  ◦ Use a dry eye questionnaire
		• Worse in females using oral contraceptives
		p. 112
			• Lipid deficiency or excess
			• Aqueous deficiency
			• Rapid tear break-up
			  ◦ Caused by inter-mixing of lipid and mucus layers
			• Increased Langerhans cell density
			p. 113

Mucin balls 	• Up to 200 small grey dots
	• Small transparent dots
	• Reversed illumination
	• Large mucin balls may collapse; doughnut-like
	• Mainly with silicone hydrogel lenses
	p. 125
		• None
		• Vision can be slightly compromised in extreme cases
		p. 127
			• Balls of mucin and lipid
			• Can indent epithelium
			  ◦ Leaves fluid-filled pits
			  ◦ Un-reversed illumination
			• Deep mucin balls may affect stromal keratocytes
			• Mucin balls compromise microbial defences
			p. 127

CONJUNCTIVA

Condition	Signs	Symptoms	Pathology

Conjunctival staining 	• Normal eye: curved lines of conjunctival staining parallel to limbus; furrow staining
	• Lens wearing eye:
	  ◦ Diffuse/coalescent stain
	  ◦ 'Lens edge' stain
	p. 137
		• Often none
		• 'Lens edge' stain may be associated with 'tight lens syndrome'
		p. 137
			• Normal eye: fluorescein pools in natural conjunctival folds
			• Lens-wearing eye:
			  ◦ Superficial epithelial cells traumatised or dislodged
			p. 140

Lid-parallel conjunctival folds (LIPCOF) 	• Parallel folds adjacent to lower lid margin • Count folds as basis of grading p. 147	• Dryness • Discomfort p. 148	• Concertina folding of conjunctiva p. 149
Conjunctival flaps 	• Tongue-like projection of conjunctival tissue • Irregular free ends • Moves with blinking • View with fluorescein p. 139	• Asymptomatic p. 139	• Focal increase in collagen • Mild collagen degeneration p. 142

Aetiology	Treatment	Prognosis	Differential Diagnosis

• Inflammation
• Lens induced changes in tear film:
  ◦ ↑ Osmolarity and pH
  ◦ Composition
  ◦ Temperature profile
  ◦ Turnover
  ◦ Break-up
	• Alter lens/solutions
	• Rewetting drops
	• Soft lens re-soaking
	• Nutritional supplements
	• Punctal plugs
	• Tear stimulants
	• Treat associated disease
	• Omega-6 fatty acids
		• Good if problem relates to lenses/solutions
		• Poor if caused by underlying pathology – e.g. keratoconjunctivitis sicca
			• Aqueous deficiency
			• Lipid anomaly
			• Lid surfacing anomalies
			• Mucus deficiency
			• Primary epitheliopathy
			• Allergic dry eye

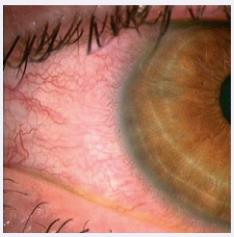
p. 113	p. 117	p. 121	p. 121
• Strong inter-facial forces • Aqueous deficient tears beneath lenses • Mucin-rich tears rolled up into discrete balls • Balls indent epithelium • Very large balls collapse to doughnut shape	• Fit lenses flatter • Rewetting drops • More frequent lens removal • Refit with lens other than silicone hydrogel	• Mucin balls and epithelial fluid-filled pits disappear within hours of lens removal • Mucin balls will recur	• Epithelial microcysts • Epithelial vacuoles • Epithelial bullae • Dimple veiling
p. 127	p. 130	p. 130	p. 130

Aetiology	Treatment	Prognosis	Differential Diagnosis

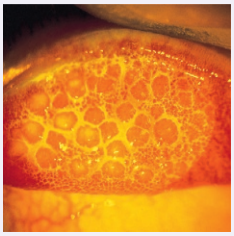
• 'Lens edge' stain caused by lens edge trauma
• Diffuse stain caused by other physical trauma
  ◦ Deposits on back of lens
  ◦ Trauma induced by excessive lens movement
	• 'Lens edge' stain:
	  ◦ Fit flatter lens
	• Lens trauma stain:
	  ◦ Improve care regimen to alleviate deposit formation
	  ◦ Improve lens fit
		• Excellent
		  ◦ Recovery within 2–4 days
			• Physiological 'furrow' vs. pathological staining
			• Conjunctival flaps
			• Conjunctivochalasis
			• Lid-parallel conjunctival folds

p. 142	p. 143	p. 144	p. 144
• Blink-induced friction • Compromised tear film	• Treat associated dry eye • Artificial tears	• Commensurate with resolution of dry eye	• Conjunctival 'furrow staining' • Conjunctival flaps • Conjunctivochalasis
p. 149	p. 149	p. 150	p. 150
• Mechanical • Tissue schisis caused by lens edge	• Monitor • Cease lens wear if troublesome	• Usually resolves 1 week after cessation of lens wear • May take several weeks to resolve	• Conjunctival 'furrow staining' • Lid-parallel conjunctival folds • Conjunctivochalasis
p. 142	p. 143	p. 144	p. 144

Condition	Signs	Symptoms	Pathology

Conjunctival redness 	• Conjunctival redness
	• May be regional variation
	• Specify location
	• Depends on lens type:
	  ◦ No lens: grade 0.78
	  ◦ Rigid lens: grade 0.96
	  ◦ Soft lens: grade 1.54
		• Often none
		• Itchiness
		• Congestion
		• Warm feeling
		• Cold feeling
		• Non-specific mild irritation
			• Vasodilatation caused by:
			  ◦ Relaxation of smooth muscle
			  ◦ Vessel blockage

	p. 151	p. 151	p. 152

Papillary conjunctivitis 	• Papillae on tarsus
	  ◦ 'Cobblestone' appearance
	  ◦ 'Giant' papillae rare
	• Redness/oedema
	• Excess lens movement
	• Coated contact lens
	• Mucus discharge
		• Early – grades 1 and 2
		  ◦ Lens awareness
		  ◦ Itching/blurring
		• Late – grades 3 and 4
		  ◦ Lens discomfort
		  ◦ Intense itching/blur
		  ◦ Reduced wearing time
			• Thickened conjunctiva
			• Distorted epithelial cells
			• Altered goblet cells
			• Inflammatory cells
			  ◦ Mast cells
			  ◦ Eosinophils
			  ◦ Basophils

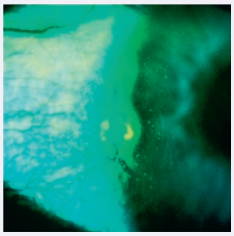
	p. 161	p. 161	p. 162

LIMBUS

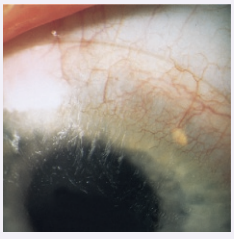
Condition	Signs	Symptoms	Pathology

Limbal redness 	• Limbal redness
	• May be regional variation around limbus
	• Depends on lens type:
	  ◦ Virtually absent with silicone hydrogel lenses
		• Depends on aetiology
		  ◦ Often none
		  ◦ Can be severe pain, e.g. with keratitis
		• Associated pathology may cause discomfort or pain
			• Vasodilatation of terminal arcades and associated vascular forms:
			  ◦ Recurrent limbal vessels
			  ◦ Vessel spikes

	p. 173	p. 173	p. 175

Vascularised limbal keratitis 	• Vascularised mass of tissue at the limbus
	• Conjunctival and limbal oedema in late stages
	• Infiltrates near limbus
	• Fluorescein staining
	• At 3 &/or 9 o'clock
	• Only in rigid lens wear
		• Early – grades 1 and 2
		  ◦ Lens awareness
		• Late – grades 3 and 4
		  ◦ Discomfort
		  ◦ Photophobia
			• Epithelial cell hyperplasia
			• Vessel engorgement
			• Vessel encroachment
			• Tissue erosion
			• Tissue oedema
			• Corneal infiltrates near limbus

	p. 180	p. 180	p. 181

Superior limbic keratoconjunctivitis 	• Superior limbic redness
	• Infiltrates
	• Micropannus
	• Corneal staining
	• Conjunctival staining
	• Hazy epithelium
	• Papillary hypertrophy
	• Corneal filaments
	• Corneal warpage
		• Lens awareness
		• Burning
		• Itching
		• Photophobia
		• Slight vision loss
		  ◦ With extensive pannus
			• Cornea
			  ◦ Epitheliopathy
			  ◦ Infiltrates
			• Conjunctiva
			  ◦ Epithelial keratinization
			  ◦ Epithelial oedema
			  ◦ Inflammatory cells

	p. 187	p. 187	p. 188

Aetiology	Treatment	Prognosis	Differential Diagnosis

• Hypoxia and hypercapnia
• Mechanical irritation
• Immunological reaction
• Infection/inflammation
• Solution toxicity
• Change in tonicity/pH
• Neural control
	• Remove cause
	  ◦ See aetiology
	• Decongestants
	• If > grade 2, cease wear
		• Excellent
		  ◦ Recovery from acute redness within hours
		  ◦ Recovery from chronic redness within 2 days
			• Cease lens wear
			  ◦ Rapid resolution implicates lens wear
			  ◦ Slow resolution suggests other cause
			• Conjunctival vs. scleral involvement?

p. 153	p. 156	p. 157	p. 157

• Anterior lens deposits
• Mechanical irritation
• Immunological reaction
• Hypoxia under lid
• Solution toxicity
• Related to meibomian gland dysfunction?
	• Suspend lens wear
	• Reduce wearing time
	• Change lens/solutions
	• Ocular lubricant
	• Mast cell stabilisers
	• Anti-inflammatory agents
	• ↑ Lens replacement
		• Papillae can remain for weeks, months or years
		• Lenses can still be worn
		• Treat according to symptoms
			• Follicle
			  ◦ Vessels on outside
			• Papilla
			  ◦ Central vascular tuft

p. 163	p. 165	p. 167	p. 167

Aetiology	Treatment	Prognosis	Differential Diagnosis

• Hypoxia and hypercapnia
• Mechanical irritation
• Immunological reaction
• Infection
• Inflammation
  ◦ Acute red eye
• Solution toxicity
	• Remove cause
	• Consider whether:
	  ◦ Acute or chronic
	  ◦ Local or circumlimbal
	• Fit silicone hydrogels
		• Excellent
		  ◦ Recovery from acute redness within hours
		  ◦ Recovery from chronic redness within 2 days
			• Re-vascularization
			• Vascularised limbal keratitis
			• Superior limbal keratoconjunctivitis

p. 176	p. 177	p. 177	p. 177

• Interruption to normal tear film dynamics around limbus
• Rigid lens with inappropriate edge design
• Severe sequel of 3 & 9 o'clock staining?
	• Early – grades 1 and 2
	  ◦ Cease extended wear
	  ◦ Reduce wearing time
	  ◦ Optimise lens edge design
	• Late – grades 3 and 4
	  ◦ Cease wear for 5 days
	  ◦ Antibiotics/steroids
	  ◦ Changes to soft lenses
		• Generally good
		• Recovery within days or weeks
		• 'Rebound' may occur
			• Neovascularization
			• Limbal redness
			• Phlyctenulosis
			• Peripheral corneal ulcer
			• Pterygium
			• Pseudo-pterygium
			• Pinguecula

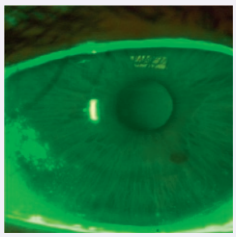
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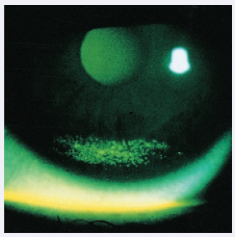
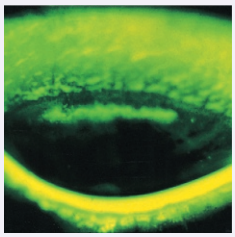
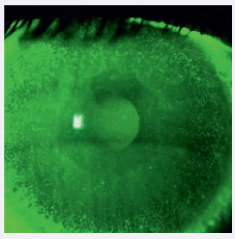
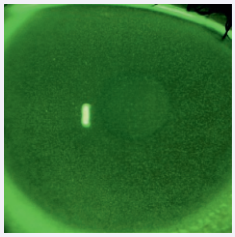
• Lens deposits
  ◦ Posterior lens surface
• Mechanical irritation
• Immunological reaction
• Hypoxia under lid
• Thimerosal
  ◦ Hypersensitivity
  ◦ Toxicity
	• Cease lens wear
	• Reduce wearing time
	• Improve solutions
	• Ocular lubricant
	• Mast cell stabilisers
	• Non-steroidal anti-inflammatory agents
	• Increase frequency of lens replacement
		• After ceasing lens wear
		  ◦ Redness resolves rapidly
		  ◦ Epithelium resolves slowly
		  ◦ Can take from 3–40 weeks to resolve
			• Superficial epithelial arcuate lesion
			• Bacterial conjunctivitis
			• Infiltrative keratitis
			• Theodore's superior limbic keratoconjunctivitis

p. 189	p. 191	p. 192	p. 192

CORNEAL EPITHELIUM

Condition	Signs	Symptoms	Pathology

3 & 9 o'clock corneal staining

	• Punctate/diffuse staining
	  ◦ 3 & 9 o'clock locations
	• Triangular patters:
	  ◦ Apex away from cornea
	  ◦ 'Base' at lens edge
	  ◦ Only in rigid lens wear
	p. 199
		• Slight discomfort
		• Dryness
		p. 199
			• Epithelial disruption at limbus
			p. 203

Inferior epithelial arcuate lesion ('smile stain') 	• Inferior arcuate stain parallel to limbus • Punctate form p. 200	• Slight discomfort p. 200	• Disruption to epithelium • Cells damaged or dislodged p. 200
Superior epithelial arcuate lesion (SEAL) 	• Superior arcuate stain parallel to limbus • Full thickness lesion • Also known as 'epithelial splitting' p. 200	• Asymptomatic p. 200	• Full-thickness splitting of epithelium p. 200
Solution-induced corneal staining (SICS) 	• Pan-corneal punctate staining • Bilateral p. 201	• Asymptomatic if mild • Severe stinging or burning if severe p. 201	• Toxic reaction of epithelium • Epithelial cell desquamation p. 203
Preservative-associated transient hyperfluorescence (PATH) 	• Pan-corneal punctate staining • Bilateral p. 202	• Asymptomatic p. 202	• Epithelium is essentially unaffected p. 203

Aetiology	Treatment	Prognosis	Differential Diagnosis

• Rigid lens bridges lid away from ocular surface
• Ocular surface adjacent to lens edge not properly wetted
	• Alter lens design
	  ◦ Reduce thickness of lens edge
	  ◦ Smaller lens diameter
	• Blinking instructions
		• After lens removal
		  ◦ Recovery: <24 hours
		• While wearing lenses
		  ◦ Slower recovery: 4–5 days
			• Vascularised limbal keratitis

p. 205	p. 207	p. 208	p. 208

• Metabolic
• Desiccation
  ◦ ↓ Post-lens tear film
  ◦ Lens adherence
  ◦ Lens dehydration
	• Alter lens fit
	  ◦ ↑Movement
	  ◦ Thicker lens
	• Alter lens type
	  ◦ Different material
		• After lens removal
		  ◦ Rapid recovery: <24 hours
		• While wearing lenses
		  ◦ Slower recovery: 4–5 days
			• Lens edge stain
			• Lens handling trauma

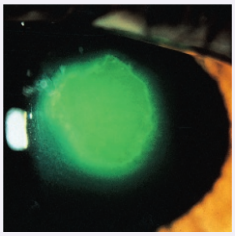
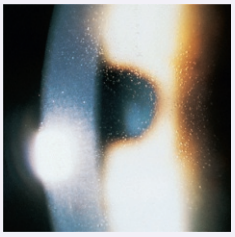
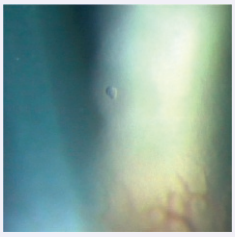
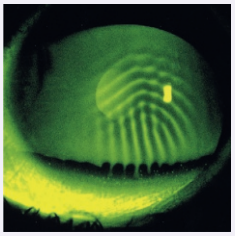
p. 200	p. 207	p. 208	p. 208

• Mechanical chaffing
• ↑ Pressure of upper lid
• Contributing factors:
  ◦ Corneal topography
  ◦ Rigid lens modulus
  ◦ Lens surface/design
	• Alter lens design
	• ↓ Mid-peripheral bearing
	• Alter lens type
	  ◦ Lower modulus material
	  ◦ Better surface characteristics
		• After lens removal
		  ◦ Recovery in 3 days
			• Lens edge stain
			• Lens insertion and removal trauma

p. 201	p. 207	p. 208	p. 208
• Occurs with certain lens-solution combinations • Can occur with direct inadvertent exposure to hydrogen peroxide	• Cease lens wear • Try different lens-solution combination • Ocular lubricants • Prophylactic antibiotics	• If mild: 2–12 hours • If severe: 2–3 days	• PATH ◦ See later • Staining observed 4 hours after lens insertion may be true SICS
p. 205	p. 207	p. 208	p. 208

• Bright fluorescence observed is attributed to fluorescein binding to preservatives on epithelial surface	• None required
	• PATH is non-pathological
		• Peak fluorescence
		  ◦ After 30 minutes with PQ-1/ Aldox solutions
		  ◦ After 120 minutes with PHMB solutions
			• SICS
			  ◦ See earlier
			• Staining observed <3 hours may be PATH

p. 203	p. 207	p. 208	p. 208

Condition	Signs	Symptoms	Pathology
Epithelial plug 	• Full thickness epithelial 'hole' • Usually circular pattern • Fills with fluorescein and fluoresces brightly p. 201	• Vision loss if plug is central • Can be asymptomatic or painful p. 201	• Epithelium removed with lens removal • ⬇ Hemidesmosomes • ⬇ Epithelial adhesion p. 201
Epithelial microcysts 	• Minute scattered dots • Spherical or ovoid shape • 5–30 µm diameter • Reversed illumination p. 211	• Can cause slight discomfort • Can reduce vision slightly p. 211	• Intra-epithelial sheets • Disorganised cell growth • Pockets of dead cells • Slowly pushed to surface p. 212
Epithelial oedema 	• Epithelial haziness • Can occur during rigid lens wear adaptation p. 216	• Asymptomatic • Appearance of haloes p. 216	• Disrupted epithelial cells • Extracellular oedema around basal epithelium p. 218
Epithelial vacuoles 	• Minute scattered dots • Spherical shape • 5–30 µm diameter • Un-reversed illumination • In corneal mid-periphery p. 217	• Asymptomatic • Do not affect vision p. 217	• Filled with gas or fluid p. 218
Epithelial bullae 	• Minute scattered dots • Irregular shape; oval • Indistinct edges • Flattened, pebble-like • 5–30 µm diameter • May coalesce • Un-reversed illumination • Centre of cornea p. 217	• Asymptomatic • Do not affect vision p. 217	• Filled with fluid p. 218
Epithelial wrinkling 	• Linear wave patterns of epithelial pooling • Patterns intersect at 70° • Discrete spots of staining at wave intersections • Seen in keratograms p. 221	• Extremely painful • Extreme vision loss • Parallel time course of discomfort and vision loss p. 223	• Epithelium forms concertina-like folds • Anterior stroma may also be slightly folded p. 223

Aetiology	Treatment	Prognosis	Differential Diagnosis
• Epithelial metabolic compromise • Chronic hypoxia	• Cease lens wear until epithelium has completely reformed • Refit with a high-oxygen permeable lens material	• After lens removal ◦ Recovery may take up to 1 week	• Lens insertion and removal trauma
p. 201	p. 207	p. 208	p. 208

• Prolonged hypoxia
• Mechanical irritation
• ↓ Oxygen uptake
• ↓ Mitosis
• Hydrogel extended wear
	• If ≤ grade 2 microcysts
	  ◦ No action/monitor
	• If ≥ grade 3 microcysts
	  ◦ Cease wear
	  ◦ Reduce wearing time
	  ◦ Change to daily wear
	  ◦ ↑ Lens Dk/t
		• After ceasing wear
		  ◦ Increase for 7 days
		  ◦ Decrease thereafter
		• Full recovery in 2 months
		• Microcysts will not recur with silicone hydrogels
			• Tear film debris
			• Mucin balls
			• Vacuoles
			• Bullae
			• Bedewing
			• Dimple veiling
			• Infiltrates

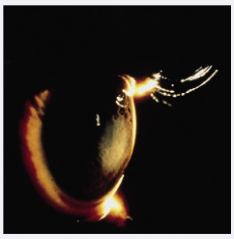
p. 213	p. 213	p. 214	p. 214
• Hypotonic tears • Rigid lens adaptation • Fluid enters epithelium	• Modify rigid lens adaptation wear regimen	• Rapid recovery upon ceasing of hypotonic stress (tearing stops)	• Generalised epitheliopathy
p. 218	p. 219	p. 219	p. 219
• Related to excess oedema?	• Generally innocuous • No management required • Note the number of vacuoles on record card	• Rapid recovery upon ceasing lens wear	• Tear film debris • Microcysts • Bullae • Bedewing • Dimple veiling • Infiltrates
p. 218	p. 219	p. 219	p. 219
• Related to excess oedema?	• Generally innocuous • No management required • Note the number of bullae on record card	• Rapid recovery upon ceasing lens wear	• Tear film debris • Microcysts • Vacuoles • Bedewing • Dimple veiling • Infiltrates
p. 218	p. 219	p. 219	p. 219

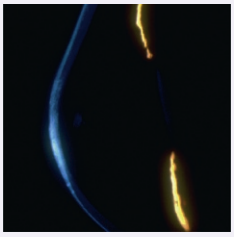
• Mechanical aetiology
• Highly elastic hydrogel material
• Very thin custom design
• 50%–55% water content
• Steep fitting
	• Remove lens immediately
	• Refit with lenses avoiding design features described in 'Aetiology'
		• Good
		  ◦ Expect complete recovery
		  ◦ Can take up to a week to fully recover
		• Rate of recovery related to period of wear
			• Fischer-Schweitzer mosaic
			• Anterior crocodile shagreen of Vogt

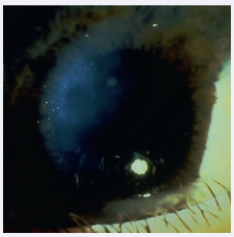
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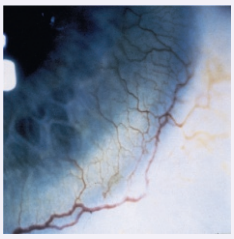
CORNEAL STROMA

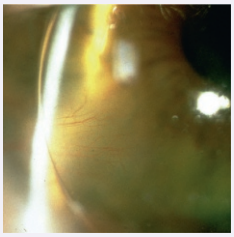
Condition	Signs	Symptoms	Pathology

Stromal oedema 	• <2% oedema: undetectable; safe
	• >5% oedema: vertical striae; caution
	• >8% oedema: posterior folds; danger
	• >15% oedema: loss of corneal transparency; pathological
	p. 230
		• <10% none
		• >10% discomfort
		p. 230
			• Oedema
			  • Increased fluid
			• Striae
			  • Separated collagen fibrils
			• Folds
			  • Physical buckling
			p. 231

Stromal thinning 	• Only detected using pachometry after oedema has resolved • Stromal thinning – true oedema – Apparent oedema • Stroma thins at about 2.1 µm per year p. 242	• None • Reduced vision if associated with corneal warpage p. 242	• Reduced stromal mass • Reduced keratocyte density • Stromal 'microdots' may represent keratocyte apoptosis p. 244

Deep stromal opacities (pseudo-dystrophy) 	• Opacities in deep stroma
	• Many appearances:
	  • Whitish dots/opacities
	  • Resembles dystrophy
	  • Lattice-like pattern
	  • Mottled cyan opacity
	• Possible associated endothelial changes
	p. 251
		• May be asymptomatic
		• Ocular discomfort and photophobia
		• May be some vision loss
		p. 252
			• Similar to pre-Descemet's dystrophy
			• Stromal 'microdots' may represent deep stromal opacities
			• Possible associated endothelial pathology
			p. 252

Superficial corneal neovascularization 	• Superficial vessels
	  • From conjunctiva
	• 'Normal' responses:
	  • No lens: 0.2 mm
	  • Si-H lens: 0.2 mm
	  • DW rigid: 0.4 mm
	  • DW soft: 0.6 mm
	  • EW soft: 1.4 mm
	p. 258
		• No discomfort
		• VA loss if extreme
		p. 260
			• Sprouting or budding
			• Solid cord of vascular endothelial cells at tip
			• Thin vessel wall
			• Pericytes
			• Inflammatory cells
			• Disrupted stroma
			• Lipid around vessels
			p. 261

Deep stromal neovascularization 	• Fine, tortuous branches • Vessels end in buds • Numerous small-vessel anastomoses • Vessels 'stop' at limbus when traced backwards from cornea • Associated pathology p. 259	• No discomfort • VA loss if extreme p. 260	• Sprouting or budding • Solid cord of vascular endothelial cells at tip • Thin vessel wall • Pericytes • Inflammatory cells • Disrupted stroma • Lipid around vessels p. 261

Aetiology	Treatment	Prognosis	Differential Diagnosis

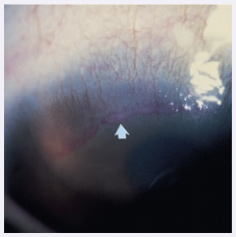
• Primarily hypoxia – 50%
  ◦ Lactate build-up
• Other factors – 50%:
  ◦ Tear hypotonicity
  ◦ Hypercapnia
  ◦ Increased temperature
  ◦ Increased humidity
  ◦ Mechanical
p. 232
	• Alleviate hypoxia
	  ◦ Increase material Dk
	  ◦ Reduce lens thickness
	  ◦ Increase lens movement
	  ◦ Increase edge lift
	• Alleviate hypercapnia
	  ◦ As per hypoxia
	p. 235
		• Acute oedema
		  ◦ Resolves in 2–3 hours
		• Chronic oedema
		  ◦ Resolves in 7 days
		• Chronic oedema thins stroma; see later
		p. 239
			• Striae
			  ◦ Nerve fibres
			  ◦ Ghost vessels
			• Folds
			  ◦ Seen in diabetes
			• Haze
			  ◦ Scarring
			  ◦ Epithelial oedema
			p. 240

• Chronic oedema
• Mechanical effect of lenses on epithelium
• Inflammatory mediators released
• Causes keratocyte apoptosis
p. 246
	• Alleviate hypoxia
	  ◦ Increase material Dk
	  ◦ Reduce lens thickness
	  ◦ Increase lens movement
	  ◦ Increase edge lift
	• Alleviate hypercapnia
	• Alleviate mechanical effect of lenses
	p. 247
		• Unknown time course
		  ◦ Thought to be permanent
		p. 248
			• Keratoconus
			  ◦ Central corneal thinning
			• Pellucid marginal degeneration
			• Terrien's marginal corneal degeneration
			p. 248

• Numerous theories:
  ◦ Long-term lens wear
  ◦ Heavy metal exposure
  ◦ Allergy to thimerosal?
  ◦ Chlorhexidine exposure
  ◦ Hypoxia/hypercapnia
  ◦ Endothelial dysfunction
  ◦ Suction effects
p. 254
	• Alleviate chronic hypoxia
	  ◦ Increase material Dk
	  ◦ Reduce lens thickness
	  ◦ Increase lens movement
	  ◦ Increase edge lift
	• Avoid noxious preservatives
	p. 254
		• Slow regression
		  ◦ Many months/years
		p. 254
			• Corneal dystrophies
			• Deep stromal opacities occur deep in stroma and may be reversible
			• Infiltrates
			p. 254

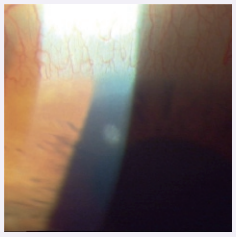
• Stromal softening
  ◦ Hypoxia-induced oedema
• Triggering agent, e.g.:
  ◦ Epithelial damage
  ◦ Solution toxicity
  ◦ Infection
p. 261
	• If severe
	• Cease lens wear permanently
	• If mild
	  ◦ Improve care system
	  ◦ Increase Dk/t
	  ◦ Reduce wearing time
	  ◦ Monitor carefully
	p. 264
		• On ceasing lens wear
		  ◦ Vessels empty rapidly
		  ◦ Ghost vessels remain
		  ◦ Years to resolve
		• On re-introducing lens
		  ◦ Ghost vessels rapidly refill
		p. 267
			• Nerve fibres
			• Striae
			• Ghost vessels
			p. 267

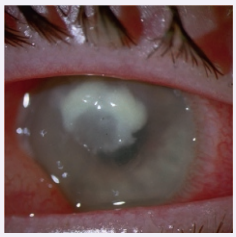
• Often other pathology
  ◦ Graft/keratoconus
• Stromal softening
  ◦ Hypoxia-induced oedema
• Triggering agent
  ◦ Epithelial damage
  ◦ Solution toxicity
  ◦ Infection
p. 261
	• Manage associated pathology
	• If severe, cease lens wear permanently
	• If mild
	  ◦ Improve care system
	  ◦ Increase Dk/t
	  ◦ Reduce wearing time
	p. 264
		• On ceasing lens wear
		  ◦ Vessels empty rapidly
		  ◦ Ghost vessels remain
		  ◦ Years to resolve
		• On reintroducing lens
		  ◦ Ghost vessels rapidly refill
		p. 267
			• Ghost vessels
			  ◦ Start at limbus
			  ◦ Relatively thick
			p. 267

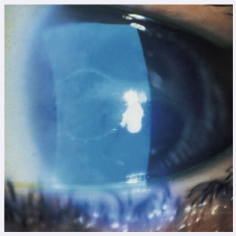
Condition	Signs	Symptoms	Pathology
Corneal vascular pannus 	• Plexus of parallel vessels from limbus onto cornea • Invading end is even • Contains fibrotic tissue • Stains with rose bengal • Active pannus: inflammatory • Fibrovascular pannus: degenerative p. 260	• No discomfort • Vision loss if extreme p. 260	• Vessels penetrate between epithelium and Bowman's layer • Ingrowth of vessels • Ingrowth of collagen • Fatty plaques • Fibrotic tissue p. 261

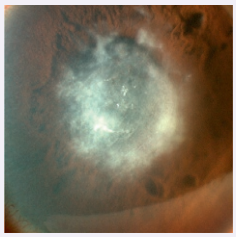
KERATITIS

Condition	Signs	Symptoms	Pathology

Corneal infiltrative event (CIE) 	• Any condition whereby there are infiltrates in the cornea
	• Ranges from minute, barely detectable infiltrate to full-blown corneal ulcer
	• Often used in the literature to denote a mild event
	p. 270
		• Depends on severity
		• Ranges from asymptomatic to very painful
		• Treat as microbial keratitis if:
		  ◦ Lenses are worn
		  ◦ Discomfort reported
		  ◦ Infiltrates observed
		p. 272
			• Infiltrates in the epithelium and/or stroma
			• Infiltrates can include:
			  ◦ Polymorphonuclear leucocytes
			  ◦ Inflammatory cells
			  ◦ Oedema
			  ◦ Microorganisms
			p. 285

Pseudomonas keratitis 	• Typically uniocular
	• Conjunctival redness
	• Lid swelling
	• Lacrimation
	• Photophobia
	• Mucopurulent discharge
	• Loss of vision
	• Culture-positive
	• Deep ulcer can form
	  ◦ Haziness in stroma
	  ◦ Overlying epithelial defect
	• Hypopyon
	• Anterior chamber flare
	p. 289
		• Initial foreign-body sensation
		• Worsening pain
		• Eye redness
		p. 289
			• Infiltrates could comprise:
			  ◦ The offending micro-organisms
			  ◦ Inflammatory cells, e.g. polymorphonuclear leucocytes
			  ◦ Bacterial endotoxins
			  ◦ Serum
			  ◦ Proteins
			• Bowman's layer destroyed
			p. 291

Acanthamoeba keratitis 	• Typically uniocular
	• Conjunctival redness
	• Lid swelling
	• Lacrimation
	• Photophobia
	• Loss of vision
	• Pseudo-dendrites
	• Radial keratoneuritis
	• Deep ulcer can form
	  ◦ Haziness in stroma
	  ◦ Overlying epithelial defect
	• Hypopyon
	• Anterior chamber flare
	p. 289
		• Initial foreign body sensation
		• Excruciating pain
		• Eye redness
		p. 289
			• *Acanthamoeba* can be observed destroying stromal tissue using confocal microscopy
			• Bowman's layer destroyed
			p. 291

Fusarium keratitis 	• Typically uniocular • Conjunctival redness • Lid swelling • Lacrimation • Photophobia • Loss of vision • Central fluffy infiltrate • Satellite infiltration • Ring infiltrate • Anterior chamber flare p. 291	• Initial foreign body sensation • Sharp pain when removing lens from eye p. 291	• *Fusarium* fungal hyphae can be observed destroying stromal tissue by using confocal microscopy • Bowman's layer destroyed p. 291

Aetiology	Treatment	Prognosis	Differential Diagnosis

• Stromal softening
  ◦ Hypoxia-induced oedema
• Triggering agent
  ◦ Epithelial damage
  ◦ Solution toxicity
  ◦ Infection
	• If severe
	  ◦ Cease lens wear permanently
	  ◦ Surgical removal
	• If mild
	  ◦ Improve care system
	  ◦ Increase Dk/t
	  ◦ Reduce wearing time
	  ◦ Monitor carefully
		• On ceasing lens wear
		  ◦ Vessels empty rapidly
		  ◦ Ghost vessels remain
		  ◦ Years to resolve
		• On reintroducing lens
		  ◦ Ghost vessels rapidly refill
			• Ghost vessels
			  ◦ Start at limbus
			  ◦ Relatively thick

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Aetiology	Treatment	Prognosis	Differential Diagnosis

• Toxic
• Allergic
• Inflammatory
• Rheumatic
• Main risk factors:
  ◦ Patient non-compliance
  ◦ Overnight use
  ◦ Smoking
  ◦ Warm climates
  ◦ Male gender
	• Depends on cause
	• Cease lens wear
	• If discomfort persists after lens removal, could be microbial keratitis
	• Assume bacterial until proven otherwise
	• Cold compresses
	• Analgesics
	• Avoid risk factors if lens wear to resume
		• Depends on cause
		  ◦ Sterile CIEs may resolve within 7 days
		  ◦ Microbial keratitis can rapidly progress to corneal perforation within hours
			• Sterile keratitis is usually self-limiting
			• Keratoconjunctivitis
			• Microbial keratitis can advance rapidly
			• In the early stages, differentiating sterile vs. microbial keratitis is difficult

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• Bacterial infection
  ◦ *Pseudomonas aeruginosa*
• Risk factors as for CIEs
	• Cease lens wear immediately
	• Advise of risks
	• Antibiotics
	• Mydriatics
	• Non-steroidal anti-inflammatory agents
	• Analgesics
	• Tissue adhesives
	• Debridement
	• Avoid risk factors if lens wear to resume
		• Depends on speed of treatment
		  ◦ Excellent if rapid action is taken
		• If untreated, can rapidly progress to corneal perforation within hours
		• If treated, condition usually worsens during initial 24 hours, then improves
			• Differentiate from *Acanthamoeba* and *Fusarium* keratitis
			• Differentiate from other bacteria
			• Corneal scraping to detect *Pseudomonas aeruginosa*
			• Bacteria cannot be seen with confocal microscopy, but *Acanthamoeba* and *Fusarium* can – see later

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• Protozoal infection
  ◦ *Acanthamoeba*
• Exists as:
  ◦ Free moving trophozoite
  ◦ Double-walled cyst
• Risk factors as for CIEs, earlier
• Relation with water critical, e.g.
  ◦ Swimming
  ◦ Hot tubs
  ◦ Water stored in tanks
  ◦ Water in stagnant lake or pond
	• Cease lens wear
	• Advise of risks
	• Propamidine isethionate 0.1% (Brolene)
	• Polyhexamethylene biguanide 0.02%
	• Neomycin
	• Mydriatics
	• Topical steroids
	• Analgesics
	• Tissue adhesives
	• Debridement
	• Avoid risk factors if lens wear to resume
		• Slow time course of recovery
		  ◦ May progress for many months despite aggressive therapy
		• Residual superficial nebula
		• Recurrence is common
		  ◦ Especially if treatment is stopped prematurely
			• Differentiate from *Pseudomonas* and *Fusarium* keratitis
			• Differentiate from other protozoa
			• Confocal microscopy can confirm presence of *Acanthamoeba* cysts and trophozoites

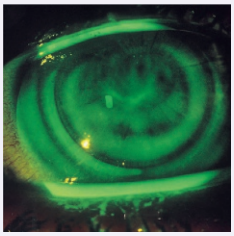
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• Fungal infection
  ◦ *Fusarium*
• Feathery colonies joining together
• Hyphae, often with septa
• Risk factors as for CIEs
• Relation with high viscosity lens care solutions
	• Cease lens wear immediately
	• Natamycin, 5%
	• Amphotericin B, 0.15%
	• Mydriatics
	• Topical steroids
	• Analgesics
	• Avoid risk factors if lens wear to resume
		• Poor prognosis
		• Slow time course of recovery
		  ◦ May progress for many months despite aggressive therapy
		• 28% of cases require penetrating keratoplasty
			• Differentiate from *Pseudomonas* keratitis and *Acanthamoeba* keratitis
			• Differentiate from other fungi
			• Confocal microscopy can confirm presence of *Fusarium* hyphae

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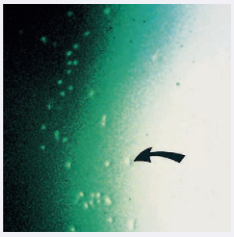
CORNEAL SHAPE

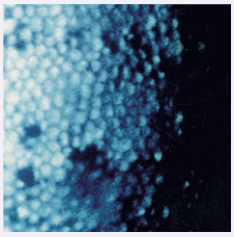
Condition/ Appearance	Signs	Symptoms	Pathology

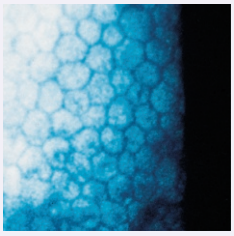
Corneal warpage 	• Can manifest as change in corneal:
	  ◦ Curvature
	  ◦ Symmetry
	  ◦ Regularity
	• Corneal indentation
	  ◦ May be associated with corneal binding
	p. 305
		• Spectacle blur
		• Haze
		  ◦ If associated with excess oedema
		p. 305
			• Surface Asymmetry Index
			  ◦ Likely with rigid lenses
			  ◦ De-centred lens flattens cornea
			• Surface Regularity Index
			  ◦ Symmetrical distortion
			  ◦ Likely with rigid lenses
			• Corneal indentation
			  ◦ Pressure from lens edge
			p. 307

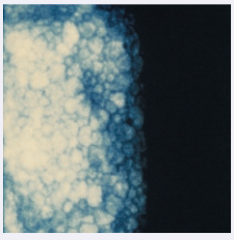
CORNEAL ENDOTHELIUM

Condition	Signs	Symptoms	Pathology

Endothelial bedewing 	• Cluster of particles
	• 20–50 in number
	• Inferior cornea, near lower pupil margin
	• Display reversed illumination
	p. 319
		• Intolerance to lenses
		• Stinging sensation
		• Reduced vision
		p. 319
			• Inflammatory cells
			  ◦ On endothelial surface
			  ◦ May become entrapped within endothelium
			p. 320

Endothelial blebs 	• Black non-reflecting areas • Apparent separation of cells p. 324	• None p. 324	• Oedema of cell nucleus • Intracellular vacuoles • Extracellular vacuoles • Posterior surface bulging p. 325

Endothelial cell redistribution 	• Redistribution of endothelial cells from corneal centre to periphery; see 'Pathology'
	• Endothelial cell density (ECD) decreases with normal ageing
	p. 330
		• None
		• Possible endothelial dysfunction leading to oedema and discomfort if severe
		p. 330
			• Spreading out of cells towards periphery
			• Reduced ECD is therefore an artefact
			  ◦ Higher peripheral ECD 'compensates' for lower central ECD
			  ◦ Overall ECD unchanged
			p. 331

Endothelial polymegethism 	• Large variation in endothelial cell size
	• Small-to-large cell ratio:
	  ◦ Normal – 1:5
	  ◦ Polymegethism – 1:20
	p. 335
		• Corneal exhaustion syndrome:
		  ◦ Reduced wearing time
		  ◦ Discomfort
		p. 335
			• Altered lateral cell walls
			• Straightening of interdigitations
			• Cell volume unchanged
			• Cell organelles normal
			• Poor oedema recovery
			p. 336

Aetiology	Treatment	Prognosis	Differential Diagnosis

• Oedema
  ◦ Increased fluid
• Physical moulding
  ◦ Pressure from rigid lenses
  ◦ Supplementary pressure from eyelids
• Associated pathology, e.g. keratoconus
	• Alleviate rigid lens bearing
	• Alleviate hypoxia
	• Corneal indentation
	  ◦ Patient dependent
	  ◦ Likely to recur again in same patient
	• Keratoplasty for keratoconus
		• Rigid lens warpage
		  ◦ Full recovery in 5 to 8 months
		• Rigid lens binding
		  ◦ Full recovery in 24 hours
		• Soft lens warpage
		  ◦ Resolves in 7 days
			• Keratoconus
			  ◦ Other signs present such as stromal thinning, Vogt's striae and Fleischer's ring

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Aetiology	Treatment	Prognosis	Differential Diagnosis

• Hypoxia
• Inflammatory mediators
  ◦ Prostaglandins?
• Inflammation of anterior uvea?
	• Reduce wearing time
	• Check for concurrent pathology
	• Check for raised intra-ocular pressure
		• Symptoms disappear in 3–5 days
		• Bedewing disappears in 3–5 months
		• Prolonged intolerance to lens wear
			• Microcysts
			  ◦ Epithelial
			• Guttae
			  ◦ Large dark spots
			• Bedewing
			  ◦ On endothelium

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• Acidic pH shift at endothelium caused by
  ◦ Hypercapnia: carbonic acid
  ◦ Hypoxia: lactic acid
• Acute response
	• Not necessary	• After inserting lens
		  ◦ Peak response in 10 minutes
		  ◦ Low-level blebs continue
		• After removing lens
		  ◦ Disappear in 2 minutes
			• Guttae
			  ◦ Permanent
			• Bedewing
			  ◦ Lasts months
			• Blebs
			  ◦ Last minutes

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• Possibly acidic pH shift at endothelium caused by
  ◦ Hypercapnia: carbonic acid
  ◦ Hypoxia: lactic acid
• Chronic response
	• General strategy
	  ◦ Alleviate acidosis
	  ◦ Higher-Dk materials
		• Possible long-term recovery (many years) after ceasing lens wear	• Effects of
			  ◦ Normal ageing
			  ◦ Disease
			  ◦ Intraocular surgery
			  ◦ Eye disease
			  ◦ Systemic disease

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• Acidic pH shift at endothelium caused by
  ◦ Hypercapnia: carbonic acid
  ◦ Hypoxia: lactic acid
• Chronic response
	• Alleviate acidosis
	• Higher-Dk materials
	• Corneal exhaustion syndrome
	  ◦ Reduce wearing time
	  ◦ Fit higher Dk/t lens
		• Possible long-term recovery (many years) after ceasing lens wear	• Guttae
			• Endothelial dystrophy

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1 Anterior Eye Examination

The slit lamp biomicroscope has been the primary instrument for examining the anterior ocular structures since its invention in the early part of the 20th century. In particular, this versatile instrument is invaluable in assessing the effect of contact lens wear on the tear film, cornea, conjunctiva and eyelids. Other simple 20th century optical instruments which were developed to aid contact lens fitting, such as the Burton lamp, or to enhance our ability to assess the tear film, such as the Tearscope, are still in common use today.

As a result of developments in digital electronics, optical technology, still and video capture imaging and computer-assisted image-analysis techniques, a range of sophisticated ophthalmic instruments have been developed over the past two decades and have expanded our capacity to examine the anterior eye. Such instruments that have been demonstrated to have considerable utility in this regard are the specular microscope, corneal confocal microscope, optical coherence tomographer, corneal topographer, pachometer and aesthesiometer. These devices provide valuable capability that supplements visual examination using slit lamp biomicroscopy.

The aim of this chapter is to review the various instruments that are now available to facilitate examination of the anterior eye and determination of anterior ocular dimensions and which have been used to capture the majority of images presented in this book. Primary attention is given to the slit lamp biomicroscope, as this technique has always been, and is likely to remain, the mainstay of ocular examination in contact lens practice.

Burton lamp

A number of manufacturers make a special hand-held magnifying device for contact lens work. This device is usually referred to as the 'Burton lamp', after the company that manufactured the original version (Burton Manufacturing Co., Chicago, Illinois, USA). The Burton lamp is essentially a large magnifying lens of about +5.00 diopters (D) housed in a broad frame, within which is mounted a combination of 4 watts (W) white light and ultraviolet light fluorescent tubes, each 11 cm long. The operator can switch between the two light sources for white light and fluorescein stain examinations. A key advantage of this instrument is that both eyes of the patient can be viewed simultaneously, facilitating inter-ocular comparisons in the course of contact lens fitting. The Burton lamp is also useful for conducting an initial screening examination (Fig. 1.1).

The main disadvantage of the Burton lamp is that it is not possible to view fluorescein fitting patterns of rigid contact lenses made of material containing ultraviolet absorbing properties. This is because the Burton lamp has its highest emission in the 300 to 400 nm range, and this short-wavelength blue light is attenuated by the lens material, resulting in decreased fluorescence.

Slit lamp biomicroscope

The slit lamp biomicroscope (Fig. 1.2) is a combined illumination and observation system that allows the eye to be examined from close distance at different magnifications. With the appropriate application of supplementary lenses and/or viewing techniques, the instrument may be used to assess the condition of the vitreous, lens and retina from the posterior pole to the ora serrata. Various ancillary instruments that enable examination of the tear film, anterior chamber angle and retina and measurement of intra-ocular pressure, corneal sensitivity and corneal thickness can be attached. Since this book is concerned with the assessment of ocular complications of contact lens wear, the discussion that follows will relate primarily to the use of the slit lamp biomicroscope in examining the anterior ocular structures.

It has long been recognised that it is not possible to sensibly prescribe and fit contact lenses, or provide ongoing care to contact lens patients, without access to a slit lamp biomicroscope.[1] This instrument is used virtually every time a contact lens patient is seen, including during the initial examination, fitting and aftercare visits. Certainly, the vast majority of complications of contact lens wear cannot be detected or assessed without the aid of a slit lamp biomicroscope. It is therefore imperative that contact lens practitioners have access to this instrument and are well versed in its operation.

This section will outline the design and construction of the slit lamp biomicroscope, review key techniques of ocular illumination and examination inasmuch as they relate to contact lens practice and suggest a recommended examination procedure.

GENERAL CONSTRUCT

The general construct of a slit lamp biomicroscope is indicated by its name; that is, there is a separate illumination system (the slit lamp) and a viewing system (the biomicroscope). These two components are mechanically linked (Fig. 1.3) so as to create a common focal point and centre of rotation; however, the mechanical linkage can be unlocked to allow the focal illumination to be directed away from the focal point of the viewing system, and this is an essential requirement for some observation techniques, such as 'sclerotic scatter' (see later). The mechanically linked illumination and observation systems are always moved simultaneously – up and down with a height control, and focusing (in and out) and lateral (side to side) movements with a joystick. This linked control system facilitates rapid and accurate positioning of the slit beam to the area of interest on the eye and ensures that the microscope and illumination systems are simultaneously in focus.

The patient is seated opposite the observer, and the head of the patient is positioned in a conventional head mount

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Fig. 1.1 Burton lamp being used in 'white light mode'. (Courtesy Lyndon Jones.)



Fig. 1.2 Slit lamp biomicroscope.



Fig. 1.3 Mechanical system of a slit lamp biomicroscope.

comprising a chin rest and a brow rest. The linked illumination/observation system can be moved about independently of the head position, and a fixation target is provided to assist eye positioning and help the patient keep his or her eyes still. The entire head mount and linked illumination/observation system are contained on an instrument table, which can be adjusted in height – as can the practitioner and patient seats – to allow a comfortable posture to be adopted by both the examiner and the patient.

The slit lamp

The illumination system is called the *slit lamp* – so called because of its capacity to project a slit of light onto the ocular surface. The light source and optical elements of the slit lamp are classically contained in a vertically oriented housing (Fig. 1.4). A bright light source (generating approximately 600,000 lux) is a fundamental requirement for a slit lamp if subtle conditions are to be seen clearly. Although halogen or xenon lamps are more expensive than tungsten lamps, they are the preferred illumination source as they provide a brighter light, last longer, have better colour rendering and generate less heat. The light is focused vertically into a slit configuration. It then reflects off a mirror mounted at 45° and is projected onto the eye.

Illumination brightness is controlled by a rheostat or multiposition switch such that brightness can be adjusted to obtain the correct balance between patient comfort and optimal visibility of the area of interest. Generally, the broader the slit, the brighter the light, the greater the patient discomfort and the lower the illumination setting must be.

The optical and aperture-masking components within the illumination system are designed such that the emergent slit of light has sharp edges and an even spread of illumination. The slit width and height are continuously variable so that a



Fig. 1.4 Illumination system of a slit lamp biomicroscope.

section of light of any shape can be projected. The ability to vary the slit width has other practical applications, such as forming a reference for estimating the size of features of interest. Furthermore, the slit can be rotated so that, for example, a horizontal rather than a vertical slit can be projected onto the eye. This facility can also be useful for measuring the degree of rotation of soft toric lenses.

A number of filters can be incorporated into the illumination system,[2] and the filters serve to enhance the visibility of certain conditions:

- Green ('red-free') filter – enhances contrast when looking for corneal and iris neovascularization, since red vessels appear black if viewed through such a filter. A green filter may be used to increase the visibility of rose bengal staining on both the cornea and conjunctiva.
- Neutral density (ND) filter – reduces beam brightness and increases comfort for the patient.
- Polarising filter – reduces unwanted specular reflections and can be useful for enhancing the visibility of subtle defects.
- Diffusing filter – diffuses the illumination source over a wide area and is used to provide broad, unfocused illumination for low-magnification viewing of the general ocular surface.
- Cobalt blue filter – provides a suitable means of exciting sodium fluorescein for examination of ocular surface integrity. Illumination of fluorescein with cobalt blue light of 460 to 490 nm produces a greenish light of maximum emission 520 nm. Any abraded area will absorb fluorescein and display a fluorescent green area against a general blue background. The filter is occasionally used on its own to aid in the diagnosis of keratoconus. A frequent finding in this corneal ectasia is a Fleischer ring, which is formed by an annular iron deposition within the stroma at the base of the cone. The iron pigment is often difficult to see in white light but will usually appear in greater contrast when viewed through the cobalt blue filter.
- Yellow (Kodak Wratten #12) filter – this is not a filter contained within the illumination system but is used as a supplementary barrier filter that is placed in front of the viewing system.[3] It significantly enhances the contrast of any fluorescent staining observed with the cobalt blue filter as it allows transmission of the green, fluorescent light but blocks the blue light reflected from the corneal surface. Custom-made barrier filters for certain slit lamps are available from some manufacturers. Inexpensive handheld versions may be constructed by using a cardboard mask and Lee filters #101 Yellow.

The biomicroscope

A biomicroscope of high optical quality is essential if the observer is to achieve a comfortable, clear, focused binocular image of the eye (Fig. 1.5). The optical system contains an objective, typically with ×3 to ×3.5 magnification, and an eyepiece with variable or interchangeable power. The normal range of total magnification is from ×6 to ×40. In some systems, magnification is continuously variable throughout this range. These systems have two key advantages: (1) There is an uninterrupted view of the eye while the level of magnification is changed, and (2) the observer is not constrained to using discrete levels of magnification and can, in effect, choose any level of magnification within the available range. However, such systems usually require additional optical elements to achieve the 'zoom' function, and this may slightly compromise the optical quality of the image.

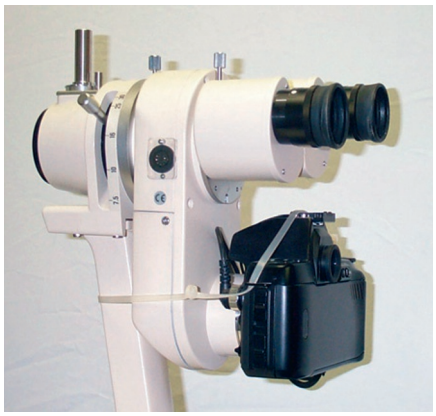


Fig. 1.5 Observation system of a slit lamp biomicroscope.

For the purposes of discussion throughout this book, the level of magnification being used can be broadly classified as follows:

- low: less than ×10 magnification
- medium: ×10 to ×25 magnification
- high: greater than ×25 magnification.

In most systems, magnification is changed in steps, with the typical progression being ×6, ×10, ×16, ×25 and ×40; these systems generally afford high optical quality, but there is the disadvantage of momentarily losing sight of the eye while the magnification is being changed. Some systems require the eyepieces to be interchanged to obtain different levels of magnification. Needless to say, these systems are cumbersome and mitigate against a smooth examination procedure. Manufacturers of slit lamp biomicroscopes could produce instruments with higher levels of magnification than ×40, but natural micronystagmoid eye movements make observation at such high magnification levels impractical.

The working distance of the biomicroscope (the distance from the eye to the front surface of the most anterior lens element of the biomicroscope) is typically set at about 10 cm, which is long enough to allow room for manipulating the eye, but not too long so as to require an uncomfortable arm position during such manipulations.

ILLUMINATION AND OBSERVATION TECHNIQUES

Being a transparent structure, the cornea lends itself to being examined with use of a wide variety of illumination and observational techniques. These are achieved by varying the illumination and observation conditions to optimise the visibility of the feature of interest in or on the cornea. There are essentially 13 illumination/observation techniques; these will be discussed in turn, with specific emphasis on those more routinely used in contact lens practice.

Although the techniques discussed next may seem daunting and somewhat confusing to the novice, it is important to realise that many combinations of these illumination and observation conditions are visible within a single field of view and are altered merely by the observer changing his or her direction of gaze. This is illustrated in Figure 1.6, where five illumination/observation conditions are simultaneously apparent in a single field of view in a case of contact lens–induced corneal neovascularization.

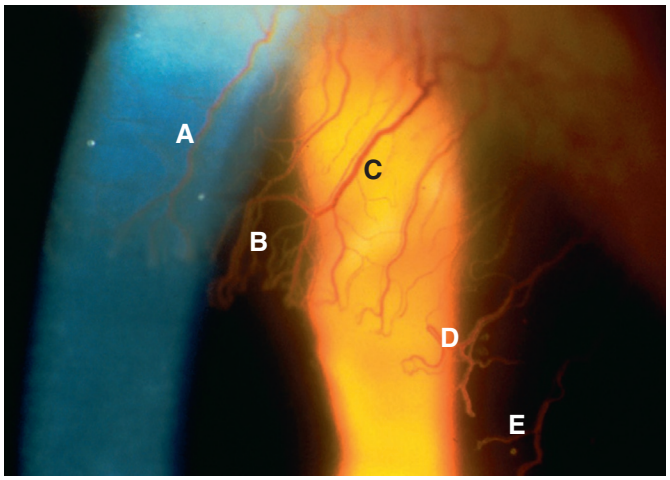


Fig. 1.6 Slit lamp photograph of contact lens–induced neovascularization, whereby the vessels can be viewed using **(A)** direct focal illumination, **(B)** indirect focal illumination, **(C)** direct retroillumination, **(D)** marginal retroillumination and **(E)** indirect retroillumination. (Courtesy Patrick Caroline, Bausch & Lomb Slide Collection.)

Diffuse illumination

A ground glass filter is placed in the focused light beam of the slit lamp. This will defocus and diffuse the light to give a broad, even illumination over the entire field of view. The angle of the illumination arm is not critical when the diffuser is in place and can be anywhere from 10° to 70° in relation to the observation arm; it is simply convenient to place it at an angle of at least 45° so as to avoid partially obstructing the field of view. The slit is generally opened wide, and high illumination will not cause too much patient discomfort in view of the diffuse nature of the light (Fig. 1.7).

Diffuse illumination is generally used to provide low-magnification views of the opaque tissues of the anterior segment (AS), including the bulbar conjunctiva, sclera, iris, eyelid margins and the tarsal conjunctiva of the everted lids. Unusual signs in these tissues could include dilated blood vessels in the bulbar conjunctiva, pigmented areas in the conjunctiva or eyelids, roughness or opacity of the conjunctiva and abnormal eyelash position or orientation. Such signs could be indicative of some conditions, such as trichiasis, bulbar redness, pterygium or papillary conjunctivitis. In assessing the eyelid margins, the apposition of the lids and puncta against the globe should be considered. Additionally, one should look for clear glands near the base of the lashes and flaking or scaling of the eyelid skin. These may indicate the presence of ectropion, blepharitis or epiphora.

Focal illumination – parallelepiped

This describes any illumination technique where the slit beam and viewing system are focused coincidentally. The illumination is turned up to a reasonably high level of brightness (ensuring that the patient remains comfortable) and the slit beam is placed at a separation of 40° to 60° on the side of the microscope corresponding to the section of the cornea to be viewed. The beam is swept smoothly across the ocular surface and the illumination system moved across to the opposite side as the beam crosses the mid-point of the cornea. Typically, a beam width of 0.1 mm to 0.5 mm is chosen initially and this may be reduced so as to bring more contrast (as a result of less light scatter) to the area of interest. The term 'parallelepiped' refers to the geometric shape of the illuminated optical section of the cornea under examination.

A slit width that is wider than 0.5 mm creates a condition known as 'broad–beam' illumination, whereby the width of the beam is greater than the depth of the cornea (effectively creating a parallelepiped, which is turned on its side). Whilst scanning the external ocular surface, a low-to-medium magnification is initially chosen, and the magnification is increased if any area of interest needs to be examined more closely.

Direct

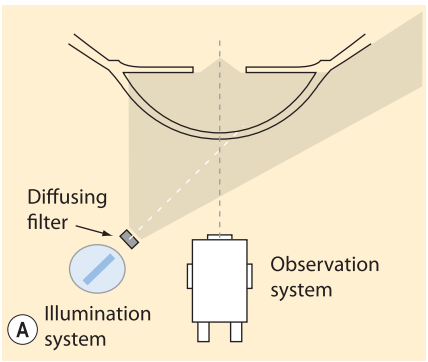
The section of the cornea *within* the illuminated beam is being observed (Fig. 1.8). This permits assessment of the location, width and height of any object within the cornea or adjacent structures. The parallelepiped is the most commonly used direct illumination technique and is employed, for example, to assess corneal scarring, infiltrates and corneal staining.

Indirect

The section of the cornea *outside* the illuminated beam is being observed. This is achieved by directing gaze to either side of the illuminated beam. To achieve this configuration, the parallelepiped is positioned to one side of the feature of interest. Thus, the feature of interest is being illuminated by side-scattering of light from the parallelepiped. This technique may reveal the presence of subtle changes in corneal transparency, which may not have been visible using direct illumination.

Focal illumination – optic section

This condition is identical to 'focal illumination – parallelepiped', except that a very thin beam of approximately 0.02 to 0.1 mm is used to essentially create a 'cross-section' of the corneal tissue. The illumination beam is placed at a separation of 40° to 60° on the side of the microscope corresponding to the section of the cornea to be viewed. Increasing the angle of the illumination arm increases the depth of the optic section in



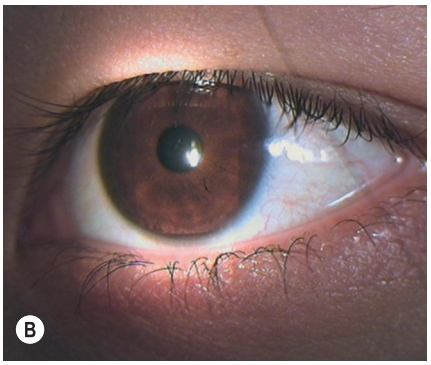


Fig. 1.7 **(A)** Diffuse illumination slit lamp technique. **(B)** Diffuse illumination view of the cornea. (A, Adapted from Jones LW, Jones DA. Slit lamp biomicroscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford, UK: Butterworth-Heinemann; 2001: 1–49. B, Courtesy Adrian Bruce. In: Efron N, editor. Contact Lens Practice. 2nd ed. Oxford, UK: Butterworth-Heinemann; 2010.)

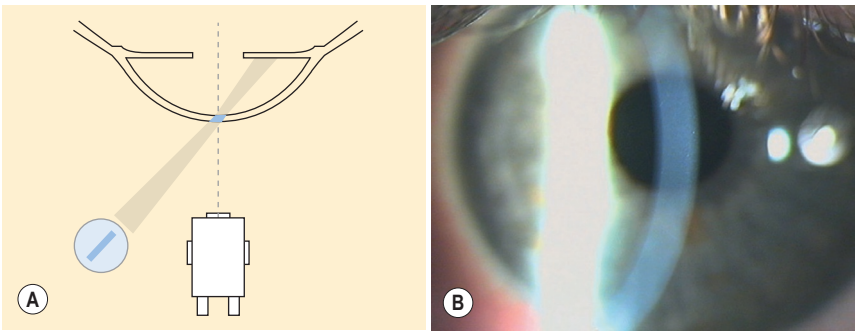


Fig. 1.8 **(A)** Direct parallelepiped illumination technique. **(B)** Direct parallelepiped view of the cornea. (A, Adapted from Jones LW, Jones DA. Slit lamp biomicroscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford: Butterworth-Heinemann; 2001: 1–49. B, Courtesy Adrian Bruce. In: Efron N, editor. Contact Lens Practice. 2nd ed. Oxford, UK: Butterworth-Heinemann; 2010.)

the cornea, but the same amount of light is spread over a greater depth of cornea, and this reduces brightness and contrast and makes the deeper corneal layers, in particular, more difficult to visualise. Because the light beam is so thin, the illumination must be turned up to maximum brightness.

Direct

The section of the cornea *within* the illuminated beam is being observed (Fig. 1.9). This provides the ability to accurately assess the depth of an object within the corneal layers. Typical uses include assessing the depth of a foreign body, locating a corneal scar and determining whether tissue within an area of staining is excavated, flat or raised.

Indirect

The section of the cornea *outside* the illuminated beam is being observed. This is achieved by directing gaze to either side of the illuminated optic section. To achieve this configuration, the optic section is positioned to one side of the feature of interest. Thus, the feature of interest is being illuminated by side-scattering of light from the optic section. Indirect focal illumination from an optic section is perhaps only a theoretical consideration; a superior indirect view of a corneal anomaly will be achieved using a wider beam (i.e. parallelepiped or broad beam).

Retroillumination

This refers to any technique in which light is reflected from the iris, anterior lens surface or retina and is used to back-illuminate a section of the cornea, which is more anteriorly positioned. The illumination and observation systems can be adjusted so that the feature of interest in the cornea is seen against a light background (e.g. light-coloured iris) or a dark background (e.g. dark-coloured iris, or the pupil in the case of indirect retroillumination).

This technique is particularly useful for examining neovascularization, scars, degenerations and dystrophies.

Direct

Direct retroillumination refers to the configuration whereby the retroillumination is directly behind the feature of interest in the cornea (Fig. 1.10). Thus, for example, a corneal scar is viewed against an illuminated iris in the background. With this technique, corneal opacities will appear black against the bright field.

Indirect

Indirect retroillumination refers to the configuration whereby the retroillumination is not directly behind the feature of interest in the cornea but is offset to one side (Fig. 1.11). Thus, the feature of interest is being observed by virtue of back-scattered light that is deflected away from the feature of interest in the cornea into the eye of the observer.

Marginal

Marginal retroillumination is a specific variant of indirect retroillumination whereby the pupil margin is deliberately chosen as the background retroilluminated field against which the corneal feature is being observed (Fig. 1.11). Simply put, the corneal feature of interest is viewed against a background of the illuminated iris–pupil margin. This technique is typically used in association with high levels of magnification and is used to assess the optical characteristics of transparent optical bodies in the tear film of the cornea, such as mucin balls, and epithelial microcysts, vacuoles and bullae.

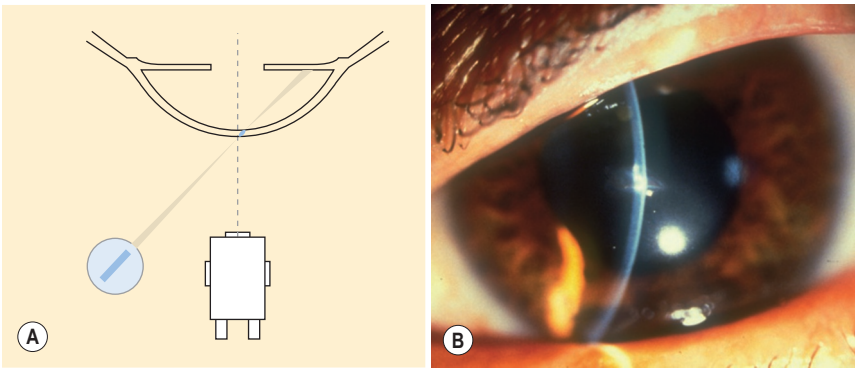


Fig. 1.9 **(A)** Direct optic section illumination technique. **(B)** Direct optic section view of the cornea. (A, Adapted from Jones LW, Jones DA. Slit lamp biomicroscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford, UK: Butterworth-Heinemann; 2001: 1–49. B, Courtesy Adrian Bruce. In: Efron N, editor. Contact Lens Practice. 2nd ed. Oxford, UK: Butterworth-Heinemann; 2010.)

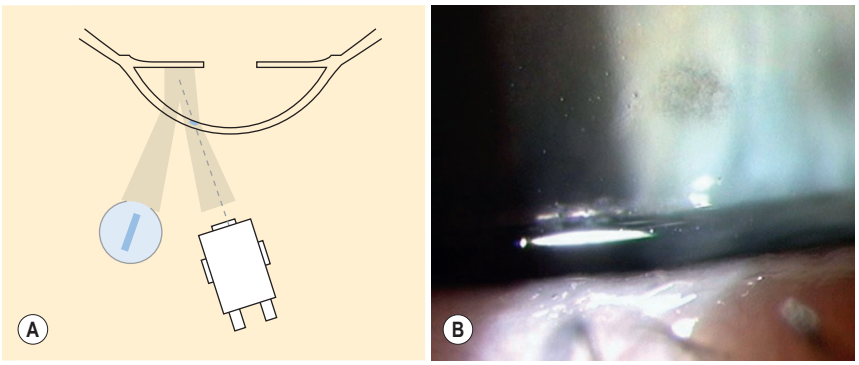


Fig. 1.10 **(A)** Direct retroillumination technique. **(B)** Corneal scar from a healed peripheral ulcer seen as a dull grey shadow in direct retroillumination. (A, Adapted from Jones LW, Jones DA. Slit lamp biomicroscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford, UK: Butterworth-Heinemann; 2001: 1–49. B, Courtesy Brian Tompkins.)

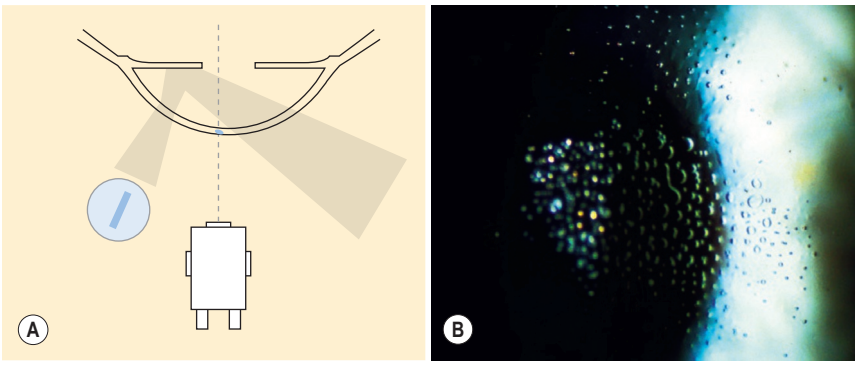


Fig. 1.11 **(A)** Indirect and marginal retroillumination technique. **(B)** Dimple veiling viewed by indirect retroillumination can be appreciated by observing the 'dimples' against both the dark pupil on the left and the illuminated iris in the right. Dimple veiling viewed by marginal retroillumination can be appreciated by observing the 'dimples' against the pupil margin; the dimples in this region clearly display unreversed illumination, indicating that they contain a material of lower refractive index than the epithelium (i.e. fluid or air). (A, Adapted from Jones LW, Jones DA. Slit lamp biomicroscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford, UK: Butterworth-Heinemann; 2001: 1–49. B, Courtesy Sylvie Sulaiman, Bausch & Lomb Slide Collection.)

Specular reflection

This is a specific case of a parallelepiped setup, where the angle of the incident slit beam is equal to the angle of the observation axis through one of the oculars (Fig. 1.12). At this angle (typically 40°–50°), the illumination beam is reflected from the smooth surfaces of the cornea and provides a mirror-like ('specular') reflection. Such specular images occur at every interface between structures of different refractive indices, the most prominent of which will be anterior epithelial or posterior endothelial surfaces. The technique of specular reflection is typically used to view the endothelium.

To begin with, the lowest magnification setting is selected, and the illumination arm is set at an angle to the normal that is greater than the angle of the observation system to the normal. The illumination arm is then brought back towards the observation system while observing the corneal surface. At the point where specular reflection is achieved, a bright reflex will fill one of the oculars (specular reflection cannot be achieved binocularly). The illumination/observation system should now remain in a fixed position, and the magnification is set to maximum so that the anterior and/or posterior corneal surface can be viewed in specular reflection. A very bright reflection from the anterior

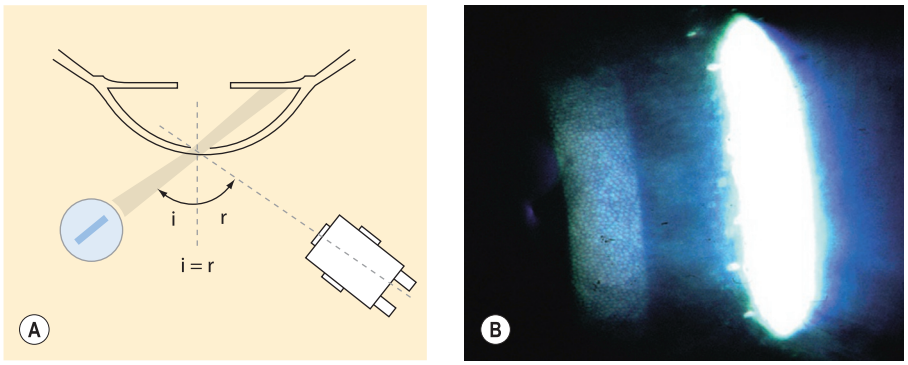


Fig. 1.12 **(A)** Specular reflection illumination technique. i angle of incidence; r angle of reflection. **(B)** Specular reflection view of the corneal endothelium. (A, Adapted from Jones LW, Jones DA. Slit lamp biomicroscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford, UK: Butterworth-Heinemann; 2001: 1–49. B, Courtesy Adrian Bruce. In: Efron N, editor. Contact Lens Practice. 2nd ed. Oxford, UK: Butterworth-Heinemann; 2010.)

surface constitutes a debilitating distraction when trying to observe the endothelium; this situation can be resolved by increasing the angle between the observation and illumination systems, although there is not much room for manoeuvre before the specular reflection is lost.

The size of endothelial cells is such that, even at ×40 magnification, only gross anomalies of the endothelium, such as large guttae, blebs, bedewing, ruptures and deep folds, can be detected. Subtle cellular characteristics of the endothelial mosaic, such as cell density or polymegethism, cannot be assessed. The tear film lipid layer, inferior tear meniscus and anterior surface of the crystalline lens can also be readily examined using specular reflection. If a contact lens is being worn, front surface wetting can be assessed and the post-lens tear film may be observed using specular reflection.[4]

Sclerotic scatter

This technique is used to investigate subtle changes in corneal clarity, such as central corneal oedema, occurring over a large area. The slit lamp is set up for a wide-angle parallelepiped (45°–60°) and the viewing system is focused centrally. The beam is manually offset ('uncoupled') and focused on the limbus. The slit beam is totally internally reflected across the cornea, and a bright limbal glow is seen around the entire cornea (Fig. 1.13). Any specific area of abnormality, such as a corneal scar, will interrupt the beam in its passage and produce a light reflection in the otherwise clear cornea; abnormalities in the cornea are especially visible when viewed against a dark pupil in the background.

Tangential (oblique) illumination

This is infrequently used in contact lens practice but is, nonetheless, a useful technique. Oblique illumination is achieved by setting up a parallelepiped and then moving the illumination system away from the observation system until the angle between them is close to 90°. The observation system is positioned at 90° to the facial plane (i.e. straight ahead) and the illumination arm is adjusted until the light beam is almost tangential to the object of interest. Any raised areas cast a shadow, making this technique particularly useful for viewing subtle irregularities on the surface of the iris, epithelium or contact lens in situ.

Conical beam

This technique is used specifically for examining the contents of the anterior chamber. A conical beam configuration is achieved by narrowing the slit beam down to about 1 to 2 mm in diameter and reducing the height of the beam to about the same dimensions. This will effectively create a circular beam of light. The illumination should be set to maximum and the room should be darkened. The arrangement of the illumination and observation system is essentially the same as for tangential illumination. The observation system is positioned at 90° to the facial plane (i.e. straight ahead) and the illumination system is moved away from the observation system until the angle between them is close to 90°. Low to medium magnification should be used.

Static

The conical beam is projected sideways into the anterior chamber and left in a fixed position. Light from the conical beam must not strike the iris because this will scatter light and make observation more difficult. Gaze is directed towards the black pupil. Any protein, debris or cellular matter floating in the aqueous will reflect light towards the observer and be detected as a glint of light (flare) against the black background of the pupil. Numerous particles will result in a glistening effect as various particles slowly move and change orientation in the aqueous.

Oscillating

The positioning of the observation and illumination systems is exactly the same as for static conical beam examination, except that the observer must rapidly oscillate the illumination arm from side to side using the offset control. This oscillation technique will increase the probability of detecting aqueous flare and glistening.

SLIT LAMP EXAMINATION PROCEDURE

No single slit lamp procedure will satisfy all observational requirements when examining a contact lens patient. However, during an examination where no abnormalities are expected to be detected (e.g. an initial assessment of a prospective contact lens wearer), it is useful to develop a systematic procedure that ensures coverage of all aspects of the assessment in a logical and consistent manner. Usually, the examination will start with low magnification and diffuse illumination for general observation, with the magnification increasing and more specific illumination techniques being employed to view structures in more detail as the examination progresses. A typical routine examination procedure using the slit lamp biomicroscope is outlined here.

Overall view

The examination should begin with a number of sweeps across the ocular surface and adnexa, whilst using a broad diffused beam and low magnification. The patient is first instructed to close his or her eyes, and the skin on the eyelids, eyebrows and surrounding areas is examined. The patient is then requested to

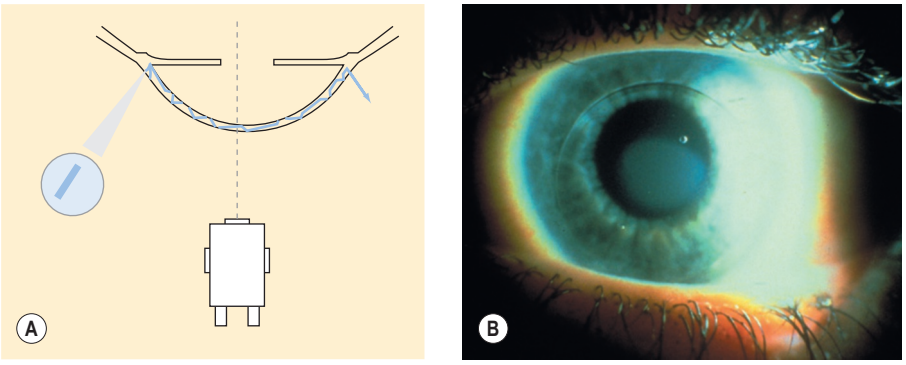


Fig. 1.13 **(A)** Sclerotic scatter illumination technique. **(B)** Central corneal oedema viewed using sclerotic scatter. (A, Adapted from Jones LW, Jones DA. Slit lamp biomicroscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford, UK: Butterworth-Heinemann; 2001: 1–49. B, Courtesy Michael Hare.)

open his or her eyes and lid margins and lashes are examined for signs of marginal blepharitis or hordeolum. The patency of the meibomian glands is assessed by gently squeezing the lids. The bulbar conjunctiva is then assessed for redness and for the presence of any abnormalities, such as pinguecula or pterygia. The superior and inferior palpebral conjunctivae are examined to check for redness, follicles and papillae. The position and action of the eyes and eyelids are noted, and the completeness of blinks can be assessed.

Cornea and limbus

The diffusing filter is removed, and the corneal examination begins by uncoupling the slit lamp illumination and observation systems and examining the cornea for signs of localised opacification using the sclerotic scatter illumination technique. The slit lamp is then recoupled and a series of observation sweeps is carried out across the cornea, using medium magnification and a broad beam (2 mm wide). The limbal vasculature is examined to assess the degree of physiological corneal vascularization (blood vessels overlaying clear cornea) and differentiating this from neovascularization (new blood vessels growing into clear cornea). Blood vessels at the limbus are best observed by using both direct illumination and indirect retroillumination. Once the limbus has been assessed, the cornea is examined with a parallelepiped to look for any abnormalities. During this procedure, a number of illumination techniques can be used simultaneously. If a corneal anomaly is detected, the beam should be narrowed to form an optic section so that the depth and fine structure of the anomaly can be determined. The endothelium should be viewed in specular reflection.

Staining examination

Irregularities of the ocular surface can be assessed by using a variety of staining agents, with fluorescein being the most readily accessible and widely used product. Fluorescein is instilled into the eye and a cobalt blue filter is interposed into the illumination system. A Kodak Wratten #12 (yellow) barrier filter should also be interposed in the observation system, if available. Gross epithelial surface irregularities can be detected by using diffuse illumination and low magnification. However, more subtle anomalies can only be detected by using medium to high magnification, employing a parallelepiped and oscillating between direct and indirect observation as the beam is swept slowly across the cornea. The illumination often needs to be set to a higher level of brightness to compensate for the loss of light through the excitation and barrier filters; however, if the illumination is too bright, the fluorescence tends to be 'flooded out', resulting in reduced contrast. Observation in white light, with or without the barrier filter, will provide an alternative view of the corneal anomaly under observation.

Various features of the tear film can be assessed with the aid of fluorescein, such as lower tear meniscus height, degree of 'sluggishness' of the tear film upon blinking and tear break-up time.

Numerous other vital stains can be applied to the eye to highlight other anomalies such as mucus accumulation, tissue devitalization and tissue necrosis. These are discussed in detail in Chapter 11.

Lid eversion

The final stage of the slit lamp examination is lid eversion, which enables examination of the palpebral conjunctiva. This procedure is performed last for the following reasons:

- The procedure is slightly uncomfortable for the patient – no matter how carefully performed – and the patient may not wish to be subjected to any further ocular examination or eye manipulation thereafter.
- The procedure may slightly traumatise the cornea – again no matter how carefully performed – confounding interpretation of any corneal anomalies observed after lid eversion.
- Since the procedure is being performed after fluorescein instillation, there is an opportunity to examine the tarsal conjunctiva both in white light and in cobalt blue light with a barrier filter. The latter procedure enhances the appearance of any papillae.

The procedure is conducted as follows: The illumination/observation system is pulled away from the patient and set in readiness for observing the tarsal conjunctiva. The best initial arrangement is low magnification and diffuse white light. Lid eversion can be performed with the head of the patient resting back against the head-rest of the consulting room chair. Alternatively, the head of the patient can be positioned in the head-and-brow rest of the slit lamp biomicroscope.

The lid is everted (Fig. 1.14) by applying light pressure beneath the brow and grabbing and lightly pulling the eyelashes of the upper lid outwards and upwards so as to evert the lid. The thumb or forefinger is then used to lightly hold the lashes of the everted lid against the upper orbital rim. To fully reveal the tarsal conjunctiva, gently pull back the eyelashes at the nasal aspect of the lid margin with a finger of the other hand. A diffuse beam is directed to the tarsal conjunctiva, which is observed at low and then medium magnification. Fluorescein is instilled if it has not already been added to the eye as part of the preceding examination, and excitation and barrier filters are interposed in the illumination and observation systems, respectively. The tarsal conjunctiva is re-examined, employing broad sweeps from side to side when using medium magnification.

When the examination has been completed, the eyelashes are pulled outwards and the lid will naturally revert to its normal anatomical configuration. Because of the unavoidable discomfort to the patient, the whole procedure of lid eversion should not last longer than about 15 seconds.

DIGITAL IMAGE CAPTURE

Digital imaging is a ubiquitous part of modern life, as anyone with a mobile phone will know. This technology is mirrored in ophthalmic consulting rooms.

'Digital imaging' refers to the electronic form of capturing and displaying pictures by using a combination of computer and camera. In contact lens practice, digital imaging is most often used to document contact lens fittings and ocular pathology. As with all forms of technology, cameras and computer systems are constantly improving in quality and resolution, and such systems are becoming more cost effective and user friendly.

In the 20th century, photographic or digital image capture was used by contact lens practitioners primarily for the purposes of publications, presentations and for teaching purposes; however, as a result of significant technological advances over the past two decades, digital image capture has become easier and cost-effective, and it is being used increasingly for routine electronic medical record keeping and to assist in real-time patient education. In addition, digital image capture is valuable in referrals and in documentation in cases of potential legal action.

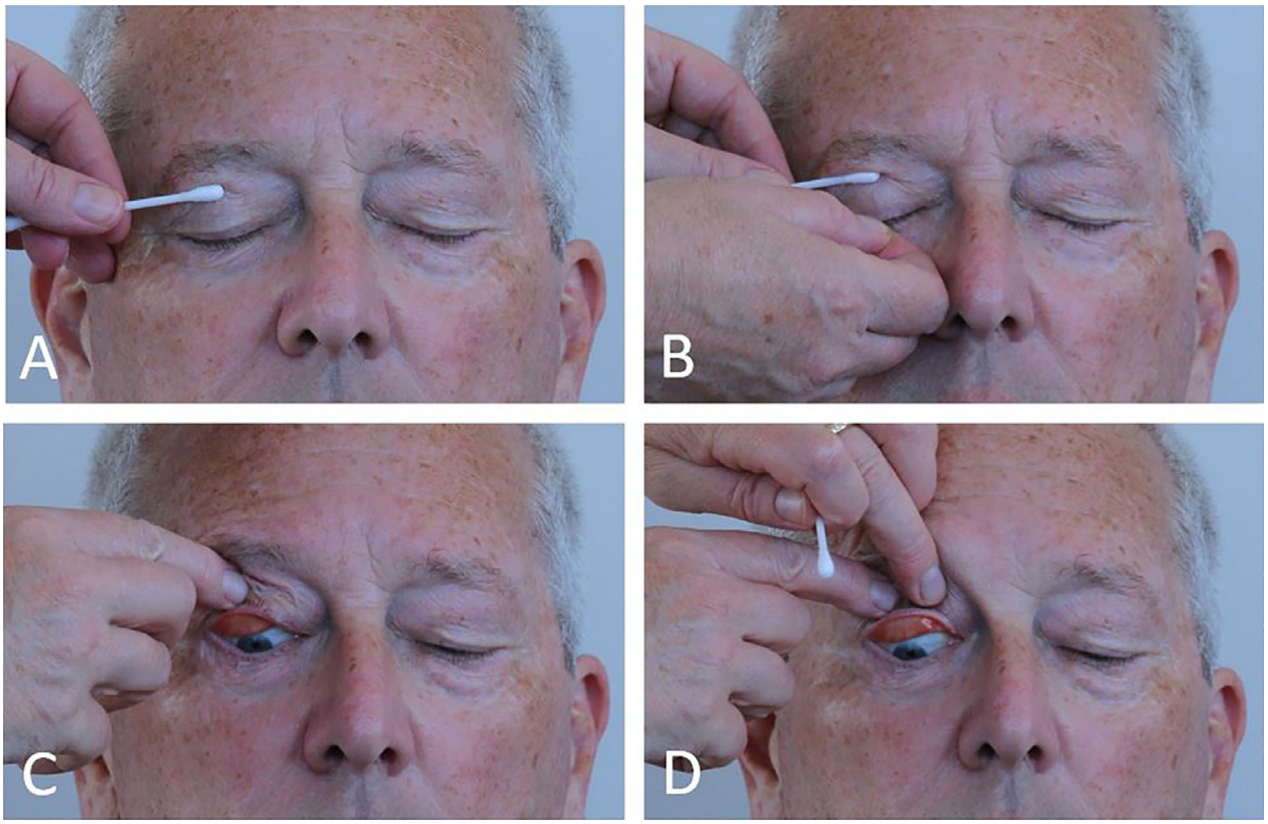


Fig. 1.14 Lid eversion technique. **(A)** With the patient looking down, place the end of a cotton tip applicator in the centre of the upper lid fold. **(B)** Grab the eyelashes of the upper lid with the other hand. **(C)** Gently pull the eyelashes slightly outwards and upwards until the upper lid everts over the cotton tip applicator, and then remove the applicator. **(D)** To fully reveal the tarsal conjunctiva, gently pull back the eyelashes at the nasal aspect of the lid margin with a finger of the other hand. When finished, gently pull the eyelashes of the upper lid outwards and downwards until the lid flips back to its normal position.

Principles of digital imaging

The basic principle of digital imaging is that a light-sensitive silicon computer chip, known as a 'charge-coupled device' (CCD), serves as the light-sensitive element in video and digital cameras. The image can be instantly displayed on the back of the camera and/or a computer screen, viewed by the practitioner and patient and then stored or printed.

A digital image may be characterised in three main ways:

- *Image resolution* refers to the image dimensions (width × height) in units of the number of dots (pixels); examples include 640 × 480 (0.3 megapixels) or 3264 × 2448 (8 megapixels).
- *Colour depth* is the number of colours that may be specified for each pixel. For true colour, this should be in the thousands or millions.
- *File format* describes the way an image is saved on a disk and affects its compatibility with different programs for viewing, e-mailing and so on. The Internet standard image file format is JPEG (JPEG is an acronym for the Joint Photographic Experts Group, which created the standard) and carries the benefit of small file size, high definition and broad compatibility with Internet e-mail and browser software.

Benefits of digital imaging for contact lens practice

There are numerous features and benefits with digital imaging. These include the following:

- Instant imaging – digital imaging is instantaneous, so any error in image focus, illumination, exposure, composition and so on can be identified and corrected immediately.
- Patient education –the patient has the benefit of immediately seeing his or her own condition.
- Image manipulation and quantification – after an image is captured, the brightness, contrast or colour can be enhanced. Furthermore, image parameters can be quantified by the computer (e.g. blood vessel length, scar dimensions and cup/disc ratio). However, care must be taken not to alter an image that may be used as legal evidence, so it is important to save the original image. Basic image editing capabilities are often incorporated into image storage software packages, but more sophisticated image editing software is available 'off-the-shelf'.
- Video movies – dynamic conditions, such as contact lens fittings or certain dynamic forms of pathology evaluation, can be captured as a short movie on the computer. For example, a movie enables recording of the intricacies of lid interactions and the effects of lens centration on fluorescein patterns. Lens performance is much easier to understand and interpret when a moving (vs. static) image is presented. Most modern digital cameras also have movie capture capabilities.

Once the digital image has been captured in an electronic format, the following possibilities are opened up:

- Paperless office – many contact lens practices are using electronic medical records for patient visits. Digital imaging is a logical adjunct to electronic records. With Cloud-based servers and other Internet-based file sharing facilities, patient records can be accessed at more than one office location.

- Minimal image costs – once a digital imaging system is set up, an image can be captured instantly and at no additional cost. With modern computers having terabyte (TB) hard disk capacity, many thousands of images may be easily stored and retrieved.
- Image transfer – e-mail is now the standard mode of communication amongst clinicians, and large-size image files can be sent as an e-mail attachment.
- Presentations – images can be transferred to computer presentation programs, which are used for training and for delivering lectures. Still and movie digital image files can easily be dropped into PowerPoint and Keynote presentation programs.

Commercial digital imaging systems

Many commercially produced digital imaging systems are available as 'ready-to-use' integrated packages, sold by ophthalmic equipment suppliers (Fig. 1.15). Such packages typically consist of a slit lamp biomicroscope with video camera, or digital still camera, beam splitter and a personal computer with database and image manipulation software. Commercial systems that can be adapted to the practitioner's existing slit lamp are also available.

Tearscope

The Tearscope-plus (Keeler, Windsor, UK) can be used to observe certain characteristics of the tear film non-invasively (Fig. 1.16A).[5] This instrument takes the form of a small, white dome with a central sight hole, surrounded by a cold cathode light source. It can be held directly in front of the eye or used in conjunction with a slit lamp biomicroscope to gain more magnification (Fig. 1.16B). The thickness distribution, quality and freedom of movement of the tears can be assessed by observing the reflected light from the featureless white dome, and the integrity of the aqueous and lipid phases can be inferred from colour fringe interference patterns. Interpretation of the appearance of various reflective patterns in the tear film is outlined in Appendix B.



Fig. 1.15 Haag-StreitBD-900 video slit lamp, with a compact off-the-shelf imaging system. There is an Apple Mac Mini running BTVPro software, interfaced to a Canopus ADVC-90 for video conversion, HP compact photo printer and flat panel LCD display.



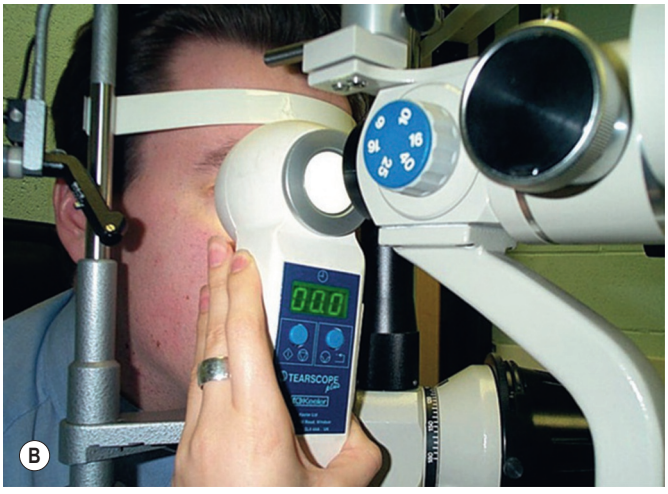


Fig. 1.16 **(A)** The Tearscope-plus. **(B)** Examining the eye with the Tearscope-plus in conjunction with a slit lamp biomicroscope to obtain higher magnification. (Courtesy Lyndon Jones.)

Specular microscope

The specular microscope allows viewing of objects through an observation system that is coaligned with an illumination source. Light passes from inside the microscope out through the objective lens to arrive at a focus near the focal plane of the lens. If this position coincides with a reflecting surface, then the focused light is reflected back through the objective lens and is viewed through the eyepiece of the microscope. The first specular microscopes used for ophthalmic research were utilised



Fig. 1.17 The Topcon SP-1P Specular Microscope. (Courtesy Topcon Corporation.)

by David Maurice in the 1960s in his work investigating corneal function. This technique made it possible to obtain high-magnification images of both the epithelium and the endothelium; this had previously been difficult because of the transparency of these structures.

In the early versions of the specular microscope, a contact dipping cone objective lens that was optically coupled to the cornea was used to provide higher magnification and resolution; however, most modern clinical specular microscopes can achieve equally high magnification without the need for ocular contact (Fig. 1.17).

These instruments are primarily used to view and photograph the corneal endothelium and to monitor its morphology. By direct viewing with the specular microscope, an overall impression of the condition of the endothelium can be established immediately. In addition, some of these instruments allow determination of corneal thickness by measuring the distance between the epithelium and the endothelium.

Typically, the features looked for are the regularity of the endothelial mosaic, the size of the individual cells, the presence of intra-cellular vacuoles and abnormal features, such as corneal guttae and keratic precipitates. From the images obtained, such factors as the number of cells per unit area, cell shape and cell area can be calculated, enabling the clinician to assess the endothelial appearance compared with that expected of normal age-matched individuals. Instruments that capture and automatically analyse the corneal endothelium are considered in more detail in Chapter 31.

Corneal confocal microscopy

A fundamental limitation of the slit lamp biomicroscope is that the highest practicable magnification possible is around ×40, with a lateral resolution of 30 μm. In certain circumstances, this places a considerable constraint upon clinical decision-making. For example, it is not possible to identify the precise nature of infiltrates in a case of keratitis. Corneal confocal microscopy became commercially available around the turn of the 21st century.[6] This technique offers clinicians the opportunity to examine the living human cornea at a magnification of around ×500 to ×700. Corneal confocal microscopy therefore enables examination of tissue structures at a cellular level, and in relation to the example given above, extraneous matter, such as infectious agents, can be identified.

This instrument is commonly referred to as a 'corneal confocal microscope' to distinguish it from a laboratory confocal microscope, which is used to examine tissue samples in vitro. However, when operated using a laser light source, the corneal confocal microscope is also capable of imaging the conjunctiva in vivo.[7] In the following sections, this ophthalmic instrument shall simply be referred to as a confocal microscope, and discussion will concentrate on imaging the cornea.

PRINCIPLE OF OPERATION

In broad terms, the optical principle of the confocal microscope is that field of view is sacrificed for resolution. In the slit lamp biomicroscope, a broad beam of light is used to view a large section of the cornea at relatively low magnification. This arrangement offers a large field of view, but resolution is limited. With the confocal microscope, a small spot of light is projected into the cornea, and the small illuminated region of corneal tissue is imaged via a confocal optical arrangement. This results in a very high resolution but virtually no field of view; the confocal microscope creates a useable field of view by instantaneously illuminating a small region of the cornea with thousands of tiny spots of light each second, with each spot of light being synchronously imaged. The spot images are reconstructed to create a usable field of view offering high resolution and magnification. A similar result can be achieved by using a scanning slit beam of light.

In the confocal microscope, therefore, a small flat field of the cornea is both optically illuminated from a point (or slit) light source and simultaneously imaged by a point (or slit) detector; that is, they are in the same focal plane, or 'confocal'.[8] Any adjacent features in the tissue outside the plane of interest are attenuated. This results in an image of good contrast with high levels of lateral and axial resolution (Fig. 1.18).

The high axial (or depth) resolution is responsible for the confocal microscope being described as an instrument that is capable of 'optically sectioning' the cornea. That is, as the instrument is focused in and out of the cornea, a section of about only 4 to 10 μm thickness is observed at any one time. This sectioning capability is essential because structures of interest to be viewed in the cornea at a cellular level, such as epithelial cells, stromal keratocytes, corneal nerves and endothelial cells, scatter or reflect light weakly. Optical sectioning allows these structures to be viewed in good contrast against a dark background. The 'sections' being viewed are en face, or 'front on', which means that only one layer of corneal tissue is observed in any given image.

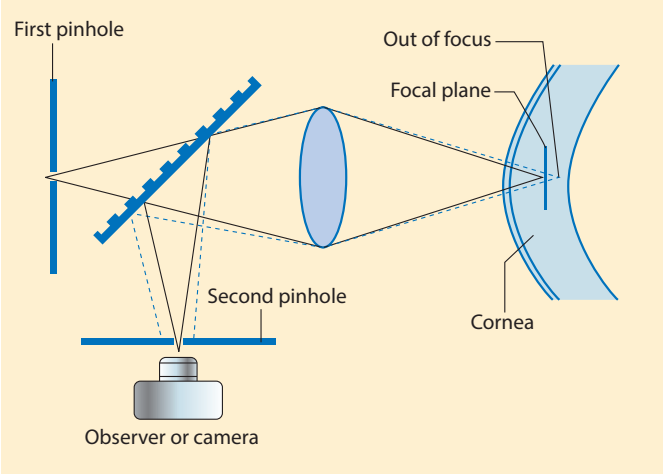


Fig. 1.18 Diagrammatic representation of the optical principles of confocal microscopy. White or laser light that passes through the first pinhole is focused on the focal plane in the cornea by the condensing lens. Returning light is diverted through the objective lens and a conjugate exit pinhole and reaches the observer or camera. Scattered out-of-focus light from below or above the focal plane (broken lines) is greatly limited by the pinholes and does not reach the observation system. (After Jalbert I, Stapleton F, Papas E, et al. In vivo confocal microscopy of the human cornea. Br J Ophthalmol 2003;87:225–36.)



Fig. 1.19 The Nidek ConfoScan 4. (Courtesy Nidek Co., Ltd. http://www.nidek.com)

CURRENT INSTRUMENTS

Slit-scanning confocal microscope

A slit-scanning confocal microscope operates by scanning the image of a slit over the back focal plane of the microscope objective. The slit width can be varied to optimise the balance of optical section thickness and image brightness. A double-sided mirror is used for scanning and descanning and a halogen lamp is used for illuminating the slit. The detector is a CCD camera. The instrument employs a non-applanating, high-numerical aperture, water immersion microscope objective, which does not touch the cornea. A methylcellulose gel is used to optically couple the tip of the microscope objective to the cornea. The high numerical aperture of the objective lens is very efficient in collecting the light from weakly reflecting corneal structures. This allows all of the epithelial layers (superficial, wing and basal cells) to be distinguished.

The only commercially available slit-scanning confocal microscope available at the time of this writing is the ConfoScan 4 (NIDEK Co., Ltd., Aichi, Japan) (Fig. 1.19). This fourth-generation instrument images corneal structures at ×500 magnification and has a field of view of 460 × 345 μm when used with a ×40 objective lens that has a numerical aperture of 0.75. It uses a 100 W/12 volts (V) halogen lamp as its illumination source and therefore produces non-coherent 'white' light consisting of a range of wavelengths. Ultraviolet and infrared filters are built into the optical path to protect the eye of the patient from these potentially harmful wavelengths. Images are acquired at a rate of 25 frames per second. Because of the relatively weak illuminating light source, subjects may be examined continuously for up to 30 minutes without inducing an afterimage.

Laser-scanning confocal microscope

A laser-scanning confocal microscope operates by scanning a laser beam spot of less than 1 μm in diameter sequentially over each point of the examined area. To scan the image, the laser beam spot must be deflected in two perpendicular directions. This is achieved by using two scanning mirrors: A resonant scanner deflects the beam horizontally to produce a scan line and a galvanometric scanner deflects this scan line vertically, producing a scan field. Descanning of reflected light is performed by the same two scanning mirrors. The reflected light is deflected to a detector, which is an avalanche photo diode (a point-like detector). The signal of the photo diode is digitised to form the image.

The only commercially available laser-scanning confocal microscope available at the time of this writing is the Heidelberg Retina Tomograph 3 with Rostock Corneal Module (Heidelberg Engineering, GmBH, Dossenheim, Germany) (Fig. 1.20). This first-generation instrument images corneal structures at ×400 magnification and has a field of view of 400 × 400 μm when used with a ×63 objective lens that has a numerical aperture of 0.9. It uses a 670-nm red-wavelength, helium-neon diode laser as its illumination source. This is a class 1 laser system and therefore does not pose any ocular safety hazard; however, the manufacturer recommends a maximum period of exposure of 45 minutes in a single examination period.

PATIENT EXAMINATION

The slit-scanning and laser-scanning confocal microscopes differ in terms of both the way in which they contact the eye and the modes of data acquisition. These instruments are generally housed in a dedicated clinical examination room, and the lights are dimmed before the microscopy procedure. The patient is seated behind the instrument, and one drop of anaesthetic (benoxinate hydrochloride 0.4%) is instilled into the eye to be examined. It has been shown that the use of anaesthetic does not appreciably alter the view of the tissue structures with these instruments.[9] The head of the patient is placed in the head-and-chin rest, and the overall height of the instrument table is



Fig. 1.20 The Heidelberg Retina Tomograph 3 with Rostock Corneal Module. (Courtesy Heidelberg Engineering, GmBH, Dossenheim, Germany).

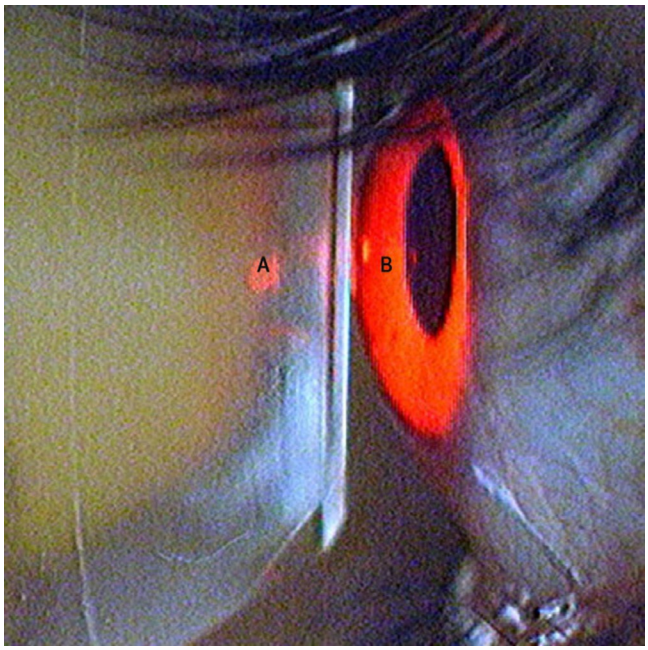


Fig. 1.21 **(A)** View captured from a side-mounted charge-coupled device camera of a Heidelberg laser scanning confocal microscope, showing the plano face of the Perspex Tomocap. **(B)** Gently contacting the cornea.

adjusted for comfort. The patient is instructed to gaze at a fixation target with the eye that is not being examined.

Slit-scanning confocal microscope

To minimise the possibility of cross-contamination between patients, the objective lens is disinfected with isopropyl alcohol before each use. A large drop of viscoelastic gel is applied to the end of the objective lens. The objective lens is brought forward until the gel comes into contact with the anaesthetised cornea (the objective lens never touches the cornea). The gel serves to optically couple the objective lens of the microscope to the cornea. As soon as the gel contacts the cornea, the computer monitor displays real-time images. The examination room is arranged in such a way that the operator can see the objective lens on the cornea and the video monitor in the same field of view. An automatic scan is then made through the anterior-posterior axis of the cornea. For each scan, 350 images are acquired at a rate of 25 frames per second, over a period of 14 seconds.

Laser-scanning confocal microscope

The objective lens of the laser-scanning confocal microscope is housed within a sterile disposable Perspex cap, known as the 'Tomocap'. A drop of viscoelastic gel is placed on the tip of the objective lens before the TomoCap is mounted on top. The gel optically couples the objective lens to the Tomocap. The surface of the Tomocap is brought gently into contact with the cornea; this procedure is facilitated by a tangentially mounted CCD camera, which displays a magnified, real-time image of the cap contacting the cornea (Fig. 1.21).

Images are obtained by using one of three possible examination modes. Section mode enables manual acquisition and storage of a single image at a time. The cornea is scanned manually in the *x*-, *y*- and *z*-axes and image capture is achieved with the aid of a foot pedal. Volume mode allows automatic acquisition of up to 30 images, 2 µm apart, in the *z*-axis. A section of cornea 60 µm in depth can be scanned in this way. A series of 100 images can be acquired at a selected rate of between 1 and 30 frames per second in sequence mode. During image acquisition, the objective lens either may remain stationary or be manually scanned in the *x*-, *y*- and *z*-axes. The result is a movie that has a duration of between 3 and 100 seconds.

It is possible to adapt the laser-scanning confocal microscope so that it operates as a non-contact instrument.[10] This is achieved by inserting a non-contact Nikon lens (CF Plan EPI SLWD) into the Rostock Corneal Module. The lens has a magnification of ×50 and numerical aperture of 0.45. Since the instrument does not come into contact with the eye, the TomoCap does not need to be fixed to the front of the lens, and no corneal anaesthetic or viscoelastic gel is required. This approach may find general use for clinical examination of the tear film, stroma and endothelium; however, a critical caveat is that the depth of stromal images cannot be determined when using this technique. This instrument also facilitates image capture of oblique sections of multiple corneal layers. However, the inability to clearly and consistently image thin corneal sub-structures – such as the tear film, the sub-basal nerve plexus and the endothelium – is a key limitation of this approach.[10]

THE NORMAL CORNEA AS VIEWED WITH THE CONFOCAL MICROSCOPE

A number of qualitative and quantitative studies have been undertaken documenting the appearance of the normal cornea as viewed with the confocal microscope. The greater image brightness and contrast of the laser-scanning confocal microscope facilitates improved imaging of certain features of the cornea,[11] as can be seen from Figure 1.22, which compares images of various corneal sub-structures obtained by using the two instruments.

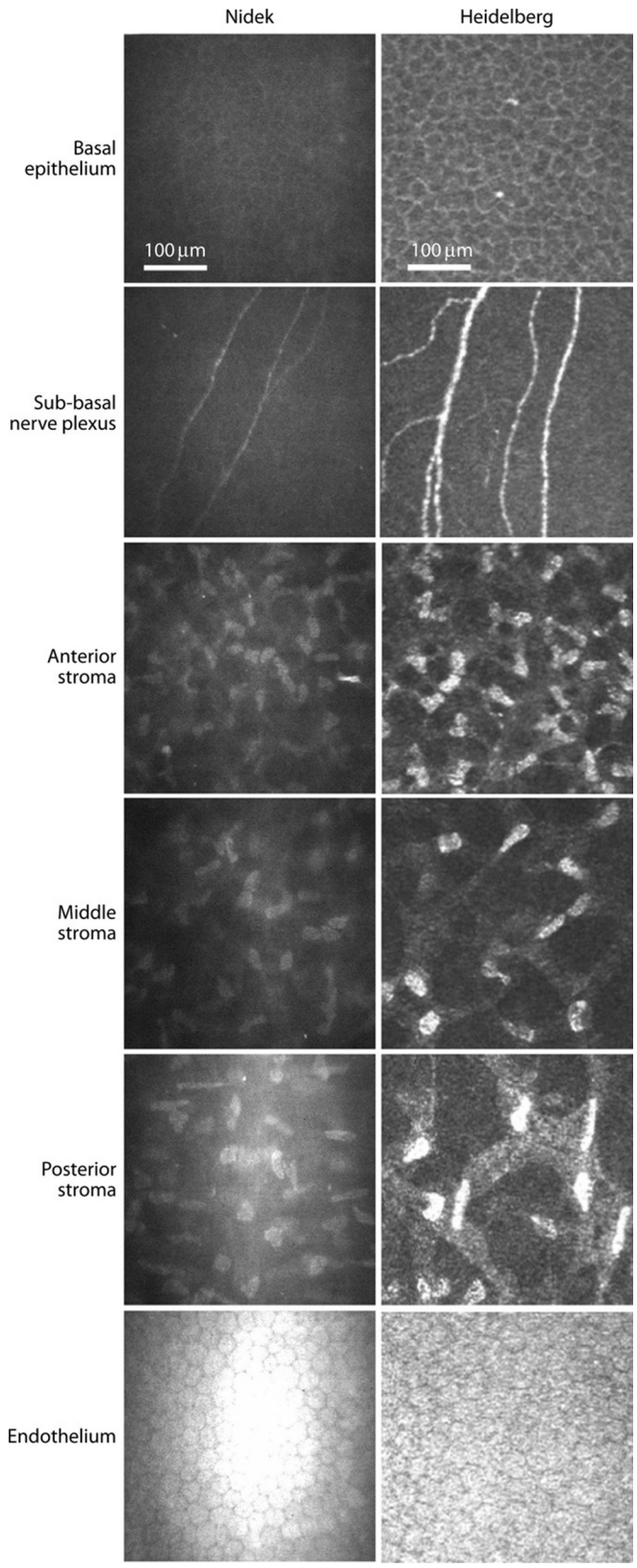


Fig. 1.22 Comparison of images of various corneal layers obtained with the Nidek (left column) and Heidelberg corneal confocal microscopes. Cellular and nerve features are seen in much higher contrast in images obtained using the Heidelberg instrument. (Courtesy Patel DV, McGhee CN. Contemporary in vivo confocal microscopy of the living human cornea using white light and laser scanning techniques: a major review. Clin Exp Ophthalmol 2007;35:71–88.)

Anterior segment optical coherence tomography

Optical coherence tomography (OCT) is capable of high-resolution, micrometer-scale, cross-sectional imaging of biological tissue.[12] This technology was originally developed to image retinal complications in which tissues have become separated or changed in structure. These include macular oedema, posterior vitreous detachment, macular holes, retinal detachment, retinoschisis and optic nerve head changes.[13]

The technique uses Michelson interferometry to compare a partially coherent reference beam to one reflected from tissue. The two beams are combined, and interference between the two light signals occurs only when their path lengths match to within the coherence length of light. The magnitude and distance within the tissue of the reflected or backscattered light at a single point are determined by using a mirror system to form a reflectivity profile (or an A-scan, analogous to ultrasonography)[14] A tomographic image, a B-scan, is generated by assembling multiple A-scans. The technique of two-dimensional (2D) OCT is thus analogous to B-mode ultrasound imaging, except that it uses light, rather than sound, and provides data on transparent ocular tissues for the computer analyser by using the differential reflectivity to coherent laser light. Reflections occur at boundaries between materials of differing refractive indices, and the greater the difference in index, the greater the amplitude of the reflected signal. The 2D-OCT scans are subsequently processed by a computer, which corrects for any axial eye movement artefacts that have occurred in the course of data acquisition. The B-scan represents a cross-sectional view of the structure under investigation, similar in appearance to a histological section.

Commercially available OCTs with anterior segment (AS) imaging capabilities are now commonplace. With resolutions between 2 and 20 µm, AS-OCT is increasingly being used to examine the cornea and has proven useful in determining epithelial and total corneal thickness changes after refractive surgery, assessing corneal central and average thickness in patients with ocular hypertension and glaucoma and in those with corneal oedema.[15] AS-OCT is also a useful tool to diagnose and document changes in corneal health. It can be used to monitor corneal infections, dystrophies, degenerations and in the assessment of glaucoma risk factors, such as central corneal thickness and narrow anterior chamber angles.[15]

Three types of OCTs are available for AS imaging: time-domain OCT (TD-OCT), spectral-domain OCT (SD-OCT) and swept-source OCT (SS-OCT). The differences in data acquisition and processing for these technologies will be briefly discussed.

TIME-DOMAIN OCT

In TD-OCT, a movable reference mirror is used to reflect the light source to generate a series of images. By taking a series of 2000 A-scans per second, a reflectivity profile is generated and the depth of ocular tissues is determined[16] One example of such a device is the Visante AS-OCT (Carl Zeiss Meditec, Inc., Dublin, Ohio, USA), which uses 1,310 nm light, allowing for deeper penetration into the tissues and facilitating greater cross-sectional visualisation and imaging of the anterior chamber, without occlusion of the angle by the scleral spur.

SPECTRAL-DOMAIN (FOURIER-DOMAIN) OCT

TD-OCT uses a moving reference mirror to reflect near-infrared light, whereas SD-OCT (also referred to as 'Fourier-domain' (FD-OCT)) uses a fixed reference mirror to reflect the light source. The interference between the ocular tissue and the reference reflections is detected by a spectrometer, which is Fourier transformed to generate an A-scan.[17] SD-OCTs use wavelengths of 820 to 879 nm, allowing improved axial resolution of images (5 μm compared with 17 μm).

However, the longer wavelength used in TD-OCTs allows deeper tissue penetration to better image AS structures.[17] As the production of A-scans are not dependent on a moving reference mirror, the speed of image acquisition with SD-OCTs is comparatively faster than TD-OCT, acquiring 25,000 to 50,000 A-scans per second.[16] An additional feature of SD-OCT is the production of a series of parallel B-scans from which three-dimensional (3D) images can be generated akin to 3D topography, which can then be rotated and otherwise manipulated.

Examples of SD-OCT devices include the 3D OCT-1000, OCT-2000 and Maestro (Topcon Medical Systems Inc., Oakland, California, USA), Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, Ohio, USA), iVue-100 (Optovue, Fremont, California, USA) and SPECTRALIS SD-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany).

SWEPT-SOURCE OCT

SD-OCT is one type of FD-OCT.[16] A second type of FD-OCT is SS-OCT, which uses a longer wavelength of 1,050 nm, permitting deeper penetration into tissues and allowing imaging with enhanced visualisation of the AS.

SS-OCT is the latest technology used in commercially available OCT instruments. This technology uses a tuneable laser that scans through a range of wavelengths of the light source to generate an interferogram. The interferogram is Fourier transformed to produce an A-scan, and several A-scans are assembled to form the cross-sectional B-scan. The scans are of high resolution, with photodetectors replacing CCD cameras to further increase resolution to 1 μm and overall scan acquisition time is faster than that of SD-OCT (up to 108,000 scans per second), which reduces any artefacts arising from eye movements.[16] For this reason, this instrumentation is also referred to as high-speed SS-OCT.

AS-OCT imaging modules also incorporate anterior and posterior corneal topography. Commercially available instruments currently include the Topcon DRI OCT Triton (Topcon Medical Systems Inc., Oakland, California, USA; Fig. 1.23) and the SS-1000 CASIA OCT (Tomey Corporation, Nagoya, Japan).

With regard to assessing the ocular complications of contact lens wear, OCT has proven useful in evaluating the tear meniscus (Fig. 1.24A),[18] tear film,[19] corneal epithelium[20] and corneal infiltrates[21] during contact lens wear, and contact lens/anterior eye fitting relationships (Fig. 1.24B).[22]

Corneal topographic analysis

The aim of corneal topography (or keratoscopy) is to accurately describe the shape of the corneal surface in all meridians. In most cases, the technique uses a similar principle to that of keratometry, in that it determines the size of the image of a target reflected in the corneal surface, the primary difference relating to the fact that for keratoscopy a series of circular concentric targets are used (a placido disc image). This arrangement allows both the central and peripheral curvatures to be determined. Historically, a photographic record of the corneal reflection images was made (photokeratoscopy) and measurements were calculated subsequently.



Fig. 1.23 Topcon DRI OCT Triton, swept-source optical coherence tomography (SS-OCT) equipment. (Courtesy Topcon Medical Systems, Inc).

Modern-generation topographers capture the image electronically on a computer and use sophisticated image-processing software to provide immediate analysis of the reflected image (videokeratoscopy). Using this technique, it has been clearly demonstrated that the cornea is aspheric and can best be described as a flattening ellipse, whose rate of flattening is asymmetrical about its centre.

Modern topographers can be categorised into two distinct forms: reflective devices and slit-scanning devices.

REFLECTIVE DEVICES

Reflective devices measure topography on the basis of the reflection of mires from the anterior surface tear film, which, of course, is essentially identical in shape to the corneal surface.

Qualitative assessment

The most basic reflective device for assessing corneal topography is the Placido disc, which is simply a series of concentric black and white rings on a flat circular disc with a central sight hole. The disc is positioned in front of the cornea and the reflections are observed. With use of this method, only gross irregularities in the corneal surface and very high astigmatism can be detected. Improved versions of the Placido disc include the internally illuminated Klein keratoscope,[23] the Loveridge grid[24] and the Tearscope-plus with corneal topography grid attachment (Fig. 1.25).[25]

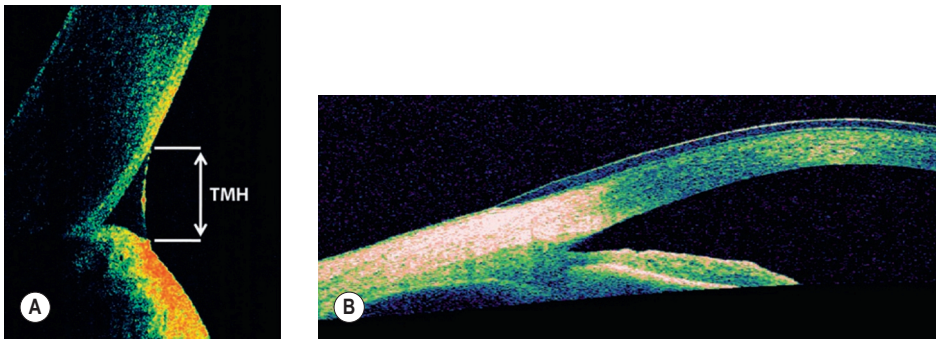


Fig. 1.24 Optical coherence tomography images. **(A)** The lower lid tear meniscus showing the tear meniscus height. TMH, tear meniscus height. **(B)** Soft lens aligning closely with the cornea. (A, Courtesy Lyndon Jones. B, Courtesy T. Hbner, British Contact Lens Association Slide Collection.)

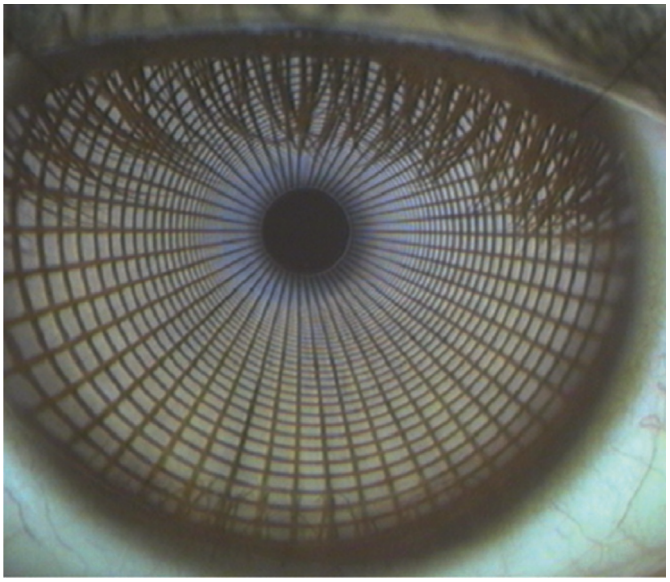


Fig. 1.25 Reflection of the non-invasive break-up time grid attachment of the Tearscope-plus (shown in Fig. 1.16) as seen in the pre-corneal tear film. The time taken from eye opening to distortion or break-up of the reflected grid pattern is recorded as the non-invasive break-up time. (Courtesy Lyndon Jones.)

Quantitative assessment

Quantitative reflective devices (Fig. 1.26) use the same basic principle of projecting a grid onto the cornea. The images are captured with a video camera, and a computational approach is adopted to analyse the data and derive a description for the corneal shape.

The images (or 'maps') produced by reflective or placido-based keratoscopes display the power distribution of the corneal surface using colour-coded displays, in which greens and yellows represent powers characteristic of those found in normal corneas, with blues or cooler colours represent flatter areas (low powers), and reds or hotter colours represent steep areas (high powers).[26] These maps permit recognition of the corneal shape through pattern recognition and swiftly reveal the presence of abnormal powers (Fig. 1.27).

All devices display simulated keratometry (SimK) values, which are analogous to standard keratometry values, and simultaneously display the power and axis of the flattest meridian.

A number of manufacturers now produce hand-held topographers (Fig. 1.28). These portable devices can prove very useful for examining children, older adults and those who are infirm, and for use in off-site consultations.



Fig. 1.26 The Atlas corneal topographer from Humphrey-Zeiss. This is an example of a topographer that uses a reflective technique to obtain topographic data. (Courtesy Lyndon Jones.)

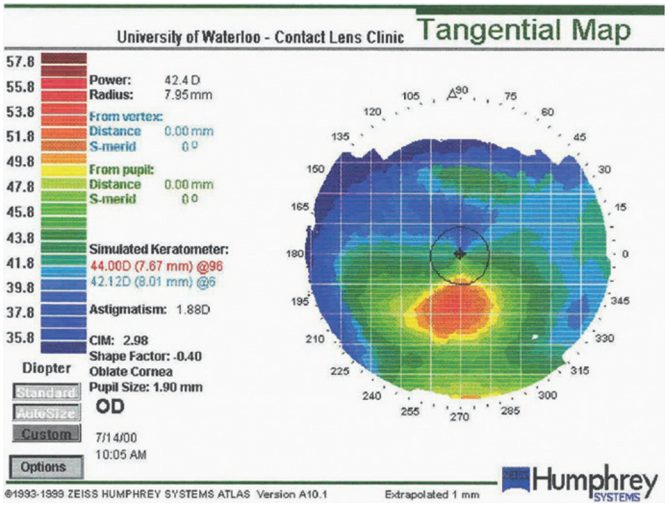


Fig. 1.27 Corneal topography map of a patient with keratoconus obtained from the Atlas corneal topographer. The steep, inferiorly positioned conus is clearly seen on this tangential map. (Courtesy Lyndon Jones.)

SLIT-SCANNING DEVICES

Orbscan

The Orbscan corneal topography system (Fig. 1.29) uses a scanning optical slit design that is fundamentally different from the



Fig. 1.28 The Marco KM-500 hand-held corneal topographer. (Courtesy Lyndon Jones.)

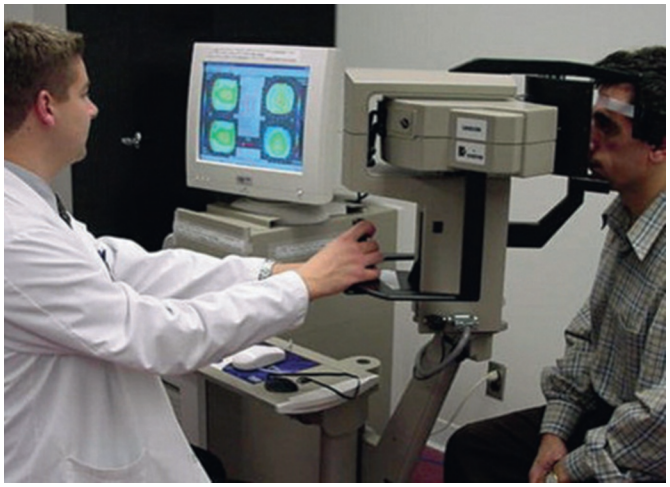


Fig. 1.29 The Orbscan corneal topographer from Bausch & Lomb. This device uses a combination of reflective and slit-scanning techniques to obtain topographic and thickness data of the cornea. (Courtesy Lyndon Jones.)

corneal topography that analyses the reflected images from the anterior corneal surface. The high-resolution video camera captures 40 light slits at a 45° angle. The software analyses 240 data points per slit and calculates corneal thickness and the posterior surface topography of the entire cornea. The topography of the anterior surface of the cornea is determined by using a combination of reflective corneal topography and optical slit-scanning data. The Orbscan generates colour-coded plots of anterior and posterior topography (Fig. 1.30).

Given that compared with the anterior surface, the posterior corneal surface contributes seven times less to the refractive power of the cornea, refractive abnormalities of the posterior surface are less significant than those of the anterior surface.

The accuracy and repeatability of the instrument are reported to be below 10 μm and, under optimal conditions, in the range of 4 μm in the central cornea to 7 μm in the peripheral cornea.[27] In clinical practice, repeatability is dependent on a range of factors, such as eye movements, the ability of patients to keep the eye wide open and optical clarity of the cornea. The other limitations of current optical slit technology are the inability to detect interfaces (e.g. after LASIK (laser-assisted in situ keratomileusis) flap) and the longer time of image acquisition and processing compared with standard placido-based topography.

Pentacam

The Pentacam (Oculus, Lynnwood, Washington, USA) uses a different method to image the cornea – Scheimpflug imaging. With this imaging paradigm, an oblique tangent can be drawn from the image, object and lens planes, and the point of intersection is the Scheimpflug intersection, where the image is in best focus. With a rotating Scheimpflug camera, the Pentacam can obtain 50 Scheimpflug images in less than 2 seconds. Each image has 500 true elevation points for a total of 25,000 true elevation points for the surface of the cornea.

The Pentacam actually has two cameras. One is for detection and measurement of the pupil, which helps with orientation and fixation. The second camera is used for visualization of the AS. The Pentacam is able to image the cornea such that it can determine anterior and posterior surface topography, including the curvature, tangential, and axial maps.

Advantages of the Pentacam include the following: (1) high resolution of the entire cornea; (2) ability to measure corneas with severe irregularities, such as keratoconus, that may not be amenable to placido imaging; and (3) ability to calculate pachometry from limbus to limbus. The Pentacam can also provide corneal wavefront analysis to detect higher-order aberrations.

Pachometry

Historically, the principal instrument used to measure corneal thickness is the pachometer, of which there are two major types, as described.

OPTICAL PACHOMETRY

Optical pachometry is based on the measurement of the apparent thickness of an optical section of the cornea, and its popularity is largely based on the commercial availability of a pachometer attachment for the Haag–Streit slit lamp. Firstly, a split image device is inserted into one eyepiece of the slit lamp. The method depends on the relative rotation of two glass plates, which are placed on top of each other. Rotation of the upper plate moves the upper half of the image of the cornea with respect to the fixed lower half. When the endothelium of the upper field is aligned with the epithelium of the lower field, the angle of rotation of the upper plate is read off an externally positioned scale. This measurement is proportional to the apparent thickness of the cornea, with true corneal thickness being determined by means of a conversion table. Because of the cumbersome methodology and subjectivity involved in image alignment, this technique is not often used today.

ULTRASONIC PACHOMETRY

With the rapid increase in interest in refractive surgery, it has become necessary for refractive surgeons to obtain rapid,

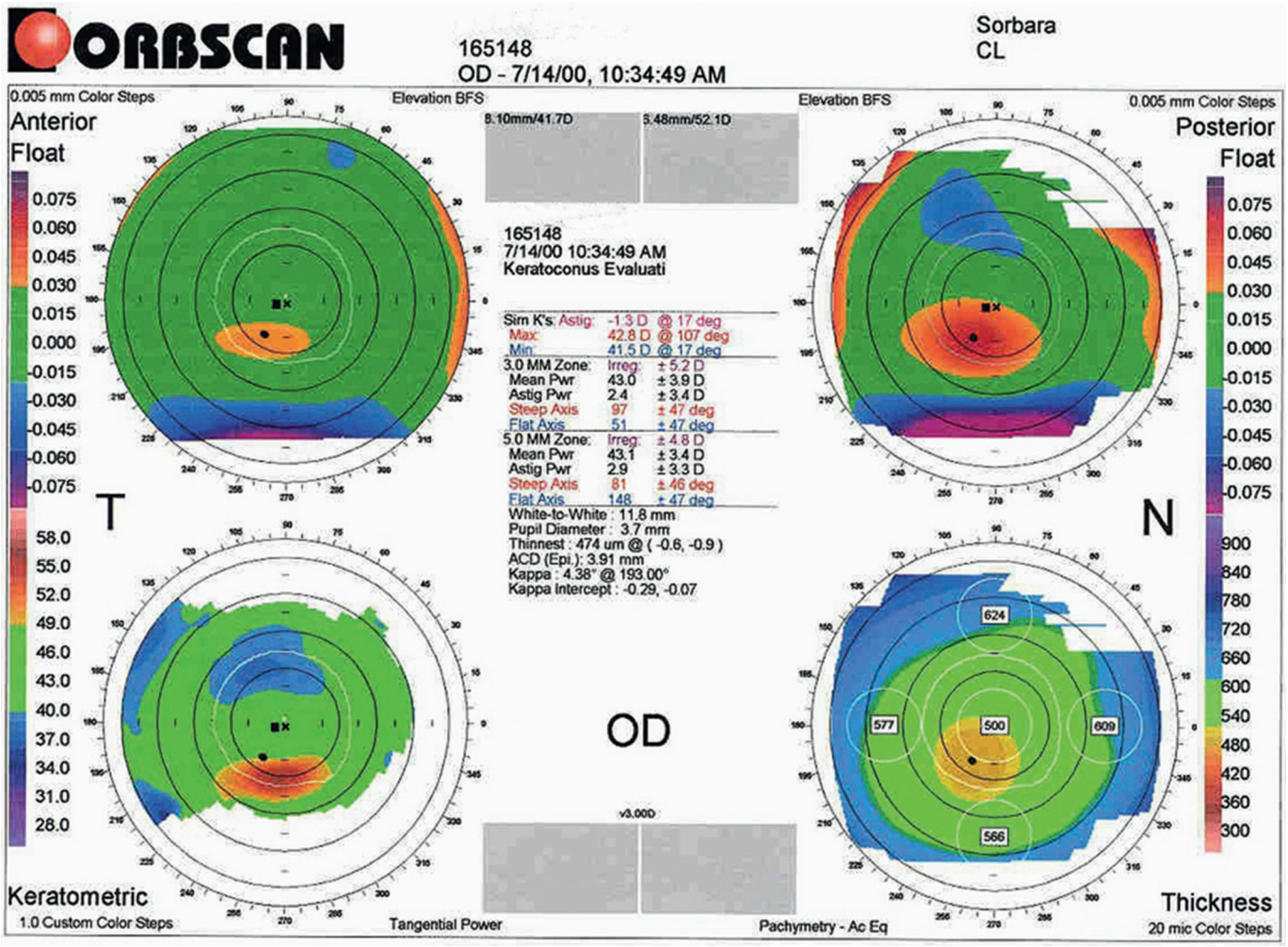


Fig. 1.30 An Orbscan map of a keratoconic cornea. The top left plot describes the anterior surface shape using an elevation map and relates the shape to a reference sphere, as obtained by the placido-disc image. The bottom left plot describes the shape in terms of a tangential power plot and clearly shows the position of the conus. The top right plot describes the posterior corneal surface shape using an elevation model, derived from the slit-scanning image. The bottom right plot provides pachometric data and indicates that the thinnest portion of the cornea is displaced inferiorly. The data in the centre provide simulated keratometry results and indicate the position and magnitude of the thinnest portion of the cornea. (Courtesy Lyndon Jones.)

repeatable measurements of corneal thickness. In many cases, this measurement is undertaken by support staff, who often have minimal slit lamp skills. These factors have resulted in the development of simpler objective methods for the assessment of corneal thickness, and ultrasonic pachometry has become the method of choice in many practice settings.

The ultrasonic pachometer is based on traditional A-scan ultrasonography, where the recording is in one dimension only, compared with B-scan instruments, which provide a 2D view of the eye. Ultrasound is transmitted to the eye from a transducer. Sound is reflected back to the transducer from tissue interfaces, which possess different acoustic impedances, enabling the distance from the ultrasound probe at the anterior epithelial interface to determine the distance between itself and the endothelium–aqueous interface. The transducer determines the time difference between the pulse signals obtained at the two interfaces and computes the corneal thickness based on this time delay and the velocity of sound in corneal tissue, which is approximately 1,580 meters per second (m/s) at body temperature. A direct measurement of corneal thickness is then displayed on a digital readout.

Before undertaking ultrasonic pachometry, the cornea is anaesthetised and the patient slightly reclined (Fig. 1.31).

Potential sources of error in measuring corneal thickness include holding the probe at an oblique angle to the cornea and measuring away from the central corneal apex, both of which would result in elevated readings of central corneal thickness (because corneal thickness increases from the centre to the periphery). The majority of modern instruments include a mechanism whereby a reading is not displayed if the probe is positioned such that there is excessive deviation from the perpendicular. The operator can use the pupil as a centring target, and the measurements obtained with the use of these adaptations are valid for clinical use.

As discussed previously, corneal topographers that are capable of imaging the anterior and posterior corneal surfaces – such as the slit-scanning Orbscan and Pentacam devices – can generate maps of corneal thickness profile across the cornea (Fig. 1.28).



Fig. 1.31 Ultrasonic pachometer evaluation. The eye is anaesthetised and the probe touched to the cornea. Readings are digitally recorded once the angle of inclination of the probe is correct. (Courtesy Lyndon Jones.)

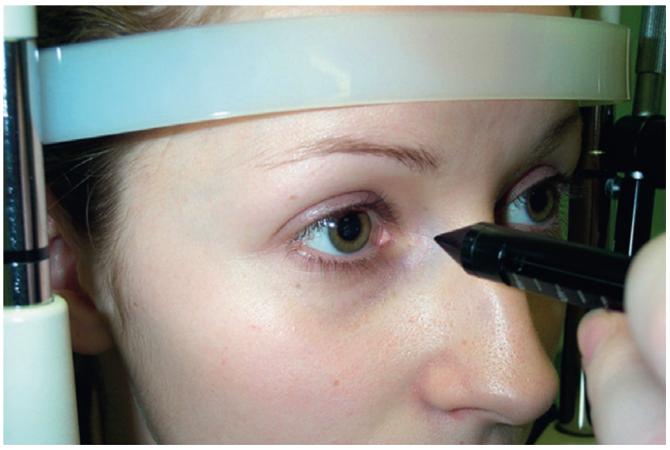


Fig. 1.32 The Cochet–Bonnet aesthesiometer being used to measure corneal sensitivity. A fine nylon thread of a set length is advanced towards the eye and the patient is asked to report when he or she first feels the thread touching the corneal surface. (Courtesy Lyndon Jones.)

Corneal aesthesiometry

The cornea is richly innervated and is one of the most sensitive tissues in the body. Corneal sensitivity is a useful indicator of corneal disease and can help determine physiological stress resulting from contact lens wear. At the most basic level, a clinician can test if a patient has an anaesthetic cornea by twisting the corner of a paper tissue, lightly touching the cornea (approaching from the side) and asking the patient whether or not he or she could feel anything. A negative response indicates an anaesthetic cornea.

Total corneal anaesthesia is rare and is more likely caused by higher neural pathology than any effects of contact lenses. However, subtle deficits in corneal sensitivity can occur in association with contact lens wear under certain conditions, such as severe hypoxic stress. To measure such deficits, quantitative techniques are required, using contact or non-contact paradigms.

CONTACT NYLON FILAMENT CORNEAL AESTHESIOMETRY

Measurement of corneal sensitivity in the clinical setting has traditionally been achieved by using a Cochet–Bonnet aesthesiometer (Fig. 1.32).[28]

This device can be hand held or mounted on a slit lamp and uses a single nylon thread to produce various forces, by varying its length in 0.5 cm steps (the longer the thread, the lighter is the force). The filament is lightly placed onto the cornea by the clinician using a support that allows manipulation in the x–y–z planes whilst being viewed through the slit lamp. The subject reports when he or she can feel the thread touching the ocular surface, and the length of thread at which this occurs is recorded. The corneal touch threshold is defined as the length of the nylon filament at which the subject responds to 50% of the number of stimulations. This length is converted into pressure by using a calibration curve, and the reciprocal of this value gives the corneal sensitivity. With the use of this technique, it has been demonstrated that corneal sensitivity varies with surface location and is altered by age, iris colour, ambient temperature, time of day, contact lens wear and pregnancy.

NON-CONTACT AIR PUFF CORNEAL AESTHESIOMETRY

Murphy et al.[29] have described how corneal sensitivity can be measured using this novel non-invasive method. The non-contact corneal aesthesiometer (NCCA) uses controlled pulses of air of varying pressures to stimulate the cornea (Figs. 1.33A & B). It measures the threshold sensitivity to a composite stimulus consisting of air pressure along with tear film evaporation and disruption.

The advantage of NCCA over the Cochet–Bonnet aesthesiometer is that a large, continuous range of stimulus intensities can be produced. Furthermore, the stimulus is more precise and sensory specific, testing is less variable than with use of a filament, there is no corneal microtrauma and patient apprehension is minimised.[29] The NCCA can assess the corneal sensation threshold in an accurate and repeatable manner, and it has been shown to be better at measuring lower stimulus thresholds than with the Cochet–Bonnet aesthesiometer.[30] The NCCA is not commercially available, is expensive to make and is not as portable as the Cochet–Bonnet aesthesiometer.

With time, it is likely that devices based on these approaches will become commercially available, and aesthesiometry will become an important technique in contact lens practice.

Conclusions

As in all fields of medical technology, significant developments have occurred in the field of ophthalmic imaging that have revolutionised our capacity to examine the anterior ocular structures in considerable detail and to quantify ocular parameters with great accuracy. Although the wide array of new and sophisticated equipment available today can greatly assist ophthalmic practitioners in understanding the ocular response to contact lens wear, the mainstay of ocular examination remains the slit lamp biomicroscope. This cost-effective and reliable instrument provides a readily accessible, magnified, stable, 3D view of the anterior eye, facilitating ready diagnosis of the vast majority of contact lens complications of immediate clinical significance.

As with any other clinical procedure, proficiency in using the slit lamp biomicroscope will only come with clinical experience.

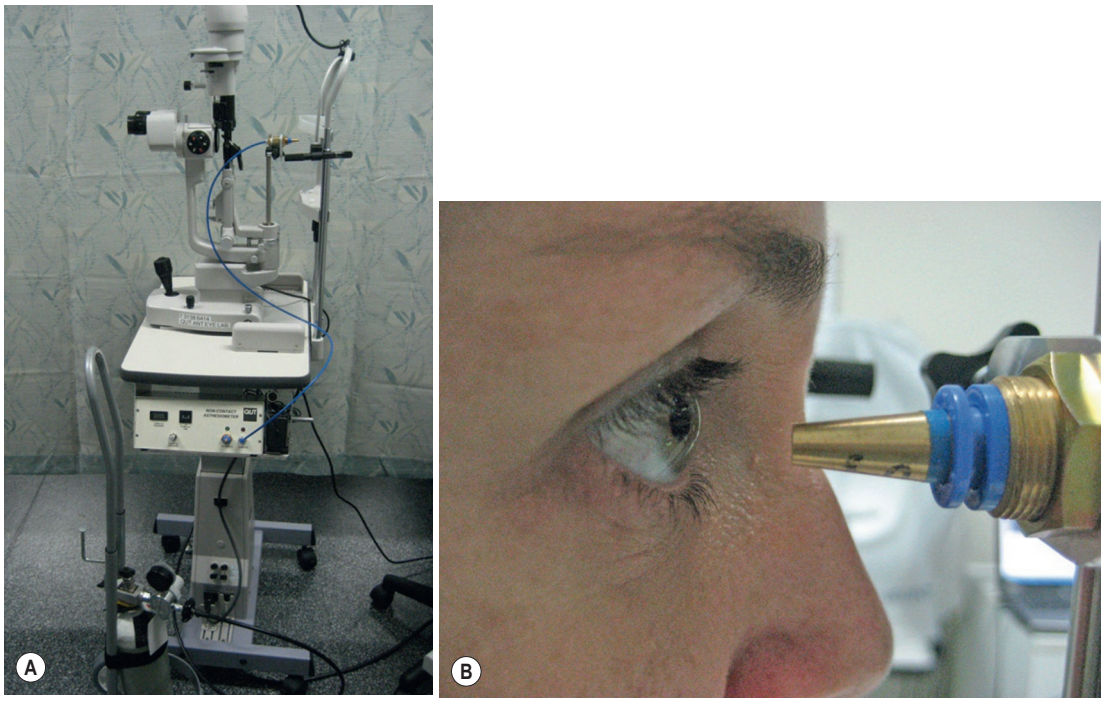


Fig. 1.33 Custom-made non-contact corneal aesthesiometer configured here as an accessory to a slit lamp biomicroscope. **(A)** The electronic control console is mounted beneath the slit lamp table. This is connected to a tank of compressed instrument-grade air. A controlled pulse of air is delivered to the cornea through a blue nylon tube to a brass nozzle mounted in front of the cornea of the subject. The air pulse is activated by a foot pedal. **(B)** Air jet nozzle positioned about 2 cm from the cornea, ready for determining puff sensation threshold. (Courtesy Nicola Pritchard.)

All practitioners, whether experienced ones or novices, should invest time in studying the features of an instrument that is being used for the first time, whether it be a newly acquired instrument or an existing instrument in a new and unfamiliar practice setting. The full diagnostic potential of a slit lamp biomicroscope can only be realised if the location and mode of operation of all controls, filters, mechanical adjustment mechanisms and so on are known, understood and used creatively.

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2 Grading Scales

In all health care disciplines, it is important to record as accurately as possible the clinical signs observed in patients. Classically, this has involved a discursive account of the condition being entered on a record card. The severity of the condition would be recorded by using wording that offers a general connotation of the level of severity, such as 'mild' or 'severe'. A potential problem with this approach is that these terms are somewhat general and can lead to miscommunication. What appears to be mild to one clinician may seem to be severe to another.

As an aid to accurate record keeping, health care practitioners of all disciplines have become accustomed to using standardised grading scales of various functions and qualities. A grading scale may be defined as 'a tool that enables quantification of the severity of a condition with reference to a set of standardised descriptions or illustrations'. In essence, grading scales offer clinicians a 'common language' for describing clinical phenomena.

In the contact lens literature, descriptive grading scales[1-3] have taken the form of an agreed series of numbers or letters, each of which corresponds to a written account of the severity of a condition. The clinician makes a judgement of the severity of a condition that is being observed with reference to the descriptive grading scale and records the appropriate number or letter.

Illustrative grading scales represent a more advanced form of denoting the severity of a clinical condition (Fig. 2.1). A series of photographs, paintings or drawings depicting a given condition in various stages of severity offers the clinician a visual reference against which the severity of a condition can be assessed and future changes in severity may be judged. A number of ad hoc photographic grading scales have been published in the contact lens literature relating to specific conditions, such as corneal staining,[4] conjunctival redness,[5] conjunctival staining[6] and papillary conjunctivitis.[7,8]



Fig. 2.1 Grading scales (A4-size card version) in use.

Various authors have developed systematic sets of grading scales for a representative range of the most frequently viewed and clinically relevant conditions encountered in contact lens practice. This chapter will review the various grading scales that have been produced and will explain in detail the clinical application of the Efron Grading Scales, which are presented in Appendix A.

Illustrative grading scales

Seven sets of illustrative grading scales have been developed for use in contact lens practice. For any given complication, a typical grading scale comprises a series of five images, from grade 0 (normal) to grade 5 (severe). These are discussed in chronological order of publication.

KOCH GRADING SCALES

These grading scales were published in 1984 as an appendix entitled 'Atlas of Illustrations' in an A5-sized soft-cover textbook published by Koch et al.[9] The grading scales were prepared by Perrin Sparks Smith, a medical artist, and are in the form of line sketches. Most of the sketches are white on black or black on white, with some use of red, green or grey block colour. Many of the illustrations are supplemented by a written description.

ANNUNZIATO GRADING SCALES

Around 1992, Annunziato et al.[10] published an atlas comprising 130 A4-sized loose-leaf pages secured in a three-ringed binder. This work was sponsored by Alcon Ltd. and was conducted under the auspices of the Southwest Independent Institutional Review Board (an ophthalmic clinical trials research group, Fort Worth, Texas, USA). The grading scales were in the form of full-colour traditional watercolour paintings by Monte Lay, an ophthalmic artist. Most of the paintings are accompanied by a brief description of the condition, and salient features are highlighted with the aid of black-and-white line diagrams.

VISTAKON GRADING SCALES

An A5-sized spiral-bound handbook of contact lens management was published by Johnson and Johnson Vision Care in 1996, under the authorship of Andersen et al.[11] All of the illustrations are slit lamp photographs. Although this book was primarily intended to be a guide to the management of contact lens complications, most of the conditions are presented in the form of a series of numbered photographs showing varying degrees of severity and, as such, essentially constitutes a series of grading scales. The photographs are accompanied by explanatory text.

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BRIEN HOLDEN VISION INSTITUTE GRADING SCALES

The Brien Holden Vision Institute (BHVI) Grading Scales were first formally published in 1997,[12] although they were released before this and distributed initially as an A2-sized poster, and subsequently in the form of an A4-sized plasticised card. These scales were originally published under the title 'Cornea and Contact Lens Research Unit (CCLRU) Grading Scales'. The term was changed to 'Institute for Eye Research Grading Scales' in 1998 and then to the current one in 2010. All of the conditions are depicted in the form of slit lamp photographs without accompanying text. Guidance is also given for grading certain conditions, but a series of graded photographs is not provided.

EFRON GRADING SCALES

The first edition of the Efron Grading Scales was published in the first edition of this book in 1999,[13] although they were released before this and distributed simultaneously in the form of an A1-sized poster and an A4-sized plasticised card in a protective slip case that contained instructions for use. These grading scales were painted by Terry Tarrant, an ophthalmic artist, and the development of the scales was sponsored by Hydron UK, Ltd. (now CooperVision Ltd.). The first edition of the grading scales depicted eight complications of contact lens wear, whereas the second edition, as presented in Appendix A of this book, depicts 16 complications.

The second edition was officially released as the 'Millennium Edition' in 2000 and has been available in card and poster forms since January 1, 2000. A handy plastic-coated A4-sized version of these grading scales, which comes in a handsome protective slipcase with comprehensive instructions for use, is available free of charge from CooperVision.

The original painted images of the Efron Grading Scales are housed in the Museum of the College of Optometrists in London; they are not on permanent display but may be viewed by appointment with the museum curator.

THE VISION CARE INSTITUTE CLINICAL GRADING SCALES

The Vision Care Institute (TVCI) Clinical Grading Scales,[14] which were adapted from the Efron Grading Scales, were first published around 2011 by Johnson and Johnson Vision Care. Unlike the Efron scales, which were painted using traditional water colours with a paint brush, the TVCI Grading Scales were generated by an artist using digital computer graphics software. As such, they can be considered as a stylised version of the Efron Grading Scales. Guidance is also given for grading certain conditions, but a series of graded photographs is not provided.

JENVIS GRADING SCALES

The Jenvis Grading Scales[15] were developed by Jenvis Research, under the authorship of Wolfgang Sickenberger et al. They were published by Alcon in 2013 under the auspices of Alcon's Academy for Eyecare Excellence. These grading scales comprise a series of slit lamp photographs of various conditions arranged in order of increasing severity. Guidance is also given for grading certain conditions, but a series of graded photographs is not provided.

Comparison of grading scale designs

Contact lens practitioners may come across clinical notes which have recorded the severity of a given complication with reference to any of the seven sets of grading scales described previously (a coherent set of grading scales is sometimes referred to as a 'grading system'). For this reason, practitioners need to be aware of the characteristics of these scales and how they compare with each other.

GRADES DEPICTED

The Koch and BHVI scales only depict grades 1 to 4 (not grade 0). Grade 0 is depicted for some of the complications depicted in the Vistakon system. The Annunziato, Efron, TVCI and Jenvis systems display grades 0 to 5 for all complications. Depiction of grade 0 is often useful as a baseline reference when grading complications of low severity.

SEVERITY DESCRIPTORS

The descriptions attached to the five grades of severity differ somewhat between grading systems; these are cited in Table 2.1. Severity descriptors are not assigned to the grades in the Koch or Jenvis systems. In the other four systems, grades 0 to 2 have slightly different meanings, whereas grades 3 and 4 are described as 'moderate' and 'severe', respectively. Thus, allowing for subtle differences in nomenclature, all seven systems have the same illustrative five-point grading system, and the five systems that offer severity descriptors (Annunziato, BHVI, Vistakon, Efron and TVCI) have adopted remarkably similar descriptors for these grades.

SUB-CLASSIFICATIONS

In the Koch and Efron systems, a single grading scale comprising five images is used to depict different levels of severity of each complication. However, in the Annunziato, BHVI, Vistakon, TVCI and Jenvis systems, a single complication can be

TABLE 2.1 Severity descriptors used in the seven grading systems

	GRADING SYSTEM						
Grade	**Koch**	**Annunziato**	**BHVI**	**Vistakon**	**Efron**	**TVCI**	**Jenvis**
0	Not stated	None	Absent	None	Normal	Normal	Not stated
1	Not stated	Trace	Very slight	Slight	Trace	Trace	Not stated
2	Not stated	Mild	Slight	Mild	Mild	Mild	Not stated
3	Not stated	Moderate	Moderate	Moderate	Moderate	Moderate	Not stated
4	Not stated	Severe	Severe	Severe	Severe	Severe	Not stated

BHVI, Brien Holden Vision Institute; TVCI, The Vision Care Institute.

sub-classified and depicted in the form of a number of grading scales so that different manifestations of that complication can be graded. For example, in the BHVI system, three grading scales are employed to facilitate an independent assessment of the severity of corneal staining in terms of type, depth and extent.

CONDITIONS DEPICTED

Putting aside sub-classifications, the number of primary conditions depicted varies markedly between grading systems – from five sets of primary grading scales in the TVCI system to 16 in the Efron system. The primary conditions depicted in each of the seven grading systems are presented in Table 2.2.

A number of interesting observations can be made from Table 2.2:

- A total of 21 complications have been depicted in all of the grading systems combined.
- A grand total of 64 grading scales have been developed in all of the grading systems combined.
- Only three conditions are depicted in all seven grading systems – conjunctival redness, corneal staining and papillary conjunctivitis.
- One condition is unique to the Koch system (epithelial edema), one to the Annunziato system (iritis), three to the Vistakon system (limbal staining, pinguecula and pterygium) and three to the Efron system (corneal ulcer, endothelial blebs and superior limbic keratoconjunctivitis).

PHOTOGRAPHIC VERSUS PAINTED SCALES

Problems with photographic scales

The advantage of photographic grading scales is that images of actual conditions are depicted. However, certain difficulties are encountered when compiling photographic grading scales. An immense slide library is required – but even if such a resource is available, a number of compromises are necessary. For example, a given condition such as neovascularization can present in many different forms, and it is generally not possible to identify a series of photographs that display precisely the same manifestation of that condition at various levels of severity.

The clinical utility of a series of photographs of a given condition at varying levels of severity may be confounded by the fact that the photographs are invariably of different patients who have different ocular characteristics, such as iris colour, conjunctival vasculature, pupil size and lid anatomy. Furthermore, photographs are taken from various angles, at different magnifications, with various illumination conditions, by using different levels of staining, and so on. Inconsistencies in colour rendering of sequential images result from the use of different types of photographic film and variations in photographic processing techniques or from the use of different electronic settings with digital image capture. The precise level of severity of a condition may not be available from the slide library, leading to further compromise.

Some complications, such as epithelial microcysts or stromal striae and folds, are extremely difficult to photograph; indeed, few photographs of such conditions exist. This artificially constrains the range of complications from which a series of graded photographic images can be compiled.

TABLE 2.2 Complications depicted in the seven grading systems

	GRADING SYSTEM							
Complication	**Koch**	**Annunziato**	**BHVI**	**Vistakon**	**Efron**	**TVCI**	**Jenvis**	**Total**
Blepharitis				✓	✓			2
Conjunctival redness	✓	✓	✓	✓	✓	✓	✓	7
Conjunctival staining			✓	✓	✓			3
Corneal distortion	✓	✓			✓			3
Corneal infiltrates		✓		✓	✓			3
Corneal neovascularization	✓	✓*		✓	✓		✓	5
Corneal edema	✓	✓†		✓	✓			4
Corneal staining	✓	✓†	✓‡	✓*	✓	✓	✓*	7
Corneal ulcer					✓			1
Endothelial blebs					✓			1
Endothelial polymegethism			✓		✓		✓	3
Epithelial microcysts	✓	✓			✓			3
Epithelial edema	✓							1
Iritis		✓						1
Limbal redness		✓	✓	✓	✓	✓	✓	6
Limbal staining				✓				1
Meibomian gland dysfunction				✓	✓	✓		3
Papillary conjunctivitis	✓	✓	✓‡	✓	✓	✓*	✓	7
Pinguecula				✓				1
Pterygium				✓				1
Superior limbic keratoconjunctivitis					✓			1
Total (21)	8	10	6	13	16	5	6	64

*Two sub-classification grading scales are presented.
†Four sub-classification grading scales are presented.
‡Three sub-classification grading scales are presented.
BHVI, Brien Holden Vision Institute; TVCI, The Vision Care Institute.

Advantages of painted grading scales

The advantages of using artist-rendered (painted, or digitally rendered using computer graphics software) versus photographic or digital image capture grading scales are as follows:

- The desired level of severity of a given condition can be depicted.
- Any chosen manifestation of a given condition can be illustrated.
- The severity of the manifestation of a given condition can be systematically advanced through the image set.
- All images of a given complication can be generated by using precisely the same colour scheme and can be standardised with respect to angle of view, magnification and associated ocular features (e.g. iris colour).
- Confounding artefacts unrelated to the complication being depicted (e.g. associated or secondary complications) can be avoided.
- Ancillary clues can be introduced to reinforce the notion of increasing severity (e.g. increasing light scatter of the slit lamp illumination reflex or increasing limbal redness).
- Artistic license can be adopted to embellish certain features or obscure others for clarity.

Many of the design features described here can be seen, for example, in the grading scale sequence for corneal neovascularization in Appendix A. The key pathological change is obvious – vessels of a given type (superficial plexus) progressively encroach into the cornea from the 6 o'clock position. Associated subtle pathological signs are deliberately painted in to reinforce the notion of a worsening condition: The limbus becomes progressively more engorged, the corneal slit lamp reflex becomes progressively more diffuse, and the central cornea becomes progressively hazier. All other factors are kept constant: The full cornea is depicted from the same angle ('front on') in each case, iris size is constant, and the iris detailing and colouring are identical in each of the five frames. All of these features combine to form a powerful, self-evident and unambiguous sequence of progressive corneal revascularization.

Efron Grading Scales: design and application

Since the Efron Grading Scales are referred to throughout this book and are featured in Appendix A, detailed consideration will be given to the design principles that have underpinned their development. Appropriate techniques for their clinical application will also be described.

DESIGN FEATURES

The primary design criteria on which the Efron Grading Scales are based are simplicity, convenience and ease of use by clinicians. Sixteen sets of grading images are depicted in two panels, each comprising eight complications. Each complication has a banner heading.

These 16 grading scales cover the key anterior ocular complications of contact lens wear. Those shown on the panel beginning with 'conjunctival redness' are frequently encountered; those in the other panel are less common and are thus less likely to be graded routinely. On each panel, complications are depicted in the approximate order in which they would be encountered in the course of a typical slit lamp examination of the eye.

As noted earlier, each complication is illustrated in a row of five images depicting progressively increasing severity, from 0 on the left to grade 4 on the right. Traffic light colouring from green (normal) to red (severe) is used to border the images to facilitate ready association of any image with its intended level of severity, without the need to cross-reference the image against the grade numbers and descriptors at the top of each panel. The gradation of severity of the complications and the maximum level of severity depicted are based on an appraisal of evidence in the literature and accumulated clinical experience.

IMAGE SIZE

Each complication has been painted to an equivalent level of magnification that addresses the compromise between (1) being large enough to depict the key features of the tissue changes and (2) having low enough magnification to relate to what practitioners can observe with available clinical techniques. The approximate magnification of each complication (relative to a whole cornea depicted as × 1) is given in Table 2.3. Figure 2.2 shows the 16 complications at grade 4 severity (each of which is identified by a letter code in Table 2.3) and indicates the approximate magnification of the images with a series of size boxes.

As a consequence of the magnification levels at which these complications have been depicted, some exceptions relating to grading technique need to be noted:

- Epithelial microcysts and endothelial blebs cannot be viewed at the resolution depicted, although they can be detected and graded at ×40 magnification on a slit lamp biomicroscope.
- Endothelial polymegethism can only be assessed with the aid of an endothelial or confocal microscope.

All other complications can be viewed at the resolution depicted and are capable of being graded by direct observation and/or using a slit lamp biomicroscope at magnifications up to ×40.

TABLE 2.3 Magnification of complications (relative to a whole cornea being 1) depicted in the Efron Grading Scales

Complication	Magnification	Image depicted in Figure 2.2
Corneal staining	× 1	A
Corneal ulcer	× 1	B
Corneal infiltrates	× 1	C
Corneal revascularization	× 1	D
Papillary conjunctivitis	× 1	E
Meibomian gland dysfunction	× 1	F
Blepharitis	× 1	G
Superior limbic keratoconjunctivitis	× 2	H
Limbal redness	× 2	I
Conjunctival staining	× 2	J
Conjunctival redness	× 2	K
Corneal distortion	× 2	L
Corneal edema	× 40	M
Epithelial microcysts	× 100	N
Endothelial blebs	× 200	O
Endothelial polymegethism	× 600	P

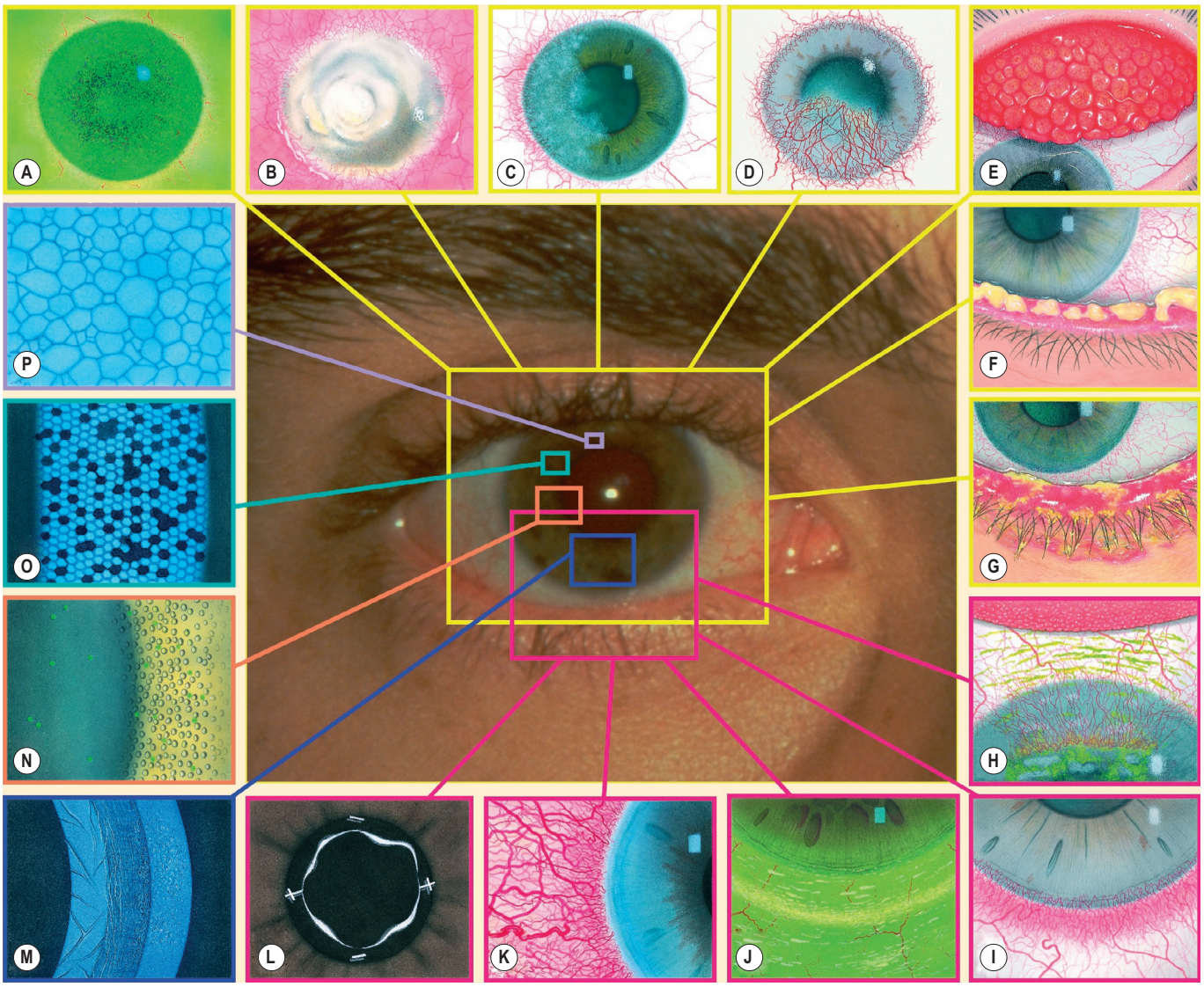


Fig. 2.2 The 16 complications represented in the Efron Grading Scales (presented in full in Appendix A), depicted here at grade 4 severity. The approximate magnification of each complication (relative to the whole cornea being ×1 magnification) is indicated by coloured boxes interposed over the image of the eye. The 16 complications are labelled with a letter code and are identified in Table 2.3.

HOW TO GRADE

Observe the tissue change of interest directly or with the aid of a slit lamp biomicroscope, under low and/or high magnification as required, and estimate the level of severity with reference to the appropriate grading scale to the nearest 0.1 scale unit. For example, a tissue change that is deemed considerably more severe than grade 2 but not quite as severe as grade 3 may be assigned a grade of 2.8 or 2.9. Although this procedure can sometimes be difficult, grading to the nearest 0.1 scale unit (rather than simply assigning a whole digit grade of 0, 1, 2, 3 or 4) affords much better grading performance by way of increasing the sensitivity of the grading scale for detecting real changes or differences in severity.[16]

HOW TO RECORD GRADING

Because various grading scales are available, it is important to clearly designate the grading system used and the specific tissue change being graded. A more expedient approach might be to print or stamp the 16 tissue changes on a record card, each with an accompanying box for entering the assigned grade. It may be necessary to make additional annotations on an accompanying set of printed sketches of the eye to more fully describe the condition (e.g. to indicate the location of the pathology) (Fig. 2.3).

INTERPRETATION OF GRADING

The five-stage 0 to 4 grading scale is based on a universally accepted concept whereby a higher numeric grade denotes greater clinical severity. In general, a level of severity of more than grade 2 is considered clinically meaningful. This schema can be applied to any tissue change, even those not depicted on any given grading scale. Severity descriptors, colour codes and clinical interpretation of the grades illustrated in the Efron Grading Scales are presented in Table 2.4; it must be recognised that the clinical interpretations are only very general guidelines and are not intended to replace sound professional judgement. There are two exceptions with respect to the interpretations

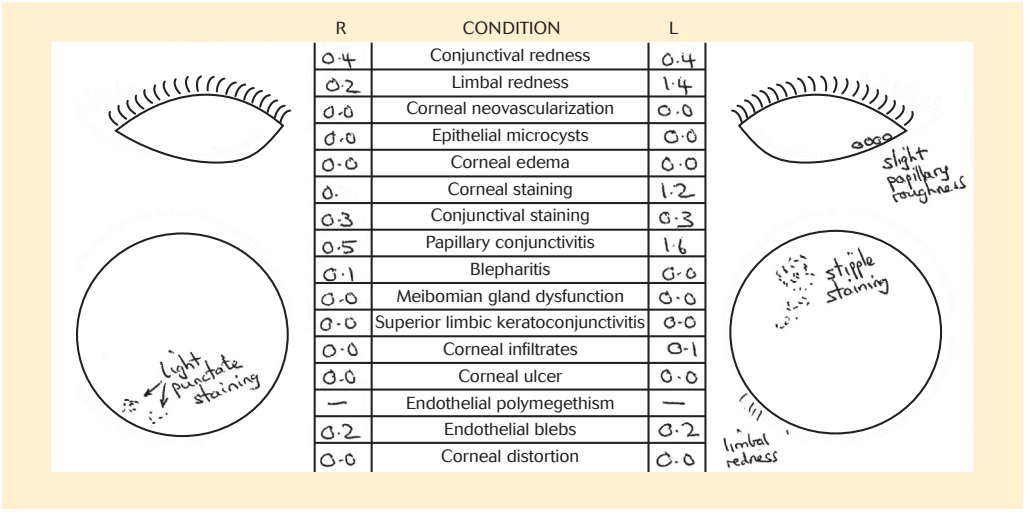


Fig. 2.3 Suggested design of record card for use in conjunction with the Efron Grading Scales.

TABLE 2.4 Severity descriptor, colour code and clinical interpretation of the grades illustrated in the Efron Grading Scales

Grade	Severity descriptor	Colour code	Clinical interpretation
0	Normal	Green	Clinical action not required
1	Trace	Lime	Clinical action rarely required
2	Mild	Yellow	Clinical action possibly required
3	Moderate	Orange	Clinical action usually required
4	Severe	Red	Clinical action certainly required

described in Table 2.4. Corneal ulceration may require urgent action when detected or even suspected at any level of severity. Endothelial blebs require no clinical action, even at grade 4.

Grading performance

Despite the apparent consistency in the construct of the five grading systems for contact lens complications, the various grading scales were developed independently and take on different appearances; therefore, grading estimates of the severity of a specific condition derived by using the different systems cannot necessarily be expected to be identical. For example, inspection of grading scales relating to papillary conjunctivitis (Fig. 2.4) in the seven systems reveals clear differences between the ranges of severity depicted.

STATISTICAL DESCRIPTORS

The classic approach for assessing grading performance is to have a clinician grade the severity of a large number of images of contact lens complications of differing severities, presented in a random sequence ('test'), and then to have the same clinician repeat this exercise some time later with the images presented in a different randomised sequence ('retest'). The clinician must grade to the nearest 0.1 grading scale unit, and the assumption is made that the clinician does not remember the grades assigned at the first attempt when making the second attempt; that is, the grading attempts are independent. Having done this, those data can be used to derive various useful indices of grading performance, as described in the following paragraphs.

Concordance

Concordance refers to the frequency of perfect agreement between grades assigned. For example, if 100 images were independently graded on two occasions, and there was perfect agreement on 12 occasions, there would be 12% concordance. The issue being addressed here is as follows: How often do the repeated grading estimates agree?

Sensitivity

'Sensitivity' is more a characteristic of the grading scale, rather than of the observer. A grading scale can be said to have 'fine' or 'coarse' sensitivity. A grading scale that accords fine sensitivity will result in superior grading performance – that is, better reliability, consistency and confidence (see later in the chapter). The converse is true of a grading scale that accords coarse sensitivity. The issue being addressed here is as follows: What is the capability of the grading scale to facilitate the detection of a change or difference in severity of an observed condition?

Precision

This refers to the differences in grading estimates among colleagues. The issue being addressed here is as follows: Is one estimator's grade higher or lower compared with those of his or her colleagues?

Accuracy

This relates to the difference between grading estimates and the 'gold standard'. The issue being addressed here is as follows: Does one estimator grade higher or lower compared with the gold standard ('the truth')?

Reliability

This is mathematically defined as ±1 standard deviation (SD) of test/retest distribution. The issue being addressed here is as follows: How tightly clustered are the repeated grading estimates?

Consistency

This is mathematically defined as (1.96 × reliability), and is also termed the 'coefficient of repeatability' or '95% confidence limits'. The issue being addressed here is as follows: What is

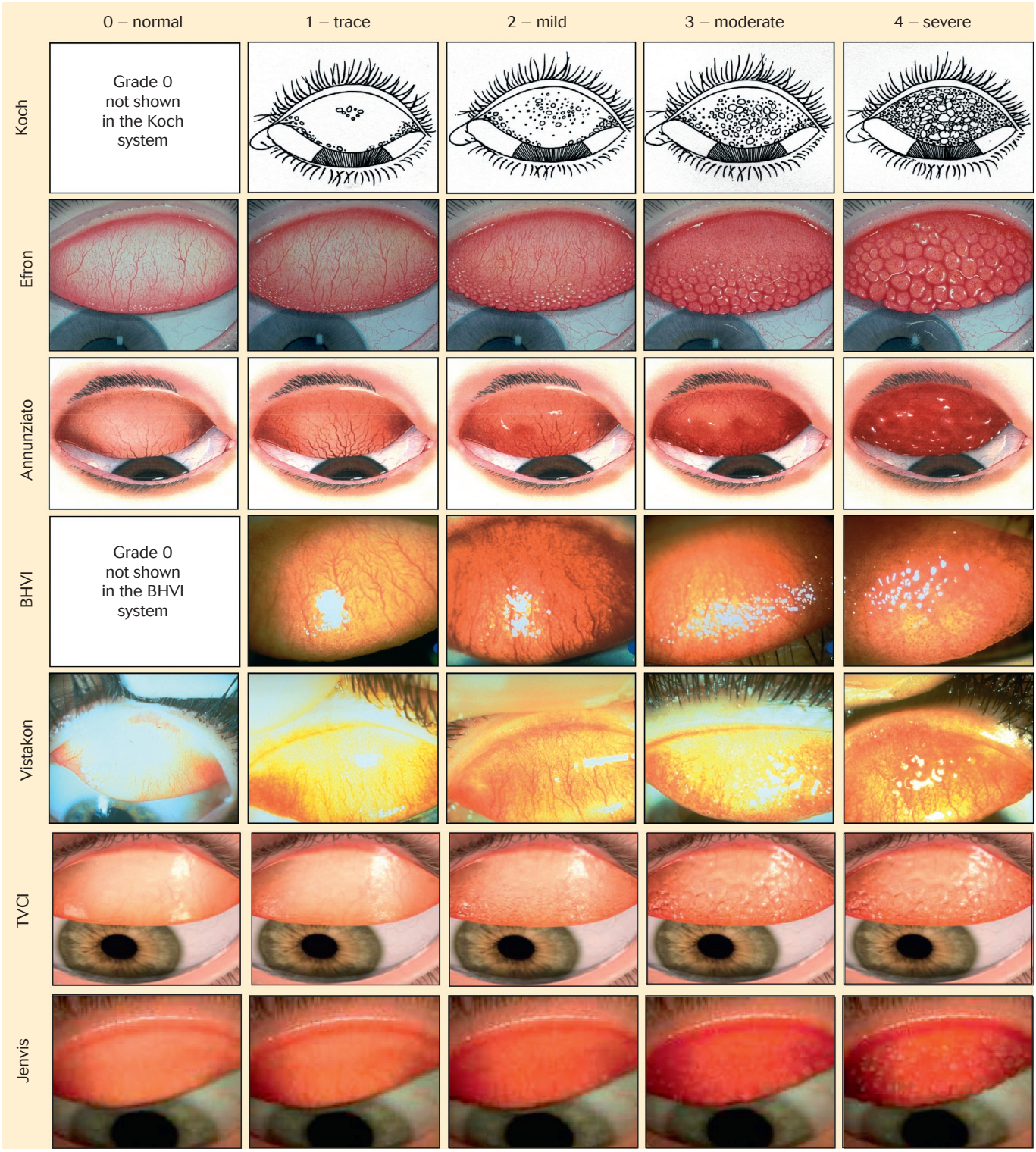


Fig. 2.4 Grading scales for papillary conjunctivitis depicted in seven grading systems. (Adapted from Efron N, Morgan PB, Katsara SS. Validation of grading scales for contact lens complications. Ophthalmic Physiol Opt 2001;21:17–29).

the range within which the grading estimates cannot be considered to differ or change? Or put another way, what is the level of sloppiness when grading?

Confidence

This refers to the extent to which grading is executed in fine increments. The issue being addressed here is as follows: To what extent does one have the confidence to grade to the nearest 0.1 grading scale unit?

Bias

This is mathematically defined as the mean of the test/retest discrepancies. The issue being addressed here is as follows: Has

there been a shift in the grading criteria between the first and second testing sessions?

GRADING STATIC VERSUS VIDEO IMAGES

A number of research studies have investigated the effect of various factors on grading performance. Typically, grading is performed with reference to clinical photographs of contact lens–associated pathology. The advantage of this approach is that the grading performance of different observers can be assessed at different times (i.e. during different experimental sessions) in respect of a single constant image.

Efron and Chaudry found little practical difference between grades assigned to various types of pathology depicted in a static image versus in a video recording of a moving, blinking eye.[17] However, Sorbara et al.[18] found that digital still image grading of corneal staining significantly underrepresented the amount of corneal staining observed through a slit lamp biomicroscope.

PRECISION AND RELIABILITY BETWEEN GRADING SYSTEMS AND OBSERVERS

The grading performance of a group of clinicians using two artist-rendered (Annunziato and Efron) and two photographic (Vistakon and BHVI) grading systems was assessed in terms of precision and reliability by Efron et al.[19] Specifically, 13 clinicians each graded 30 images – by interpolation or extrapolation to the nearest 0.1 increment – of each of the three contact lens complications that were common to all four grading systems, namely, corneal staining, conjunctival redness and papillary conjunctivitis. This entire procedure was repeated approximately 2 weeks later, yielding a total database comprising 9360 individual grading estimates.

Analysis of variance (ANOVA) revealed statistically significant differences in both precision and reliability among systems, observers and conditions. The artist-rendered systems generally afforded lower grading estimates compared with the photographic systems.[19] The reason for this becomes readily apparent upon inspection of Figure 2.4. It is clear that higher grades of papillary conjunctivitis depicted in the painted grading scales (Annunziato and Efron) represent greater levels of severity compared with those depicted in the photographic grading scales (BHVI and Vistakon). For example, a grade 4 image in the BHVI Scale would perhaps be equivalent to about grade 2.5 on the Efron Scale. It is unlikely that the narrow severity range of the photographic systems was a deliberate design strategy, but instead, it was caused by lack of suitable photographs of severe conditions.

Because of these significant between-system differences in grading performance, it is advisable to use the same grading system consistently. However, it is sometimes necessary to compare grading estimates obtained using different scales (e.g. when evaluating results from published clinical trials from groups that use different grading scales). Such comparisons can be made with the aid of conversion tables, such as those published by Schulze et al.[20]

As an illustration of this approach, Schulze et al.[21] determined the between-scale agreement of grading estimates obtained with cross-calibrated McMonnies/Chapman-Davies, BHVI, Efron and Validated Bulbar Redness Grading Scales. They found that (1) the use of cross-calibrated reference grades for bulbar redness grading scales allows for comparison of grading estimates obtained with different scales; and (2) perceived redness is dependent on the dynamic range of the reference images of the scale, with redness estimates generally being found to be higher for scales with a shorter dynamic range.

Complications could be graded more reliably by using the artist-rendered systems than with the photographic systems.[19] This finding may be related to the greater control over the progression of severity that an artist can depict compared with photographic grading scales, in which the selection of images designed to represent a systematic progression of severity is constrained by the availability of suitable images.

Conjunctival redness and papillary conjunctivitis could be graded more reliably compared with corneal staining.[19] This may be attributed to the greater variability in the manifestations of corneal staining patterns that can be observed versus the more characteristic and predictable clinical presentations of conjunctival redness and papillary conjunctivitis. Grading reliability was generally unaffected by the *severity* of the condition being assessed.

Efron et al.[19] concluded that, notwithstanding the previously mentioned differences, the four grading system studies are validated for clinical use. It was determined that practitioners can initially expect to use these systems with an average reliability of ± 0.6 grading scale units. In the report by Efron et al.,[19] the estimates of grading reliability were somewhat inferior compared with those reported elsewhere (Table 2.5). Sorbara et al.[18] reported that clinical investigators graded corneal staining with a high degree of consistency when using the Centre for Contact Lens Research corneal staining scale that combines grades of both extent and type to provide an overall 'global staining score' from 0 to 10,000. Ishak et al.[22] found good inter- and intra-observer agreement between two observers grading papillary conjunctivitis by using the BHVI Grading Scales. These differences may be related to the use of different scales and the level of experience and/or training of the subjects used in their experiments (see later).

Perhaps one way of interpreting the data in Table 2.5 is that when using grading scales for the first time, a confidence interval of about 1.2 is to be expected; however, with experience, this may improve to 0.7 grading scale units. Peterson and Wolffsohn[32] reported similar findings: they found that when using the Efron Grading Scales, subjects were able to differentiate images of conjunctival redness with differences in grade of 0.70 to 1.03. Rounding these values to the more conservative estimate, it can be considered that in general, a change or difference of greater than about 1.0 grading scale unit is considered both statistically significant and clinically meaningful. This conclusion was also reached by Efron[33] in an experiment conducted on more than 400 observers, who all performed the same grading exercise. Practitioners can determine their own grading precision by using a Grading Tutor (see Chapter 3).

Efron et al.[19] reported that they were disappointed, but not surprised, to observe that the experimental subjects tended to grade to the nearest whole-digit or half-digit grading scores, as revealed by inspection of the frequency distribution of all grading estimates made during the experiment (Fig. 2.5). This occurred despite constant encouragement given to the subjects to grade to the nearest 0.1 grading scale increment. This observation highlights the natural reluctance of clinicians to grade using fine increments.[16]

Surveys of grading behaviours in clinical practice[34] revealed that 76% of optometrists surveyed in Australia and 53% of optometrists surveyed in a number of other countries[35] used

TABLE 2.5 Grading reliability and subject experience/training reported in various studies

Author	Number of subjects	Level of experience/training of subjects	Grading tool	CONDITION		
				Corneal staining	Conjunctival redness	Papillary conjunctivitis
Chong et al., 2000[23]	5	'highly experienced in using clinical grading systems'	Photographic*	±0.25	±0.19	±0.20
			Verbal†	±0.20	±0.21	±0.21
			Morphs‡	±0.25	±0.16	±0.19
Dundas et al., 2000[24]	2	'trainee optometrists'	BHVI*	±0.18		
Papas, 2000[25]	7	'highly trained and accustomed to using the grading scale for over one year'	BHVI*		±0.40	
Twelker & Bailey, 2000[26]	2	'experienced'	Efron§		±0.30	
Efron et al., 2001[19]	13	'minimal experience in using grading scales'	Efron§	±0.67	±0.55	±0.54
			Annunziato§	±0.61	±0.58	±0.60
			BHVI*	±0.76	±0.53	±0.64
			Vistakon*	±0.76	±0.59	±0.63
MacKinven et al., 2001[27]	2	'trainee optometrists'	BHVI*			±0.12
Efron et al., 2002[28]	9	'experienced users of grading scales'	Efron§	±0.34	±0.38	±0.56
			Morphs¶	±0.48	±0.49	±0.36
Efron & Chaudry, 2007[17]	38	'final-year optometry students'	Efron§	±0.55	±0.54	±0.67
Efron & McCubbin, 2007[29]	25	'final-year optometry students'	Efron§	±0.32	±0.50	±0.38
Murphy et al., 2007[30]	2	'trained observers'	BHVI*		±0.32	
Efron et al., 2011[31]	100	'optometrists in practice'	Various	±0.60		

*Printed grading scales based on photographs.
†Verbal descriptor grading scales.
‡Computer-generated grading morphs based on photographs.
§Printed grading scales based on artist-rendered paintings.
¶Computer-generated grading morphs based on artist-rendered paintings.
BHVI, Brien Holden Vision Institute.

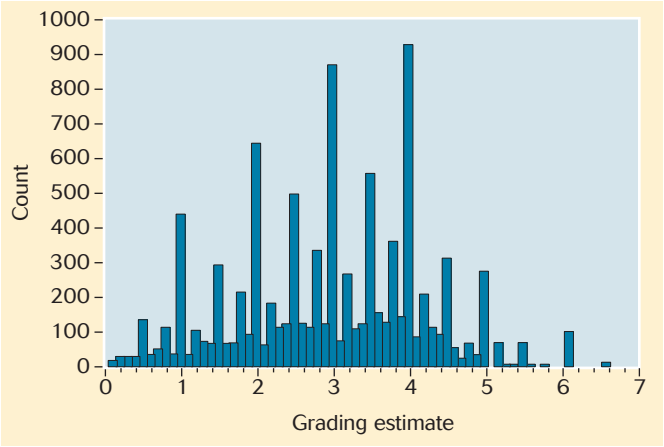


Fig. 2.5 Frequency distribution of all grading estimates of the severity of a range of contact lens complications (N = 9,360). (Adapted from Efron N, Morgan PB, Katsara SS. Validation of grading scales for contact lens complications. Ophthalmic Physiol Opt 2001;21:17–29).

a method of incremental grading, rather than simply grading with whole numbers.

INFLUENCE OF KNOWLEDGE, TRAINING AND EXPERIENCE

A number of factors are likely to influence the accuracy and reliability of grading estimates when using clinical grading tools, including the design and presentation of the grading tool, the complexity and/or severity of the condition being graded and the time constraints within which grading must be executed (or other extraneous pressures on performance). There are also a number of attributes of the person executing the grading that are likely to influence grading performance; these attributes can be broadly defined as a 'clinical skill set', the components of which fall into the three categories discussed in the next paragraphs.

Knowledge

This attribute refers to the relevant knowledge of the person executing the grading.[36,37] Specifically, it relates to the broad knowledge base that underpins the clinical task under consideration, which, in this case, is the use of grading scales for complications of contact lens wear. The knowledge base that underpins this task would be acquired through broad education in ophthalmic science and clinical practice and specific education in the field of contact lenses and related ophthalmic pathology such as would be gained by having trained as an optometrist or ophthalmologist.

Training

This refers to the extent of instruction/learning with the specific grading tool. This attribute is concerned with dedicated instruction and training in the theoretical development and clinical application of grading scales for contact lens complications. Such training could occur in the form of lectures, tutorials or clinical workshops or via the use of purpose-designed training packages, such as the Efron Grading Tutor (see Chapter 3).

Experience

This is the accumulated amount of time spent in the use of a grading tool. This attribute relates to the repeated use of a

grading scale whereby grading performance might be expected to improve over time because of accumulated experience and ongoing learning by trial and error.

Grading performance of those with the 'clinical skill set'

It might be supposed that a professional with the earlier-defined clinical skill set would demonstrate superior grading performance compared with a person who does not possess this clinical skill set. However, it could be argued that clinical grading with the use of a pictorial grading scale is a simple visual matching task and that such a clinical skill set is not necessarily required for good accuracy and reliability.

Efron et al.[38] conducted a study to investigate the combined influence of knowledge, training and experience (i.e. the possession of a clinical skill set) on various aspects of grading performance (i.e. accuracy, reliability, bias and interpolation) when assessing the severity of complications of contact lens wear.

Nine optometrists (who were in possession of a relevant clinical skill set) and nine non-optometrists (management and engineering university students, who, by definition, did not have the relevant clinical skill set) were each invited to grade – to the nearest 0.1 increment – an image of each of 16 complications of contact lens wear by using the Efron scales. This procedure was repeated 2 weeks later, yielding a total database comprising 576 individual grading estimates. The mean of the test and retest grading estimates was the same for the optometrists (2.8 ± 0.7) and the non-optometrists (2.6 ± 0.9); that is, non-optometrists can grade accurately. The median grading reliability of the optometrists (±0.41) was statistically significantly lower (i.e. superior) than that of the non-optometrists (±0.67) (Fig. 2.6). Non-optometrists tended to display some reluctance to grade by interpolation and to grade subtle clinical signs less reliably.

Efron et al.[38] concluded that when averaged over several attempts, non-optometrists will arrive at similar estimates of severity as optometrists when grading ocular complications of contact lens wear; however, they will do so less reliably. Thus, possession of the clinical skill set is not required to grade accurately, but at least certain elements of the clinical skills set are required for reliable grading.

Cardona and Seres[39] came to similar conclusions. They noted that knowledge intensity and specificity both contribute to improved grading skills, albeit through different mechanisms. They also suggested that an intermediate knowledge of complications of contact lens wear and a basic training in pathology is required to attain good grading accuracy.

Effect of experience and training on grading performance

The experiment described earlier did not address the question of the *relative* contributions of the three attributes of the clinical skill set to grading reliability. To examine this, Efron et al.[40] conducted a further experiment whereby the influence of experience and training on grading reliability was assessed on a group of subjects with a common knowledge base.

Twenty-three optometry students who were unfamiliar with the use of grading scales each used the Efron Grading Tutor computer program (described in Chapter 3) to ascertain grading reliability at an initial experimental session and a final session 3 weeks later. Twelve subjects were given a tutorial on grading techniques and were asked to complete two grading exercises between the initial and final sessions; this was designated as the trained group. The other 11 subjects (the untrained group) received no such training between the two sessions. Differences in grading reliability between the initial and final grading sessions were evaluated for both groups.

Grading reliability was superior (lower score) for the combined subject cohort at the final visit (mean ± SD 0.33 ± 0.12) compared with the initial visit (0.46 ± 0.25). However, there was no difference in improvement in grading reliability between the two groups. From this, Efron et al.[40] concluded that grading reliability improves statistically with some experience, although perhaps not to a clinically meaningful extent. No added benefit can be derived from supplemental training in terms of grading reliability.

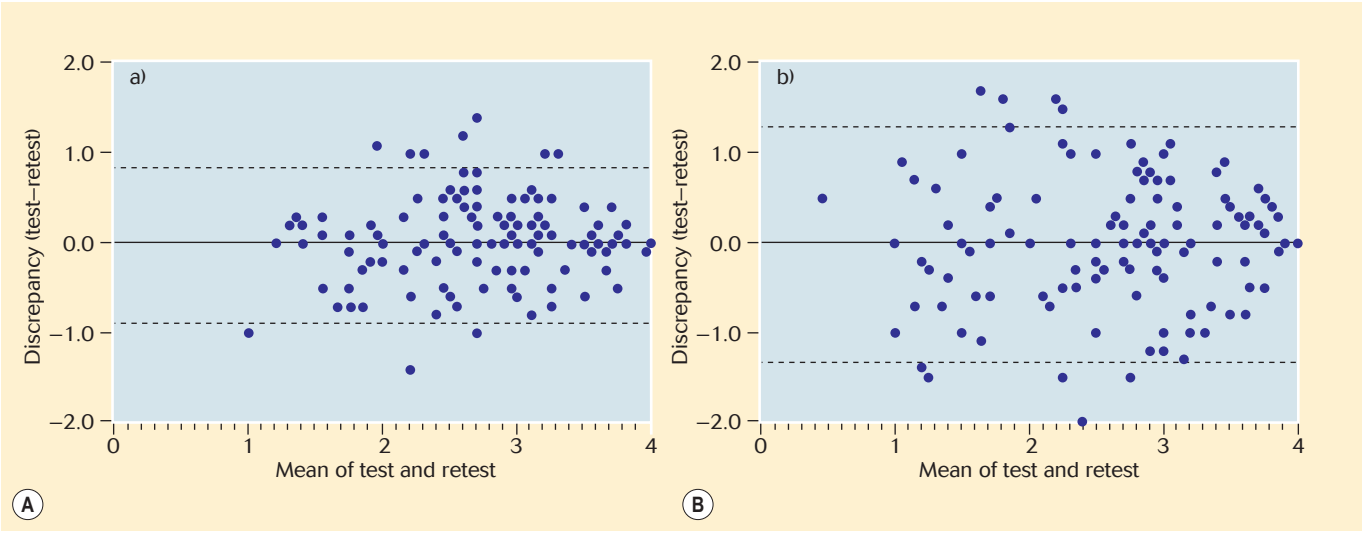


Fig. 2.6 Plot of test–retest grading discrepancies versus mean of the test–retest grading estimates of the severity of a range of contact lens complications, for optometrists (left graph) and non-optometrists (right graph). The solid line in each graph represents the mean of the test–retest discrepancies and the dotted lines represent the 95% confidence limits of the test/retest discrepancies (n = 144 for each graph). (Adapted from Efron N, Morgan PB, Jagpal R. The combined influence of knowledge, training and experience when grading contact lens complications. Ophthalmic Physiol Opt 2003;23:79–85).

GRADING UNDER TIME CONSTRAINTS

To investigate the effect of observation time on the precision of grading the severity of complications of contact lens wear, Efron and McCubbin[29] asked 25 optometry students to use the Efron Grading Scales to grade the severity of one image of each of the 16 forms of anterior eye pathology depicted in these scales. This procedure was repeated for observation times of 0.1, 2 and 60 seconds. Overall, significantly greater grading precision (smaller SD of mean grades) was demonstrated for longer observation times ($p < 0.004$); however, certain complications appear to require longer observation times for precise grading. There was a highly significant dependence of the mean grade on image ($p < 0.0001$), observation time ($p < 0.0001$) and observation time–image interaction ($p < 0.0001$). It was concluded that a brief viewing time of a few seconds is typically all that is required for precise grading of ocular complications of contact lens wear. Some forms of pathology are more complex and may require more time for precise grading.

GRADING IN PRACTICE

Efron et al.[41] conducted a study to investigate the extent and pattern of use of grading scales in optometric practice in Queensland, Australia. An anonymous postal survey was sent to 756 optometrists, and information relating to level of experience, practice type, location and mode of usage of grading scales was elicited. Survey forms were returned by 237 optometrists, representing a 31% response rate. The majority of respondents (61%) reported using grading scales frequently in practice; 65% of these preferred to use the Efron Grading Scales.

Grading scales are more likely to be used by optometrists who (1) have graduated more recently ($p < 0.001$), (2) have a post-graduate certificate in ocular therapeutics ($p = 0.018$), (3) see more contact lens patients ($p = 0.027$) and (4) use other forms of grading scales ($p < 0.001$). The most frequently graded ocular conditions were corneal staining, papillary conjunctivitis and conjunctival redness. The main reasons reported for not using grading scales included preference for sketches, photographs or descriptions (87%) and unavailability of scales (29%).

Grading scales were used for a variety of purposes, including assessment of severity of conditions, communication with other professionals, making comparisons between patients, informing treatment decisions and patient education.

Wolffsohn et al.[35] conducted an online survey of eye care practitioners from around the world regarding their current practice for anterior eye health recording, including the use of grading scales. Surveys returned by 809 practitioners revealed that grading scales were used for recording anterior eye health more in contact lens patients than in other patients. Of the respondents, 84.5% used one grading scale, and 13.5% used two grading scales, with the Efron (51.6%) and BHVI (48.5%) systems being the most popular. The median number of features graded was 11 (range 1–23), with the frequency of grading specific conditions ranging from 91.6% (bulbar hyperaemia) to 19.6% (endothelial blebs).

Conclusions

The grading scales presented in Appendix A have been devised as a clinical aid to accurate record keeping. These grading scales provide a practitioner-friendly means of recording adverse responses to contact lens wear and monitoring changes in severity over time. The assignment of general guidelines relating to the necessity for clinical action with respect to each level of severity can be of assistance to clinicians in formulating a general framework for patient management. The grading scales will also nurture a common language that can assist practitioners communicate clinical information within and beyond the confines of contact lens practice.

Clinicians are encouraged to use grading scales as part of their routine contact lens practice so as to foster a disciplined and consistent approach to clinical decision-making, which will ultimately benefit patients. As a general rule, a change or difference of greater than about 1.0 grading scale unit or an absolute level of severity of greater than grade 2 is considered clinically meaningful.

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3 Grading Morphs

Although grading performance can be enhanced by interpolation to the nearest 0.1 grade unit,[1] most practitioners find the process of mental interpolation between two discrete grading steps to be quite difficult, notwithstanding the fact that this task becomes easier with practice. One way of partially overcoming this difficulty is to re-engineer the grading scales into a continuous movie sequence, progress through which can be controlled by the clinician attempting to decide on a grade. Modern computer software technology is available to undertake such tasks; the process of merging discrete images into a continuous movie sequence is known as 'morphing'. The results of morphing will be familiar to many readers because this technique is used extensively in the visual arts to change the appearance of an object or person into another – for example, changing the face of one person seamlessly into that of another.

Morphing is a technique that allows accurate interpolation of numerous progressively changing images between a 'start' image and an 'end' image, which are calculated pixel by pixel. When these images are presented one after the other in rapid succession, a movie or animation results, allowing one to observe the 'start' image being transformed into the 'end' image. The greater the number of interpolated images, the smoother will be the movie sequence. If the 'start' and 'end' images are not identical, the morphing technician can use software to link common elements in these images, and these elements are identified manually. The only limitation to the number of interpolated images is the amount of computer memory available because a high-resolution image in many colours can be memory intensive.

Efron Grading Morphs

Morphing animation sequences have been developed for each of the 16 complications depicted in Appendix A and have been incorporated into a computer program called 'Efron Grading Morphs'. This can be downloaded from the Expertconsult website (www.expertconsult.com) by using the code in the front of this book.

Efron Grading Morphs and 'The Efron Grading Tutor' (described later) can be operated on either IBM-compatible personal computer platforms (Windows 7, Vista, XP or higher) or Apple Macintosh platforms (Mac OS X or higher). The software may also operate on other computer configurations, although full testing has only been performed on the previous configurations.

The operation of the Efron Grading Morphs program is described later.

PROGRAM OPERATION

When the Efron Grading Morphs program is opened, a title page appears. Click on 'Skip'. A second window appears, from which you can choose any one of the 16 available grading morphs shown in the vertical scrolling menu along the left of the window.

The choice of available morphs can be viewed by either (1) clicking on the scroll handle and dragging it up or down or (2) clicking on the up or down arrows until the desired complication can be seen. Once located, click on the desired complication. It will become highlighted in a yellow box, and the corresponding grading morph will be displayed in the centre of the window. The slide bar immediately beneath the grading morph can be adjusted by clicking and holding the small white rectangular slide bar control handle and moving it in the appropriate direction. When the slide bar control handle is moved to the right, the grading morph advances and the level of severity increases. Moving the slide bar control handle to the left will reverse the grading morph to a lower level of severity. The slide bar control handle can be moved back and forth in this way until the desired level of severity is achieved.

The numeric grading indicating the level of severity of the condition being displayed is indicated in the box on the right-hand side as the grading morph is adjusted. This numeric grading is indicated to the nearest 0.1 grading scale unit, with the range being 0.0 (normal) to 4.0 (severe). The slide bar control handle can be released, re-engaged and moved as many times as required, before selecting an alternative grading morph or quitting.

The Efron Grading Morphs program window is shown in Figure 3.1. In this example, papillary conjunctivitis has been selected; this is highlighted by a yellow box in the vertical scrolling menu on the left-hand side of the window. The slide bar control handle has been advanced to grade 2.7; this numeric grade is also displayed in the right-hand-side panel.

For masking purposes, the numeric grading can be 'hidden' by clicking on the button 'Hide Grade' button beneath the numeric grade window. The numeric grading can then be revealed again by clicking on same button, which is now called 'Show Grade'. The operator can toggle between the 'Show Grade' and 'Hide Grade' modes as often as required.

To view a movie sequence of the selected morph, click on 'Play movie'. A movie sequence of the morph, which lasts approximately 10 seconds, will be shown.

A different grading morph can selected by clicking on a different complication in the vertical scrolling menu. The operating procedure as described previously is identical for all 16 grading morphs.

Clicking the '?' (Help) button in the top right corner of the window opens a separate window, which pictorially indicates how the program should be used. In this view, clicking on the 'Close' button in the upper right corner will reopen the main window platform, from which any of the 16 grading morphs can again be selected.

Simply close the window in the usual manner to quit the program.

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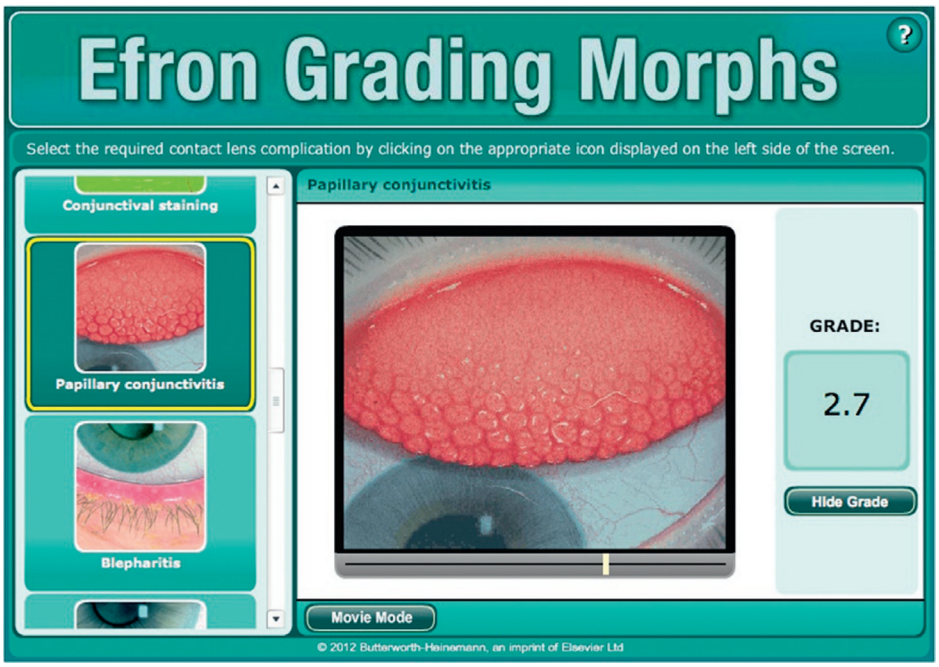


Fig. 3.1 Efron Grading Morphs program window. In this example, the papillary conjunctivitis morph is active.

EFRON GRADING SCALES VERSUS EFRON GRADING MORPHS

Technical differences

The creation of printed scales involves computer-based scanning of the original artwork. The resulting RGB (red/green/blue) electronic files are used for storing and displaying colour images on computers. These must be converted to CMYK (cyan/magenta/yellow/black) electronic files, which are used to control CMYK-coloured inks when printing to paper. This conversion alters the stored colour information and results in a shift in the hue, saturation and value (brightness) of the colours of the grading scales when they appear in printed form. Computer morphs, however, are viewed on a display monitor in the RGB format.

As a result of the previous considerations, printed scales on paper might be expected to look different from computer morphs on a computer screen. Additionally, the individual images on the printed scales are relatively small (36 × 27 mm) and static, whereas the computer morph images on screen are relatively large (e.g. 97 × 79 mm on a 15-inch computer screen displaying 1024 × 768 pixels) and dynamic. In view of the differences described previously, computer morphs may or may not be accurate or accord the same reliability as the generally accepted and well-established printed scales.

Performance differences

In contrast to the recommended method of using printed scales – by interpolation of the score to the nearest 0.1 grading scale unit – no such interpolation is required when using continuously variable computer morphs. Because there is no 'guesswork' required by way of interpolation of grades when using computer morphs, it might be expected that grading can be executed with greater reliability when using this tool versus printed scales.

Efron et al.[2] evaluated the performance of the Efron Grading Morphs computer program by (1) determining grading accuracy when using this program in relation to that obtained using the original five discrete printed images of the Efron Grading Scales, from which the morphs were constructed; and (2) comparing grading reliability between these two grading tools. The aim of this experiment was to determine whether computer morphs accord superior grading performance compared with printed scales.

Nine experienced optometrists were each invited to grade – to the nearest 0.1 increment – an image of each of 16 contact lens complications, using printed Efron Grading Scales and the electronic Efron Grading Morphs computer program. This entire procedure was repeated approximately 2 weeks later, yielding a total database comprising 576 individual grading estimates. Good accuracy was achieved by using computer morphs, as evidenced by the similarity between the mean of the test and retest grading estimates for the printed scales (2.8 ± 0.7) and the computer morphs (2.6 ± 0.8).

There was no difference in median reliability between the printed scales (±0.41) and the computer morphs (±0.43). Figure 3.2 depicts the grading discrepancies versus the mean of the test and retest grading estimates for the printed scales and computer morphs. It is clear by inspection that there is no general relation between the discrepancies and the means, indicating that grading reliability is unaffected by the severity of the condition being assessed by using either grading tool.

The differences in grading estimates between the two grading tools versus condition severity are presented in Figure 3.3. Again, there does not appear to be any relationship between these discrepancies and condition severity.

Chong et al.[3] reported inferior grading reliability (i.e. higher standard deviations (SDs)) for grading conjunctival redness and papillary conjunctivitis and no difference for grading corneal staining when using printed scales versus computer morphs. However, the differences with respect to grading conjunctival redness and papillary conjunctivitis were small, and the authors failed to verify the statistical significance of these differences.



Fig. 3.2 Plot of test–retest grading discrepancies versus mean of the test–retest grading scores for all observers and ocular complications, for printed scales **(A)** and computer morphs **(B)**. The solid line in each graph represents the mean of the test–retest discrepancies and the dotted lines represent the 95% confidence intervals of the test–retest discrepancies (n = 144 for each graph). (Adapted from Efron N, Morgan PB, Jagpal R. Validation of computer morphs for grading contact lens complications. Ophthalmic Physiol Opt 2002;22:341–9.)

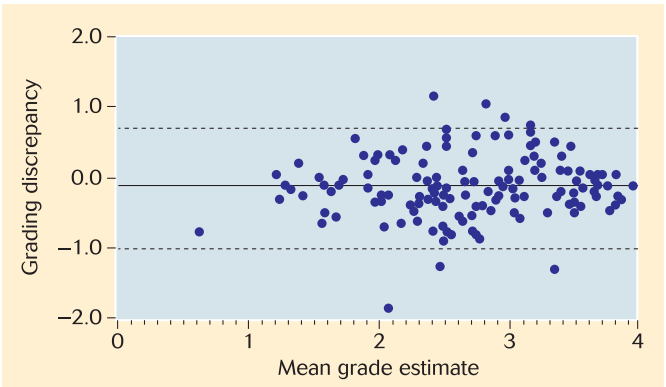


Fig. 3.3 Differences in grading estimates when using printed scales and computer morphs versus mean of grading estimates for all observers and ocular complications. The solid line represents the mean of the grading differences, and the dotted lines represent the 95% confidence intervals of the differences (n = 144). (Adapted from Efron N, Morgan PB, Jagpal R. Validation of computer morphs for grading contact lens complications. Ophthalmic Physiol Opt 2002;22:341–9.)

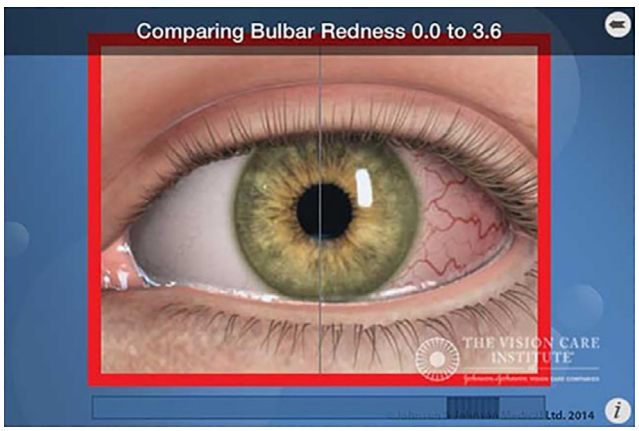


Fig. 3.4 Split-screen grading of bulbar conjunctival redness by using the Vision Care Institute Clinical Grading Scales App on an iPhone. (Courtesy The Vision Care Institute, Johnson and Johnson Vision Care.)

The study of Efron et al.[2] found no overall statistically significant difference in grading reliability when grading a broad range of conditions by using printed scales versus computer morphs. Computer morphs were thus considered to have been validated in view of their accuracy and reliability compared with printed scales. The notion that computer morphs offer superior grading reliability compared with printed scales must therefore be rejected.

The Vision Care Institute Clinical Grading Scales App

The Vision Care Institute, under the auspices of Johnson and Johnson Vision Care, has produced a grading scale morphing program called the 'Vision Care Institute Clinical Grading Scales App'.

The app allows practitioners to evaluate nine common eye conditions – bulbar conjunctival redness, corneal staining, papillary conjunctivitis (separate morphs for assessing tarsal conjunctival redness and roughness), limbal redness, meibomian gland dysfunction, pterygium, pinguecula and cortical cataract. The level of severity is adjusted with a finger-touch sliding control. A readout of the level of severity is indicated in increments of 0.1 grading scale units, from 0.0 to 4.0. The morphs were created from the still images that were developed for the Vision Care Institute Clinical Grading Scales.

A novel feature of the app is a split-screen function that allows left and right fields of the image to be set to different levels of severity. This would allow, for example, comparison of bulbar redness before and after overnight contact lens wear. In the simulation in Figure 3.4, the left side of the split-screen is set to the level of bulbar conjunctival redness before overnight lens wear (grade 0.0), and the right side of the split-screen is set to the level of severity of bulbar conjunctival redness after

overnight lens wear (grade 3.6), facilitating ready appreciation of the ocular response to overnight lens wear in this patient.

The app also presents assessment guides, such as slit lamp illumination techniques, corneal inflammation versus infection, signs of oxygen deficiency, staining and lid assessments.

This app is compatible with the iPhone and can be downloaded for free via the Apple App Store; however, it is not available in all countries.

The Efron Grading Tutor

The Efron Grading Tutor computer program, which was developed for use by students, practitioners and researchers, has a variety of potential applications. The program can be downloaded from the Expertconsult website (www.expertconsult.com) by using the code in the front of this book. Computer operating requirements are the same as for the Efron Grading Morphs program, as outlined previously.

An important application of this program is to help practitioners assess, and possibly enhance, their grading performance. Specifically, The Efron Grading Tutor will do the following:

- help hone grading skills;
- identify whether there is any grading bias;
- determine grading consistency;
- calculate grading accuracy;
- compare performance with that of experts;
- explain what all this means clinically.

The Efron Grading Tutor has a similar interface to the Efron Grading Morphs program. It is assumed that the user is familiar with the Efron Grading Morphs program, which provides instructions on general principles of how to grade the severity of a condition by using morphs. The Tutor invites the user to grade the severity of 16 images of contact lens complications, twice in random sequence (32 gradings are performed). A given complication is graded by adjusting a slide bar until the severity of the condition as depicted in the morph matches that of the image under consideration. Severity is graded on a continuous scale, which ranges from 0.0 (normal) to 4.0 (severe). The numeric gradings are revealed to the user only after all 32 gradings have been attempted. On completion of this grading exercise, a series of windows appears and will give the user the information listed previously.

A supplementary 'Help' window can be called up, and it presents further tips on grading and provides other useful information.

PROGRAM OPERATION

When the file 'The Efron Grading Tutor' is opened, the program will begin to run, and a title page appears. Click on 'Skip' to begin the program. In the next frame, enter your name, and then click 'Continue' or hit the 'Return' key.

You are now presented with a set of instructions, which explains how to use this program. Click 'Start Tutor' to begin grading. The first image to be graded appears, together with the matching morph.

To grade the image, the slide bar beneath the grading morph movie frame is adjusted by clicking and holding the small rectangular slide bar control handle and moving it in the appropriate direction. When the slide bar control handle is moved to the right, the grading morph movie advances and the level of severity increases. Moving the slide bar control handle to the left will reverse the grading morph movie to a lower level of severity. The slide bar control handle can be moved back and forth in this way until the desired level of severity is achieved and matches that of the image under consideration. The slide bar control handle can be released, re-engaged and moved as many times as required before advancing to the next image.

The Efron Grading Tutor program window is shown in Figure 3.5. In this example, the user was invited to grade an image of epithelial microcysts (the left-hand-side image); the condition being graded (in this case, epithelial microcysts) is

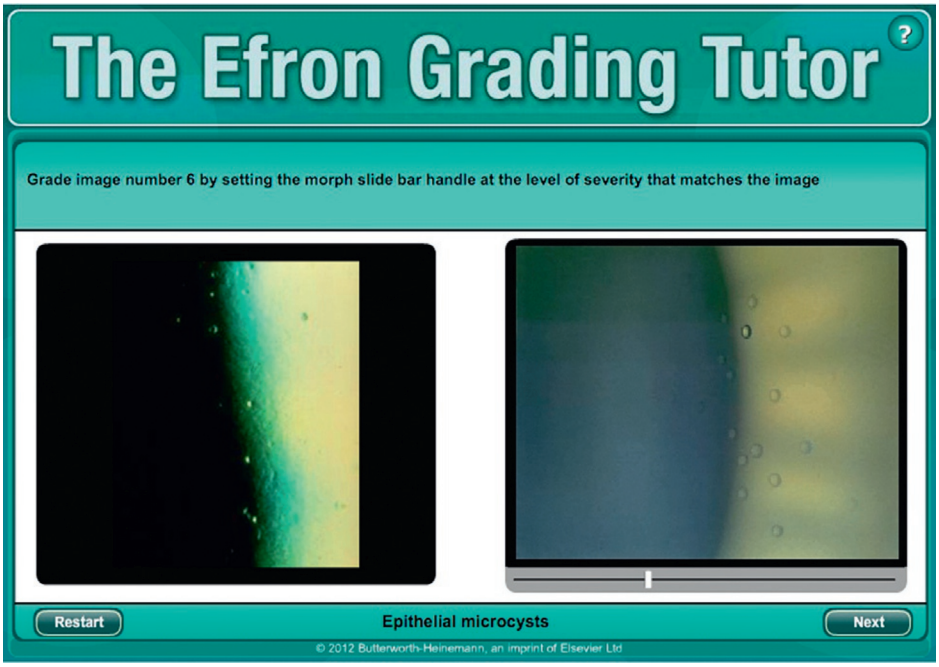


Fig. 3.5 The Efron Grading Tutor program window. In this example, the operator is invited to grade an image of epithelial microcysts.

indicated on the bottom bar. The top bar indicates that this is the 16th image being graded. The slide bar control handle beneath the morph on the right-hand side has been adjusted so that the level of severity displayed in the morph matches that of the left-hand-side image; this numeric grade is deliberately *not* displayed (to avoid observer bias).

When you are satisfied that you have matched the first image as accurately as possible, click the 'Next' button in the bottom right corner to advance to the second image. You can keep track of how many images you have graded (up to the maximum 32 images) by referring to the grading instruction along the top of the window.

Click 'Next' again, and so on, until all 32 images have been graded. You can stop grading and restart the program at any time by clicking on the 'Restart' button at the bottom left.

After grading the 32nd image, click on the 'Results' button in the bottom right corner. You will be led through a series of windows that will present you with information concerning your own grading performance. The first result you are presented with is your bias score.

Click 'Consistency' to reveal your consistency score. An arrow will appear from the right and stop at your consistency score. An explanation as to what this means is provided (Fig. 3.6).

Click 'Accuracy' to reveal your accuracy scores. Your name and a date and time stamp will appear in the heading bar. You can scroll through all 16 complications by either (1) clicking on the scroll handle and dragging it up or down or (2) clicking on the up or down arrows, until the desired complication can be seen (each complication is named and is accompanied by a small image of that complication). For each complication, the mean (±1 SD) grading estimate assigned by a panel of 10 'experts' is presented, along with your score and the difference between your score and that of the experts (Fig. 3.7).

A more detailed analysis of your grading performance with respect to any given complication can be analysed in detail by clicking anywhere along the row relating to the complication of interest. This will open the 'Accuracy Analyser' window for the chosen complication, which is stated at the bottom of the window (Fig. 3.8). An image of the complication that was graded is shown on the, and a grading morph movie frame of the complication appears on the right. The slide bar beneath the grading morph movie frame is moved in the usual way and can be adjusted with reference to the image on the left and the grading level of the morph, which is indicated in a small window above the morph. The expert mean (±1 SD) grade and the score you obtained when undertaking the masked grading previously is shown in the top left corner. In this way, you can dynamically compare your estimate with that of the experts.

Click the 'Return' button on the bottom right to return to the 'Grading Accuracy' window. Another complication may be selected to go to the 'Accuracy Analyser' for that complication, and so on. The full set of grading accuracy scores can be printed out by hitting the 'Print' button.

Clicking 'Next' takes you to the window that presents your average grading accuracy, which advises whether your grade is typically higher, lower or the same as that of the group of experts.

An overall summary of your results can be seen in the next window by clicking 'Summary' on the bottom right. Again, your name and a date and time stamp will appear in the heading bar. A table through which you can scroll to view your first and repeat grading scores and the score difference for each of the 16 complications is presented (Fig. 3.9). Three results boxes appear on the right, which display your grading bias, consistency and accuracy. The full set of summary data can be printed out by hitting the 'Print' button. Click 'Finish' to end the program.

Conclusions

Although there is no difference in grading performance when using printed scales versus computer morphs,[2] there are clearly advantages to using both tools. Printed scales offer the

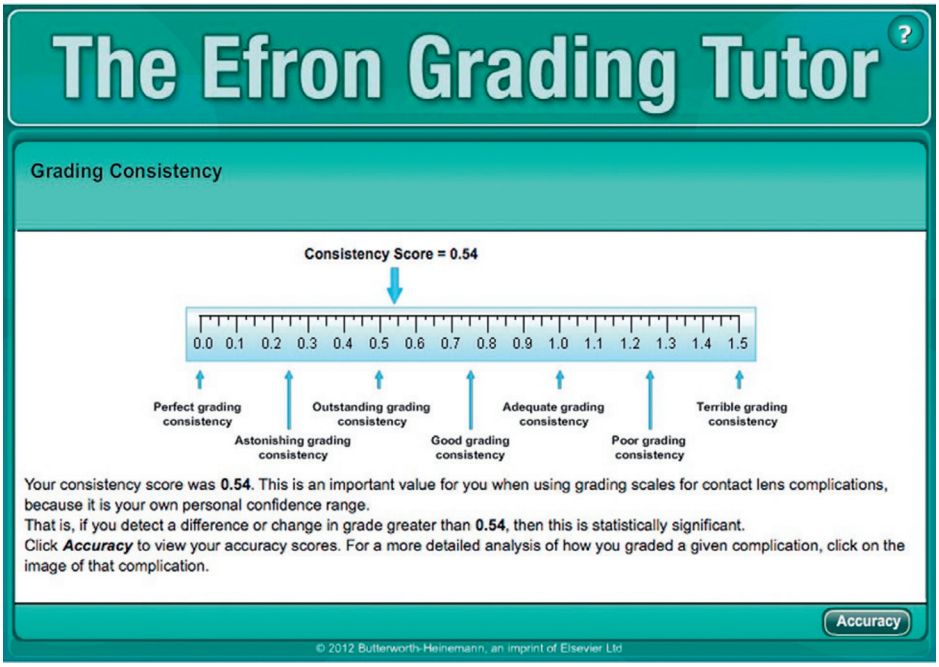


Fig. 3.6 The Efron Grading Morphs program window for analysing grading consistency.

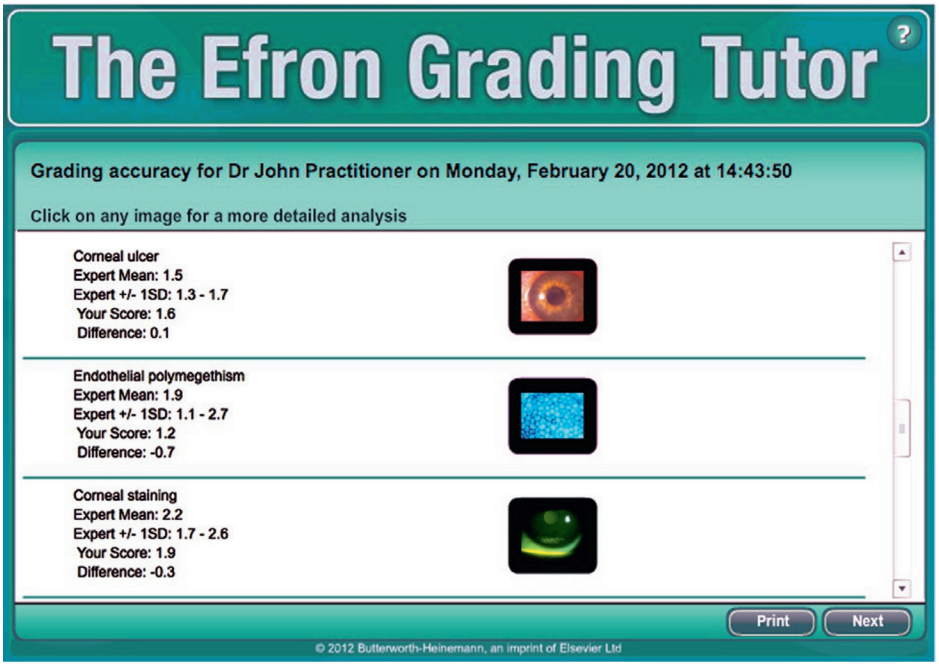


Fig. 3.7 The Efron Grading Morphs program window, which gives scroll bar access to grading accuracy results for all 16 complications.

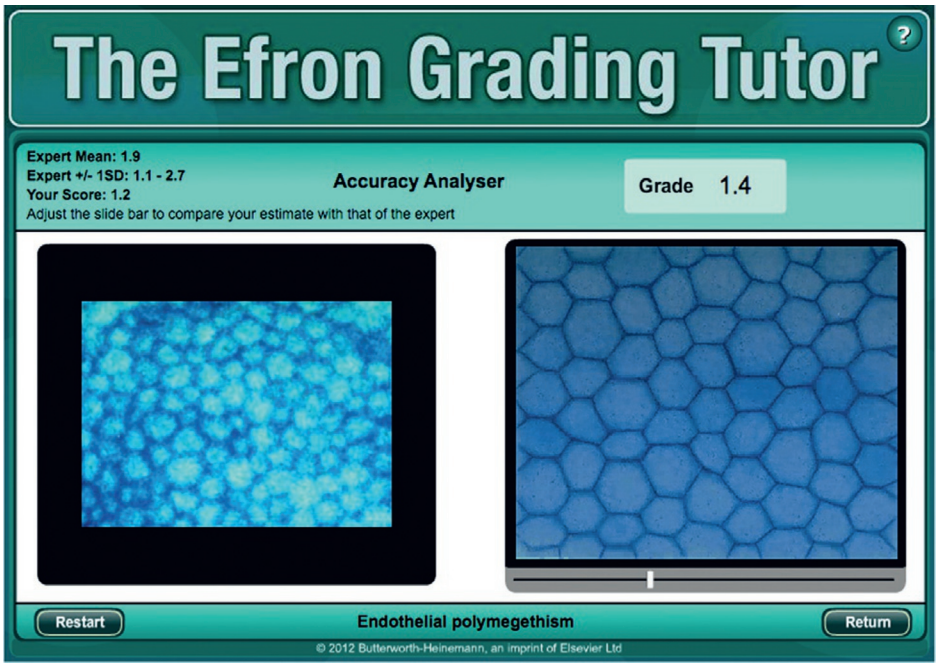


Fig. 3.8 The Efron Grading Morphs program 'Accuracy Analyser' window. In this example, grading performance in relation to endothelial polymegethism is being analysed.

convenience of being readily accessible and thus they may be kept next to the slit lamp biomicroscope. The use of computer morphs ensures that grading estimates will be made to the nearest 0.1 grading scale increment, obviating the tendency observed with printed scales to grade to the nearest whole-digit or half-digit grade.

Computer morphs also offer the opportunity of integration with computer-based record-keeping systems. For example, a grading determined on a morphing tool can be entered automatically into a patient's electronic record. Computer morphs have the advantage of allowing students and practitioners to better conceptualise the continuum and range of severity of various forms of contact lens–induced ocular pathology and can be incorporated into self-help grading tutorial programs, such as The Efron Grading Tutor; in this context, computer morphs constitute a valuable learning, teaching and research tool.

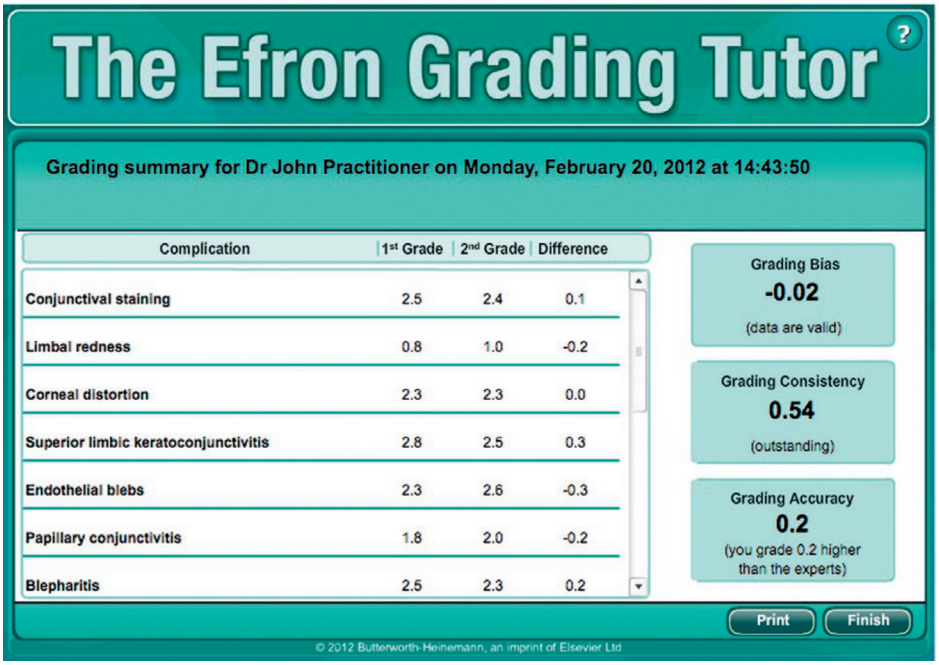


Fig. 3.9 The Efron Grading Morphs program summary window, which gives scroll bar access to grading scores for all 16 complications. Grading bias, consistency and overall accuracy are indicated in the boxes on the right side.

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4 Blinking Abnormalities

Blinking is a high-speed closure movement of the eyelids of short duration and has both reflex and spontaneous origins.[1] Reflex blinking can be elicited by a variety of external stimuli, such as strong lights, approaching objects, loud noises and corneal, conjunctival or ciliary touch.

Contact lenses will cause reflex blinking during lens insertion and removal and other instances of manual manipulation. Furthermore, as a result of a reflex blink, contact lenses may mislocate or become dislodged from the eye. Besides these phenomena, there is no reason to suppose that contact lens wear alters the essential nature of the reflex blink. For this reason, this chapter will concentrate on spontaneous blinking activity associated with contact lens wear, and the term 'blink' should generally be taken to mean 'spontaneous blink'.

Blinking serves a number of useful functions both with and without contact lenses. Eye care practitioners have long subscribed to the notion that their contact lens patients should execute full and regular blinks during lens wear. This chapter will review characteristics of the normal blink and will examine how contact lens wear can affect, and be affected by, blinking behaviour. Complications that arise from poor blinking behaviour with contact lenses (e.g. lens surface drying as shown in Fig. 4.1) will be reviewed, along with the question of clinical management of blinking abnormalities.

The normal spontaneous blink

MECHANISM OF BLINKING

Eyelid closure during blinking is effected by the orbicularis oculi muscle, which is innervated by the seventh cranial nerve. The act of blinking is accomplished primarily by the upper lid. The lower lid remains virtually stationary. Closure is characterised by a progressive narrowing of the palpebral fissure, in a zipper-like fashion, from the outer canthus to the inner canthus. This moving wave of closure serves to force aqueous in the inter-palpebral fissure toward the lacrimal puncta, thus aiding tear drainage.[2]

Spontaneous blinking occurs in all terrestrial vertebrates possessing eyelids, although the rate of blinking varies considerably among species. Large predatory cats execute less than one blink per minute, whereas some species of small monkeys have blink rates as high as 45 times per minute. Infants have a very low spontaneous blink rate.[1]

Spontaneous blinking occurs in patients who have total congenital blindness, indicating that it is a phenomenon that is not learned or dependent on visual input.[1] The rate of spontaneous blinking may alter in response to changes in the level of visual activity and in different emotional states. General environmental changes, such as the level of dryness or wind flow, may also alter the spontaneous blink rate. The frequency and completeness of blink is reduced during intense concentration, for example, when reading[2] or working on a visual display unit.

TYPES AND PATTERNS OF BLINKING

Researchers must employ covert methods to monitor types and patterns of spontaneous blinking; this is necessary because of the methodological problem that subjects will alter their blinking activity if they are aware that this is being assessed.[2] Typically, subjects under such circumstances will execute an increased proportion of voluntary forced blinks and a greater overall blink frequency. For this reason, hidden observers or video cameras are employed to record blinking activity while the subject, for example, is engaged in discussion or is asked to observe a silent movie.

Zaman and Doughty[3] have highlighted other potential methodological pitfalls in quantifying blinking behaviour. For example, simple averaging of blink rates may not always be appropriate because of the high chance of a non-Gaussian data distribution. These authors concluded that eye-blink monitoring for at least 3 minutes is required for valid data analysis. Fortunately, almost all blink researchers have used observation times in excess of this.

According to Abelson and Holly,[4] blinking can be classified into four basic types:

- Complete blink – the upper eyelid covers greater than 67% of the cornea.
- Incomplete blink – the upper eyelid covers less than 67% of the cornea.
- Twitch blink – a small movement of the upper eyelid.
- Forced blink – the lower lid raises to complete eye closure.

The percentage of all blinks that can be characterised by each of these four blink types, as determined by Abelson and Holly,[4] is illustrated in Figure 4.2. Subsequent research has confirmed these findings.[5,6]

Tsubota et al.[7] developed a computer-interfaced 'blink analyser' to accurately measure the time course and pattern of blinking in 64 normal volunteers. They found that the average time taken to execute one complete blink (which they defined as the upper lid covering greater than 85% of the cornea) was 0.20 ± 0.04 second and that the average inter-blink period (IBP) was 4.0 ± 2.0 seconds. Taking one complete blink cycle as the sum of the blink time and IBP ($0.2 + 4.0 = 4.2$ seconds) gives an average blink frequency of 14.3 blinks per minute (i.e. 60/4.2). This result is consistent with previous estimates of the spontaneous blink rate in humans.[5,8]

The small interruption to visual input during a blink is only thought to be of practical significance in occupations or tasks requiring constant monitoring of rapidly changing visual images. (Paradoxically, blinking is problematic for researchers monitoring blinking activity of experimental subjects, either directly or via video replays; in the latter case, viewing in slow motion solves this problem.) Volkmann et al.[9] proposed that suppression of the visual pathway is associated with blinks, so the momentary interruption to visual input does not produce a conscious interruption to visual perception.

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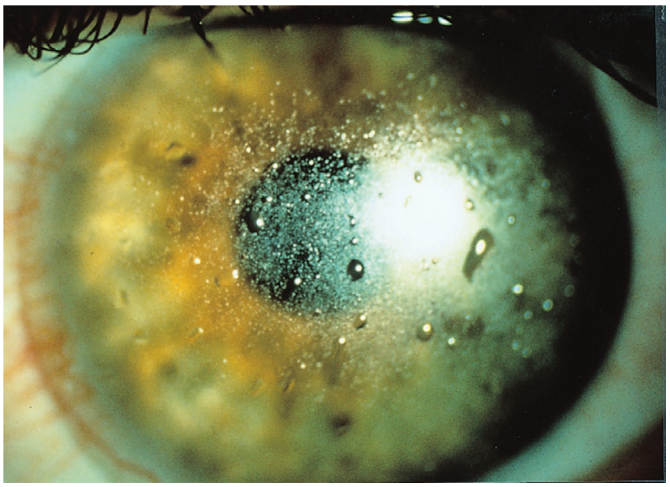


Fig. 4.1 Non-wetting surface of a silicone elastomer lens. (Courtesy Timothy Grant, Bausch & Lomb Slide Collection.)

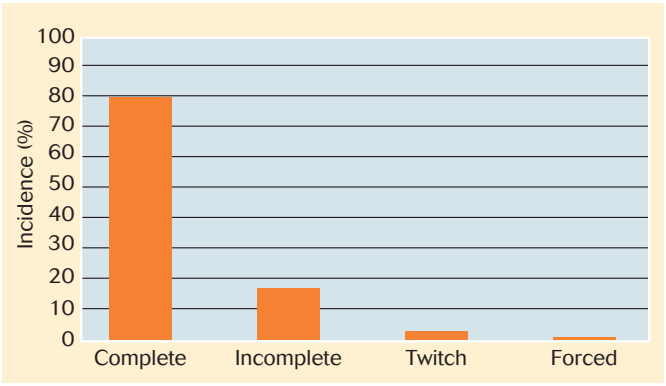


Fig. 4.2 Frequency of occurrence of various blink types. (Adapted from Abelson MB, Holly FJ. A tentative mechanism for inferior punctate keratopathy. Am J Ophthalmol 1977;83:866–70.)

Various authors have suggested that there is a gender difference in blink rate. Hart[1] proposed that males blink more frequently compared with females, whereas Tsubota et al.[7] have suggested the opposite; neither group has statistically validated their claims. Yolton et al.[8] shed light on this issue by measuring the spontaneous blink rate in males, females not using oral contraceptives and females using oral contraceptives. The blink rates observed in these three groups were 14.5, 14.9 and 19.6 blinks/min, respectively. This finding indicates that there is no intrinsic gender difference in the blink rate, but the use of oral contraceptives causes a significantly greater blink rate, for reasons which are unclear.

PURPOSE OF BLINKING

Spontaneous blinking in non–lens wearers serves the following beneficial functions:

- Maintenance of an intact pre-corneal tear film by constantly spreading the tear film evenly across the corneal surface.
- Removal of intrinsic and extrinsic particulate matter by forcing such debris into the lower lacrimal river.
- Facilitation of tear exchange by constantly swiping tears toward the puncta located at the inner canthus.

Paradoxically, blinking may also be harmful to the already-compromised ocular surface. This has been discussed by Cher,[10] who introduced the concept of 'blink-related microtrauma'. A prime example is superior limbic keratoconjunctivitis, which is a mechanical result of blinking under prolonged non-physiological conditions. Other ocular surface disorders regarded as primarily derived from blink microtrauma are filamentary keratitis, blepharospasm and severe ptosis, canthal/palpebral froth, conditions resulting from disordered eyelid lining and contact lens–related damage.

The importance of maintenance of an intact pre-corneal tear film has been demonstrated in a number of studies that have examined blinking behaviour in patients suffering from symptoms of dry eye.

Prause and Norn[11] proposed the theory that spontaneous blinking is, in part, a stimulus to rupture of the pre-corneal tear film. They tested this hypothesis by measuring tear break-up. time (TBUT) and the IBP in normal individuals and in patients with dry eye. In both groups, there was a statistically significant positive correlation between these two parameters; that is, the more rapidly the tear film breaks up, the more frequently the patient blinks. That finding was subsequently confirmed by Yap[12] in a group of normal subjects, although two other research groups found no such association.[8,13]

Prause and Norn[11] also demonstrated that, in general, IBP was slightly less than TBUT, suggesting that patients adopt a blink rate that will prevent tear break-up. Using quantitative videographic analysis, Tsubota et al.[7] found that IBP in patients with dry eye was 1.5 ± 0.9 seconds, compared with 4.0 ± 2.0 seconds in normal subjects.

Indirect evidence of the link between TBUT and IBP comes from the work of Tsubota and Nakamori,[14] who measured the tear evaporation rate from the ocular surface (TEROS) in 17 normal volunteers and found an increase in the blink rate with increasing TEROS. This result is consistent with previous demonstrations of the positive correlation between IBP and TBUT because tear break-up associated with more rapid blinking would be expected to result in higher rates of tear evaporation.

Although the weight of evidence does suggest that the blink rate is, in part, dependent on the integrity of the tear film, other factors must also be involved. This fact was demonstrated by Collins et al.,[15] who found that blinking persisted after the instillation of a corneal topical anaesthetic in a group of normal subjects. The blink rate did, however, drop from 24.8 to 17.2 blinks/min. If tear break-up was the sole determinant of the blink rate, blinking would have stopped in the eyes with anaesthetised corneas.

Alterations to blinking caused by contact lenses

BLINK RATE

It has long been recognised that contact lens wear can alter blinking activity.[16] Hill and Carney[17] demonstrated, in a group of seven subjects, that blink rate increased from 15.5 blinks/min to 23.2 blinks/min after being fitted with rigid polymethyl methacrylate (PMMA) contact lenses. A similar result was reported by York et al.,[18] although Brown et al.[19] did not confirm this

result. It appears, however, that PMMA lens–induced alterations to the blink rate may be more related to reflex blinking rather than to spontaneous blinking; that is, the increased blink rate may be a result of continual irritation caused by the lens edge buffeting against the lid margin.

In another group of seven subjects, Carney and Hill[20] demonstrated that the blink rate increased from 12.1 blinks/min to 20.3 blinks/min after the subjects were fitted with soft contact lenses (presumably hydroxyethyl methacrylate (HEMA)). The reason for this is less clear, as soft lenses would be expected to be more comfortable and thus to induce less reflex blinking activity, although it should be noted that the earlier study of Brown et al.[19] found that the blink rate was essentially unaffected by soft lens wear.

Although the blink rate may be altered during contact lens wear, a supplementary consideration is whether or not any alteration to blinking activity is permanent. Yolton et al.[8] reported that the blink rate (16.2 ± 8.9 blinks/min) in a cohort of habitual contact lens wearers (the lens type was not specified) who had stopped lens wear at least 24 hours before the blinking assessment was identical to that of a matched control group of subjects who had never worn contact lenses (16.2 ± 9.5 blinks/min), suggesting that contact lens–induced alterations to the blink rate are only evident during lens wear.

Contact lens wearers experiencing end-of-day dryness have been observed to display an increased blink rate.[21] It is thought that the increased blink rate could act to improve the ocular surface environment and relieve symptoms.[21]

Lopez-de la Rosa et al.[22] reported that the blink rate increased when wearers of hydrogel contact lenses were exposed to simulated adverse environmental conditions (in-flight air cabin environment: 5% relative humidity, localised air flow, 23°C temperature and 750 millibars (mb) atmospheric pressure) for 90 minutes in an environmental chamber, compared with standard environmental conditions (50% relative humidity, 23°C temperature and 930 mb of atmospheric pressure). The authors suggested that contact lens dehydration was the stimulus for the increased blink rate. Kojima et al.[23] reported similar findings.

The type of contact lens care solution used can affect blink rate during contact lens wear. Yang et al.[24] reported that lens care solutions incorporating wetting agents are associated with a significantly reduced blink rate, presumably because of improved pre-lens tear film (PLTF) quality.

BLINK TYPE

Carney and Hill[17,20] have examined the effects of rigid and soft lens wear on the pattern of blinking. A decrease in the frequency of long IBPs was observed in association with rigid lens wear, but not soft lens wear. Neither rigid nor soft lens wear altered the proportion of complete, incomplete, twitch and forced blinks. An example of an incomplete blink in a soft lens wearer is shown in Figure 4.3.

Jansen et al.[25] found that blink frequency increased amongst soft contact lens wearers when they were concentrating on near tasks. The authors suggested that wearing of soft contact lenses, even when the subjects were fully adapted, provides enough extrinsic ocular surface stimulation to override internal controls and affect blink parameters.

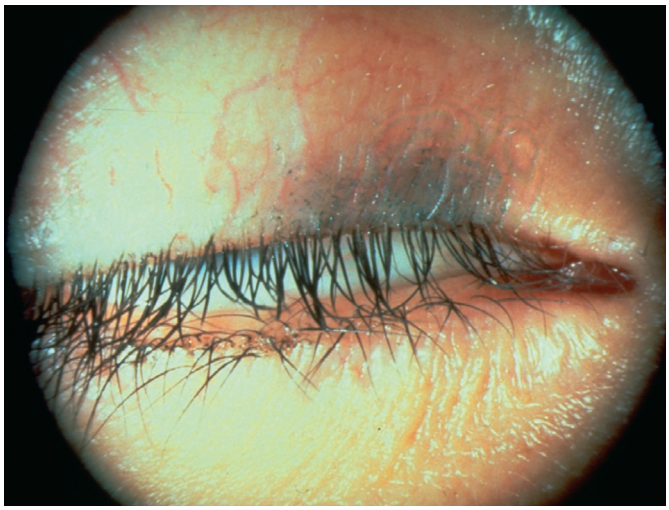


Fig. 4.3 Incomplete blink in a soft lens wearer. (Courtesy Hilmar Bussaker, Bausch & Lomb Slide Collection.)

Complications of abnormal blinking with contact lenses

LENS SURFACE DRYING AND DEPOSITION

The tear film on the front surface of both soft and rigid lenses has a different structure compared with the pre-ocular tear film (POTF), with the lipid layer being thinner or absent and the aqueous layer being of variable thickness, depending on the lens material and design.[26-28] Similarly, the tear film on the front surface of soft and rigid lenses is less stable than that of the POTF. The POTF in normal human subjects has a TBUT of at least 15 seconds.[29] The PLTF has a TBUT of between 3 and 10 seconds for soft lenses[30] and between 4 and 6 seconds for rigid lenses.[27] Bearing in mind that mean IBP in humans is 4.0 ± 2.0 seconds and that contact lens wear has little effect on IBP, it is clear that in some patients, IBP will exceed the TBUT of PLTF, leading to intermittent lens surface drying.

Alonso-Caneiro et al.[31] used a dynamic-area high-speed videokeratoscopy technique to assess tear film surface quality with and without the presence of soft contact lenses on eyes. The authors were able to distinguish and quantify the subtle, but systematic, worsening of tear film surface quality during the inter-blink interval in contact lens wear. Overall, wearing hydrogel and silicone hydrogel lenses caused the tear film surface quality to worsen between blinks compared with that of the bare eye condition.

A case of severe drying of the surface of a silicone elastomer lens (which is naturally hydrophobic) is depicted in Figure 4.1. In view of the rapid TBUT of such a lens, an unsustainable inter-blink frequency of approximately 2 seconds would be required to prevent drying of the lens surface.

It is generally recognised that a full and continuous tear film on the lens surface is important for maintaining a clean surface with minimal deposition. The greater the discrepancy between the IBP and the TBUT of PLTF and the longer the tear disruption is maintained, the greater will be the possibility for both extrinsic and intrinsic material to adhere to the lens surface.

It would also seem theoretically plausible that a discrepancy between the IBP and the TBUT of PLTF of soft lenses could result in a greater degree of lens dehydration, as water from

the lens could evaporate directly into the atmosphere from a dry lens surface. This theory was tested by Young and Efron,[30] but no association could be demonstrated between the TBUT of PLTF and lens dehydration.

In general, therefore, lens surface characteristics can be optimised by ensuring that the IBP is shorter than the TBUT of PLTF.

VISUAL DEGRADATION

Ridder and Tomlinson[32] found that with soft lenses, vision was considerably degraded when a target was presented less than 100 milliseconds (msec) after the blink. They explained their finding in terms of blink suppression and prismatic shift of the retinal image induced by movement of the contact lens produced by the blink. This explanation was reinforced by the observation that loose-fitting contact lenses caused an even greater decrement in immediate post-blink vision.

Blink-induced lens movement causes a reduction in visual performance that is potentially greater with toric soft contact lenses than with spherical soft contact lenses because of the combination of vertical lens movement and rotation. Tomlinson et al.[33] found that prism-ballasted lenses gave better overall visual performance compared with dynamic stabilization design lenses at all times after the blink.

PROLONGED LENS SETTLING

Golding et al.[34] postulated that the extent of lens settling and the degree of post-insertion lens movement are determined by the time-average pressure for post-lens tear film expulsion exerted on the lens by the eyelids. Specifically, they found that lens settling was prolonged (i.e. lens movement was significantly higher) for slower blink rates (10 blinks/min) compared with faster blink rates (30 blinks/min) or the eye closure condition.

EPITHELIAL DESICCATION

Severe desiccation staining of the corneal epithelium is known to occur as a result of fitting extremely thin, high-water-content hydrogel contact lenses.[35] This phenomenon relates primarily to the fitting of lenses that are not properly designed. However, Guillon et al.[36] have demonstrated that epithelial desiccation can occur with well-fitting, high-water-content lenses of adequate thickness. They attributed this phenomenon to a break-up of the tear film at the inferior tear prism margin. This complication is theoretically avoidable if the blink rate is sufficient to prevent such TBUT of PLTF.

POST-LENS TEAR STAGNATION

The anterior ocular surface is host to a plethora of organic material, such as desquamated superficial epithelial and conjunctival cells, mucus, proteins, lipids, microorganisms and inflammatory cells. Environmental antigens, such as iron particles, dust, pollen, smoke, smog and other atmospheric pollutants and particulate matter, can also easily enter the tear film. The material listed rarely poses a problem because it is constantly being washed away with the tear film, primarily as a result of blinking. However, when such material gets behind the lens, problems can arise if the post-lens tear film is allowed to stagnate (Fig. 4.4).

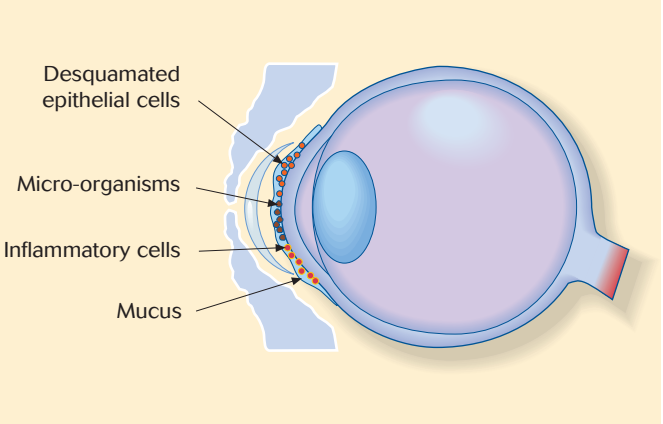


Fig. 4.4 Various types of debris trapped beneath a soft lens.

Infrequent and/or incomplete blinking during contact lens wear can be theoretically problematic because the residency time of ocular pollutants in the post-lens tear film is increased, thus heightening the potential for traumatic, toxic, allergic or infectious insult of the cornea. Blinking serves to flush such debris out from beneath the lens, to be replaced by 'fresh' tears containing a new set of pollutants. As long as there is this constant turnover of tears beneath the lens, which is referred to as 'tear exchange', high resident times of pollutants can be avoided.

Daily wear of rigid contact lenses is known to be associated with a tear exchange of 10% to 17% with each blink.[37] This contrasts with a tear exchange of only about 1% with each blink during hydrogel lens wear[38] and a slightly greater amount with silicone hydrogel lenses.[39] These research findings, as well as accumulated clinical experience, have led practitioners to be aware of the importance of fitting soft lenses such that there is adequate movement of contact lenses (in particular soft lenses) with each blink. Failure to ensure adequate lens movement may allow the stagnating post-lens tear film debris to induce an adverse reaction via a variety of different mechanisms, leading to lens discomfort. Reducing the diameter of soft lenses can enhance tear exchange[40]; however, smaller lenses tend to be less comfortable. Theoretical analyses suggest that fenestrations and channels can facilitate greater tear exchange in soft lenses by enhancing transverse (in–out) lens motion.[41]

Problems relating to post-lens tear film stagnation are uncommon in daily wear because an awake, conscious patient can manipulate or remove an uncomfortable lens, thus minimising any ocular trauma. Furthermore, lenses are removed each day, allowing recovery from any sub-clinical insult that may have occurred.

Post-lens tear stagnation is, however, of real concern in patients who sleep wearing lenses, and the problems with rigid and soft lenses manifest differently. In the case of rigid lenses, the aqueous phase is depleted overnight, leaving a mucus-rich post-lens tear film, which tends to create adhesion between the lens and the cornea (Fig. 4.5).[42] In patients who have slept wearing rigid lenses, blinking upon awakening is critical because the blinking action tends to mechanically dislodge the adherent lens so that a normal post-lens tear film can be re-established.

In the absence of blinking during overnight lens wear, material that was present in the post-lens tear film immediately before going to sleep, in addition to desquamated epithelial cells

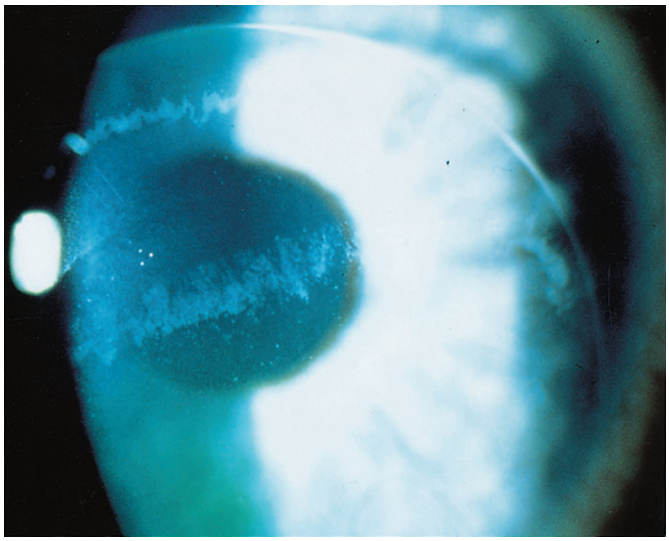


Fig. 4.5 Mucus at the centre and periphery of the cornea in the tear film beneath a rigid lens that has been worn overnight. (Courtesy Donna LaHood, Bausch & Lomb Slide Collection.)

and inflammatory cells that will have accumulated throughout the night, will be present beneath the lens upon waking in the morning.[43] Various forms of toxic, infectious, inflammatory or immunological reactions may be initiated. If the patient continues to wear lenses during the waking hours, the rate of tear exchange, especially with soft lenses, may be insufficient for rapid clearance of the post-lens tear film, allowing continuation of any adverse reactions that have been initiated.

In a patient who sleeps wearing soft contact lenses, a model can be constructed to illustrate the sequence of events that lead to corneal ulceration resulting from inadequate blink-assisted clearance of debris from the post-lens tear film upon waking (Fig 4.6). Desquamated epithelial cells are trapped beneath a soft lens. These cells undergo lysis and irritate the underlying corneal epithelium, causing corneal staining. The epithelium is unable to repair itself in the toxic post-lens tear film environment, and a sterile ulcer results.

Factors governing the removal of debris from the post-lens tear film have been investigated by McGrogan et al.,[44] who inserted soft lenses containing polystyrene microspheres of various sizes and monitored the rate of removal of these microspheres from the post-lens tear film during blinking (Fig. 4.7). The key determinant of microsphere removal was the size of the microspheres; larger microspheres were less easily dislodged from beneath the lens compared with smaller microspheres. Lens modulus and lens fit had little effect on microsphere clearance.

HYPOXIA AND HYPERCAPNIA

The normal cornea is constantly drawing oxygen from the atmosphere to sustain its high levels of metabolic activity. At the same time, carbon dioxide – an unwanted byproduct of corneal metabolism – is released into the atmosphere from the corneal surface. Contact lenses form a potential barrier to both corneal oxygenation and carbon dioxide efflux, resulting in reduced oxygenation (hypoxia) and increased levels of carbon dioxide (hypercapnia). Complications arising from lens-induced hypoxia and hypercapnia will be discussed throughout this book. A key goal of contact lens fitting is minimization of hypoxia and hypercapnia.

All contact lenses fitted today have some degree of gas transmissibility that allows oxygen to flow through the lens into the cornea and carbon dioxide to flow out of the lens into the atmosphere. This necessary gaseous exchange can be further

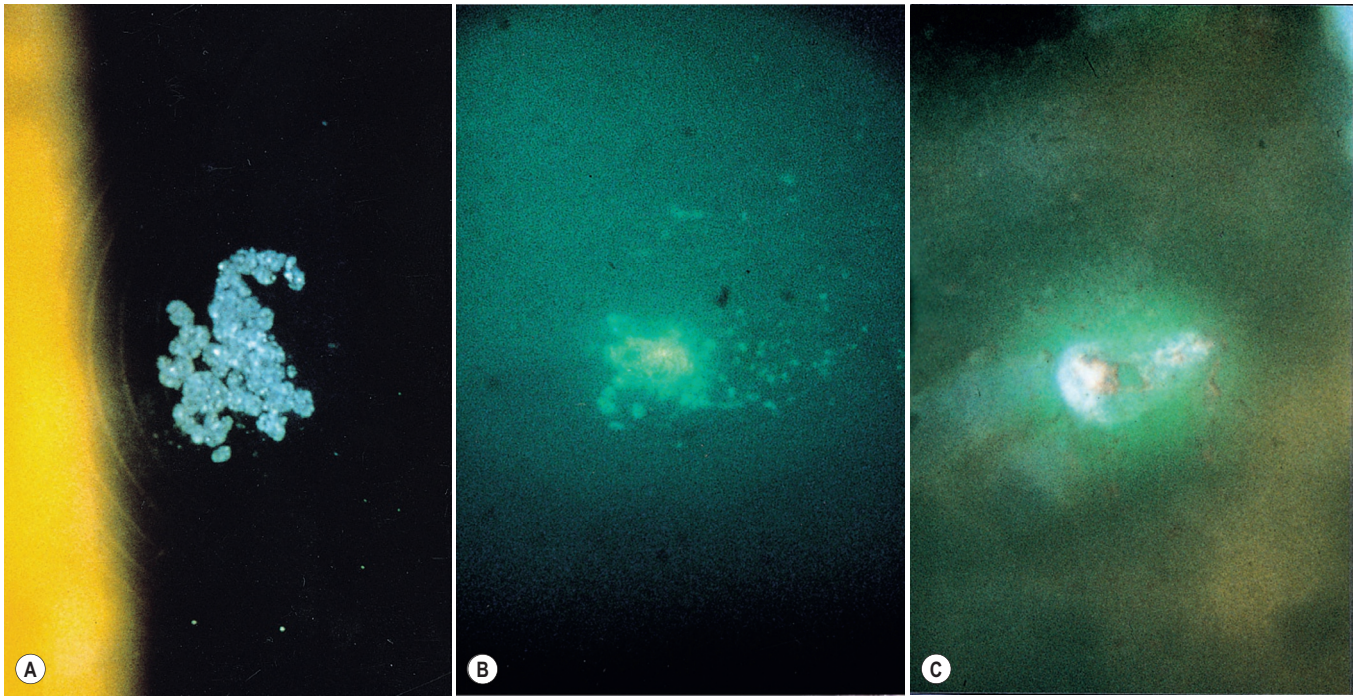


Fig. 4.6 Complications caused by stagnating debris in the post-lens tear film. **(A)** Epithelial cells are trapped by the lens. **(B)** Cell lysis leads to epithelial disruption and staining. **(C)** A small sterile corneal ulcer forms. (Courtesy Brien Holden, Brien Holden Vision Institute.)

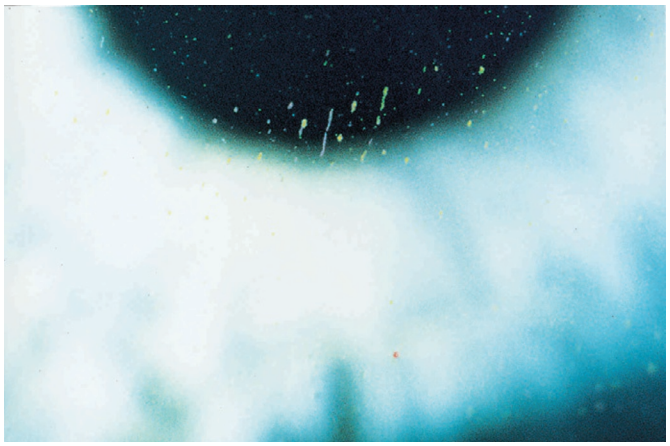


Fig. 4.7 Polystyrene microspheres visible as single spheres and small 'tracks' (the latter as a result of a slow photographic shutter speed). The microspheres have a diameter of 10 μm (yellow) and 6 μm (pink). (Courtesy Lucia McGrogan.)

enhanced by tear exchange, whereby the oxygen-depleted and carbon dioxide–rich tear film beneath the lens is partially replaced by freshly oxygenated and carbon dioxide–free tears from outside the lens. The higher the gas permeability of the lens fitted, the lower will be the reliance on tear exchange for the alleviation of hypoxia and hypercapnia. This is generally the case, for example, with silicone hydrogel lenses.

The effect of blinking on corneal hypoxia and hypercapnia beneath rigid and soft lenses has been studied extensively.[45,46] It has been demonstrated that blinking can partially alleviate corneal hypoxia and hypercapnia in both soft and rigid lenses.

Blinking also plays an important role in re-distributing oxygenated tears evenly across the corneal surface beneath soft lenses, via a process known as 'tear mixing'.[47] This function is particularly important during the wearing of lenses of non-uniform thickness. For example, in the absence of effective tear mixing with a minus-powered lens (thicker in the lens periphery than the lens centre), the corneal periphery will suffer from greater levels of hypoxia compared with the central cornea, potentially resulting in pathology of the peripheral cornea and limbus. In this example, effective tear mixing would allow highly oxygenated tears beneath the centre of the lens to become interspersed with oxygen-deprived tears beneath the lens periphery, resulting in an 'averaging' of available oxygen and reduced peripheral hypoxia.

SOFT LENS STAINING

Collins et al.[48] investigated the blinking patterns of non–contact lens wearers and soft contact lens wearers to determine whether these blinking characteristics were associated with corneal fluorescein staining. High-speed filming (100 frames per second) was used to capture the natural blinking patterns of 15 soft lens wearers and 11 non-lens-wearing control subjects for approximately 3 minutes. Custom software was used to measure the vertical palpebral aperture at the start and at the end of the downward motion of the upper eyelid. The vertical gap between the lids at the lowest point of the upper lid movement during each blink was measured (the 'closed palpebral aperture'). The authors observed that the distribution of closed palpebral apertures of non–contact lens wearers and soft contact lens wearers showed no clear distinction between complete and incomplete blinks. Both groups of subjects showed evidence of an association between the mean closed palpebral aperture size (degree of incomplete blinking) and the grade of corneal fluorescein staining, with the association being stronger in soft contact lens wearers.

RIGID LENS 3 & 9 O'CLOCK STAINING

This is a common problem with rigid lenses, and it is thought to be caused by lens-induced disturbance of the normal blink movement of the upper lid over the lens and the cornea. A rigid lens tends to bridge the upper lid away from the cornea so that, during the downward movement of the upper lid in the course of a blink, the lid is unable to re-wet the 'bridged' regions of the cornea at the 3 & 9 o'clock locations. This leads to local drying and consequent staining of these 'bridged' corneal locations.

van der Worp et al.[49] found that rigid lens wearers experiencing 3 & 9 o'clock staining exhibit a different eye blink frequency for individual types of eye blinks, but not for overall eye blinks. Fewer complete eye blinks, more incomplete eye blinks and more eye blink attempts were observed in rigid lens wearers with 3 & 9 o'clock staining compared with wearers with minimal staining and non-wearers.

LENS DESIGN AND FITTING

With respect to the eyelids, rigid lenses can be fitted according to two basic philosophies – the intra-palpebral fit and the lid attachment fit. The intra-palpebral fit entails fitting a lens, typically of small diameter, such that it rests on the cornea between the upper and lower lid margins during primary gaze. The upper lid rides over the lens during the blink, resulting in lens movement (essential for tear exchange) and lens repositioning (essential for proper lens alignment with the optical axis of the eye). van der Worp et al.[49] also found that fewer complete eye blinks and more eye blink attempts ($p < 0.01$ for both) are associated with inter-palpebral lens fits compared with lid attachment fits.

Inappropriate lens design and fitting can result in an interference with proper blink-mediated lid–lens interaction. For example, an edge standoff that is too great (as a result of a peripheral lens curvature that is too flat or excessive edge lift) could lead to discomfort during the blink because of the constant buffeting of the lens edge against the lid margin. The lid may even gain leverage beneath the lens edge, causing the lens to be dislodged from the eye.

With a lid attachment fit, the upper lid lies over the lens periphery, into which a negative lens carrier may be designed. The purpose of this type of fit is to aid central lens positioning. The lens will typically move synchronously with each blink. A poorly designed lens carrier or the use of a lens of inappropriate diameter may result in a loss of synchrony of movement of the lid and lens, leading to lens mislocation, discomfort and intermittent blur.

Management of abnormal blinking with contact lenses

Practitioners essentially have two options when faced with a clinical problem relating to non-pathological abnormalities of spontaneous blinking activity, such as infrequent or incomplete blinking. These options are to either (1) train the patient to modify the blinking activity or (2) alter the lens type or lens fit.

Early anecdotal reports proposed a variety of strategies for enhancing blinking activity. These ranged from simple instructions and reminders[50] to the employment of a small buzzer that sounded every 10 seconds, acting as a prompt to execute a full blink.[51] Although it was realised that such strategies were stimulating only reflex, rather than spontaneous blinks, the underlying assumption was that spontaneous blinking activity could be learned via training by using reflex stimulation techniques.

Collins et al.[6] tested the hypothesis that blinking could be trained by subjecting a group of unsuspecting contact lens–wearing volunteers to blink exercises (the volunteers were told that the purpose of the exercises was to improve vision). The exercise consisted of placing the index finger of each hand just lateral to the outer canthus to hold the lids taught while performing 10 complete forced blinks. This exercise was repeated three times daily for 2 weeks. Blinking exercises resulted in an increased frequency of complete blinks and a decreased frequency of incomplete and twitch blinks (Fig. 4.8).

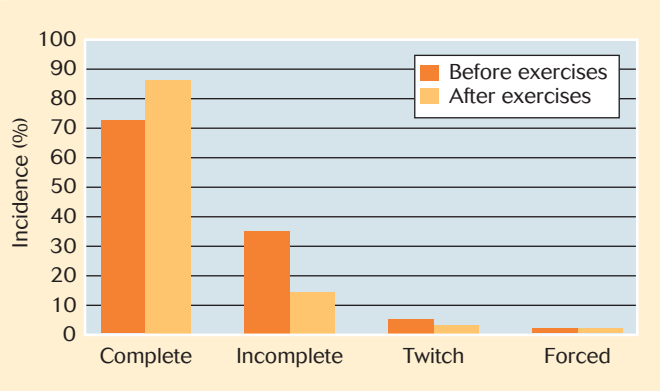


Fig. 4.8 Percentage distribution of the various types of blink before and after blink training. (Reproduced with permission from: Collins M, Heron H, Larsen R, Lindner R. Blinking patterns in soft contact lens wearers can be altered with training. Am J Optom Physiol Opt 1987;64:100–3. ©The American Academy of Optometry 1987.)

If blink training is thought to be impractical or inefficacious, alternative management strategies to alleviate blink-related contact lens problems are to alter the lens type, design or fit and to possibly provide supplementary eye lubrication.[28] The following strategies are advocated as examples.

Blink-associated problems relating to debris removal, hypoxia and hypercapnia can be alleviated by:

- changing from soft lenses to rigid lenses;
- changing a rigid lens design from an aspheric design to a multi-curve design; and
- changing a rigid lens fit from a lid-attachment fit to an intra-palpebral fit.

Blink-associated problems relating to lens surface drying can be alleviated by changing from rigid lenses to soft lenses. The same strategy will solve 3 & 9 o'clock staining.

Sabau and Raad[52] conducted a theoretical analysis of blink-induced dynamics of rigid lenses. They concluded that the motion of a rigid lens can be controlled by proper choice of the lens material microstructure and that lens motion can be enhanced by lowering the 'slip coefficient' and increasing lens material permeability. Thicker lenses and thicker tear films were predicted to cause the lens to squeeze faster and to slide more slowly.

Differential diagnosis of blinking abnormalities

Practitioners should be alert to the possibility that apparent anomalies in the type or pattern of blinking activity in a contact lens wearer may be attributable to coincidental disease states. Interruptions to the neural input and/or muscular systems of the eyelids can adversely affect normal spontaneous blinking activity. For example, patients with Parkinson's disease exhibit a low blink rate.[53] Increased mechanical resistance to eyelid movement as in Graves' disease can also reduce blink frequency. Local pathology of the eyelids, such as ptosis, chalazia and carcinomas, can alter eyelid function and movement and thus interfere with normal blinking activity. It is therefore essential to rule out the possibility of concurrent pathology before ascribing blinking abnormalities to contact lens wear.

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5 Lid Wiper Epitheliopathy

The concept of the 'lid wiper' and a proposed condition brought about by disturbance to this structure, referred to as 'lid wiper epitheliopathy' (LWE), were first described by Korb et al. in 2002.[1] The terms 'lid wiper' and 'LWE' are becoming increasingly common when referring to the aetiology, diagnosis and management of dry eye in contact lens wearers and non–lens wearers.

The lid wiper is proposed to be that portion of the marginal conjunctiva of the upper eyelid that acts as a wiping mechanism for spreading the tear film over the ocular surface or over the surface of a contact lens. There is also a lid wiper in the lower lid, but its role in spreading tears is less certain, as discussed later. LWE is the term used to describe disruption to the surface epithelium of the lid wiper, typically observed using vital dyes.[2]

Keen interest in the concept of the lid wiper and LWE possibly stems, at least in part, from the apparent difficulty encountered by clinicians and scientists in diagnosing, reconciling signs and symptoms and treating dry eye syndrome. Moreover, little progress has been made in understanding the root cause of contact lens discomfort,[3] which, in turn, is a major reason for discontinuation from contact lens wear,[4] causing great inconvenience to lens wearers[5] and missed economic opportunity for contact lens practitioners and the contact lens industry.[6]

Terminology

In broad terms, the lid margin is divided into three distinct anatomical sub-zones: (1) the skin epidermis extending over the meibomian gland orifices; (2) the mucocutaneous junction, which is the transition region between the skin epidermis and the conjunctival tissue – the surface that represents the line of Marx; and (3) the lid wiper (Fig. 5.1).[7]

Ehlers[8] appears to have first connected the action of the lid to that of the windscreen wiper of a car. He did not specifically provide terminology for the region, but when referring to the part of the lid that rubs against the bulbus during blinking, he stated: 'This soft (unkeratinised) bead gliding over the cornea must be assumed to be a perfect "wind screen wiper"'. Fatt[9] later referred to the 'wiper blade' action of the upper lid in spreading tears over the ocular surface.

In their initial paper on this topic, Korb et al.[1] carefully defined the lid wiper region and precisely mapped out its location in relation to adjacent commonly recognised anatomical landmarks. Accordingly, the location of the lid wiper is clear and unambiguous in all subsequent papers by Korb and other researchers who have coined this specific term. However, some have adopted different terminology. For example, Munger and Halata[10] referred to the 'angle'. McGowan et al.[11] used the terms 'marginal zone' and 'marginal angle'. Navascues-Cornago et al.[12] were clearly examining the lid wiper but used the terms 'lid margin' and 'marginal conjunctiva', both of which were apparently considered to be synonymous with 'lid wiper'. Golebiowski et al.[13] also used the term 'lid margin' to indicate the lid wiper region for staining purposes but measured 'lid margin sensitivity' at the 'occlusal surface'.

With respect to the term 'lid wiper epitheliopathy', it is perhaps worth considering the appropriateness of the suffix '-pathy', which indicates a 'morbid condition or disease; generally used to designate a non-inflammatory condition'.[14] Two questions arise: (1) To what extent is LWE truly a 'disease'? (2) Is there evidence that it has an inflammatory component? If the answer to the latter question is in the affirmative, then the term 'lid wiper epitheliitis' may be more appropriate.

Structure of the eyelid margin

The anatomy and histology of the eyelid margin have been described in a small number of papers throughout the 20th century, although the structure of the lid wiper as a defined anatomical region has only been investigated fairly recently.

GROSS ANATOMY

According to Korb et al.[1] the anatomical area of the lid wiper region is the portion of palpebral marginal conjunctiva in the upper and lower lids that is in contact with the globe. In the upper lid, it extends from the crest of the sharp posterior (inner) lid border (i.e. the mucocutaneous junction, or line of Marx) to the subtarsal fold superiorly and from the medial upper punctum to the lateral canthus horizontally. This configuration is similar in the lower lid.

The idea that the lid wiper is essentially the only part of the upper lid wiping tears across the ocular or contact lens surface assumes that the tarsal conjunctiva does not contact the opposing ocular or contact lens surface. Part of this reasoning is that the lid wiper is the only part of the eyelid to exhibit non-keratinised stratified squamous epithelium, a characteristic feature of other body tissues that experience frequent rubbing.[8]

Ehlers[8] made the further observation that blinking would be impeded if the tarsal region of the lid was sucked closely against the eye. Kessing[15] investigated the notion that there is a gap between the tarsal conjunctiva and ocular surface, which extends vertically from the lid wiper to a region approaching the upper fornix; this has become popularly known as 'Kessing's space'.[15]

The word 'space' in the term 'Kessing's space' implies an empty area; however, this may not be the case. Using electron microscopy, Doughty[16] observed a very thick, fixed gel layer across the palpebral conjunctiva in rabbits. He suggested that this mucus layer is important in providing a robust lubrication system to facilitate regular blink activity. Doughty[16] went on to propose that the mucus-based material likely fills Kessing's space, although this has yet to be confirmed in humans.

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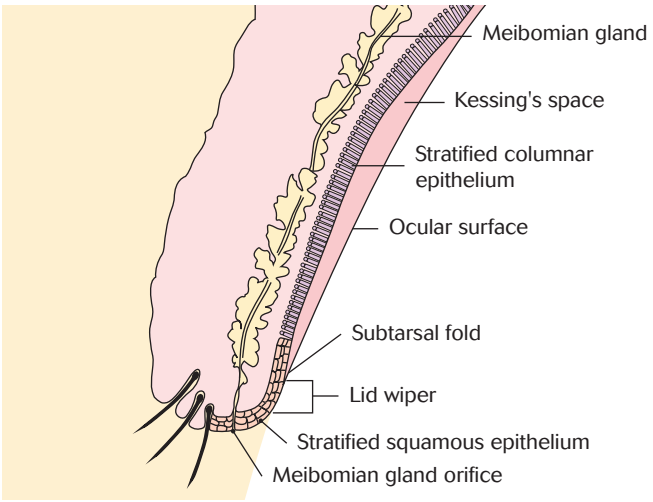


Fig. 5.1 Relationship of areas of contact and non-contact between the upper eyelid and ocular surface. The area of the lid wiper starts posterior to the meibomian glands, where the stratified conjunctival epithelium changes from keratinised to non-keratinised tissue and extends superiorly to the subtarsal fold. (Reproduced from Korb DR, Greiner JV, Herman JP, Hebert E, Finnemore VM, Exford JM, Glonek T, Olson MC. Lid-wiper epitheliopathy and dry-eye symptoms in contact lens wearers. CLAO J 2002;28:211–6, with permission of Lippincott Williams & Wilkins, via Copyright Clearance Center.)

Knop et al.[17] measured the upper lid wiper in human cadaver eyes and noted that it is of variable width, ranging from 0.3 to 0.5 mm, and forms a slope. This was confirmed by Shaw et al.,[18] who rested the lid margin of a series of subjects against pressure-sensitive paper and determined the lid wiper to be to 0.60 ± 0.16 mm wide (range 0.33–0.84 mm).

HISTOLOGY

There are two regions of interest here, namely, the mucocutaneous junction and the newly proposed lid wiper.[17] These two adjacent structures will be considered separately.

Mucocutaneous junction (line of Marx)

The first detailed account of the mucocutaneous junctions was provided in 1924 by Marx,[19] hence the eponymous name of this anatomical feature as the 'line of Marx'.

Knop et al.[7] and Doughty[20] characterised the mucocutaneous junction as being composed, at least in part, of squamous cells; however, the description provided by Jalbert et al.[21] is more consistent with non-squamous cells. This discrepancy may relate to a number of factors, including the use of different staining techniques, assessment of the line of Marx in the upper lid[21] versus the lower lid[20] and the observation of non–contact lens wearers only[20] versus a mixed cohort of lens wearers and non–lens wearers.[21]

The width of the line of Marx was measured by Knop et al.[17] to be 0.2 to 0.3 mm wide. Doughty[20] determined the line of Marx to be up to 0.3 mm wide but noted that when stained with lissamine green, it could be close to 0.5 mm wide in some subjects. These values are somewhat greater than the estimates of Donald et al.[22] (0.10 ± 0.09 mm) and Shaw et al.[18] (0.09 ± 0.02 mm) (Fig. 5.2). Differences in accounts of the width of mucocutaneous junction may be attributed to differences in in vitro versus in vivo measurement.

Lid wiper

Knop et al.[7] described the lid wiper as an epithelial elevation that typically has an initial thickness of about 100 μm. They

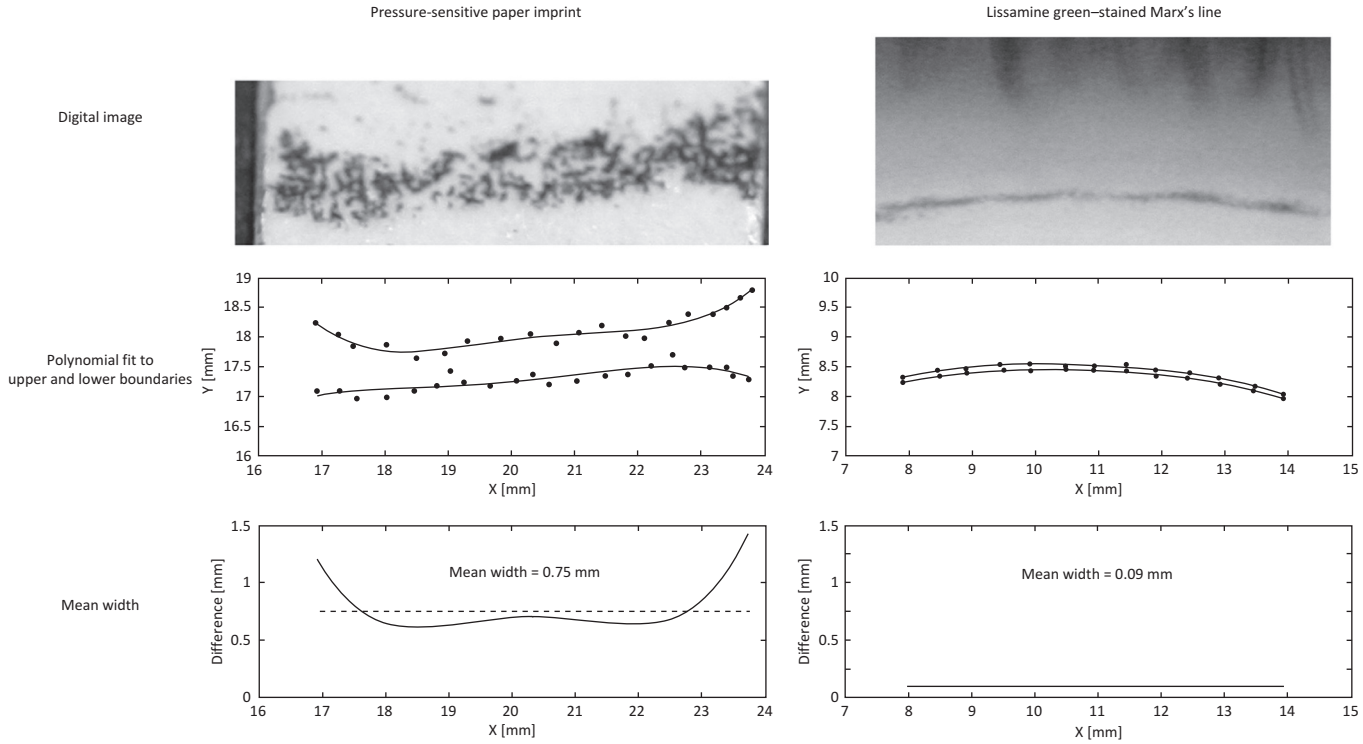


Fig. 5.2 Examples of the digital images (top) and analysis (middle and lower) from one subject of a contact imprint of the lid wiper (mean width 0.75 mm) and lissamine green staining of the line of Marx (mean width 0.09 mm). Both widths were averaged over approximately the central 6 mm of the eyelids. (Reproduced from Shaw AJ, Collins MJ, Davis BA, Carney LG. Eyelid pressure and contact with the ocular surface. Invest Ophthalmol Vis Sci 2010;51:1911–7, with permission of Association for Research in Vision and Ophthalmology, via Copyright Clearance Center.)

described the lid wiper as consisting of stratified epithelium with a conjunctival structure of cuboidal cells, some parakeratinised cells and goblet cells, with a superficial flattened polygonal mesh of small vessels. The goblet cells observed in the lid wiper occur either singly or in clusters. Specifically, they are located in both superficial and deeper layers of the epithelium and along epithelial crypts that are connected to the surface (Fig. 5.3).[17] These goblet cells secrete soluble mucins onto the lid wiper surface. Along with the tear film, the mucins form a hydrated gel between the lid wiper and the ocular surface to provide lubrication so that the lid wiper and ocular surface are separated by a fluid film consisting of mucin and aqueous components.

NEUROANATOMY

Munger and Halata[10] conducted a histological investigation of the neural tissue of a region they referred to as the 'angle between occlusal and conjunctival surfaces', which approximates to the lid wiper region. They observed a few special nerve endings consisting of scattered simple corpuscles and scant Meissner corpuscles. Simple corpuscles are often associated with presumptive intra-epithelial free nerve endings.

Further aspects of lid wiper neuroanatomy can be inferred from measures of tactile sensitivity of this tissue. Although a number of authors claimed to have measured the sensitivity of the lid margin, only two appear to have genuinely measured

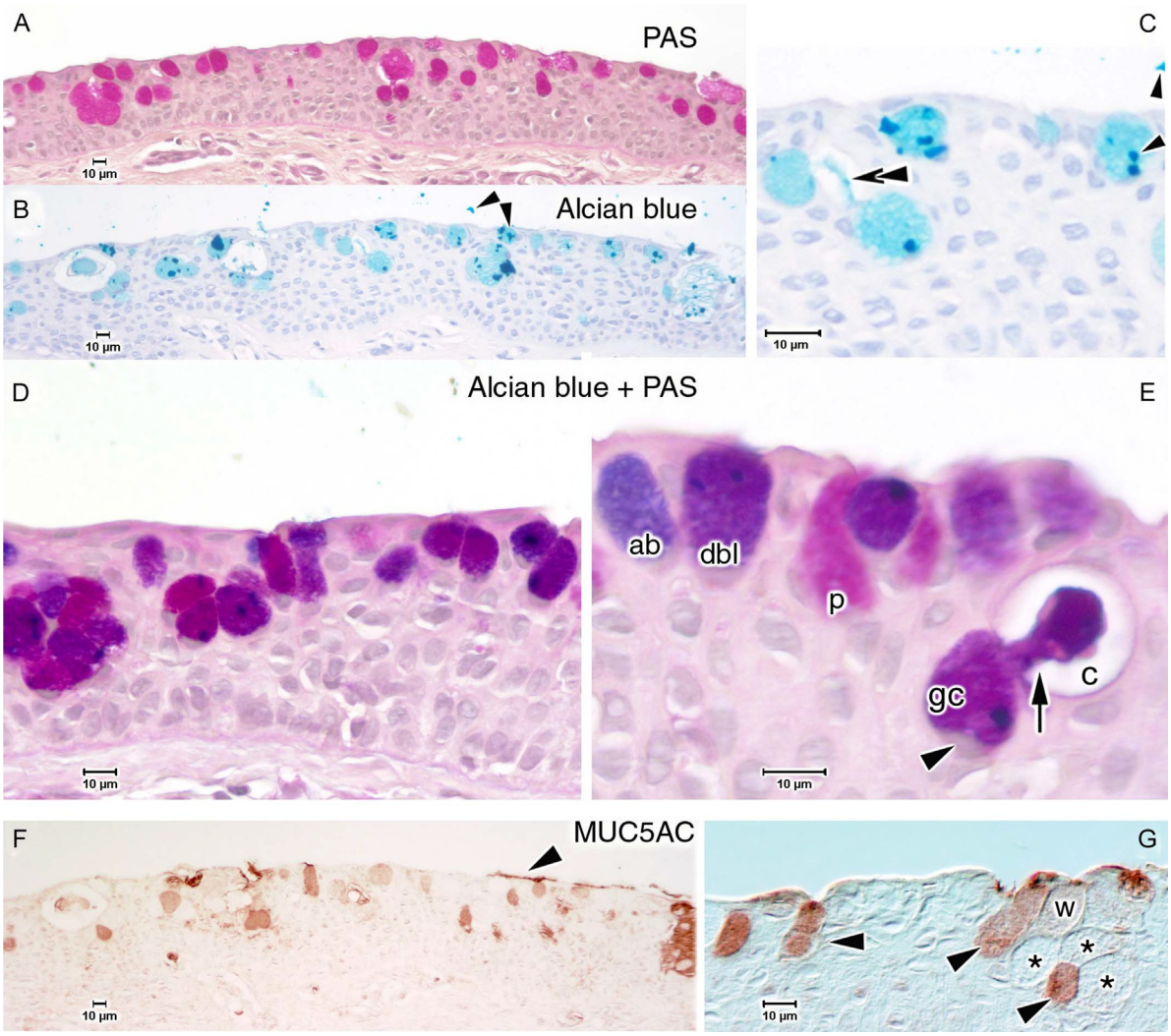


Fig. 5.3 Overview of a lid wiper shows several goblet cells, some of them arranged in groups at the surface and others deep in the epithelium. Goblet cells are stained in serial sections either by Periodic Acid–Schiff (PAS) **(A)** and Alcian blue **(B, C)** or by combined staining **(D, E)**. One isolated goblet cell deep inside the epithelium (**C**, Alcian blue) shows a narrow stained extension (double arrowhead) of the cytoplasmic content that points to the surface and conceivably indicates the delivery of mucus into a cryptal lumen or directly toward the surface. Staining with Alcian blue plus periodic acid–Schiff **(D, E)** shows that most goblet cells are double stained (dbl in **E**) and have an intermediate color. **(E)** Some goblet cells stain preferably for either Alcian blue (ab) or periodic acid–Schiff (p). Stained mucus material from a goblet cell (gc) with basal flat nucleus (arrowhead) deep in the epithelium of the lid wiper is seen to be continuous (arrow) with mucus in a cryptal lumen (c), suggesting delivery of mucus into a luminal space. Immunohistochemistry for MUC5AC **(F, G)** revealed that some goblet cells are strongly positive for MUC5AC (arrowheads in **G**), whereas others are weakly stained (w) and yet others are negative (asterisks). In places, MUC5AC-positive material is seen deposited on the epithelial surface (**F**, arrowhead). Note that Alcian blue shows artificial stain concrements (**B, C**, small arrowheads) on the section and on the glass slide. Paraffin histology: **(A)** periodic acid–Schiff; **(B, C)** Alcian blue; **(D, E)** Alcian blue plus periodic acid–Schiff; **(F, G)** MUC5AC. Size marker in **A–G** = 10 µm. (Reproduced from Knop N, Korb DR, Blackie CA, Knop E. The lid wiper contains goblet cells and goblet cell crypts for ocular surface lubrication during the blink. Cornea 2012;31:668–79, with permission of Lippincott Williams & Wilkins, via Copyright Clearance Center.)

the sensitivity of the lid wiper. McGowan et al.[11] used a Cochet-Bonnet aesthesiometer to measure touch thresholds of three regions of the eyelid: the middle of the tarsus, the lid wiper (referred to as the 'marginal angle') and the non–lid wiper region of the lid margin (referred to as the 'occlusal surface'). The lid wiper was the most sensitive of the three regions.

Navascues-Cornago et al.[12] also used the Cochet-Bonnet instrument to measure the touch sensitivity of the cornea, bulbar conjunctiva, lid wiper and tarsal conjunctiva. They found that the cornea was the most sensitive of these tissues but that the lid wiper was more sensitive than other regions of the conjunctiva. The implication from these works is that the lid margin is more richly innervated compared with the surrounding conjunctival and lid tissues but is less richly innervated compared with the cornea.

Signs and symptoms

With the upper eyelid everted, the lid wiper can be seen in white light as a long, thin pale band of tissue beneath the eye lashes extending laterally from inner to outer canthus (Fig. 5.4). Disturbance to the superficial epithelium of the lid wiper is not visible in white light but can be observed with the aid of vital dyes. A key question to be addressed is the extent to which lid wiper staining correlates with symptoms of discomfort.

STAINING TECHNIQUES

In their original paper, Korb et al.[1] described the application of fluorescein followed by rose bengal stain but subsequently[23] advocated use of a mixture of 2% fluorescein and 1% lissamine green stains.

Different research groups subsequently used a variety of staining approaches when examining the lid wiper, including the use of fluorescein only, lissamine green only, fluorescein and rose bengal, fluorescein and lissamine green and a triple combination of fluorescein, lissamine green and rose bengal stains (Fig. 5.5). In more recent times, the trend has been to use lissamine green only.

Varikooty et al.[24] described an optimised technique for staining the lid wiper as follows: Moisten two strips with 1 mg lissamine green; hold the strips together; then, apply to the eye with 50 µL of saline. Repeat this procedure 1 minute later. Evert the eyelid 3 minutes after the second instillation to visualise the lid wiper.[24] The beam of the slit lamp is set to maximum width and 10 mm height, and the potentiometer is set to provide maximum illumination.

STAINING PATTERNS OBSERVED

In assessing the lid wiper after contact lens wear, Korb et al.[1,25] simply considered the lateral extent of the band of staining as the basis for grading LWE. However, complex patterns of staining have been reported.

Varikooty et al.[24] investigated staining patterns observed in those wearing silicone hydrogel contact lenses. At times, no staining was observed. Staining that was present was categorised into six patterns: vertical streaks, short horizontal band, broad horizontal band, speckled appearance, comb-shaped appearance and atypical appearance (Fig. 5.6). Little difference was observed between the patterns of stains reveled by fluorescein and lissamine green.

GRADING THE SEVERITY OF STAINING

Korb et al.[26] advocated a grading technique that accounted for staining observed with both fluorescein and lissamine green. Specifically, fluorescein staining of the lid wiper was graded from 0 to 3 for each of two characteristics: the linear area of involvement (Table 5.1) and the severity of the staining (Table 5.2). The total grade for fluorescein staining of the lid wiper is the average of the grades for the linear area and severity of staining. This procedure was repeated for lissamine green. The *higher* of the final fluorescein or lissamine green staining grades is used as the LWE severity grade, whereby 0.5 to 1.0 = grade 1 LWE (mild); 1.25 to 2.0 = grade 2 LWE (moderate); and 2.25 to 3.0 = grade 3 LWE (severe).

Korb et al.[1] made the point that it is very important to differentiate any staining across the proposed lid wiper zone/region from that staining seen at the line of Marx, which invariably stains bright as a clearly delineated thin line at the distal border of the lid wiper with all three staining agents. Others have noted that grade 0 LWE shows staining only of the line of Marx, but grade 1 LWE, for example, shows a slight staining of the lid wiper lesion in addition to the staining of the line of Marx.[27] In attempting to objectively assess overall staining across the marginal zone, the line of Marx may also be included in the measurements and still be referred to as the 'lid wiper'.[28]

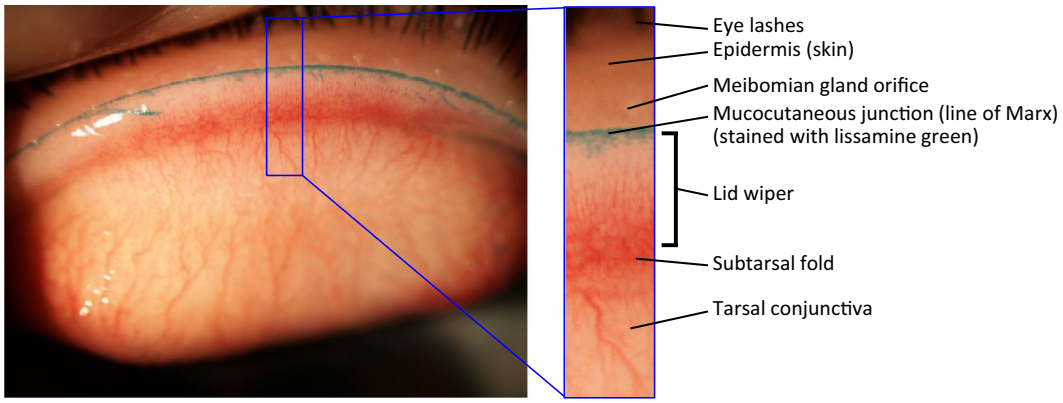


Fig. 5.4 Normal everted eyelid, showing the location of the lid wiper and adjacent anatomical structures. Lissamine green stain highlights the mucocutaneous junction (line of Marx). (Courtesy Maria Navascues Cornago.)

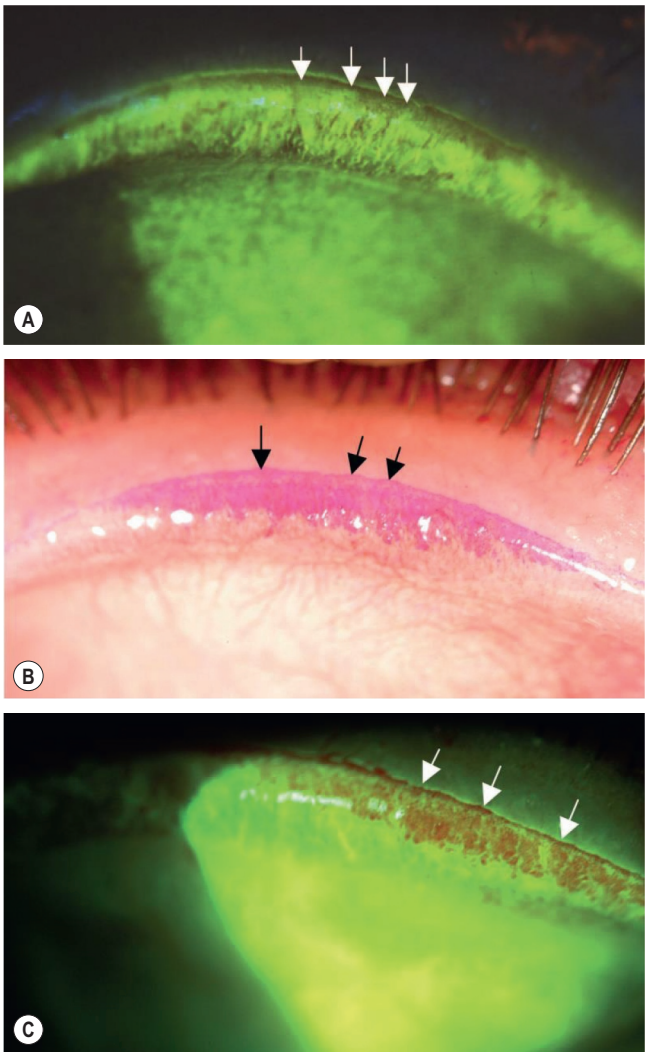


Fig. 5.5 **(A)** The everted upper eyelid with moderate lid wiper epitheliopathy (LWE) shown by fluorescein staining. The lid wiper was photographed with black light after two instillations of fluorescein dye and a single instillation of rose bengal dye. Rose bengal did not stain this lid wiper. **(B)** The everted upper eyelid with moderate LWE shown by rose bengal staining. The lid wiper was photographed with white light illumination after two instillations of fluorescein dye and a single instillation of rose bengal dye. Because fluorescein did not stain this lid wiper, the ocular surfaces were irrigated with normal saline to remove the fluorescein and enhance the photograph. **(C)** The everted upper eyelid with severe LWE shown by fluorescein and rose bengal staining. The lid wiper was photographed with black light illumination after two instillations of fluorescein dye and a single instillation of rose bengal dye, but without irrigation of the ocular surfaces. (Reproduced from Korb DR, Herman JP, Finnemore VM, Exford JM, Blackie CA. An evaluation of the efficacy of fluorescein, rose bengal, lissamine green and a new dye mixture for ocular surface staining. Eye Contact Lens 2008;34:61–4, with permission of Lippincott Williams & Wilkins, via Copyright Clearance Center).

Guillon and Maissa[29] judged the extent of lissamine green staining of the lid wiper in terms of staining type (0 = none; 1 = broken line; 2 = thin line; 3 = thick line/patch) and staining severity (0 = none; 1 = slight; 2 = mild; 3 = moderate; 4 = severe).

Kunnen at al.[30]compared a semi-objective method of grading LWE with subjective assessment. They found that human observers tended to overestimate the height and underestimate the width of LWE staining.

LWE IN PRESENTING POPULATIONS

Guillon and Maissa[29] evaluated the incidence and type of lid margin staining in 75 consecutive patients (30 males, 45 females) aged 18 to 62 years (mean age 33.1 ± 11.5 years) presenting to an eye clinic; the population included non–contact lens wearers and contact lens wearers. The upper and lower lid margin staining was evaluated with lissamine green and was judged by using their grading system as described previously.[29]

In the majority of cases, staining was rated as mild or moderate for both the upper (mild = 39.6%; moderate = 37.6%) and lower (mild = 38.9%; moderate = 38.3%) eyelid margins. The staining observed was most commonly of the 'thin line' type (upper lid = 65.3%; lower lid = 63.3%). Clinically significant 'thick line/patch' staining was observed in about 1 in 4 eyelids (upper = 23.3%; lower = 25.3%). The results were highly correlated between the upper and lower lid margins ($r = 0.895–0.918$; $p < 0.001$) and between the right and left eyes ($r = 0.820–0.987$; $p < 0.001$). The authors[29] concluded that LWE is present in 25% of a population presenting to an eye clinic.

The prevalence of upper and lower LWE was examined by using combined fluorescein and lissamine green staining in 405 eyes of 208 soft contact lens wearers, 135 eyes of 71 rigid contact lens wearers and 443 eyes of 229 non–lens wearers by Shiraishi et al.[31] Tear break-up time (TBUT) and corneal and conjunctival staining were also assessed. The prevalence/mean grade of lower LWE (39.5% (0.79)) was significantly higher than that of upper LWE (12.5% (0.21)) in non–lens wearers ($p < 0.001$). The prevalence/mean grade of upper LWE was significantly higher in rigid contact lens wearers (84.4% (1.3)) compared with soft lens wearers (58.1% (2.1)) ($p < 0.001$). There was no difference in prevalence/mean grade of lower LWE between rigid and soft lens wearers.[31]

The prevalence of both upper LWE and lower LWE were significantly correlated with age and corneal and conjunctival staining, but not sex and TBUT, in non–lens wearers. The prevalence of both upper LWE and lower LWE was significantly higher in younger subjects ($p < 0.001$). Upper LWE and lower LWE were detected in a higher percentage of contact lens wearers than in non–lens wearers ($p < 0.001$).[31]

Alghamdi et al.[32] examined the lid wiper in 60 current contact lens wearers, 20 previous contact lens wearers and 20 non–lens wearers. They found no difference in the severity of LWE amongst the three groups.

RELATION BETWEEN LWE AND SUBJECTIVE DISCOMFORT IN CONTACT LENS WEARERS

A number of studies have explored the relationship between LWE and symptoms of dryness or discomfort in contact lens wearers. This question has generally been approached by assessing the incidence and/or severity of LWE among symptomatic versus asymptomatic contact lens wearers. The findings of research so far addressing this question are equivocal.

Publications demonstrating a link between LWE and contact lens–associated dryness/discomfort

Korb et al.[1] reported a mean score for symptoms of 0.3 points for a group of asymptomatic lens wearers versus 7.2 points for a symptomatic group, out of a possible 12 points. Twenty-four (80%) of the 30 symptomatic subjects displayed LWE compared with 10 (13%) of 75 asymptomatic subjects ($p = 0.0001$). The

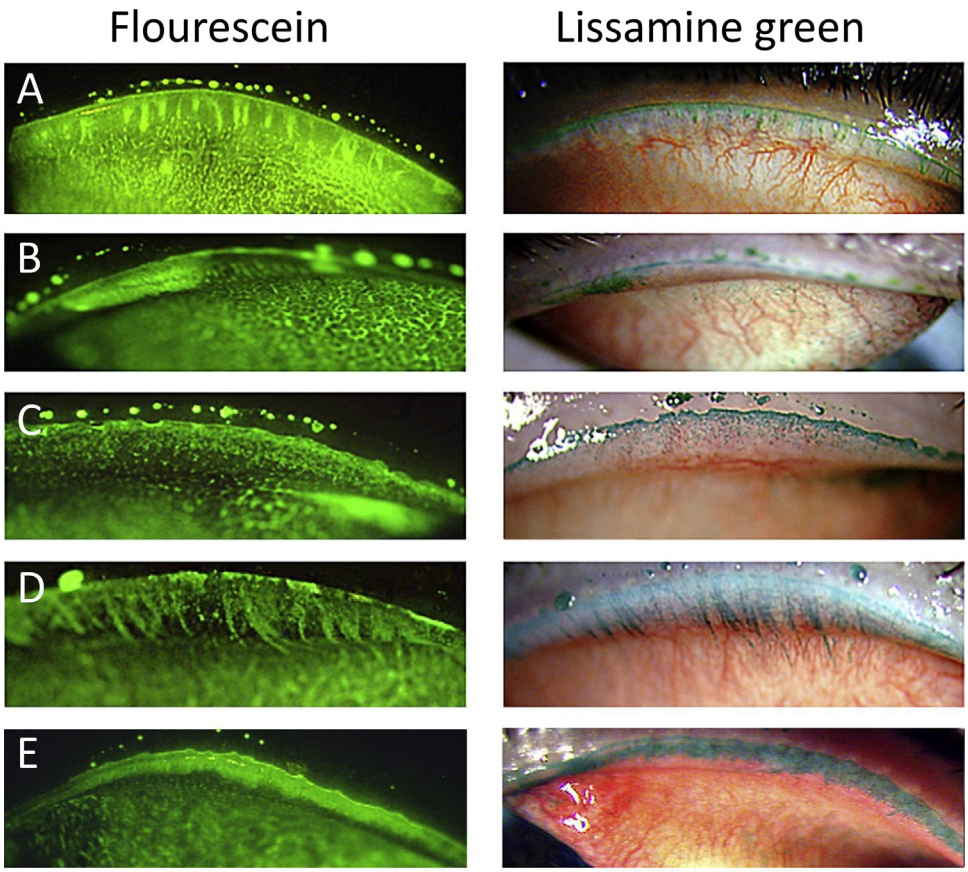


Fig. 5.6 Various appearances of lid wiper epitheliopathy (LWE) revealed by fluorescein (left column) and lissamine green (right column): **(A)** vertical streaks, **(B)** short horizontal band, **(C)** speckled appearance, **(D)** comb appearance, **(E)** broad horizontal band. (Reproduced from Varikooty J, Srinivasan S, Subbaraman L, Woods CA, Fonn D, Simpson TL, Jones LW. Variations in observable lid wiper epitheliopathy (LWE) staining patterns in wearers of silicone hydrogel lenses. Cont Lens Anterior Eye 2015;38:471–6, with permission of Elsevier, via Copyright Clearance Center.)

TABLE 5.1 Grading of linear area of staining of lid wiper

Linear Area of Staining	Grade
<2 mm	0
2–4 mm	1
5–9 mm	2
≥10 mm	3

Based on Korb DR, Greiner JV, Herman JP, Hebert E, Finnemore VM, Exford JM, Glonek T, Olson MC. Lid-wiper epitheliopathy and dry-eye symptoms in contact lens wearers. CLAO J 2002;28:211–6.

TABLE 5.2 Grading of severity of staining of lid wiper

Severity of Staining	Grade
Absent	0
Mild	1
Moderate	2
Severe	3

Based on Korb DR, Greiner JV, Herman JP, Hebert E, Finnemore VM, Exford JM, Glonek T, Olson MC. Lid-wiper epitheliopathy and dry-eye symptoms in contact lens wearers. CLAO J 2002;28:211–6.

authors suggested that LWE is associated with symptoms of dry eye in contact lens wearers.

Berry et al.[33] found that upper LWE scores were significantly greater in symptomatic versus asymptomatic contact lens wearers ($p < 0.035$), although there was no such association demonstrated for lower LWE.

Pult et al.[34] reported that severity scores for LWE were significantly greater in symptomatic versus asymptomatic patients (U-test; $p < 0.03$). They noted that the predictive values derived from the receiver operating characteristic (ROC) curve indicated that LWE served better as a test for *excluding* dry eye symptoms.

Yan et al.[35] found an association between LWE and dry eye irrespective of whether or not contact lenses are worn.

Pult et al.[36] reported that LWE was significantly increased when wearing contact lenses; however, the LWE score was found to be of little value in predicting contact lens–induced dry eye.

Varsani and Wong[37] reported that LWE staining was greater for symptomatic lens wearers versus asymptomatic lens wearers for both lids and the lower lid.

Yeniad et al.[38] assessed LWE by using fluorescein, rose bengal and lissamine green in 42 symptomatic contact lens wearers and 27 asymptomatic contact lens wearers. Dry eye was assessed in all participants by using a subjective questionnaire and three objective tests – Schirmer I test, fluorescein break-up time and fluorescein corneal staining. The prevalence of staining with the three dyes in the symptomatic and asymptomatic contact lens wearers were as follows: fluorescein 67% and 32%, respectively ($p = 0.001$); rose bengal 59% and 41% (no statistics provided); and lissamine green 61% and 39% (no statistics provided). The authors were unable to demonstrate a correlation between LWE

and fluorescein break-up time or Schirmer I test results. The authors concluded that LWE should be investigated in symptomatic contact lens wearers who yield normal results with tests for dry eye.

Publications failing to demonstrate a link between LWE and contact lens–associated dryness/discomfort

Best et al.[39] fitted monthly replacement silicone hydrogel contact lenses to 60 subjects who had never worn contact lenses previously and monitored them for 6 months. The authors reported that LWE was unable to discriminate between those who dropped out of lens wear trial versus those who completed the 6 months of the trial (ROC area under the curve = 0.511).

Read et al.[40] assessed symptoms and lissamine green staining of the upper and lower lid wipers in 10 symptomatic lens wearers, 10 asymptomatic lens wearers and 10 non–lens wearers, at afternoon visits. They concluded that inspection of the lid wiper region with lissamine green staining does not appear to differentiate between symptomatic and asymptomatic contact lens wearers.

Navascues-Cornago et al.[41] reported that among lens wearers, a significant increase in lower lid wiper staining was found after 12 hours of lens wear compared with baselines measures ($p = 0.04$). However, lid margin staining was not significantly different between symptomatic and asymptomatic lens wearers (Mann-Whitney U test; all $p > 0.05$).

In a large multi-centre study, Schulze et al.[42] assessed subjective comfort in 246 participants wearing their habitual soft contact lenses. After lens removal, the lid wiper was graded by using fluorescein and lissamine green. The authors were unable to demonstrate a relationship between comfort scores and the severity of LWE.

Stahl and Jalbert[43] conducted a randomised, cross-over study on 20 subjects who wore comfilcon A and lotrafilcon A lenses for 10 days separated by a 7-day washout period. Tear and contact lens osmolarity; ocular symptoms, including comfort, tear stability and production; and LWE were measured. The authors were unable to demonstrate an association between comfort LWE.

Efron et al.[44] reported the results of a meta-analysis of data extracted from six studies examining the relationship between LWE and contact lens comfort. A total of 587 subjects were enrolled in these studies, comprising 180 males and 407 females (age 28.5 ± 7.8 years (range 18–62 years)). LWE was assessed using fluorescein and lissamine green staining, and comfort was assessed using a validated patient reported outcomes instrument, known as the 'contact lens user experience' (CLUE) metric.[45] The authors were unable to demonstrate a significant relationship between grade of LWE and CLUE score ($F = 1.21$; $p = 0.298$) (Fig. 5.7).

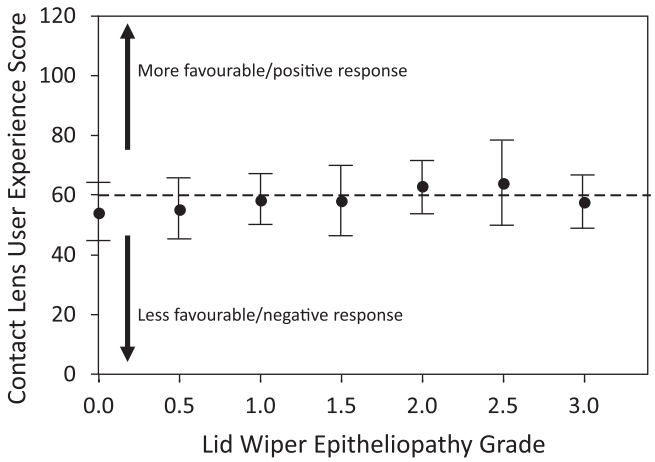


Fig. 5.7 Contact lens user experience score versus lid wiper epitheliopathy grade. There was no significant association between these two parameters ($F = 1.21$; $p = 0.298$).

Pathology

Preliminary studies employing immunocytochemistry, impression cytology, functional slit lamp biomicroscopy and corneal confocal microscopy have shed some light on the likely tissue pathology underlying LWE, and aesthesiometry of the lid wiper margin has highlighted possible functional deficits associated with this condition.

IMMUNOCYTOCHEMISTRY

Jalbert et al.[21] performed immunocytochemistry for the keratinization-related proteins filaggrin, transglutaminase1 and cytokeratin 1/10 on impression cytology samples collected from a broad region of the upper lid margin. The authors demonstrated expression of all of these proteins from lid margin epithelium, suggesting the possibility of pathological processes occurring in superficial epithelial cells of the lid wiper.

STRUCTURAL CHANGES

Evidence from studies using invasive techniques (impression cytology) and non-invasive approaches (laser scanning confocal microscopy and functional slit lamp biomicroscopy) shed some light on contact lens–induced structural changes in the lid wiper.

Lid wiper epithelial cell morphology

Jalbert et al.[21] performed impression cytology on the lid margin, including the lid wiper, in 19 soft contact lens wearers and 21 non–lens wearers and observed lissamine green staining in 17% of subjects. There was no difference between contact lens and non–contact lens wearers for lid margin staining or Nelson grade ($p = 0.4$; Fisher's exact test). The authors did not report any differences between samples obtained from those who did and those who did not display lissamine green staining of the lid wiper region in respect of cell morphology, histochemistry or immunocytochemistry.

Muntz et al.[46] described an optimised method of collecting, staining and imaging cells from the lid wiper region by using impression cytology. Cells are collected from the inner surface of the upper eyelid of human subjects by using hydrophilic polytetrafluoroethylene membranes and are stained with cytological dyes to reveal the presence of goblet cells, mucins, cell nuclei and various degrees of pre- and parakeratinization. Immunocytochemical dyes show cell esterase activity and compromised cell membranes on a confocal scanning laser microscope. Up to 100 microscopic digital images are captured for each sample and stitched into a high-resolution, large-scale image of the entire impression cytology span.

Fractal dimensions of the lid wiper microvascular network

Deng et al.[47] used functional slit lamp biomicroscopy to capture images from the lid wiper of 16 healthy subjects before and after lens wear. The microvascular network density of the lid wiper increased from 1.411 ± 0.116 to 1.548 ± 0.079 after 6 hours

of contact lens wear ($p < 0.01$). The decrease in ocular discomfort was strongly related to the change in microvascular network density of lid wiper ($r = 0.61$; $p < .05$).

FUNCTIONAL CHANGES

Presumed tissue structure compromise indicated by staining of the lid wiper may be associated with functional alterations. A functional attribute of the anterior ocular structures that can be readily investigated is sensitivity to touch.

Navascues-Cornago et al.[12] measured mechanical sensitivity at eight locations on the ocular surface and adnexa (cornea, upper and lower lid wipers and bulbar and tarsal conjunctivae) of 35 soft contact lens wearers and 35 non-wearers by using a Cochet-Bonnet aesthesiometer. The lid wiper was found to be the most sensitive conjunctival region (all $p < 0.001$), which is consistent with a previous report.[11]

Measurements were repeated by Navascues-Cornago et al.[12] at 12 hours in 11 non-wearers and 10 symptomatic lens wearers. At this time, the sensitivity of the lower lid wiper, but not the upper lid wiper, was found to be reduced in lens wearers compared with non-wearers (all $p < 0.05$). The upper lid primarily travels in a vertical direction during blinking, and the vertical distance traversed by the lid margin is much greater than that of the lower lid; however, the lower lid translates in short horizontal movements during blinking.[48] This lower lid horizontal shift may result in a different physical interaction with the anterior cornea or contact lens surface than occurs with predominantly large vertical sweeps of the upper lid, possibly differentially affecting lid wiper sensitivity.

Aetiology

The primary hypothesis for the aetiology of LWE can be summarised as increased friction between the lid wiper and ocular or anterior contact lens surface as a result of inadequate lubrication. Numerous theories have been proposed regarding the mechanism; some are based on solid evidence, some on preliminary evidence and some are conjecture. These theories relate to either the association between LWE and dry eye or between LWE and contact lens–induced discomfort/dry eye, and some relate to both.

FRICTION AND CONTACT LENS WEAR

Coles and Brennan[49] compared coefficient of friction data[50] and comfort data relating to six silicone-hydrogel and three hydrogel materials. End-of-day comfort data from over 700 1-month wearing trials were available for analysis. A strong correlation between comfort and coefficient of friction was evident ($p < 0.01$) (Fig. 5.8). Regression analyses excluded oxygen transmissibility, modulus and water content as predictors of comfort, leaving only coefficient of friction as a significant factor.

TRIBOLOGY

Characterising the role of the lid wiper and the aetiology of LWE requires consideration of the principles of tribology, which is the science and engineering of interacting surfaces in relative motion. This involves investigation of the relationship between coefficient of friction, load, relative speed and lubricious fluid properties.

Pult et al.[51] have applied these tribological principles to model the dynamic interaction between the lid wiper and the ocular or contact lens surface during normal and abnormal blinking and dry eye situations. They begin by pointing out that classic tribological theory is not strictly applicable to the process of blinking, because of the presence – in a healthy tear film – of the glycocalyx and the gel-forming, mucinous, brush-like structure on the ocular surface and lid wiper. The expected high coefficient of friction at low blink speeds does not occur because of the presence of the brush. In addition to the hydrophilic polymer brushes formed by the mucins, the tribological model of the eye may be influenced by (1) physical parameters, such as lid pressure (see later), blink speed, surface roughness and texture; (2) material parameters, such as the elastic modulus

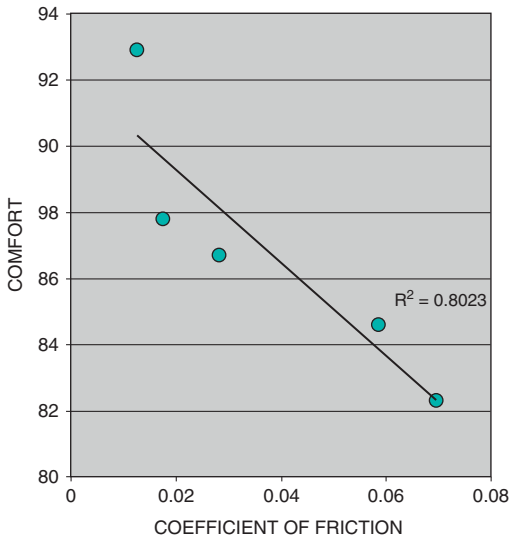


Fig. 5.8 Plot of median end-of-day comfort with contact lenses versus contact lens coefficient of friction. (Courtesy of Dr Noel Brennan.)

of the tissue or contact lenses; and (3) tear film composition, which ultimately has an influence on tear film viscosity and lubricant thickness. Tear film viscosity is also influenced by temperature.[51]

Kato et al.[52] investigated a broad range of dry eye measures (tear meniscus radius, tear film spread rate, lipid layer thickness, fluorescein break-up time, upper lid wiper staining grade and Schirmer 1 test) and blinking activity (blink rate, palpebral aperture height and upper lid ascending/descending distance and maximum velocity) on 45 eyes of 45 female patients with dry eye (mean age 57.6 years). Significant correlations were found between LWE and tear film spread rate ($r = 0.75$; $p < 0.0001$) and fluorescein break-up time ($r = -0.79$; $p < 0.0001$). Maximum upper eyelid descending velocity was also a determinant of LWE grade. The authors suggested that their results provide evidence to support the notion that LWE is caused by sheer friction.

SACCADIC EYE MOVEMENTS

Saccadic eye movements – the small, jerky ocular rotations that occur between two periods of visual fixation – may affect the lid wiper. Depending on the task, from reading a book to scanning a scene, the distance of movement of the cornea relative to the eyelid will normally be from 0.2 mm to 0.8 mm. Saccadic eye movements occur about 10% of the time during the waking hours. In total, an eye will likely make more than 150,000 such movements during the waking hours (eye movement characteristics during sleep are different, but these will not be considered here as this discussion is limited to open-eye lens wear). The sliding speed during these movements is generally below 1 cm per second, and the lubricity in this regime is likely to be the determining factor for lubricity-related comfort.

Because the majority of saccadic eye movements are horizontal, different considerations are required for modelling frictional dynamics at the lid wiper. In vertical movement of the eyelid, a leading edge of contact with the cornea is apparent, but that is no longer the case for horizontal eye movements. Greater lid wiper staining is observed on the lower lid compared with the upper lid,[12,13] which may be explained, in part, by differences in friction and lubrication with saccadic eye movements versus blinks.

INFLAMMATION

Korb et al.[25] proposed that LWE in contact lens wearers represents friction-induced microtrauma as a result of movement of the anterior lens surface across the lid wiper epithelium; they suggested that this, in turn, initiates a classic inflammatory cascade, as seen in dermal tissue. One way of testing this hypothesis is to examine the lid wiper in lens wearers with dry eye symptoms for evidence of inflammation. In this regard, various approaches have been applied, including non-invasively assessing cells in the lid wiper known to modulate inflammation, measuring vascular changes in the lid wiper and monitoring the temperature of the lid wiper.

Cellular response

Alzahrani et al.[53] set out to determine if Langerhans cells in the lid wiper are upregulated in contact lens–induced dry eye. The lid wiper of one eye of each of 46 contact lens wearers was examined by using a Heidelberg laser scanning confocal microscope (Fig. 5.9) after 6 months of wearing daily disposable hydrogel contact lenses (Biomedics 1 day Extra). Seventeen participants were assessed as having contact lens–induced dry eye, and 29 participants were assessed as not having contact lens-induced dry eye by using a subjective test (Contact Lens Dry Eye Questionairre-8) and objective tests (non-invasive TBUT, phenol red cotton thread tear test and fluorescein corneal staining). Twenty non–contact lens-wearing controls were also examined. Langerhans cell density in each participant was taken as the mean cell count, calculated manually from six clear, randomly selected images of known dimensions (Fig. 5.10).

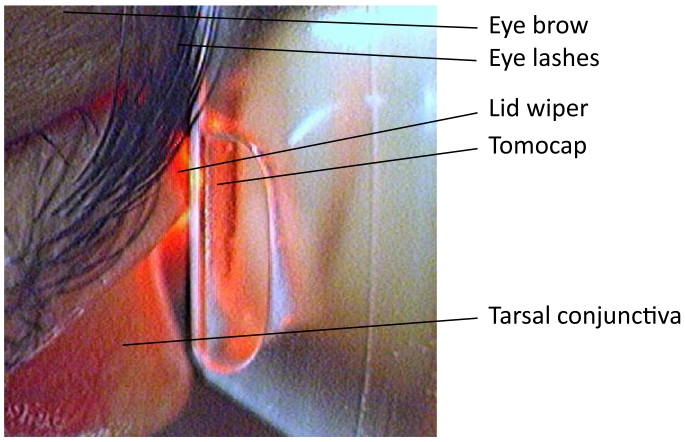


Fig. 5.9 View captured from side-mounted charge-coupled device camera of Heidelberg laser scanning confocal microscope while imaging the lid wiper. The upper section of the plano face of the Perspex TomoCap can be seen gently applanating the lid wiper. The TomoCap does not contact the exposed tarsal conjunctiva of the everted upper lid, eye lashes or brow. (Reproduced with permission from Alzahrani Y, Colorado L, Pritchard N, Efron N. Inflammatory cell upregulation of the lid wiper in contact lens dry eye. Optom Vis Sci 2016;93:917–24.)

There were significant overall differences in Langerhans cell density in the lid wiper among the three groups ($p < 0.001$) (Fig. 5.11). Langerhans cell density was significantly greater in the lid wiper in those with contact lens–induced dry eye (17 ± 10 cells/mm^2) compared with controls (8 ± 4 cells/mm^2) ($p < 0.001$); however, there was no difference in Langerhans cell density between those without contact lens–induced dry eye (10 ± 5 cells/mm^2) and controls ($p = 0.489$). Langerhans cell density was significantly greater in those with contact lens–induced dry eye than in those without contact lens–induced dry eye ($p = 0.002$). Alzahrani et al.[53] concluded that Langerhans cells in the lid wiper are upregulated in contact lens–induced dry eye, suggesting an inflammatory component in the aetiology of this condition.

Vascular response

The lid wiper is highly vascularised, so it would be expected that any inflammation of this tissue structure would be associated with hyperaemia. Certainly, Korb et al.[1] made the anecdotal observation that severe cases of LWE were associated with lid wiper hyperaemia. The finding of Deng et al.[47] that the microvascular network density of the lid wiper increased after 6 hours of contact lens wear supports the notion that LWE is

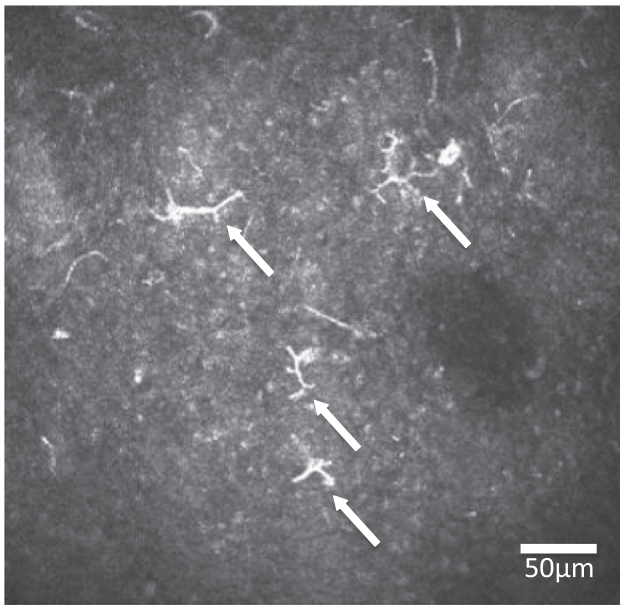


Fig. 5.10 Laser scanning confocal microscope image of Langerhans cells in the stroma of the lid wiper of a participant with contact lens–induced dry eye. Arrows indicate mature Langerhans cells with long dendrites. This image was captured at a depth of 46 µm from the epithelial surface. (Reproduced with permission from Alzahrani Y, Colorado L, Pritchard N, Efron N. Inflammatory cell upregulation of the lid wiper in contact lens dry eye. Optom Vis Sci 2016;93:917–24.)

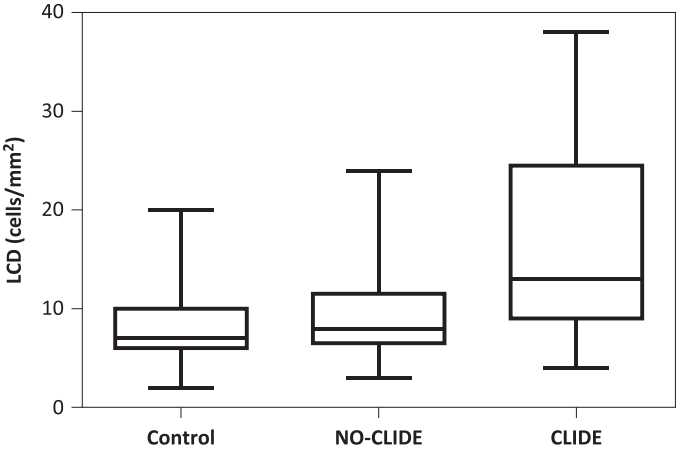


Fig. 5.11 Langerhans cell density (LCD) in the lid wiper of participants with contact lens–induced dry eye (CLIDE), participants without contact lens–induced dry eye (NO-CLIDE) and non-lens-wearing control participants. Box shows 25th and 75th percentiles; whiskers show data range; horizontal bar in box shows mean. (Reproduced with permission from Alzahrani Y, Colorado L, Pritchard N, Efron N. Inflammatory cell upregulation of the lid wiper in contact lens dry eye. Optom Vis Sci 2016;93:917–24.)

inflammatory, in the context of hyperaemia being one of the five cardinal signs of inflammation, as observed clinically.

In contrast, Read et al.[40] assessed changes in redness of the lid wiper (as an analogue of vascular response) for contact lens wearers and non–lens wearers and reported that lid wiper redness did not alter significantly through the day or after contact lens wear. No association was observed with lid wiper redness or subjective comfort (either the Contact Lens Dry Eye Questionnaire (CLDEQ-8) or the 0–100 comfort score). Inspection of the lid wiper region with respect to either redness or lissamine green staining did not appear to differentiate between symptomatic and asymptomatic contact lens wearers.

LID WIPER ELASTICITY AND EYELID PRESSURE

The extent to which eyelid pressure is involved in the development of LWE was investigated directly in two experiments by Yamamoto et al.[27] In the first experiment, eyelid pressure was measured with a blepharo-tensiometer, and the degree of upper and lower LWE was assessed using lissamine green staining in 79 eyes of 43 non–contact lens wearers. Upper LWE was detected in 24 (30.4%) of 79 eyes, and no significant difference was detected in eyelid pressure between any grade of upper LWE. Lower LWE was detected in 41 (51.9%) of 79 eyes, and eyelid pressure (27.9 ± 2.8 mmHg) in eyes with grade 3 LWE was significantly higher than that in eyes with grade 0 LWE (19.7 ± 1.3 mmHg; $p < 0.05$).

In the second experiment by Yamamoto et al.,[27] movements of the eyelids and displacement of the eyes during spontaneous blinking were photographed with a high-speed camera. Eyelid pressure was also measured in 34 normal eyes of 19 non–contact lens wearers. The authors observed that lower eyelid pressure was significantly correlated with the length of the horizontal movement of the lower eyelids ($p < 0.05$) and also with the degree of posterior movement of the globe ($p < 0.05$). The authors concluded that higher pressure from the eyelid may be one of the causes of lower LWE development.

UPPER LWE VERSUS LOWER LWE

Shiraishi et al.[31] offered an interesting hypothesis to explain the observation of greater staining of the lower lid wiper versus that of the upper lid wiper (Fig. 5.12), which, upon initial consideration, seems counterintuitive. They noted that during a blink, the upper eyelid has a large vertical movement, whereas the lower lid has a shorter horizontal nasalward movement, as revealed by high-speed photography of the eye during blinking.[48] The large excursion self-evident in the upper eyelid has perhaps captured the attention of most researchers attempting to investigate and explain LWE.

Because the lower eyelid moves horizontally, the lower eyelid margin rubs over the same restricted region of the contact lens or over ocular surface. As a result, frictional effects, and therefore LWE, may be greater in the lower eyelid than in the upper eyelid – the latter gliding over a vast expanse of generally well-lubricated ocular surface (in a non-dry eye situation).

AGE

Pult et al.[54] reported a significant positive correlation between LWE and age ($r = 0.340$; $p < 0.034$) in a cohort of 17 males and 30 females aged 19 to 70 years. This indicates that LWE is more likely in older patients.

The findings of Pult et al.[54] contradicted those of Shiraishi et al.,[31] who assessed LWE in 443 eyes of 229 non–contact lens wearers (100 men and 129 women; age 3–94 years; mean ± standard deviation (SD) 52.1 ± 24.0 years). When the subjects were divided into younger (≤39 years) and older (≤40 years) groups, both the prevalence and average lid wiper scores were significantly higher in the younger groups for both upper and lower LWE.

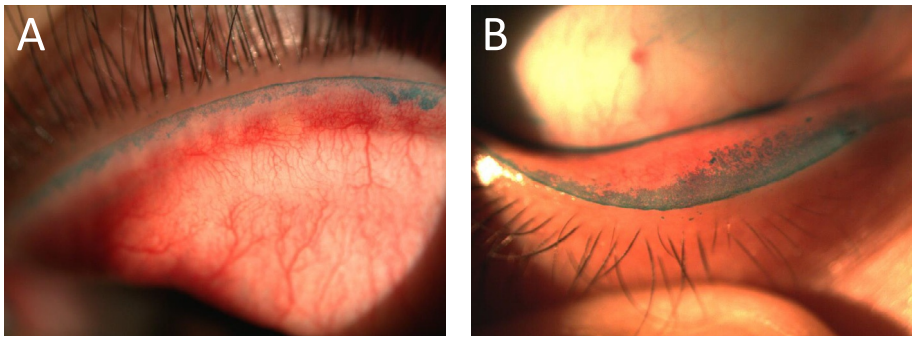


Fig. 5.12 Staining of the lid wiper with lissamine green. **(A)** Moderate LWE of the upper eyelid. **(B)** Severe LWE of the lower eyelid. (Courtesy Maria Navascues Cornago.)

SEX

Research to date has failed to demonstrate an association between sex and LWE. Pult et al.[54] found no relationship between sex and LWE (U test; $p > 0.05$). Shiraishi et al.[31] also could not detect a significant difference in sex between those with LWE and those without LWE. Using lissamine green staining, Doughty et al.[55] observed that staining of the line of Marx was quantitatively similar in both men and women.

ETHNICITY

Craig et al.[56] investigated the influence of eyelid shape on tear film quality, ocular surface characteristics and dry eye symptomatology by comparing non–contact lens wearing Asian and Caucasian populations. The authors observed higher levels of LWE in the Asian group compared with the Caucasian group (all $p < 0.05$).

HUMIDITY

The effect of a low-humidity environment on the status of LWE was investigated by Jones et al.[57] Ten symptomatic contact lens wearers were randomised to contralateral lens wear with narafilcon A and etafilcon A lenses. Lens wear was discontinued 48 hours before assessments, and Refresh Plus artificial tears were instilled three times per day in both eyes. Upper LWE and lower LWE were assessed by using fluorescein and lissamine green at baseline before lens insertion and entry into a low humidity environmental exposure chamber (temperature 22 ± 3° C, relative humidity 10% ± 3% and air velocity 5 ft/sec) for 180 minutes. Upon exit, lenses were removed, and artificial tears were instilled every 15 minutes for 120 minutes. LWE was evaluated immediately after post-chamber exposure and at 30 minutes, 90 minutes and 120 minutes.

After 180 minutes in the chamber, from baseline to post-chamber assessment, upper LWE increased from 1.25 to 2.23 for narafilcon A and from 1.18 to 1.93 for etafilcon A. Lower LWE increased from 1.00 to 2.48 for narafilcon A and from 0.90 to 2.03 for etafilcon A (all $p < 0.05$). The mean upper and lower LWE grades did not return to baseline levels at 120 minutes after leaving the chamber and were 2.47 and 2.11 for narafilcon A and 2.42 and 1.89 for etafilcon A, respectively. These LWE responses were similar for the two lenses despite their markedly different material properties.

These results suggest that low-humidity environments can have an adverse effect on upper and lower LWE during contact lens wear, presumably as a result of degradation of the PLTF and consequent exacerbation of frictional contact between the lid wiper and anterior lens surface.

PSYCHOLOGICAL FACTORS

McMonnies[58] suggested that there may be an important psychological component to the development of LWE. He proposed that higher expectations of comfort may be established for soft lens wearers on the basis of their initial experience with diagnostic lenses. These expectations are usually reinforced by the high comfort levels experienced on daily insertion of fully hydrated lenses and before significant lens front surface drying occurs after many hours of wear, resulting in greater lid wiper friction and typical end-of-day symptoms.

McMonnies[58] proposed that lens awareness can increase under provocative conditions for front surface drying, such as prolonged reading and/or computer use, air conditioning, air movement and incomplete and/or infrequent blinking. Such adverse environmental conditions could compromise the tear film and exacerbate frictional effects between the lid wiper and lens surface. Failure of lens wearers to appreciate the potential significance of these factors may contribute to discomfort experiences; conversely, understanding the potential significance of these factors may help patients to reduce exposure to, or even to avoid, some of these adverse influences.[58]

MULTIPLE LID WIPER EPITHELIOPATHIES?

The term 'lid wiper epitheliopathy' implies that this is a unitary condition, but the earlier discussion on the different forms of clinical presentation and the various possible aetiological factors contributing to this condition suggests that there may be many different forms of LWE. An analogy would be corneal staining – an overarching descriptor of a range of conditions with different aetiologies, such as solution-induced corneal staining, 3 & 9 o'clock corneal staining, desiccation corneal staining, superior epithelial arcuate lesions and peroxide burn. Although all of these conditions can be included under the overarching descriptor 'corneal staining', they represent a wide range of clinical presentations with different causes, requiring different treatments.

Treatment

The choice of strategies for the treatment of LWE is confounded by uncertainty as to the link between LWE and ocular comfort

and by lack of a complete understanding of the aetiology of the condition, which may be multi-factorial and vary among individuals. Despite these uncertainties, a number of reports have advocated various management strategies for alleviating LWE. Some authors have directly assessed the benefits of certain therapies on LWE, whereas some others have demonstrated an effect of therapies on LWE in the course of alleviating dry eye or contact lens discomfort. In the latter case, improvements in LWE essentially served as a surrogate marker for alleviation for dry eye.

REBAMIPIDE

Itakura et al.[59] presented two case reports of patients who were successfully treated with topical rebamipide to alleviate LWE. Rebamipide is an amino acid derivative of 2-(1H)-quinolinone and is used for mucosal protection, healing of gastroduodenal ulcers and treatment of gastritis. It works by enhancing mucosal defense, scavenging free radicals and temporarily activating genes encoding cyclooxygenase-2. It is also thought to have anti-inflammatory properties.[60] Administration of topical rebamipide increases secretion of mucins from goblet cells and improves the ocular surface in the 'short break-up time' type of dry eye.[61]

In both cases, fluorescein staining of the cornea and lid margin was remarkably improved, ocular symptoms decreased and TBUT increased with rebamipide eye drops administered four times daily for 2 to 3 weeks.

In an in vitro study, Kase et al.[62] observed that lid wiper tissue in patients who have been using rebamipide before tissue biopsy (obtained during involutional entropion surgeries) contained a significantly higher number of goblet cells and expressed higher levels of epidermal growth factor receptors compared with those who had not used rebamipide.

Rebamipide is used in a number of Asian countries, including Japan, South Korea, China and India, but it is not approved by the U.S. Food and Drug Administration for use in the United States.

CORTICOSTEROIDS

The efficacy of a corticosteroid, Lotemax (Bausch & Lomb), for the treatment of LWE was investigated by El-Rayess et al.[63] Forty subjects were treated with Lotemax (Bausch & Lomb), and 30 served as untreated controls. After a 1-month treatment phase with patients using one drop twice daily, there was an improvement in signs ($p < 0.001$) and symptoms ($p < 0.001$) in the treatment groups. The authors claimed that their study demonstrated the effectiveness of a corticosteroid for the initial treatment of LWE.

EYELID CLEANSING

Sung et al.[64] applied cleaning solutions to the eyelids of 43 patients with signs of clinical blepharitis. Diluted baby shampoo (Johnson's No More Tears) was applied to one eye, and a dedicated eyelid cleanser (TheraTears SteriLid) was applied to the fellow eye, twice daily for 4 weeks. Significant improvements in LWE were observed after application of both treatments (all $p < 0.05$), but there was no difference *between* treatments (all $p > 0.05$).

Similarly, Yanchenko et al.[65] reported that the prescription of eyelid hygiene (Blepharolotion or Blepharosalfetka plus Blepharogel-1 to be used 2 times daily) to relive meibomian gland dysfunction resulted in the resolution of LWE after 2 to 3 months.

LUBRICANT EYE DROPS

El-Rayess et al.[63] examined the efficacy of an oil-in-water emulsion lubricant for the treatment of LWE. Forty subjects were treated with Soothe Emollient Eye Drops (Bausch & Lomb), and 30 served as untreated controls. After a treatment phase (one drop twice daily) of at least 1 month, followed by a 1-year maintenance phase, there was an improvement in signs ($p < 0.001$) and symptoms ($p < 0.001$) in the treatment groups. Of subjects completing the maintenance phase, 85% demonstrated sustained improvement ($p < 0.01$). According to the authors, the oil-in-water emulsion eye drop was efficacious for both the initial treatment of LWE and maintaining long-term improvement of the lid wiper epithelium.

Guthrie et al.[66] examined the clinical effect of using Systane Balance Lubricant Eye Drops (Alcon, Fort Worth, Texas, USA), an oil-in-water emulsion, as a re-wetting eye drop in symptomatic contact lens wearers. The authors reported that comfort, wearing time, LWE and corneal staining all showed statistically significant improvements in the test group with use of Systane Balance Lubricant Eye Drops at the 1-month visit compared with baseline data (all $p < 0.01$) and compared with the control group at the 1-month visit ($p < 0.01$; $p = 0.01$; $p < 0.01$; and $p < 0.03$, respectively).

A new contact lens re-wetting drop containing both carboxymethylcellulose and hyaluronic acid was compared with a standard drop containing carboxymethylcellulose only in a study conducted by Nichols et al.[67] on 365 subjects. Symptoms of discomfort typical in lens wear and LWE were assessed over a 3-month period. The combination of carboxymethylcellulose and hyaluronic acid was superior in terms of alleviating ocular symptoms, reducing end-of-day discomfort and alleviating LWE.

BASIC FIBROBLAST GROWTH FACTOR

The treatment of LWE with basic fibroblast growth factor was investigated by Zhang and Mo.[68] Eighty-six patients were divided into a treatment group administered preservative-free artificial tears combined with basic fibroblast growth factor and a control group administered preservative-free artificial tears. After 3 weeks of treatment, all patients were assessed for LWE, and a questionnaire survey was used to evaluate dry eye.

The therapeutic effect of LWE in the treated group was deemed excellent in 74 eyes (86%) and effective in 12 eyes (14%), with a cure rate of 86%. The therapeutic effect in the control group was deemed excellent in 51 eyes (59%), effective in 34 eyes (40%) and ineffective in 1 eye (1%), with a cure rate of 59%. There was a statistically significant difference between the two groups ($p < 0.05$). The authors concluded that artificial tears combined with basic fibroblast growth factor were effective in treating LWE.[68]

LIPIFLOW THERMAL PULSATION SYSTEM

Satjawatcharaphong et al.[69] sought to identify patient characteristics – including LWE – at a baseline ocular surface evaluation that correlated with improvement in dry eye symptoms at a follow-up visit after treatment with the LipiFlow Thermal Pulsation System. Only initial symptoms and sex (and not LWE) were found to be predictive of improved post-treatment dry eye symptoms.

PUNCTAL PLUGS

The benefits of punctal plug insertion in alleviating the symptoms and signs of aqueous tear-deficient dry eye, including LWE, were investigated in 13 subjects by Yokoi et al.[70] Symptoms and signs before and at more than 1 month after punctal occlusion were assessed. The authors reported that a range of symptoms, including dryness, difficulty opening the eye, foreign body sensation, pain, redness, blurred vision, sensitivity to light, heavy eyelid and eye fatigue were significantly improved (all $p < 0.01$), along with tear meniscus radius, interference grade/spread grade of the tear-film lipid layer, non-invasive break-up time, ocular surface epithelial damage score (both corneal and conjunctival), corneal filament grade and LWE grade (all $p < 0.02$). Punctal plug insertion was therefore deemed efficacious in alleviating LWE.[70]

FITTING CONTACT LENSES OF HIGH SURFACE LUBRICITY

A strategy that may alleviate LWE associated with contact lens wear is fitting a lens with high surface lubricity. Roba et al.[50] demonstrated that contact lenses have a wide range of surface lubricity values. Further to this, Coles and Brennan[49] showed that contact lenses with higher lubricity values tend to be more comfortable. However, no studies to date have demonstrated a relationship between contact lens surface lubricity and LWE. Such an experiment would be difficult to conduct as lenses would have to be custom manufactured for such an experiment, whereby a range of lenses that are identical in all respects except surface lubricity would need to be fabricated.

ALTERING LENS WEARING MODALITIES

It also remains to be seen whether alterations to lens wearing modalities could alleviate LWE. Such strategies might include reducing lens wearing time, increasing lens replacement frequency, changing lens material properties (modulus of elasticity, silicone/water content, surface-active agents or packaging wetting agents),[71] changing lens dimensions (thickness, diameter and radius of curvature) or altering lens fit.

IMPROVING BLINKING BEHAVIOUR

McMonnies[72] proposed that improved blink efficiency, achieved through a reduction in the rate of incomplete blinking, may be an important component in the management of LWE related to dry eye in contact lens wearers and non–lens wearers.

Prognosis

Korb[73] noted anecdotally that cessation of contact lens wear usually leads to the resolution of most cases of LWE. Apart from this, there have no reports of the natural history of LWE. It is likely that LWE exists as a low-grade, chronic condition in lens wearers who are asymptomatic or have low levels of discomfort since there is a high prevalence of LWE in the presenting populations.[29]

The prognosis for the recovery of LWE after cessation of lens wear is unknown. If the resolution of LWE staining is analogous to that of general bulbar conjunctival staining, then resolution may be expected to occur within a few days of cessation of lens wear.

Differential diagnosis

It is important to be able to differentiate LWE from other physiological and pathological eyelid conditions that may take on a similar appearance. Although there is no clear evidence that the lid wiper increases in redness in cases of LWE, other pathological conditions in adjacent anatomical structures of the eyelid may be associated with lid wiper staining; clinicians may need to differentially diagnosis such conditions from LWE.

LINE OF MARX

Korb et al.[1] emphasised the importance of differentiating between LWE and staining of the line of Marx. With the patient looking upwards, it is possible to view the line of Marx without lid eversion; however, lid eversion is required for observation of the lid wiper.[74]

LID IMBRICATION SYNDROME

Hinkle[75] suggested that LWE needs to be differentiated from lid imbrication syndrome – a condition in which patients have a lax upper eyelid that does not easily evert and a normal tarsal plate.[76,77] Korb[73] noted the following points of differentiation between LWE and lid imbrication syndrome:

- The typical population with lid imbrication syndrome is much older than that with LWE.
- All patients with lid imbrication syndrome exhibit overriding of the upper lid on the lower lid, a feature not observed in patients with LWE.
- Surgery is often required to treat lid imbrication syndrome. LWE does not require surgery.
- LWE is a very common feature of contact lens wear, and cessation of contact lens wear usually leads to resolution in most cases of LWE, indicating that LWE may be induced by contact lenses.

BLEPHARITIS

The term ‘posterior blepharitis’ refers to inflammatory conditions of the posterior lid margin, and meibomian gland dysfunction is a possible cause. The resulting lid margin redness may result in a similar appearance to LWE, so the two conditions need to be differentiated. Although the symptoms of blepharitis and LWE may be similar in mild cases, all forms of blepharitis involve tissue anterior to the line of Marx and thus can be differentiated from LWE, which only involves the lid wiper, which is posterior to the line of Marx.

PAPILLARY CONJUNCTIVITIS

Differentiation of LWE from papillary conjunctivitis can be achieved by lid eversion and careful inspection of the underlying palpebral tissue to see which is affected. Instillation of fluorescein will reveal papillae on the tarsal conjunctiva in the case of papillary conjunctivitis and staining of the lid wiper in LWE, or both if the two conditions co-exist.

DEMODICOSIS

Demodex (mite) infestation of the eyelashes (demodicosis) is common and generally sub-clinical, but if the mites are present in excessive numbers, adverse signs and symptoms may

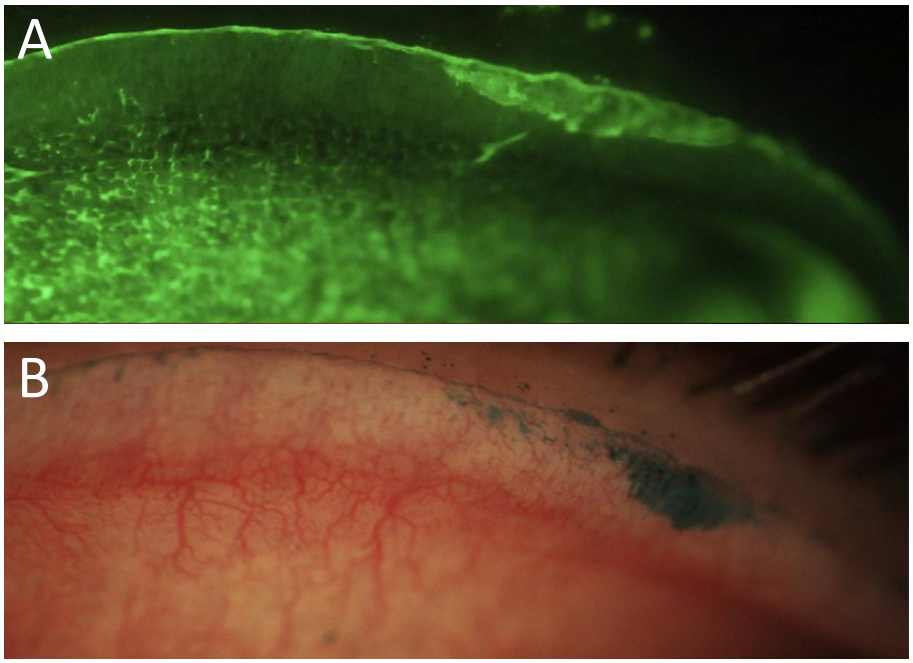


Fig. 5.13 False-positive lid wiper staining artifact. Short horizontal bands of staining seen on the lid wiper, caused by the finger touching the lid margin region, before instillation of **(A)** fluorescein and **(B)** lissamine green. (Reproduced with permission from Varikooty J. What is lid wiper epitheliopathy? Contact Lens Spect 2015;30:36—38, 40, 41.)

develop. Although the symptoms of demodicosis may be similar to those in LWE, careful inspection of the lashes for signs of mites or collarettes will assist with differential diagnosis.

In a group of 40 female Asian subjects, Jalbert and Rejab[78] were unable to detect significant differences in lid wiper staining between *Demodex*-infested subjects and those without *Demodex* infestation, regardless of whether or not they wore contact lenses.

MEIBOMIAN GLAND DYSFUNCTION

The absence of oil globules at the meibomian gland orifices could indicate normal function, hyposecretion or obstructive meibomian gland dysfunction. If oil globules are not observed on the lid margins of a symptomatic contact lens wearer, the patient may have a condition that Blackie et al.[79] referred to as 'non-obvious obstructive meibomian gland dysfunction'. Such cases may appear similar to LWE, and it may be necessary to conduct a provocative test to establish the state of health of the meibomian glands by manual expression of the glands so that the nature of the expressed oils can be assessed. Abnormal secretions will assist differentiation of meibomian gland dysfunction, especially the 'non-obvious' form, from LWE.

Willis et al.[80] evaluated the grade of LWE in individuals symptomatic for dry eye meibomian gland dysfunction and found that patients reporting dry eye symptoms are very likely to display meibomian gland dysfunction and LWE as comorbidities.

In cases where LWE and meibomian gland dysfunction coexist, clinicians should remain aware that the precise location of the line of Marx – a key anatomical landmark for the assessment of LWE – varies in location relative to the meibomian gland orifices, tending to run on the eyelid-margin side of gland orifices in more severe cases.[27]

IATROGENIC LID WIPER STAINING

In the course of research experiments characterizing the various appearances of lid wiper staining, Varikooty et al.[24] occasionally observed a false-positive artefact on the lid wiper if a finger of the examiner touched the lid margin region before instillation of fluorescein or lissamine green (Fig. 5.13). Care must therefore be taken when manipulating the lids during eversion and while maintaining lid eversion to avoid causing iatrogenic lid wiper staining.

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6 Eyelid Ptosis

Contact lens practitioners routinely examine the tarsal conjunctiva and lid margins of their patients, but little attention is generally given to the overall integrity of the eyelids. Eyelid dysfunction, whether caused by contact lens wear or other factors, can pose a problem for contact lens wearers because this could interfere with some of the important roles played by the eyelids.

This chapter will concentrate on a condition that is often overlooked by eye care practitioners – contact lens–induced ptosis (CLIP) of the eyelids. Ptosis is defined as 'prolapse, abnormal depression, or falling down of an organ or part; applied especially to drooping of the upper eyelid'.[1] Because ptosis is not confined to the eyelids, some authors prefer to use the more exact term 'blepharoptosis'. An assortment of other eyelid disorders that may be of relevance to contact lens wear will also be considered.

CLIP is perhaps the only complication of contact lens wear for which surgical intervention is contemplated and occasionally executed (notwithstanding infectious keratitis associated with corneal ulceration, which sometimes requires hospitalisation and can result in keratoplasty). It is for this reason that clinicians should have an appreciation of the typical manifestation of this condition, its likely causation, indications for surgery and other management options.

Signs

The classic appearance of ptosis is of narrowing of the palpebral fissure and a relatively large gap between the upper lid margin and the skin fold at the top of the eyelid (Fig. 6.1). In a normal individual without ptosis, the skin fold at the top of the eyelid is only slightly higher than the upper eyelid margin. In some patients, these anatomical features can become virtually co-aligned toward the outer canthus.

It is possible to detect CLIP if (1) a patient reports that he or she detects narrowing of the palpebral apertures; (2) palpebral aperture height is measured accurately on many occasions over time (to detect a trend); or (3) one eye is affected more than another. Because contact lenses are typically worn in both eyes, any contact lens–induced narrowing of the palpebral apertures will be expected to be bilateral. However, Kersten et al.[2] reported CLIP to be unilateral in 58% of a series of presenting patients. Unilateral CLIP can arise as a result of lens handling-related trauma, whereby the patient is more forceful with lens insertion or removal on either the right or the left side. Unilateral CLIP can also result from uniocular lens wear or the highly unusual scenario of wearing of a different lens type in each eye of (i.e. rigid lens in one eye and soft lens in the other eye).

Fonn and Holden[3,4] conducted a longitudinal trial designed to compare the ocular response to rigid and hydrogel contact lenses worn for an extended period. The experimental protocol called for inter-ocular comparison; that is, a rigid lens was worn in one eye and a hydrogel lens was worn in the other eye. It was observed that the palpebral aperture of the eye wearing the rigid lens was noticeably narrower than that in the eye fitted with the soft lens in 77% of the 40 subjects who participated in the trial[4] (Fig. 6.1).

SEVERITY

Various studies have quantified the extent of palpebral aperture closure resulting from various modalities of contact lens wear. Fonn et al.[5] measured the palpebral aperture size to be 10.10 ± 1.11 mm in non-wearers, 10.24 ± 0.94 mm in soft lens wearers and 9.76 ± 0.99 mm in rigid lens wearers. The difference in palpebral aperture size between the rigid lens wearers and the soft lens wearers (0.48 mm) and between the rigid lens wearers and the non–lens wearers (0.34 mm) was statistically significant, but there was no significant difference in palpebral aperture size between soft lens wearers and non-wearers (0.14 mm). The rigid lens wearers had been wearing lenses for 11.6 ± 8.4 years, and the soft lens wearers had been wearing lenses for 8.2 ± 5.5 years. No gender difference in the development of CLIP was noted.

Satariano et al.[6] determined that the mean ptosis measurement was 1.00 mm among those who did not wear contact lenses, 1.41 mm among those who wore soft contact lenses and 1.84 mm among those who wore rigid contact lenses.

A study by van den Bosch and Lemij,[7] similar to that described earlier, found that the upper lid had lowered by 0.5 mm in a group of patients who had been wearing rigid lenses for an average of 16.3 years. The reason for a greater amount of ptosis in this study (vs. that of Fonn et al.[5]) may be attributed to the greater lens wearing experience of the subjects examined (16.3 vs. 11.6 years), although Fonn et al.[5] noted no such



Fig. 6.1 Unilateral right eye ptosis induced by rigid lens extended wear approximately 4 weeks after initiating wear. The left eye was wearing a soft lens as part of a research experiment. The skin folds, which are used as the reference point for assessing the degree of ptosis, are indicated by the white arrows. (Courtesy Desmond Fonn, Bausch & Lomb Slide Collection.)

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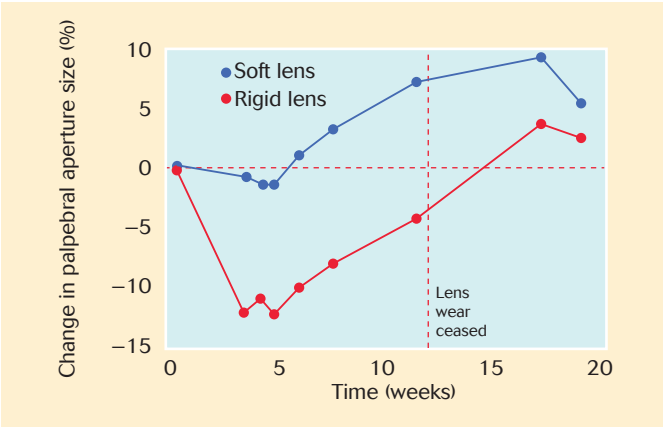


Fig. 6.2 Changes in palpebral aperture size (%) over 13 weeks of extended wear of a rigid lens in one eye and a soft lens in the other eye and 7 weeks of recovery. (Reproduced with permission from Fonn D, Holden BA. Rigid gas-permeable vs. hydrogel contact lenses for extended wear. Am J Optom Physiol Opt 1988;65:536-42. ©The American Academy of Optometry, 1988.)

relationship within their own study group. The position of the lower lid was unaltered by rigid lens wear.[7]

Reddy et al.[8] reported mild to moderate bilateral CLIP in nine soft lens wearers with a mean age of 24.2 years (range 15–35 years). All had been wearing soft contact lenses for at least 2 years before presentation, with a mean exposure of 5.6 years. None of the lens wearers had papillary conjunctivitis, which can also induce CLIP.

TIME COURSE OF ONSET

Fonn and Holden[4] monitored the time course of onset of CLIP in 17 subjects who wore a soft lens in one eye and a rigid lens in the other. In the eye wearing the rigid lens, maximum ptosis (12% closure) was observed between 4 and 6 weeks after commencing lens wear; this was followed by a relative lessening of the ptosis to a point where the palpebral aperture size was 3% smaller compared with baseline after 13 weeks (Fig. 6.2). The palpebral aperture size remained fairly stable in the eye wearing the soft lens for the first 7 weeks but, paradoxically, began to increase thereafter to become 7% wider compared with baseline after 13 weeks. (Apparent widening of the palpebral aperture as a result of soft lens wear is discussed later in this chapter).

In the longer term, the pattern of onset can be variable. In one study,[7] all but 2 of 17 patients presenting to a clinic complaining of CLIP reported that the condition had developed gradually over the past 12 to 24 months; most of these patients could illustrate this with photographs.[7] The other two patients in this study noted that the ptosis had existed for 6 and 16 years, respectively, and had gradually become worse.

Symptoms

Based on their observation of 17 patients presenting to a clinic complaining of advanced CLIP, van den Bosch and Lemij[7] demonstrated that 'generally' this is a condition that will be noticed by patients. No associated signs or symptoms were noted in any of these patients.

It is also interesting that, in prospective studies of palpebral aperture height in asymptomatic contact lens wearers,[5,7] none of the patients deemed to be suffering from CLIP were aware that they had this condition.

Prevalence

RIGID LENSES

Ptosis is defined by van den Bosch and Lemij[7] as a condition wherein the distance between the centre of the pupil and the lower margin of the upper lid is less than 2.8 mm. By using this criterion, these authors determined that the prevalence of ptosis in a consecutively presenting group of 46 rigid lens wearers was 11% versus 1% in a control group of non–lens wearers. Jupiter and Karesh[9] reported the prevalence of ptosis in a population of rigid lens wearers to be 4.7%. Kersten et al.[2] noted contact lens wear to be the only identifiable cause of acquired ptosis in 47% of a series of 91 patients who were 15 to 50 years of age and had this condition between 1986 and 1994.

Thean and McNab[10] published a report of a total of 15 consecutive patients who presented over a 4-year period (1997–2001) with blepharoptosis in the context of prolonged contact lens use. Four of the 15 patients (27%) were wearing rigid gas-permeable lenses. The rest had been wearing polymethyl methacrylate (PMMA) lenses. Thirteen patients (87%) had been wearing their contact lenses for more than 17 years. The age of the patients ranged from 15 to 71 years (mean age 46 years). All 15 patients had normal levator palpebrae superioris function. Four patients (27%) had bilateral involvement.

SOFT LENSES

Reddy et al.,[8] who used the same definition of ptosis as that used by van den Bosch and Lemij,[7] noted that although only 13% of all Americans wear soft contact lenses, the prevalence of soft contact lens use in their series of patients with acquired ptosis and no other clinically evident cause for ptosis, irrespective of age, was much higher at 52%. In their study, the prevalence of soft contact lens use in patients under age 35 years with unspecified acquired ptosis was 69%. They concluded that (1) soft contact lens use was approximately five times more common in young patients, who developed otherwise unexplained acquired ptosis than in the general population, and (2) soft lens wear was the most common risk factor for ptosis in patients under age 35 years.

Bleyen et al.[11] reported on a consecutive retrospective series of 35 patients diagnosed with unilateral or bilateral ptosis. The history of contact lens wearing in these patients was as follows: 20 (57%) (ages 18–50 years; average 37 years) had been wearing hard contact lenses for, on average, 17.6 years (range 6–27 years); 9 (26%) (ages 18–45 years; average 30 years) had been wearing soft contact lenses for, on average, 9 years (range 1.5–20 years); and 6 (17%) (ages 23–39 years; average 33 years) had no history of contact lens wear. The odds ratio (OR) for soft contact lenses was 14.7 (95% confidence interval (CI) 4.2–50.7) and for hard contact lenses 97.8 (22.5–424). The authors concluded that not only hard contact lens wear but also soft contact lens wear may be associated with ptosis.

Risk factors

Hwang and Kim[12] conducted a systematic review to evaluate the risk for blepharoptosis in contact lens wearers. In a PubMed search, 393 papers were found using the terms 'lens and ptosis'. The abstracts were read, and 16 full-text articles were reviewed. Among them, five articles were analysed. Five studies were subgrouped and a meta-analysis of these data suggested that there is an increased risk for blepharoptosis in rigid lens wearers over

non–lens wearers (n = 7426; OR 17.38; 95% CI 3.71–81.29; p < 0.00001). One study was sub-grouped, and these data suggested that there is also an increased risk for blepharoptosis in soft lens wearers over non–lens wearers (n = 90; OR 8.12; 95% CI 2.68–24.87; p < 0.0002).

An age-matched case-control study was performed by Kitazawa[13] in a hospital in Japan. The rate of rigid lens use in ptosis cases was compared with that in a control group, and then the OR was estimated. A history of wearing rigid lenses was significantly higher in patients (90.2%) versus controls (31.6%). Rigid lens wearers had a 20 times increased risk for ptosis (OR 19.9; 95% CI 6.32–62.9) compared with non-lens-wearing subjects.

Satariano et al.[6] assessed the environmental factors that may contribute to eyelid ptosis in a population of identical twins. Photographs of 286 sets of twins from a prospectively collected database from 2008 to 2010 were reviewed and digitally analysed; 96 sets of identical twins (192 individual persons) had differing severity of ptosis. Wearing either hard or soft lenses was associated with an increased risk for ptosis, and these influences are independent of genetic predisposition.

Watanabe et al.[14] investigated the effect of myopia, duration of rigid contact lens wear and patient age on the progression of ptosis among 194 eyes of 98 patients with either bilateral or unilateral ptosis. The average best-sphere refractive error was −8.34 diopter (D) in those with severe ptosis; −6.28 D in those with moderate ptosis; −5.57 D in those with mild ptosis; and −4.80 D in those with no ptosis. The average duration of rigid lens wear was 34 years in those with severe ptosis, 30 years in those with moderate ptosis, 29 years in those with mild ptosis, and 31 years in those with no ptosis. The authors concluded that high myopia, patient age and long-term rigid lens wear are risk factors associated with the progression of ptosis.

de Silva and Collin[15] observed that increased severity of ptosis was directly related to patient age and refractive error (p < 0.005), but not to the duration of contact lens wear.

Pathology

There is general agreement that the pathological basis of CLIP is either (1) oedema leading to lid swelling or (2) disinsertion, dehiscence (splitting), thinning or lengthening of the levator aponeurosis.[2,7,8,10,16] The relatively large gap between the upper lid margin and the skin fold at the top of the eyelid described earlier (also referred to as a 'high skin crease') develops because the posterior fibres of the levator aponeurosis on the tarsal plate disinsert, split or lengthen, whereas the anterior insertion of the levator aponeurosis into the orbicularis muscle and skin remains intact.[7] Thinning of the eyelid is also sometimes observed.

Aetiology

A number of mechanisms have been advanced as possible causes of CLIP. These can broadly be categorised into aponeurogenic (i.e. involving some form of dysfunction of the aponeurosis) and non-aponeurogenic causes.

APONEUROGENIC CAUSES OF CLIP

Forced lid squeezing

The unnatural 'forced blink' rigid lens removal technique places simultaneous, but antagonistic, forces on the orbicularis and levator muscles. Because rigid lens wearers are instructed to open their eyes wide while executing a powerful blink, both the levator and orbicularis muscles are attempting to contract at the same time. The opposed actions of these two muscles might cause increased traction on the levator aponeurosis, leading to disinsertion or dehiscence.[17]

Lateral eyelid stretching

To effect rigid lens removal, patients are often instructed to pull firmly on the outer canthus to create increased tension in the eyelids so that a greater leverage force is created to cause the lens to be blinked out of the eye. Although this action primarily may lead (if anything) to a disinsertion or dehiscence of the lateral canthal ligament or the medial canthal tendon, it should not by itself lead to a disinsertion or dehiscence from the levator aponeurosis.[7] However, in combination with the antagonistic contraction of the orbicularis and levator muscles during forced blink removal, as described previously, stretching or thinning of the levator aponeurosis cannot be discounted.

Consideration of these two aetiological factors – forced lid squeezing and lateral eyelid stretching – leads to the disturbing conclusion that actions undertaken by both practitioners and patients may be responsible for CLIP in some cases. This conclusion is supported by the report of five cases of CLIP by Epstein and Putterman,[17] who observed that two of these cases developed directly after the patients were fitted with rigid lenses. The ptosis in these two patients did not resolve after cessation of lens wear.

Rigid lens displacement of tarsus

During repeated attempts to remove a rigid lens, the lid will occasionally be pulled across the lens, which will, in turn, exert pressure on the palpebral conjunctiva. This unnatural pressure against the palpebral conjunctiva, effectively in an anterior direction against the posterior surface of the lid, could be directed against the levator aponeurosis, especially if the lens has migrated a little superiorly. This, in turn, could lead to disinsertion, dehiscence and/or thinning of the aponeurosis.[7]

Blink-induced lens rubbing

It has been argued by van den Bosch and Lemij[7] that every blink made during the regular wearing of a rigid lens causes the lens to rub against the eyelid structures, albeit less forcefully than during lens insertion and removal. This chronic rubbing and displacement of the lid away from the globe by the lens may cause a gradual thinning and stretching of the levator aponeurosis. Thus, the way in which the lens is fitted, and the size, thickness and positioning of the lens, may have a bearing on CLIP.

Excessive force used in handling of soft lenses

The method of lens insertion and removal was determined by Reddy et al.[8] to be the likely cause soft lens–induced ptosis. Specifically, they suggested that ptosis may occur in patients who either apply abnormal force to their eyelids while manipulating their lenses or have an intrinsically weak levator aponeurosis.

NON-APONEUROGENIC CAUSES OF CLIP

Oedema

Constant physical irritation of any tissue in the body can result in a mild, sub-clinical inflammatory status and subsequent oedema.[3-5] Thus, constant rubbing of a rigid lens against the



Fig. 6.3 Apparent rigid lens–induced lid oedema in the region above and below the upper skin fold of the right eye, leading to ptosis. The left eye was wearing a soft lens as part of a research trial. (Courtesy Meng Poey Soh.)

tarsal conjunctiva is a possible cause of the ptosis. Specifically, oedema could lead to ptosis because of a physical enlargement of the eyelid in all dimensions (including a downward displacement) as the lid absorbs increased levels of fluid. The increased mass of the oedematous upper lid, combined with the effects of gravity, may cause a lowering of the lid (Fig. 6.3).

Rigid lens–induced ptosis in the right eye of a patient who also wore a soft lens in the left eye (as part of a research study) is shown in Figure 6.3. The region above and below the upper skin fold of the right eye appears slightly oedematous, which would suggest that oedema caused by mechanical rubbing of the lens is the cause of the ptosis in this eye.

Blepharospasm

Rigid lenses are intrinsically uncomfortable, especially during the adaptation phase of lens wear. Discomfort primarily results from buffeting of the lens edge against the lid margins. Involuntary narrowing of the palpebral aperture (blepharospasm) is often adopted as a mechanism to stabilise the lens and prevent lens-lid buffeting. Blepharospasm is therefore another possible explanation for CLIP. Chronic involuntary blepharospasm may strain the levator muscle and, in turn, cause a higher tonus of the levator muscle. However, van den Bosch and Lemij[7] discount this mechanism as an important aetiological factor in CLIP because the lower lid – which would be expected to adopt a slightly higher position as a result of blepharospasm – is unaffected by rigid lens wear.

Papillary conjunctivitis

Severe (grade 4) contact lens–induced papillary conjunctivitis can be associated with excessive inflammation and oedema of the eyelids, which can cause lid swelling and drooping.[18] Since papillary conjunctivitis typically manifests bilaterally, a bilateral CLIP results.[19] This situation will be more prevalent in soft lens wearers. Papillary conjunctivitis also occurs in association with rigid lens wear, but it is rarely more severe than grade 2.

Patient management

A key diagnostic criterion in deciding on an appropriate course of action to alleviate CLIP is to determine whether the CLIP is caused by:

- Aponeurogenic disorders, such as disinsertion, dehiscence or thinning of the aponeurosis;
- non-aponeurogenic disorders, such as oedema or involuntary blepharospasm); or
- contact lens–induced papillary conjunctivitis.

To differentiate between these possible causes, patients demonstrating CLIP should be required to cease lens wear for at least 1 month (to detect any trends toward recovery) and perhaps as long as 3 months (to demonstrate complete resolution).

If CLIP resolves partially or completely after ceasing lens wear for 1 month, then the cause was lid oedema and/or involuntary blepharospasm. The decision as to whether action needs to be taken is based largely on cosmetic considerations, although a severe ptosis can also interfere with vision if the lid wholly or partially covers the pupil. If the extent of ptosis is cosmetically unsightly, or it is more prominent in one eye leading to a noticeable asymmetry in palpebral aperture size, the patient may need to be refitted with soft lenses, which are less likely to be associated with ptosis.

The eyelids should also be inverted to determine if papillary conjunctivitis is involved, and if so, appropriate action should be taken to alleviate that condition. If the ptosis persists after resolution of the papillary conjunctivitis, then it is likely that the aponeurosis has also been damaged by lens wear.

PROPHYLAXIS

Many cases of CLIP can be averted in the first place by instructing contact lens wearers to be very gentle with their eyelids during any form of in-eye lens manipulation, especially during insertion and removal. The key time point for issuing such advice is during the initial teaching visit, when a patient is new to lens wear. As well, patients should be required, from time to time, to demonstrate insertion and removal techniques at aftercare visits, and any evident heavy-handed habits should be rectified with further instruction and demonstration. These principles apply to both soft and rigid lens wear, although it is recognised that more forceful techniques typically are required for rigid lens removal.

SURGICAL CORRECTION

If CLIP does not resolve after ceasing lens wear for 1 month, then the most likely cause is damage to the aponeurosis. Surgical correction is the preferred option in such cases.[20] The typical procedure is reinserting the levator aponeurosis on the anterior surface of the tarsal plate under general anaesthesia and reconstructing the skin crease. This procedure was carried out successfully by van den Bosch and Lemij[7] in a series of 10 patients who had developed ptosis as a result of rigid lens wear. After surgery, patients should not be refitted with rigid contact lenses – the obvious remaining alternatives being soft contact lenses, spectacles or refractive surgery.

Teo et al.[21] reported on the results of Müller's muscle conjunctival resection surgery conducted on 31 eyelids of 20 contact lens–wearing patients with ptosis. Lenses had been worn for 20.6 ± 12.1 years. More than half (60%) wore soft contact lenses, as opposed to rigid lenses. Pre-operative margin-to-reflex distance was lower in patients who wore rigid contact lenses (0.8 ± 0.7 mm) compared with patients with soft contact lenses (1.7 ± 1.1 mm) ($p = 0.01$). Surgery was successful in 93.5% of cases.

A fascinating report by Levy and Stamper[22] reinforces the importance of observing the eyes after a prolonged period of cessation of lens wear to exclude non-aponeurogenic causes

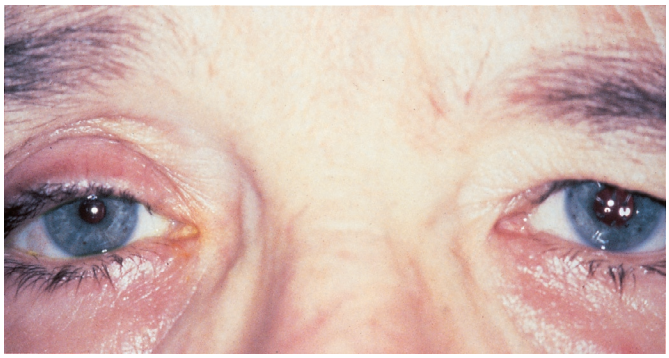


Fig. 6.4 Ptosis in the right eye caused by rigid lens wear in that eye. The left eye was emmetropic (because of intra-ocular lens wear) and did not require a contact lens. (Courtesy Desmond Fonn, Bausch & Lomb Slide Collection.)

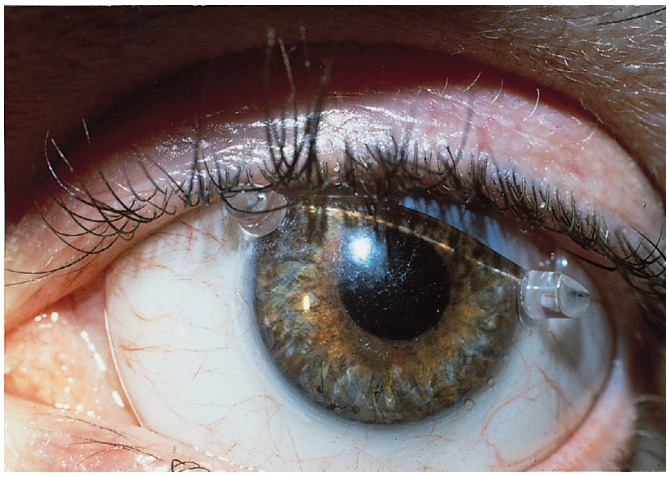


Fig. 6.5 Scleral lens with ptosis lugs and shelf. (Courtesy Frank Pettigrew, British Contact Lens Association Slide Collection.)

of CLIP. They reported the case of a rigid lens wearer who had undergone extracapsular cataract surgery in the right eye. After surgery, the right eye was emmetropic, and the patient continued to wear a rigid lens in the left eye. However, as a result of the surgery, the right eyelid became oedematous, and the palpebral aperture of that eye was the same as that of the left eye, which was also reduced because of the pre-existence of CLIP. Eight weeks after surgery, the patient presented with an apparent ptosis of the lens-wearing (left) eye. The palpebral aperture size was 12 mm in the right eye and 8 mm in the left eye.

Lid surgery was contemplated, but as a precaution, the surgeon advised cessation of lens wear for a period to determine if the lens was the cause. The palpebral aperture size was reduced by half within 1 month and disappeared after 3 months. Surgery was therefore not performed.

Figure 6.4 illustrates the previous point; it depicts the case of patient who was fitted with an intra-ocular lens to the left eye. The ametropic right eye that was fitted with a rigid lens displays an obvious ptosis.

NON-SURGICAL MANAGEMENT

Management strategies are available for patients who have severe CLIP but do not wish to undergo lid surgery. Katsoulos et al.[23] described three patients (five eyes) with ptosis resulting from levator dehiscence caused by long-term wear of rigid gas-permeable contact lenses for keratoconus, phthisis bulbi, and myopathy due to Kearns-Sayre syndrome, who were fitted with scleral contact lenses to provide cosmesis by lifting the upper eyelid with the bulk of the lens and simultaneously provide vision correction, where applicable. The lenses provided comfortable wear and significantly improved cosmesis, as both palpebral aperture and marginal reflex distance were increased. Visual acuity was also subjectively and objectively improved. Two of the patients opted for the scleral contact lenses, whereas the parents of the third patient, a 10-year-old girl with Kearns-Sayre syndrome, chose ptosis surgery for their daughter because of issues with handling of the scleral lenses. The authors concluded that scleral lenses can be a useful treatment option for patients with complex ptosis.

The patient may be fitted with a 'ptosis crutch', 'ptosis prop' or 'ptosis lugs'.[24] This is a scleral lens that has either a cemented ledge or lugs fixed to the front surface, and/or a shelf cut into the front surface of the lens. In both cases, the lower border of the upper lid rests on the ledge or shelf, thus keeping the eyelid open to the desired extent.

Figure 6.5 depicts the case of a blind eye with inoperable ptosis that was fitted with an impression scleral prosthetic moulded shell with a superior shelf and ptosis crutch legs. In this photograph, the lid appears to be supported more by the left lug, and the shelf (the white line connecting the two lugs) appears to be displaced from the upper lid margin. This appliance has been successfully worn for 10 years.

This approach in a patient with CLIP constitutes something of a paradox because the patient is being fitted with a scleral lens – which can be considered to be an extreme form of rigid lens – which was the likely cause of the problem in the first place. That is, the scleral lens with ptosis crutch may be perpetuating or even exacerbating the very problem it is supposedly curing.

Other options for non-surgical correction of CLIP include the following:

- instructing the patient to periodically raise the ptotic lid with a finger and relying on residual tone to keep the lid open for a period thereafter;
- employing a spectacle frame-mounted lid prop; or
- attaching one end of a small piece of surgical tape to the eyelid just above the lashes and the other end to the smooth skin below the eyebrow.

Prognosis

The prognosis for recovery from aponeurogenic CLIP is poor; the condition can be reversed by surgical correction or other management options, as described earlier.

The prognosis for recovery from non-aponeurogenic CLIP is good. If the cause of ptosis is papillary conjunctivitis, the time course of resolution of the ptosis will parallel the time course of recovery of the papillary conjunctivitis. A noticeable diminution of ptosis associated with a reduction of the severity of papillary conjunctivitis from grade 4 to grade 1 or 2 would take 4 to 8 weeks.

According to Fonn and Holden,[4] complete resolution of non-aponeurogenic CLIP will occur within 6 weeks. In severe cases, resolution may take as long as 3 months.[22]

de Silva and Collin[15] reported that among 31 contact lens wearers who underwent ptosis surgery during a 12-month

period (2005–2006) at Moorfields Eye Hospital in London, UK, the outcome of surgical ptosis correction was successful in only 72% of cases versus 89% among 46 non-lens-wearing control subjects ($p < 0.005$).

Differential diagnosis

If a contact lens wearer presents with ptosis, other possible causes of this condition must be considered so that the appropriate course of management can be adopted.

APONEUROGENIC PTOSIS

Any ptosis caused by disinsertion, dehiscence, thinning or lengthening of the levator aponeurosis can be referred to as *aponeurogenic ptosis*, of which there are two categories based on aetiology – traumatic or involutional.

Surgery is the most common cause of traumatic aponeurogenic ptosis; specifically, damage to the levator aponeurosis can be caused by traction on the eyelids during surgery or clumsy attempts by the patient to remove a patch over the eye after surgery. Trauma induced by forceful rigid lens removal and the chronic presence of a rigid lens are other possible causes of traumatic aponeurogenic ptosis.

Involutional aponeurogenic ptosis describes the process of damage to the levator aponeurosis as a result of ageing. Ocular inflammation and the use of steroids can exacerbate this condition.[7]

van den Bosch and Lemij[7] compared the age profile of patients presenting with contact lens–induced aponeurogenic ptosis with that of a patients presenting to the same clinic with involutional aponeurogenic ptosis. The age range was 18 to 56 years (mean 38.5 years) in the lens-wearing group and 48 to 88 years (mean 69 years) in the group with involutional aponeurogenic ptosis. Thus, patient age provides an important clue as to the cause of aponeurogenic ptosis. By measuring lid and vertical eye saccades with electromagnetic search coils, Wouters et al.[25] were able to differentiate between congenital ptosis and aponeurogenic ptosis (involutional or rigid lens-induced).

NON-APONEUROGENIC PTOSIS

Non-aponeurogenic causes of ptosis include the following:

- neurogenic diseases, such as pathway interruption or palsy of the third cranial nerve supplying the levator, Horner's syndrome or the Marcus Gunn sign;
- myogenic disease, which may be congenital or acquired – examples of the latter being muscular dystrophy or myasthenia gravis;
- oedema after lid surgery;
- oedema caused by traumatic eye injury;
- oedema resulting from prolonged rigid contact lens wear (as described in detail in this chapter);
- contact lens embedded in upper eyelid (see later);
- chalazion;
- tumour;
- dermatochalasis;
- blepharospasm, possibly caused by photophobia secondary to other ocular diseases;
- vernal and giant papillary conjunctivitis; or
- forms of nervous disposition leading to idiosyncratic partial eye closure.

Other contact lens–associated eyelid disorders

INCREASE IN PALPEBRAL APERTURE SIZE

Hori-Komai et al.[26] reported the pre-operative and post-operative palpebral fissure width in eyes undergoing laser in situ keratomileusis. In patients who had previously worn rigid lenses, palpebral aperture size increased from 7.6 ±1.6 mm before surgery to 8.7 ± 1.2 mm after surgery. In patients who had never worn lenses previously, palpebral aperture size increased from 7.7 ± 1.9 mm before surgery to 8.9 ± 1.9 mm after surgery. The postsurgical increase in palpebral aperture size in the rigid lens group could be attributed to a resolution of previous lens-induced ptosis; however, the reason for the increase in the control group is unclear.

Mutti and Seger[27] noted – in two unilateral soft lens wearers – a relative ptosis of 19% in the contralateral non-lens-wearing eyes. As these authors had no baseline data, they were unsure as to whether this appearance resulted from a widening of the palpebral aperture of the lens-wearing eye or a narrowing of the palpebral aperture of the non-lens-wearing eye.

Interestingly, Fonn and Holden[4] observed an 8% widening of the palpebral aperture in eyes wearing soft lenses but failed to validate their data statistically. Fonn et al.[5] noted that the palpebral aperture size of soft lens wearers was 1.4% greater than that of controls, but statistical analysis failed to reveal a significant difference.

Although soft lens–induced *widening* of the palpebral aperture can only be considered as an anecdotal observation at the present time, it is interesting to speculate as to a possible cause. Mutti and Seger[27] have tentatively attributed this phenomenon to neural feedback from stimulation of the lid by the lens edge and/or lens mass, resulting in increased reflex tonus of the levator or Müeller's muscle, thus causing a slight raising of the eyelid.

RETAINED AND EMBEDDED LENS

'Lost' cosmetic lenses

Cases of a rigid lenses becoming 'lost' and, in some cases, embedded in the upper palpebral conjunctiva were reported as early as 1963.[28,29] Since then, numerous accounts of similar occurrences have been published.[30-40]

In the case reported by Tossounis et al.,[39] a 52-year-old man presented with right upper eyelid ptosis and requested cosmetic correction. However, in the majority of these cases, patients presented with complaints of an otherwise 'quiet' lump in the upper lid, which can be misdiagnosed as a chalazion.[30-32] Jahn[30] reported the case of a 41-year-old female patient who had lost a rigid lens 12 months before noticing a lump in her left eye. She failed to associate the previously lost lens with the lid lump. The condition was diagnosed as chalazion, and to the great surprise of the surgeon, a lens was extracted from the lump during surgical treatment of the 'chalazion'. In one case, a rigid lens embedded in the upper lid was recovered 40 years after a failed trial of rigid lens wear.[40]

In two cases,[33,34] the embedded lens was inverted; that is, the convex surface of the lens faced the globe. Jones and Hassan[33] suggested that this inversion leads to greater mechanical irritation (compared with a non-inverted lens) and is a predominant factor in reducing the time taken for distressing symptoms to occur.

They also suggested that if the lens does not invert, deeper migration into a pretarsal or even orbital location is more likely.[35] Excessive lid swelling as a result of a lost[37] or embedded[36] lens can also give the appearance of ptosis in the affected eye.

Patel et al.[37] described the case of a 56-year-old woman who presented with unilateral ptosis induced by a non-embedded soft contact lens, which had been in place for approximately 2 years. The authors surmised that the unilateral ptosis most likely resulted from localised inflammation and the physical presence of the soft contact lens. Symptoms resolved completely after double lid eversion and lens removal.

Although numerous other cases, such as those reported earlier, of 'lost lenses' re-appearing later in the upper lid have been published, two extraordinary stories stand out. Kelly[38] reported the case of a female patient who presented to a clinic claiming that she had lost a lens, which she suspected was still in her eye. A mucous-coated pellet was removed from beneath the upper eyelid, leaving a well-defined depression on the upper globe. On further questioning, the patient reported having lost, and subsequently reordered, a number of lenses over the previous 3 months and having reported to other clinicians that she thought a lens was in her eye (with nothing being found). The mucus-coated pellet removed from her eye was found to consist of eight PMMA lenses and one rigid gas-permeable lens.

Morjaria et al.[41] presented an account of a 67-year-old woman who attended a day surgery for routine cataract surgery. She had no previous ocular complaints. During peribulbar anaesthesia, a bluish foreign body emerged from the superior fornix as a hard mass of 17 soft contact lenses bound together by mucus. The patient had worn soft lenses for 35 years and, more recently, had been wearing monthly disposable lenses. The authors noted that the patient had poorer vision in the right eye and deep-set eyes, which might have contributed to the unusually large number of retained lenses.

These cases highlight the importance of appropriate candidate selection and monitoring of contact lens wearers. Double lid eversion and fluorescein staining of the ocular surface can reveal dislocated contact lenses in the upper fornix.

'Lost' bandage lenses

Ho and Mathews[42] reported the case of a patient who was treated with a pair of soft bandage contact lenses for persistent ocular pain secondary to dry eye symptoms. At her subsequent visit, the bandage contact lens was removed from her left eye, but none was found in the right eye. Documentation from subsequent visits noted that the bandage contact lenses were no longer in situ. At a visit 6.5 years after the lenses were initially inserted, lid eversion revealed a 'foreign body' retained beneath her right upper eyelid, which was noted to be a folded, discoloured bandage lens.

Trauma

Contact lenses can become embedded in the eye as a result of trauma. Kang et al.[43] reported the case of a 36-year-old female who presented with mild swelling in the right upper eyelid. She had lost her rigid lens 7 months before her first visit as a result of trauma from being accidentally kicked in the right eye by her child. At the first examination, the authors could feel a firm lump inferior to the right brow. Eversion of the upper eyelid revealed a firm sub-conjunctival mass superior to the upper tarsus. After incising the conjunctiva, the lens was found with a fibrous capsule and granulation tissue in the sub-conjunctival space. Three years after removal of the lens, the ptosis had resolved, and the patient did not show any other complications.

ECTROPION

Ectropion is an outward turning of the eyelid from the globe and is frequently associated with epiphora and chronic conjunctivitis. Four types of ectropion can be defined:

- Involutional – senile change
- Cicatricial – caused by scarring and contracture of skin and underlying tissue, which pulls the eyelid away from the globe
- Congenital – rare and typically associated with blepharophimosis syndrome
- Paralytic – typically caused by a facial nerve palsy[44]

The implications of ectropion in contact lens wearers is that the lower lid cannot be relied on to help position the lens; that is, both rigid and soft lenses may mislocate inferiorly in an ectopic eye. An ectopic eyelid will have a reduced effectiveness in cases where the lower lid is required for lid-assisted lens translation (e.g. alternating vision bifocals) or location (e.g. truncated toric lens). In addition, an eye with an ectopic eyelid may tend to be relatively dry because of an excessive rate of loss of tears.

ENTROPION

Entropion, inversion of the eyelid toward the globe, usually causes discomfort as a result of rubbing of the eyelashes against the cornea. This latter phenomenon is known as *pseudotrichiasis* and should not be confused with 'true' trichiasis, which is a term that describes actual ingrowth of lashes from an otherwise normal lid margin.

Four types of entropion can be defined:

- Involutional – senile change
- Cicatricial – caused by scarring and contracture of the palpebral conjunctiva that pulls the eyelid towards the globe. This condition can be caused by cicatricial pemphigoid, Stevens-Johnson syndrome, trachoma and chemical burns, and can involve the upper and lower lids
- Congenital – rare, but can be dealt with surgically
- Acute spastic – caused by spasm of the orbicularis arising from ocular irritation; this condition typically resolves with removal of the irritation[44]

An important implication of entropion in contact lens wearers is that the lower lid may interfere with correct lens positioning. An entropic eyelid with associated pseudo-trichiasis can lead to corneal irritation; as an interim measure, soft contact lenses can be fitted to protect the cornea.

A pseudo-entropion can arise as a result of pressure on the eyelids from external forces. An example of such a case is shown in Figure 6.6; the lower lid has been temporarily folded inward because of the fitting of a scleral lens of insufficient diameter.

LAGOPHTHALMOS

Lagophthalmos, which refers to incomplete eyelid closure, can be caused by a number of factors, such as facial nerve lesions, orbicularis weakness, ectropion or mechanical displacement caused by tumours. This condition can lead to corneal exposure and consequent keratitis. A soft lens will provide protection, although lenses can fall out of the eye if the lagophthalmos is severe. In such cases, partial tarsorrhaphy or temporary taping together of the eyelids is indicated.

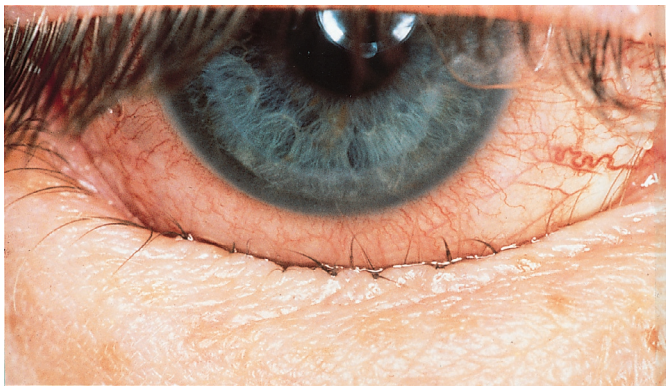


Fig. 6.6 Pseudo-entropion caused by the fitting of a scleral lens of insufficient diameter. (Courtesy Jan Kok, Bausch & Lomb Slide Collection.)

Rigid lenses are problematic because they do not completely cover the cornea. This can lead to corneal desiccation outside the lens edge, typically in the 3 & 9 o'clock positions.[44]

Nocturnal lagophthalmos (partial eye opening during sleep) is an anatomical variant in the normal human population; indeed, it occurs in 23% of the population.[45] Excessive 3 & 9 o'clock staining in some patients who sleep wearing rigid lenses could be explained by the presence of nocturnal lagophthalmos.

RIGID LENS 'BRIDGING'

Contact lenses act to displace the eyelids away from the globe. This action has been implicated in the aetiology of traumatic aponeurogenic ptosis in rigid lens wear because of the greater displacement caused by such lenses. Rigid lenses also cause a 'bridging' of the tarsal conjunctiva away from the corneal surface at the lens edge, which is thought to be of aetiological significance in the development of 3 & 9 o'clock corneal staining. The areas of cornea immediately adjacent to the lens edge, especially at the 3 & 9 o'clock positions, are prone to dry out because these regions are not being re-wetted by the passage of the eyelid against the eyeball.

ABSENCE OF EYELID

The destruction of an eyelid by a tumour or other disease is a potentially blinding situation. The reason for one of the first recorded contact lens fittings (by a Dr. Sämisch in Germany) was for a patient whose lower eyelid in one eye was completely destroyed by carcinoma. The upper lid of this eye was partially missing, with the remaining portion thickened and entropic.[46] (Contact lens historians point out that, technically, a contact 'shell' was fitted, rather than a 'lens', because it had no power[47]). The other eye was totally blind. The patient obtained useful vision with the aid of this prosthetic device, which was worn continually day and night without ever being removed for over 20 years until the patient died.

Lids as a lens-positioning tool

The eyelids are employed in a variety of ways to stabilise, position and translocate contact lenses to achieve various fitting and optical objectives. A detailed analysis of these strategies is beyond the scope of this book, but they are listed here so as to provide a clue to solving contact lens–related eyelid problems that may have a direct bearing on lens performance.

Specifically, eyelids are employed to:

- move the lens with each blink so as to effect an exchange between the tears beneath the lens and the remaining tears on the ocular surface; this serves to remove of particulate matter from beneath the lens, to facilitate corneal oxygenation, and to prevent build-up of carbon dioxide beneath the lens;
- continually re-wet the front surface of the lens with each blink;
- position truncated rigid and soft toric lenses;
- squeeze the 'thin zones' of toric lenses against the globe to provide correct lens orientation;
- position rigid lenses by way of 'lid attachment' or 'interpalpebral' fitting philosophies; and
- translate alternating vision bifocals across the cornea so as to align the appropriate portion of the lens over the pupil.

Deformities or swelling of the eyelids – such as scarring of the lid margins (Fig. 6.7) or swellings of the palpebral conjunctiva (Fig. 6.8) – can interfere with lid-mediated positioning of contact lenses.



Fig. 6.7 Distortion of the lower lid margin caused by scarring of the inferior palpebral conjunctiva, which may adversely affect lens positioning. (Courtesy Robert Terry, Brien Holden Vision Institute.)



Fig. 6.8 Mass of vascularised oedematous tissue adjacent to the lid margin of a soft lens wearer, which could lead to lens mislocation. (Courtesy Sylvie Sulaiman, Bausch & Lomb Slide Collection.)

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7 Meibomian Gland Dysfunction

The meibomian glands in the upper and lower eyelids play a critical role in forming and maintaining a viable tear film. Specifically, these glands produce a clear, oily secretion that serves two main functions: (1) forming a hydrophobic lining along the lid margins, thus preventing epiphora, and (2) maintaining a thin lipid layer over the surface of the aqueous tear phase, which retards evaporative fluid loss.

Meibomian gland dysfunction (MGD) may be defined as a chronic, diffuse abnormality of the meibomian glands, commonly characterised by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation and ocular surface disease.[1]

Some authors previously used the terms 'posterior blepharitis' and 'MGD' as if they were synonymous, but these terms are not interchangeable. *Posterior blepharitis* is a term used to describe inflammatory conditions of the posterior lid margin, of which MGD is only one cause (see Chapter 8).[1]

Figure 7.1 sets out a classification schema for MGD, as devised by the International Workshop on Meibomian Gland Dysfunction.[1] As will be discussed throughout this chapter, there are differing opinions as to whether contact lens wear causes, exacerbates or coincidentally co-exists with MGD. Whatever the answer, the classification schema shown in Figure 7.1 provides a useful framework for considering contact lens–associated MGD (CL-MGD).

Structure of meibomian glands

ANATOMY

The meibomian (tarsal) gland orifices emerge just anterior to the mucocutaneous junction. By using broad diffuse illumination at high magnification (×40), round or slightly oval meibomian gland orifices can be seen just in front of the mucocutaneous junction (Fig. 7.2).

There are about 30 to 40 vertically oriented meibomian glands in the upper lid, which open onto small, round orifices in the upper margin. There are slightly fewer meibomian glands – about 20 to 40 in number – which open into the lower lid margin. The meibomian glands in the lower lid margin are shorter in length and slightly wider than those in the upper lid. In both the upper and lower lids, the meibomian glands are approximately uniformly distributed from inner to outer canthus (Fig. 7.3).

HISTOLOGY

The tarsal plates contain the acini and ducts of the meibomian (tarsal) glands. The vertically oriented ducts, which run perpendicular to the lid margins, are connected to multiple secretory acini, which open laterally onto each duct (Fig. 7.4A). The glands occupy nearly the full length and width of each tarsus.

Acini are lined by a layer of undifferentiated basal cells that divide, and cells are displaced from the basement membrane. As they progress toward the duct, they gradually enlarge and

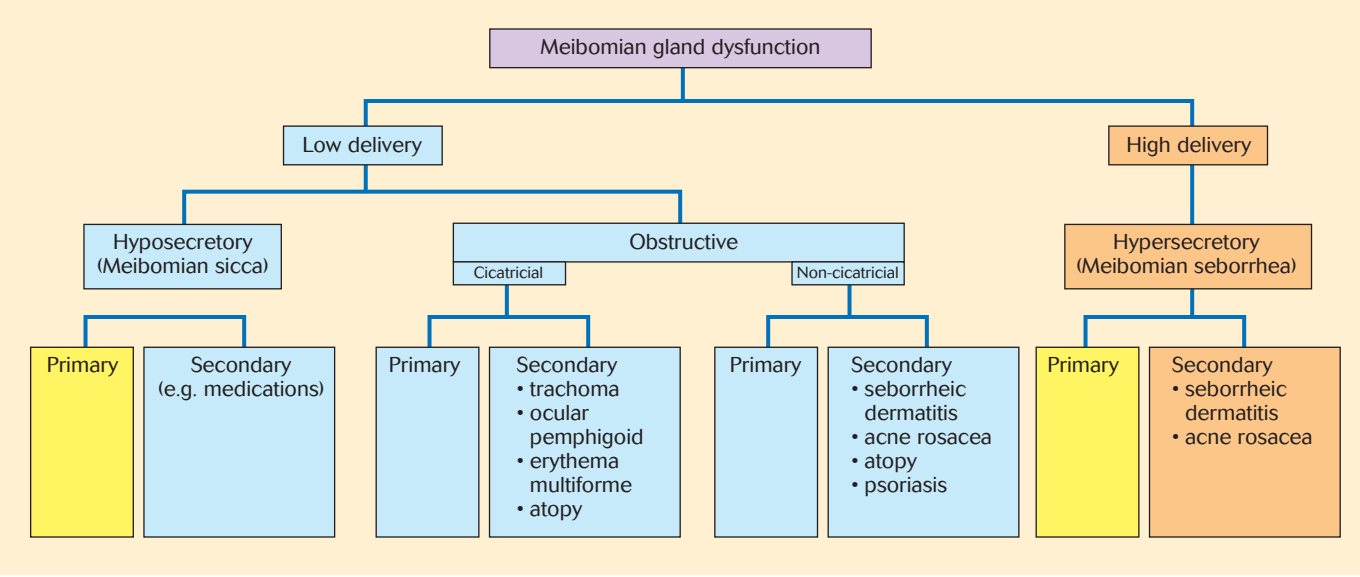


Fig. 7.1 Classification schema for meibomian gland dysfunction (MGD). (Adapted from Nelson JD, Shimazaki J, Benitez-del-Castillo JM, Craig JP, et al. The International Workshop on Meibomian Gland Dysfunction: report of the Definition and Classification Subcommittee. Invest Ophthalmol Vis Sci 2011;52:1930–7.)

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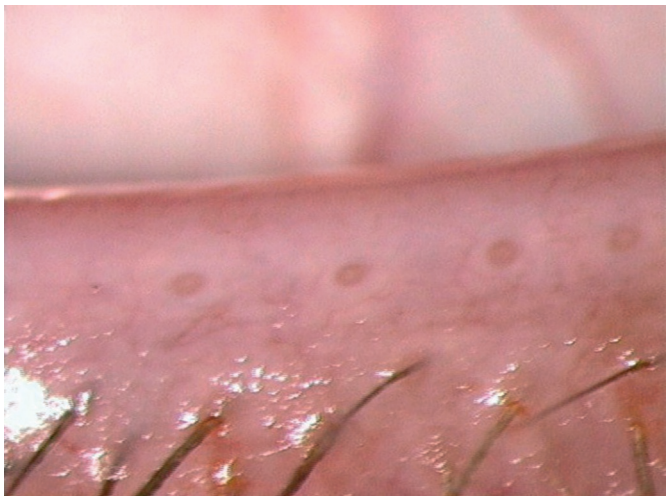


Fig. 7.2 Normal meibomian gland orifices in the lower lid margin. (Courtesy Brian Tompkins.)

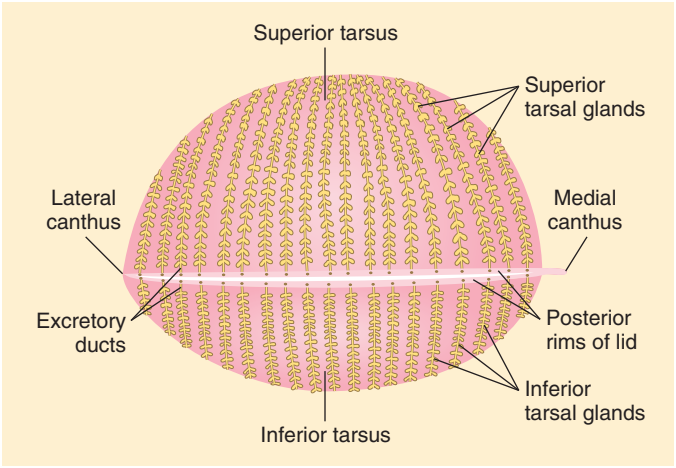


Fig. 7.3 Anatomy of the meibomian glands. (Redrawn based on Sobotta D. Atlas der Anatomie des Menschen. In: Ferner H, Straubesand J, eds. 18th ed. Vol. 1 [p. 215]. Munich, Germany: Urban & Schwarzenberg; 1982.)

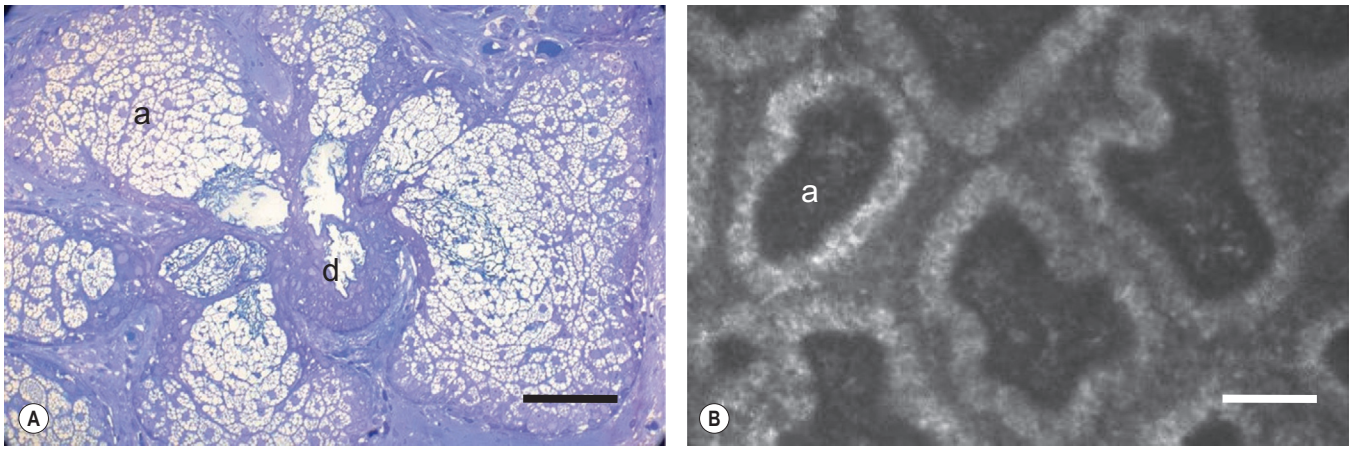


Fig. 7.4 Histology of the meibomian glands. **(A)** Light micrograph of section through meibomian gland. A number of acini (a) are seen surrounding the central duct (d). The secretory cells within the acini are resolved. **(B)** Meibomian gland acini (a) viewed with the laser scanning confocal microscope. Large cells can be seen lining the acini, and fine cellular material can be resolved within the acini lumen. The complete borders of three acini are visible. Size bar in both images = 50 μm. (**A,** Courtesy Professor John Lawrenson.)

develop lipid droplets in their cytoplasm. Ultimately, cell membranes rupture and cellular debris, together with the lipid product, is discharged into the duct (Fig. 7.4B).

Meibomian gland acini can also be imaged by using laser scanning confocal microscopy (Fig. 7.4B). The layer of undifferentiated basal cells that line the acini can be clearly identified, and granular material can be seen within the acini, which are presumed to be ruptured cells and lipid droplets.

NEUROLOGY

The stimulus for meibomian gland secretion is unclear. Although a modest autonomic innervation of the meibomian glands has been demonstrated, there is still some doubt regarding a neuromodulation of glandular secretion, and it is likely that the principal control of the glands is hormonal and that both androgen and oestrogen have been shown to regulate meibomian secretion. A long ductal system carries the secretion to the lid margin, and the compressive action of the palpebral division of the orbicularis oculi on the meibomian ducts facilitates the flow of lipid and its eventual delivery onto the lid margins.

Prevalence

Korb and Henriquez[2] found that 36.6% of symptomatic contact lens wearers manifested abnormalities of meibomian gland orifices versus 2.5% of asymptomatic wearers. Ong[3] examined the eyes of 81 contact lens wearers and 150 age- and gender-matched non–lens wearers for evidence of MGD. The prevalence of CL-MGD was 49% versus 39% among the controls; this difference was not statistically significant, and this suggests that contact lens wear is not a cause of MGD.

Hom et al.[4] conducted a survey of 398 normal individuals presenting for a routine eye examination. Based on the principal clinical criterion of an absent or cloudy meibomian gland secretion upon expression, 39% of the patients were found to have MGD. The prevalence of MGD was significantly increased with increasing age, and this is in accordance with the finding of Stanek.[5] Hom et al.[4] reported that the prevalence of MGD was 41% among contact lens wearers and 38% among non–lens wearers. These figures broadly agree with those of Ong[3] (49% and 39%, respectively).

Molinari and Stanek[6] reported that 22% of contact lens wearers exhibited MGD. In a retrospective study of 141 patients

attending a hospital outpatient clinic with complaints of discomfort while wearing contact lenses, blepharitis and CL-MGD were noted in 32% of cases.[7] Young et al.[8] reported that the prevalence of CL-MGD among 226 symptomatic contact lens wearers was 14% in a multi-centre study.

Stanek[5] evaluated the meibomian gland status of active-duty military forces (younger population) and US military veterans (older population). One examiner observed 113 consecutive patients in both groups during a 2-week period. MGD was observed in 9.7% of the younger population (about half of these were contact lens wearers) versus 71.1% of the older patients (none wore contact lenses). These finding suggest a higher prevalence of MGD with increasing age.

Sapkota et al.[9] reported that MGD represented 8.6% of complications relating to contact lens wear in cases seen during the period 2003 to 2010 in a large hospital in Nepal.

Ong and Larke[10] reported that the prevalence of MGD[4] and CL-MGD[10] is unrelated to gender.

Signs

There are various signs of CL-MGD, but not all will be evident in any given lens wearer. Although slit lamp biomicroscopy is the cornerstone procedure when investigating this condition, ancillary procedures may need to be employed to assist in making a definitive diagnosis and for assessing the severity of the condition. The various signs of CL-MGD and investigative techniques are considered here.

MEIBOMIAN GLAND ATROPHY AND DROP-OUT

The procedure of observing the morphology of the meibomian glands using specialised illumination and observation techniques is known as *meibography*. When using this method, the structure of the meibomian glands, including the ducts and acini, can be observed.

Before observing meibomian glands in the upper lid, the tarsal conjunctiva must be exposed by everting the lid. Before observing meibomian glands in the lower lid, the tarsal conjunctiva must be exposed by placing the forefinger on the skin just beneath the lower lid margin and gently pulling downward.

Two forms of meibography have been described. A transillumination technique, in which the eyelid is everted over a light source, can be used. The most basic version uses white light, for example, from a Finoff transilluminator. This is applied to the cutaneous side of the everted eyelid and allows for observation from the palpebral conjunctival surface. As such, this is a contact technique that can cause mild discomfort to the patient.

Direct, non-contact infrared meibography involves the employment of an infrared charge-coupled device video camera and infrared light source that does not touch the patient during the procedure. An infrared transmitting filter is required to facilitate observation of the everted lid. The meibomian glands appear as white structures against a dark background (Fig. 7.5).

Although meibography has been conducted for many years in a research setting, a number of non-invasive, clinician-friendly devices have recently been released, making meibography possible as a routine procedure within clinical practice. Two of these devices include the Keratograph 5M (OCULUS, Wetzlar, Germany) and the LipiScan Dynamic Meibomian Imager (TearScience, Johnson and Johnson Vision, Morrisville, North Carolina, USA) (Fig. 7.6). The LipiScan offers a feature that combines dynamic illumination and adaptive transillumination

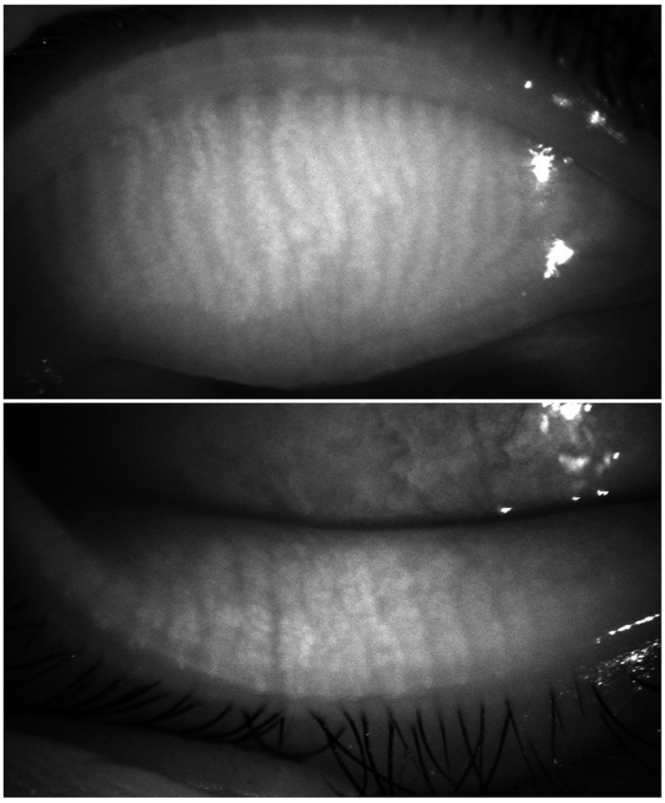


Fig. 7.5 Infrared imaging of the meibomian glands viewed in the everted upper lid (top) and everted lower lid (bottom). (Courtesy Reiko Arita.)



Fig. 7.6 The LipiScan Dynamic Meibomian Imager. (Courtesy TearScience, Johnson and Johnson Vision, Morrisville, North Carolina, USA.)

to generate an enhanced view of meibomian gland structure (Fig. 7.7).

Pult and Riede-Pult[11] devised a schema for grading the level of severity of meibomian gland pathology of the lower lid, known as the *meiboscale*. This instrument was subsequently enhanced to contain separate scales for the upper and lower lids (Fig. 7.8). Each scale consists of a series of meibography images that progress from 'degree 0' (normal; 0% gland dropout/atrophy) to 'degree 4' (severe; > 75% gland drop-out/atrophy). Each meibography image is accompanied by a schematic drawing of the level of severity. The progression of severity is also indicated by colour coding, from green (normal) to red (severe). A central



Fig. 7.7 Enhanced meibography image, captured with the LipiScan Dynamic Meibomian Imager, showing fine detail of meibomian glands in the everted lower lid. Gland drop-out is evident in the middle of the lid. (Courtesy TearScience, Johnson and Johnson Vision, Morrisville, North Carolina, USA.)

panel illustrates meibomian glands with various forms of pathology.

Arita et al.[12] investigated the influence of contact lens wear on meibomian glands by using non-contact meibography. Partial or complete loss of the meibomian glands was scored for each eyelid using four grades (meiboscores): grade 0 (no loss of meibomian glands) through grade 3 (the area characterised by gland drop-out was >66% of the total area containing the meibomian glands). The meiboscore was significantly higher ($p < 0.0001$) in contact lens wearers (mean 1.72; 95% confidence interval (CI) 1.47–1.96) compared with that in the control group (0.96 (95% CI 0.73–1.19)). The average meiboscore of contact lens wearers was similar to that of the 60- to 69-year-old age group from the normal population. A significant positive correlation was observed between the duration of contact lens wear and the meiboscore. The authors concluded that contact lens wear is associated with a decrease in the number of functional meibomian glands. This decrease is proportional to the duration of contact lens wear.

Tang et al.[13] evaluated meibomian gland morphology, by using meiboscore and digital analysis, among 60 subjects categorised as non–contact lens wearers, short-term contact lens wearers (≤ 3 years) and long-term contact lens wearers (> 3 years). The median percentage area of meibomian gland loss in the upper eyelid of the non-wear, short-term wear and long-term wear groups was 9.2%, 13.3% and 16.7%, respectively ($Hc = 6.390$; $p = 0.041$). The total (upper and lower lid) median percentage area of meibomian gland loss of the non-wear, short-term wear and long-term wear groups were 6.6%, 8.8% and 13.0%, respectively ($Hc = 7.019$; $p = 0.030$). The authors concluded that long-term (> 3 years) contact lens wear can cause meibomian gland loss.

Pucker et al.[14] graded upper and lower eyelid meibomian gland atrophy with both digital meibography and visual meiboscore methods in 70 contact lens wearers (case) and 70 age- and gender-matched non–contact lens wearers with no history of lens use. All subjects were administered the Ocular Surface Disease Index questionnaire and a comprehensive battery of clinical tests (e.g. tear break-up time (TBUT), bulbar and limbal redness, meibography, etc.) were performed. The association between contact lens wear and meiboscore was not significant in univariate analysis, but the best-fitting multivariate regression model showed that higher meiboscores were associated with being a contact lens wearer (odds ratio (OR) 2.45). Percent gland atrophy was not associated with contact lens wear in the regression analysis ($p = 0.31$). In view of these findings, the authors considered that associations between contact lens wear and meibomian gland atrophy were inconclusive.

MEIBOMIAN GLAND DISTENTION AND DISTORTION

The presence of distended or distorted meibomian glands[15] confirms the diagnosis of cicatricial obstructive CL-MGD. These are sometimes visible when viewed with the slit lamp biomicroscope under low magnification (×6) and a broad illumination beam of white light.

On eversion of the lids, the distended glands appear as broad yellowish, linear formations perpendicular to the lid margin (Fig. 7.9).

EXPRESSIBILITY OF MEIBOMIAN GLANDS

Meibomian gland expression is a simple and rapid provocative test that causes only mild discomfort to the patient. Anatomical

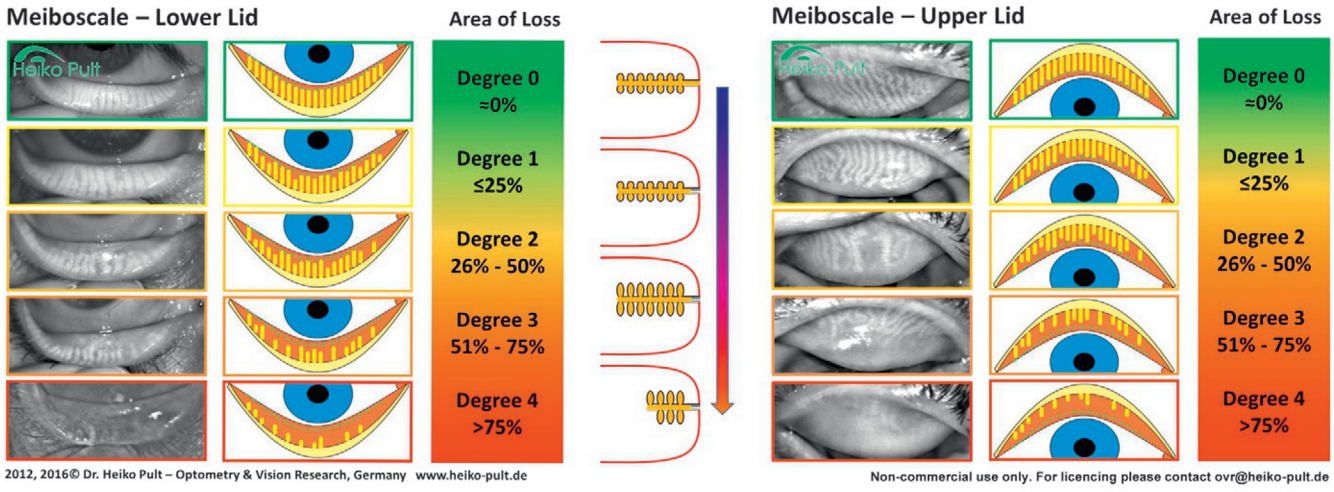


Fig. 7.8 Meiboscale for assessing the severity of meibomian gland dysfunction (MGD) in the lower and upper lids. The central panel illustrates various forms of pathology of the meibomian glands; from top to bottom, normal gland; blocked orifice; gland distention; gland atrophy (partial drop-out). (Courtesy Heiko Pult.)



Fig. 7.9 Distended meibomian glands in the lower lid. (Courtesy Brian Tompkins.)

considerations dictate that expression of the meibomian glands in the lower lid is the preferred procedure. The patient is instructed to gaze superiorly. In cases of mild meibomian orifice blockage, gentle pressure with the finger or thumb immediately below the lower lid margin, together with a slight rolling action of the finger or thumb toward the lid margin, will generally result in the appearance of a small amount of expressed material.

If nothing is expressed with use of the procedure described previously, a more complete or even total meibomian blockage is indicated. In such cases, a support needs to be placed behind the lower lid margin so that increased pressure can be applied to force expression of meibomian oils. This can be achieved by using a Mastrota paddle (OcuSOFT, Rosenberg, Texas, USA) (Fig. 7.10), which is designed to gently and effectively express meibum from the meibomian glands. The lower lid is gently retracted, and the Mastrota paddle is positioned between the eyelid and the eye, parallel to the glands. A finger or cotton tip applicator applies gentle pressure to the outer lid. This procedure can be carried out with or without anaesthesia.

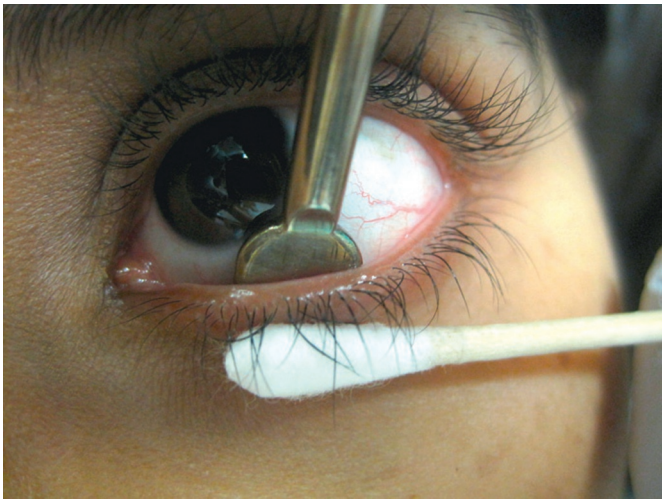


Fig. 7.10 Mastrota paddle being used to evaluate the functioning of the meibomian glands. (Courtesy Lyndon Jones.)



Fig. 7.11 Instrument for meibomian gland expression. (Courtesy Donald Korb.)

Korb et al.[16] have designed a custom diagnostic hand-held meibomian gland expression instrument that can be used as an alternative to manual expression (Fig. 7.11). The Meibomian Gland Evaluator (TearScience, Morrisville, North Carolina, USA)[16] delivers constant force for meibum expression. The instrument has a flat rectangular contact surface area, of approximately 40 mm^2, with rounded edges that applies pressure to approximately one-third of the lower eyelid, allowing for direct application of force to, and the simultaneous expression of, approximately eight meibomian glands. The precise contact surface area dimensions are 8.76 × 4.45 mm = 38.95 mm^2. The instrument is designed to exert a constant force of 1.25 g/mm^2.

Sudden release of a blockage when applying firm pressure can result in copious expression of apparently dehydrated material in the form of a thick stream, akin to the result of forcefully squeezing a toothpaste tube; this is referred to as an 'inspissated' secretion. The extent of these inspissated secretions can be graded by using the grading scale for CL-MGD presented in Appendix A. It is not certain whether increased lipid is a result of (1) true hypersecretion of the meibomian glands or (2) damming of secretions in the presence of mild obstruction.[1] This appearance is accompanied by symptoms of blurry vision, greasy lenses, dry eyes and reduced tolerance to lens wear. In severe cases where the meibomian orifices are blocked, gland secretion may be absent.

The absence of oil globules at the meibomian gland orifices when applying gentle pressure to the lids could indicate normality, hyposecretion or obstructive CL-MGD. If oil globules are not observed on the lid margins of a symptomatic contact lens wearer after application of gentle pressure, the patient may have a condition that Blackie et al.[17] referred to as 'non-obvious MGD'. In such cases, it may be necessary to conduct a provocative test to establish the state of health of the meibomian glands. This can be achieved be manual expression of the glands so that the quality of the expressed meibum can be assessed (see later).

CLOUDY MEIBUM

Examination of the lid margins using diffuse illumination at approximately ×20 magnification often reveals the presence of small, oily globules at the orifices of the meibomian glands in patients suffering from CL-MGD.

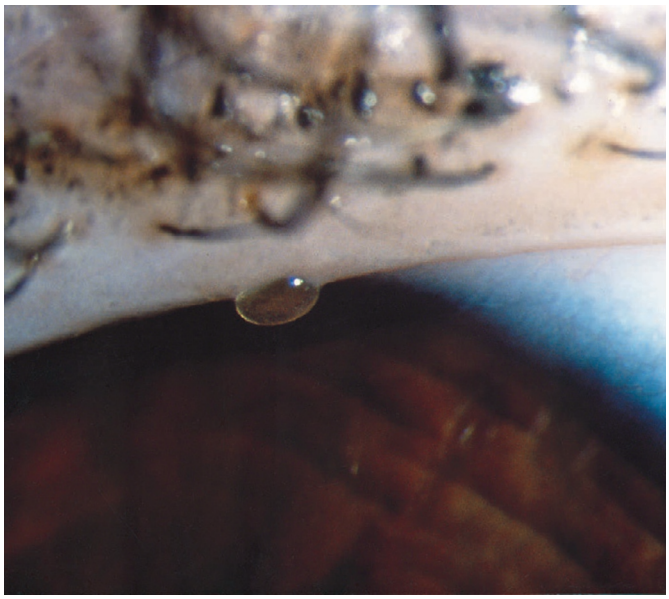


Fig. 7.12 Clear secretion expressed from a normal meibomian gland in the upper lid. (Courtesy Xavier Llobet, Bausch & Lomb Slide Collection.)

The clarity of expressed meibum can be observed by examining the lid margins by using diffuse illumination at approximately ×0 magnification. The expressed meibum in a patient without CL-MGD can appear as small, clear, oily globules at the orifices of the meibomian glands (Fig. 7.12). Viewing the lid margins against the dark background of the pupil or against a dark coloured iris, as shown in Figure 7.12, will enhance the view of the expressed material.[18]

In patients with CL-MGD, the meibum may appear to be slightly murky (Fig. 7.13). In more severe cases of CL-MGD, the meibum takes on an almost opaque waxy, milky-yellow colour (Fig. 7.14).

According to Ong and Larke,[10] 20% of non–contact lens wearers show some loss of clarity of expressed meibomian oils, and opaque oils can be expressed from 6% of non–contact lens wearers. These figures rise to 30% and 11%, respectively, in contact lens wearers.

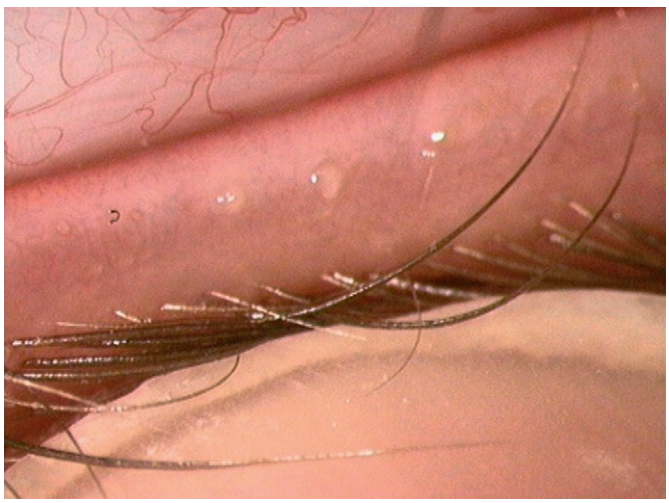


Fig. 7.13 Slightly murky secretion expressed from a contact lens wearer with mild meibomian gland dysfunction. (Courtesy Brian Tompkins.)



Fig. 7.14 Inspissated secretion from the meibomian glands in the lower lid of a contact lens wearer. (Courtesy Brian Tompkins.)

Ong and Larke[10] reported that among contact lens wearers, about 10% of patients who complain of blurred vision and dryness can be demonstrated to have abnormal meibum.[10]

Meibum samples collected by Hagedorn et al.[19] from contact lens wearers without MGD showed large, circular aggregates with low surface roughness, whereas meibum samples from those with CL-MGD showed more lipid aggregates, greater size variability and higher surface roughness. Worn lenses of those with CL-MGD had a few large tear film deposits with lower surface roughness, whereas lenses from those without MGD had many small lens deposits with higher surface roughness.

Care must be exercised when interpreting studies of expressed meibum, given that expression technique influences the relative amount of phospholipids in the resulting sample. Kunnen et al.[20] found that the meibomian gland evaluator method returned smaller polar lipid quantities than the cotton bud approach. The highest amounts of phospholipids were detected with the cotton bud expression technique and the lowest with the meibomian gland evaluator technique. Cleaning the eyelid margin before expression was not found to affect the lipid composition of the sample. This may be a consequence of the more forceful expression resulting in cell membrane contamination or higher risk for tear lipid contamination as a result of reflex tearing.

TEAR FROTHING

Frothing or foaming of the lower tear meniscus is sometimes observed in CL-MGD (Fig. 7.15), especially toward the outer canthus.[10] This may be caused by lowering of the surface tension of the tear film as a result of the lipid layer being absent or abnormal.

BLOCKED MEIBOMIAN GLAND ORIFICES

Clinical and cytological studies indicate that obstructive MGD is caused by blockage of the meibomian gland orifices by desquamated epithelial cells that tend to aggregate in keratotic clusters, which results in alteration of the contribution of meibomian glands to the pre-corneal tear film.[2] Plugs of keratinised epithelium and dried lipid secretions that block meibomian gland

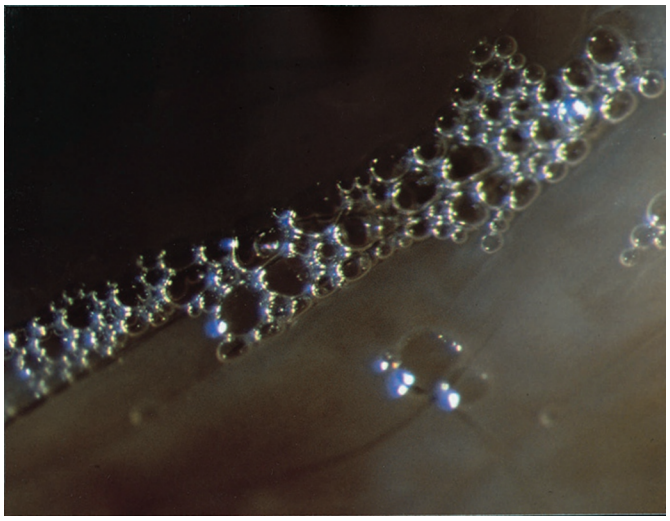


Fig. 7.15 Frothing of the tear film. (Courtesy Lourdes Llobet, Bausch & Lomb Slide Collection.)

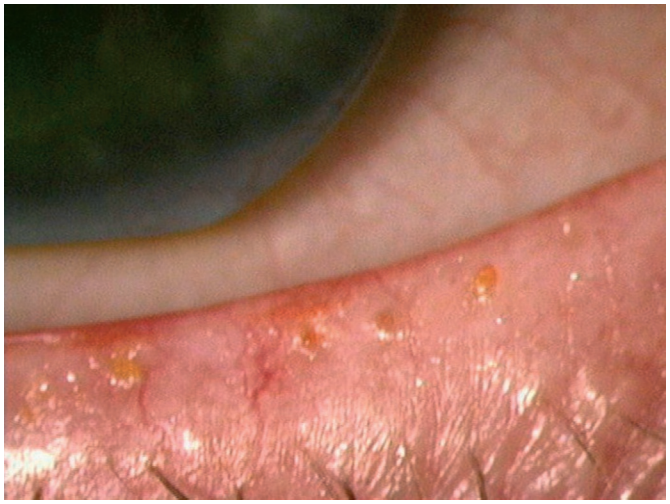


Fig. 7.16 Plugs of keratinised epithelium and dried lipid secretions blocking meibomian gland orifices. (Courtesy Brian Tompkins.)

orifices in CL-MGD[21] can sometimes be observed with the slit lamp biomicroscope (Fig. 7.16).

IRREGULAR, DISTORTED AND THICKENED LID MARGINS

Long-standing cases of CL-MGD (a low delivery state) may be associated with additional signs, such as irregularity, distortion and thickening of eyelid margins (as in cicatricial obstructive CL-MGD); slight distension of glands; mild to moderate papillary hypertrophy; vascular changes (Fig. 7.17) and chronic chalazia. The vascular changes have been described as neovascularization, but it is more likely in the majority of cases where this change is observed that existing vessels have become distended and thus more visible.

CORNEAL STAINING

Hope-Ross et al.[22] reported that in a series of 30 patients with recalcitrant recurrent corneal erosions, the prevalence of MGD was 100%. Marren[23] reported statistically significant links among MGD, contact lens wear and corneal staining. These findings suggest that increased corneal staining (i.e. more than is typically observed in asymptomatic contact lens wearers) is associated with CL-MGD; however, neither Hope-Ross et al.[22] nor Marren[23] could explain the basis for this link.

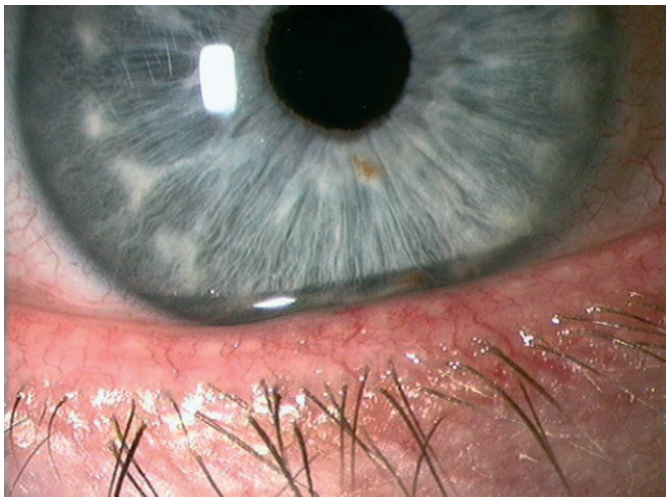


Fig. 7.17 Enlargement and tortuosity of vessels and distortion of lid margin of a contact lens wearer. Blocked meibomian glands can be seen as intermittent pale, slightly raised areas of tissue along the lid margin. (Courtesy Brian Tompkins.)

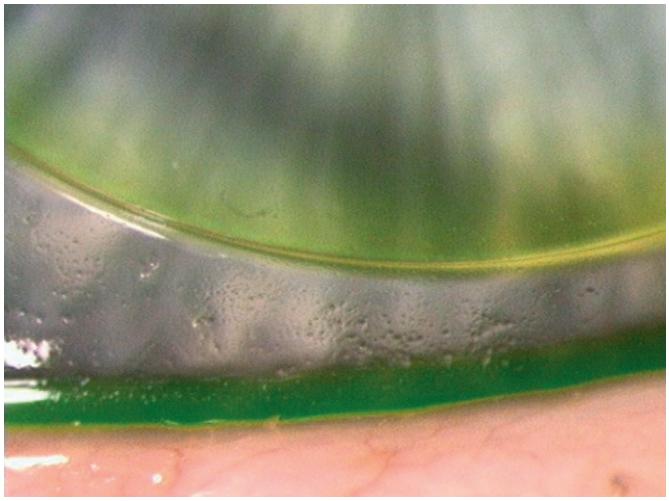


Fig. 7.18 Oily debris in the tear film of a rigid contact lens wearer with meibomian gland dysfunction. (Courtesy Brian Tompkins.)

TEAR LIPID ABNORMALITIES

Hypersecretory CL-MGD can result in the appearance of oily debris in the tear film (Fig. 7.18) and lipid deposits on the surface of contact lenses (Fig. 7.19). Conversely, patients suffering from hyposecretory or obstructive CL-MGD may display a reduced TBUT (measured either with fluorescein or non-invasively).[18]

Examination of the tear layer in specular reflection with the use of a tearscope may reveal a contaminated lipid pattern, which is exacerbated by the use of cosmetic eye make-up[24] (see Appendix B). This approach is difficult because a considerable amount of subjectivity is required in making the assessment. More sophisticated techniques with automated image analysis,

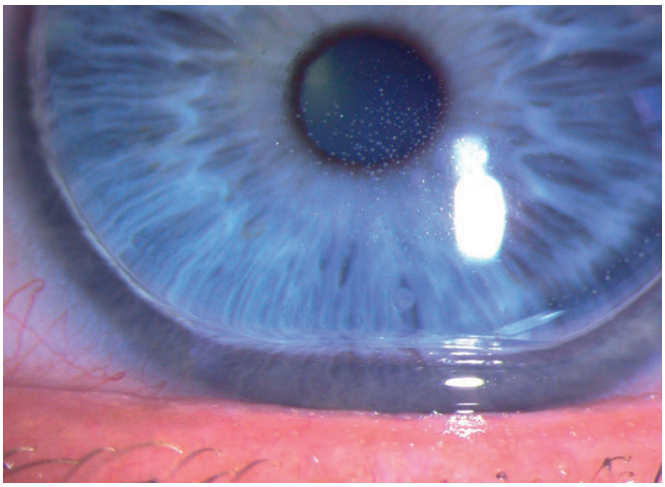


Fig. 7.19 Greasy lipid deposits on the surface of a rigid contact lens, observed adjacent to the bright light reflex of the slit lamp, in a patient with hyposecretory contact lens-associated meibomian gland dysfunction (CL-MGD). (Courtesy Brian Tompkins.)

such as the LipiView Interferometer (TearScience Inc., Morrisville, North Carolina, USA), are capable of delivering quantitative values of the tear-film lipid layer thickness. For example, Finis et al.[25] reported a positive correlation between the lipid layer thickness and expressible meibomian glands, suggesting a higher probability of MGD in patients with low lipid layer thicknesses. This automated assessment of the lipid layer thickness might therefore be a suitable screening test for detecting CL-MGD.

Tear fern analysis is likely to reveal a disrupted pattern in the form of minimal fern, again indicating a contaminated and poorly formed tear layer.[26]

Effect of duration of lens wear on CL-MGD

Alghamdi et al.[27] investigated the effects of the duration of contact lens wear on the meibomian glands. The sample comprised three groups of lens wearers with different duration profiles (short, moderate and long experience of lens wear), a group of previous lens wearers who had ceased wear for at least 6 months before the study and a group of healthy non-wearing control subjects. Compared with non–lens wearers, those wearing contact lenses exhibited reduced meibomian gland expressibility ($p < 0.001$), more plugged orifices ($p = 0.001$), fewer expressed orifices ($p < 0.001$), greater meibomian gland drop-out ($p = 0.001$), a higher Marx line score ($p < 0.001$), increased palpebral redness ($p = 0.003$) and roughness ($p = 0.002$), reduced non-invasive TBUT ($p < 0.001$), reduced Phenol red thread test findings ($p = 0.005$) and reduced tear meniscus area ($p = 0.029$).

Duration of wear was not a significant factor. Although the onset of these changes occurred during the first 2 years of wear, prolonged contact lens exposure beyond this point did not appear to be associated with further ocular compromise. Cessation of wear for up to 6 months does not lead to resolution.

Symptoms

Siddireddy et al.[28] investigated symptomatology in CL-MGD. The authors found that grades of foam at meibomian gland orifices, expressibility and quality of secretions, tear evaporation rate, fluorescein TBUT and tear lipid layer thickness were significantly associated with symptoms of discomfort in symptomatic lens wearers ($r^2 > 0.45$; $p < 0.05$).

Cox et al.[29] examined 203 habitual contact lens wearers (67.5% female) with mean (±SD) age of 30.3 ± 9.6 years and assessed symptomatology and clinically observable features relating to the meibomian glands. The most commonly observed characteristics were orifice pouting/plugging, compromised meibomian gland expressibility and lid margin vascularity (35%, 30.3% and 20.4% of subjects, respectively). Mucocutaneous junction displacement had an effect on comfort upon insertion ($p = 0.01$), comfort after 5 minutes ($p = 0.03$), end-of-day comfort ($p = 0.01$) and ability to maintain ocular moisture ($p = 0.030$). Meibomian gland expressibility had a significant effect on general comfort ($p = 0.01$), comfort throughout the day ($p = 0.02$) and the ability to maintain ocular moisture ($p = 0.02$). The authors concluded that mucocutaneous junction displacement and meibomian gland expressibility have an effect on contact lens comfort.

Arita et al.[30] cautioned against studies that purport to demonstrate a relationship between contact lens discomfort and CL-MGD, in part because of the lack of specificity of the applied questionnaires.

Multi-factorial clinical trials

Machalinska et al.[21] investigated 41 daily soft lens wearers and 31 age-matched non–lens wearers in respect of functional and morphological aspects of MGD. Contact lens use was associated with abnormal meibum quality ($p = 0.0057$); more frequent bulbar ($p = 0.0028$) and palpebral ($p = 0.028$) conjunctival hyperaemia; lid margin telangiectasia ($p < 0.00001$); rounding ($p = 0.04$), notching ($p = 0.019$) and hyperaemia ($p = 0.015$) of the posterior lid margin; and orifice plugging ($p = 0.015$) and retroplacement ($p = 0.037$). The authors suggested that contact lens wear may predispose individuals to MGD.

Pathology

Changes to both the ductal lining of meibomian glands and the meibomian secretion in MGD have been reported in the literature.[31] An increase in the turnover of epidermal epithelium around the orifices of the glands and an increase in the turnover of the epithelium lining of the ducts have been described; these changes can lead to mechanical clogging of the meibomian glands.[2,31,32] Blepharitis is frequently a secondary complication of MGD.[33]

Laser scanning confocal microscopy is capable of imaging posteriorly projecting acini of the meibomian glands in vivo, and this can serve as a basis for assessing for tissue damage associated with MGD. Matsumoto et al.,[34] using confocal microscopy, have shown a decrease in meibomian gland density in patients with MGD (47.6 ± 26.6 mm^2, compared with 101.3 ± 33.8 mm^2 in a control group). These authors also introduced the measurement of meibomian gland diameter as a new parameter reflecting the health of the glands. In their study, MGD was associated with an increase in residual gland width (98.2 ± 53.3 μm in MGD vs. 41.6 ± 1.9 μm in controls) that was attributed to accumulated, inspissated debris within the acini.

In a separate study, Matsumoto et al.[35] noted that inflammatory cell densities observed by in vivo confocal microscopy decreased significantly in a group of patients with MGD receiving anti-inflammatory treatment.

Villani et al.[36] reported the following pathological changes in meibomian glands in patients with CL-MGD (compared with controls): decreased basal epithelial cell density ($p < 0.01$), lower acinar unit diameters ($p < 0.05$), higher glandular orifice diameters ($p < 0.05$), greater secretion reflectivity ($p < 0.01$) and greater inhomogeneity of the periglandular interstices ($p < 0.05$). The duration of contact lens wear was correlated with the acinar unit diameters ($p < 0.05$). These signs were interpreted as indicating meibomian gland drop-out, duct obstruction and glandular inflammation. The authors concluded that a comprehensive confocal microscopy evaluation of the meibomian glands in contact lens wearers could assist in diagnosing CL-MGD.

An important attribute of tear film lipids is that they not only appear to be essential for ease and comfort in contact lens wear but also form deposits on these lenses. It is possible that contact lens wear disrupts the meibomian glands and/or lipid layer and leads to tear film evaporation and ocular surface discomfort.[37] Ong and Larke[10] failed to find any difference in the biochemical composition of meibomian secretions of contact lens wearers and non-wearers. They did, however, observe that abnormal meibomian oils began melting at 35° C (vs. 32° C for normal meibomian oils) and that the melting profile of abnormal meibomian oils comprised five or six components (vs. five to 12 components for normal meibomian oils). The results of this physical melting point analysis of meibomian secretions are consistent with the observation of a more free-flowing meibomian secretion in normal individuals.

Chen et al.[38] observed approximately the same reduction (20%) of diesters and very-long-chain wax esters in meibum samples obtained from contact lens wearers and non-lens-wearing controls.

In a contact lens–wearing patient not suffering from MGD, the lipid layer is always separated from the lens surface by the aqueous phase of the tear layer. Some lipid can deposit on the lens surface – the magnitude and extent of which are determined, in part, by the polymeric nature of the lens material. Such lipid deposits are easily removed in practice by using routine surfactant cleaning.

In CL-MGD, symptoms of blurred or greasy vision can probably be attributed to adhesion of waxy dysfunctional meibomian oils to the surface of the contact lens, which can migrate more readily down to the lens surface as a result of the generally disrupted nature of the tear layer.[39]

As more lipid rapidly deposits on the lens, the surface becomes increasingly hydrophobic and is less able to sustain a continuous tear film. In addition, the abnormal and irregular lipid layer is less capable of preventing evaporation of the aqueous tear fluid covering the lens and from exposed anterior ocular structures. These factors combine to dehydrate the lens and to lead to a sensation of dryness; the association between hydrogel lens dehydration and dryness has been established by Efron and Brennan.[40]

Watters et al.[41] reported that the ocular biome in patients with MGD was no different among contact lens wearers versus non-wearers, ruling out an infectious aetiology of CL-MGD.

Aetiology

Some interesting but largely unproved theories about the cause of CL-MGD have been advanced. Rengstorff[42] suggested that CL-MGD may be attributed to the fact that contact lens wearers rub their eyelids less frequently compared with non–lens wearers for fear of damaging or mechanically dislodging (and possibly losing) their lenses. This deprives the eyelid of the contact lens wearer of periodic rubbing which, Rengstorff[42] claimed, is essential to mechanically stimulate meibomian glands so that they will remain unblocked and free flowing.

This theory of Rengstorff[42] was tested by Marren,[23] who postulated that non–lens wearers using eye make-up would be similarly reluctant to rub their eyes for fear of messing up the make-up. However, no difference was found in the prevalence of MGD between those who wear eye make-up and those who do not.

An alternative 'eye rubbing' theory has been proposed to explain CL-MGD, but to the opposite effect. Various authors[43,44] have suggested an association between CL-MGD and contact lens–associated papillary conjunctivitis. Martin et al.[43] proposed that the itching created by contact lens–associated papillary conjunctivitis causes eye rubbing, which, rather than having a positive and stimulatory effect as proposed by Rengstorff,[42] causes mechanical damage to the meibomian glands and consequent dysfunction.

Since there is no difference in the prevalence of MGD between contact lens wearers and non–lens wearers,[3,4] neither the meibomian stimulation theory of Rengstorff[42] nor the meibomian trauma theory of Martin et al.[43] can be supported.

From a tissue pathology standpoint, the cause of obstructive MGD is increased keratinization of the epithelial walls of meibomian gland ducts.[2,31,32] This leads to the formation of keratinised epithelial plugs that form a physical blockage in meibomian ducts, which, in turn, restricts or prevents the outflow of meibomian oils (Fig. 7.16). Increased levels of keratin proteins have been found in the meibomian oils of patients suffering from MGD.[45] It is thought that the creamy-yellow colour of meibomian oils is a result of the presence of keratin proteins.[31]

The obstructive process is thought to be influenced by endogenous factors, such as age, gender and hormonal disturbances, and by exogenous factors, such as topical medications.[46]

The increase in the prevalence of MGD with age, as reported by Hom et al.,[4] may be attributed to the fact that overall gland width decreases with age,[47] presumably as a result of the loss of gland acini. Other age-related factors that could lead to MGD include general morphological changes[9] and orifice displacement.[48]

Patient management

Although it is not possible to treat the underlying cause of MGD (epithelial keratinization of meibomian gland ducts and consequent contamination of meibomian oils with keratin proteins), it is possible to provide symptomatic relief by adopting one or more of the procedures described in the following sub-sections. All of these procedures should be undertaken after removal of the contact lenses.

WARM COMPRESSES

Henriquez and Korb[49] advocated the use of warm compresses and lid scrubs to alleviate symptoms associated with CL-MGD.

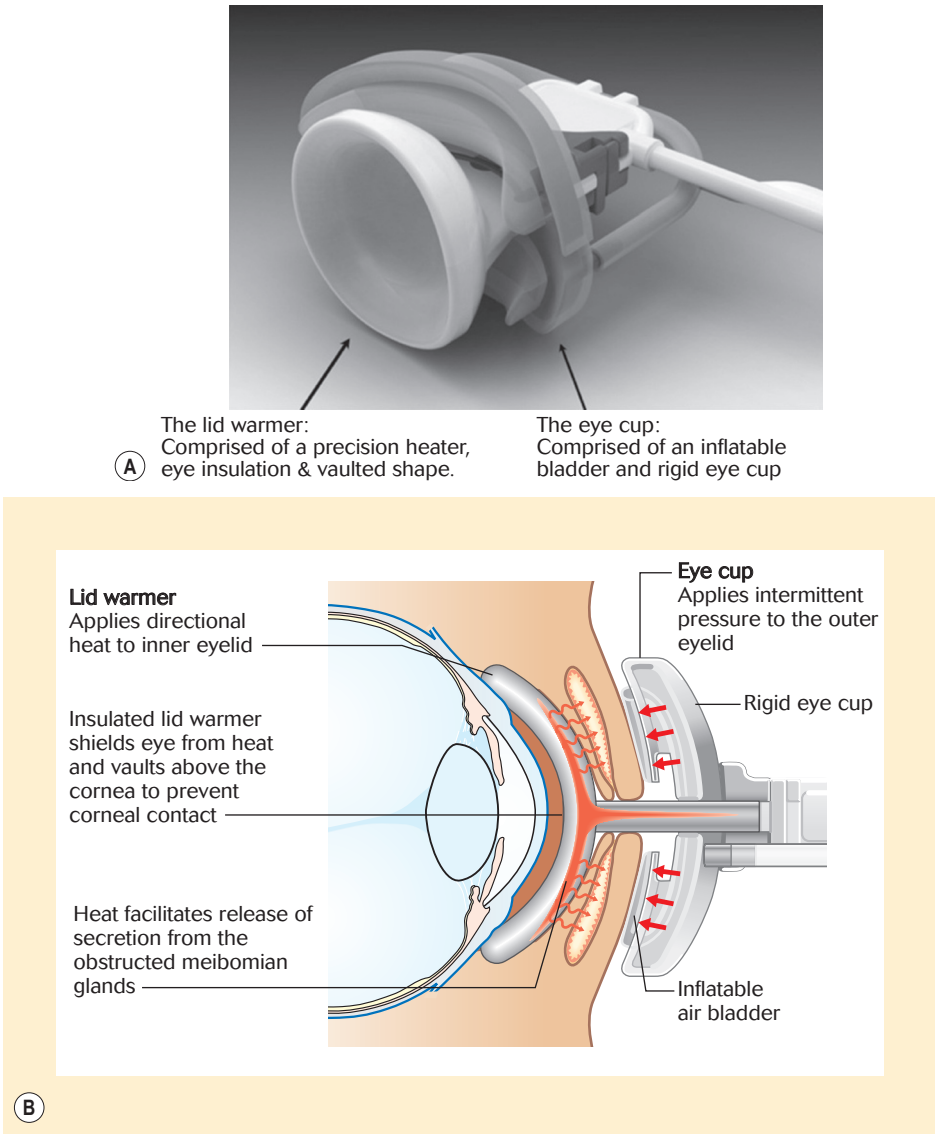


Fig. 7.20 **(A)** Thermodynamic treatment device for meibomian gland dysfunction (MGD). **(B)** Features and mode of operation. (Adapted from Korb DR, Blackie CA. Restoration of meibomian gland functionality with novel thermodynamic treatment device-a case report. Cornea 2010;29:930–3.)

Cotton wool pads soaked in hot water (boiled water that has been allowed to cool for a few minutes) are firmly massaged against the closed eyelids. This procedure is intended to melt solidified lipids and thus un-block the meibomian orifices, allowing lipids to escape and reconstitute a tri-laminate tear layer. A protocol to optimise warm compress treatment has been published by Blackie et al.,[50] and it recommends the continuous application of 45° C hot compresses for at least 4 minutes with optimal contact between the compress and the eyelid, the compress being replaced every 2 minutes with a new one pre-heated to 45° C to achieve adequate warming to alter secretions.

HEATING DEVICES

Alternative sources of heat for warm compress therapy include eye warmer devices,[51] delivering infrared irradiation[52,53] and use of moist air[51] or eye warmer masks.[54]

A sophisticated thermodynamic treatment device has recently been described by Korb and Blackie (Fig. 7.20A).[54] The device is composed of two primary parts (Fig. 7.20B). The first part (lid warmer) resembles a large scleral contact lens (approximately 24 mm in diameter), which is designed to rest on the sclera and vault the cornea. The concave side of the scleral lens comprises an insulating material, which, in addition to the air gap created by the corneal vault, prevents heat from reaching the cornea and the ocular surface. The convex side of the scleral lens contains an embedded precision heater, which warms the palpebral conjunctiva overlying the upper and lower eyelid meibomian glands. Multiple temperature sensors are built into the precision heater to regulate the temperature bladder, which rests over the closed eyelids once the scleral lens has been inserted. During heating, the bladder inflates, sandwiching the eyelids between the heated lid warmer and the bladder. This bladder cyclically inflates and deflates to massage the eyelids in the direction of the meibomian gland orifices. This creates a

milking action over the glands. As such, the device is capable of expressing material from all meibomian glands of the upper and lower eyelids simultaneously.

For the treatment of MGD, Hynes et al.[55] designed an ultrasound hyperthermia device, which consists of a transducer contained inside a contact lens with an internal air gap. The transducer heats the posterior of the tarsus, and the air gap provides an air backing to the transducer, preventing direct heating of the cornea. In an in vivo porcine experiment, a prototype device was built, and hyperthermia experiments were performed. A therapeutic temperature rise of 5° C to 7° C was achievable in 10 to 15 minutes. The temperature of the cornea did not rise by greater than 2° C during any of the experiments.

LID SCRUBS

The maintenance of clean and healthy lid margins is likely to provide benefit by (1) preventing additional debris from blocking the meibomian orifices and (2) reducing the probability of contamination of the meibomian glands, which could result in infection. The patient is advised to clean the lid margins each morning and evening by gently rubbing or 'scrubbing' with a clean face cloth pre-soaked in mildly soapy water.

Alternatively, a cotton-tipped bud pre-soaked in a weak solution of baby shampoo may allow a more controlled lid clean. Commercially available lid hygiene kits are available. Proper attention to lid hygiene will reduce the likelihood of MGD developing into a meibomian cyst (chalazion).

Paugh et al.[18] conducted a controlled, single-masked clinical trial examining the symptomatic and therapeutic benefits of a combined treatment of warm compresses and lid scrubbing in patients suffering from CL-MGD. These procedures were applied to one eye only, chosen at random, for 2 weeks, with the contralateral eye acting as the control. After 2 weeks, there was a significant improvement in the tear film quality of the treated eye, which displayed a greater increase in TBUT (4 seconds greater than baseline) versus the non-treated eye (0.2 seconds greater than baseline). Improved comfort was also reported in the treated eye, but it should be noted that the experiment was single masked (i.e. the patient knew which eye was being treated) and the possibility of subject bias in recording comfort levels cannot be discounted.

MECHANICAL EXPRESSION

The patient can be instructed to manually express the meibomian glands by using the techniques described previously. If this procedure is adopted after the application of warm compresses, and lid hygiene procedures have been followed, gentle pressure is usually all that will be required to facilitate expression of meibomian gland oils.

ANTIBIOTICS

The uncertain role of bacteria in the pathophysiology of MGD and the incompletely understood optimal balance of normal lid microbiota make the role of topical antibiotics in therapy indeterminate. Although CL-MGD is not an inflammatory condition, it is thought that topical antibiotics, such as fucidic acid, metronidazole, fluoroquinolones and macrolides, may be effective against the pathogens most likely to be present in this condition.[56] Systemic antibiotics, such as tetracycline, may also be beneficial; these act by killing bacteria that normally split neutral lipids into irritating fatty acids.

CALCINEURIN INHIBITORS AND CYCLOSPORINE

Steroid-sparing strategies are commonly used to control chronic inflammatory ocular conditions. Topical non-steroidal anti-inflammatory drugs are generally not included in a long-term treatment strategy because of the frequency of development of corneal epitheliopathy. Calcineurin inhibitors, such as cyclosporine, are used in the treatment of many inflammatory ocular conditions, such as uveitis, atopic keratoconjunctivitis and vernal keratoconjunctivitis.[56] Topical cyclosporine was is used to increase tear production in patients with inflammatory dry eye disease. Perry et al.[57] advocated the treatment with cyclosporine for MGD occurring in conjunction with rosacea and/or aqueous-deficient dry eye.

DIQUAFOSOL

Yamaguchi et al.[58] evaluated the efficacy and safety of diquafosol ophthalmic solution in patients who were wearing contact lenses and had dry eye or concomitant MGD or conjunctivochalasis. Diquafosol sodium 3% ophthalmic solution is a purinergic P2Y2 receptor agonist, which may stimulate the secretion of water and mucin from conjunctival epithelial cells and goblet cells. Diquafosol treatment resulted in significant improvement in total symptom score, corneal and conjunctival fluorescein staining score and TBUT, without significant differences between the patient sub-group with contact lens use versus that without contact lens use, MGD or conjunctivochalasis. Comparable proportions of patients showed perceived symptomatic improvements in all sub-groups. There were no adverse reactions specifically associated with the contact lens use or any comorbidity of MGD or conjunctivochalasis. The authors concluded that diquafosol can be used effectively and safely as a monotherapy for the treatment of patients with dry eye wearing contact lenses or have concomitant MGD or conjunctivochalasis.

SEX HORMONES

Extensive basic science research has probed the relationship between sex hormones and the meibomian gland. Androgens have been shown to influence gene expression in mouse meibomian glands, especially to suppress the genes associated with keratinization and stimulate the genes related to lipogenesis.[56] Worda et al.[59] described successful treatment of dry eye with use of an androgen-containing eye drop in a 54-year-old male, resulting in a restored lipid phase of the tear film.

ESSENTIAL FATTY ACIDS

Dietary supplements of omega-3 fatty acids have gained popularity over recent years because of the beneficial effects on anti-inflammatory byproducts of prostaglandin metabolism. Clinical studies have demonstrated an association between the use of oral supplements of omega-3 and symptoms of dry eye. Pinna et al.[60] reported the superiority of oral omega-3 supplementation over lid hygiene or placebo treatment in patients with MGD.

ARTIFICIAL TEARS

Although aqueous tear deficiency is not a central pathophysiological mechanism in MGD, it is a concomitant disease in many patients with MGD. Supplementing the tear film with artificial viscosity agents may help by increasing tear volume and prolonging the formation of a tear layer over the lens and ocular surface. This should at least provide symptomatic relief and lessen the 'dryness' sensation.

TOPICAL LIPID SUPPLEMENTS

Supplementation of tear film lipids has been attempted by the use of lipid-containing eye drops and sprays, emulsion-type eye drops and ointments. Historically, lipid-containing lubricant eye drops have not been used widely because of the induced blurring of vision after their use. In recent years, newer formulations have been better accepted.[56] A lipid-containing liposomal spray has been studied in patients who have evaporative dry eye, as defined by low TBUT and inflammatory lid margin changes.[61,62] Patients received hyaluronate eye drops, triglyceride gel or a phospholipid liposome eye spray, each for a minimum of 6 weeks. Phospholipid liposomal spray achieved a significantly greater reduction in lid-parallel conjunctival folds and lid margin inflammation and improvement in TBUT compared with hyaluronate eye drops or triglyceride gel.

INTRA-DUCTAL PROBING

Minor surgical procedures, such as probing, appear capable of provide long-lasting improvement in MGD. Maskin[63] inserted small stainless-steel probes (2 or 4 mm in length) into the meibomian gland orifices and ducts in 25 consecutive cases of obstructional MGD (Fig. 7.21). This procedure was reported to alleviate symptoms that were not apparent before the probing but were only noted by the patient to have been present in retrospect, when recognizing the overall improvement of ocular comfort. These improvements included relief of ocular symptoms, such as mucus, tearing, burning, soreness, tiredness, irritation, friction, dry contact lens, foreign body sensation, redness, aching, photophobia, stickiness, pain, itching and dryness, and reduced use of artificial tears. Patients also noted increased comfort, moisture, lubrication, vision and lid excursion. The surface of the eye was felt to be smoother and cooler by some.

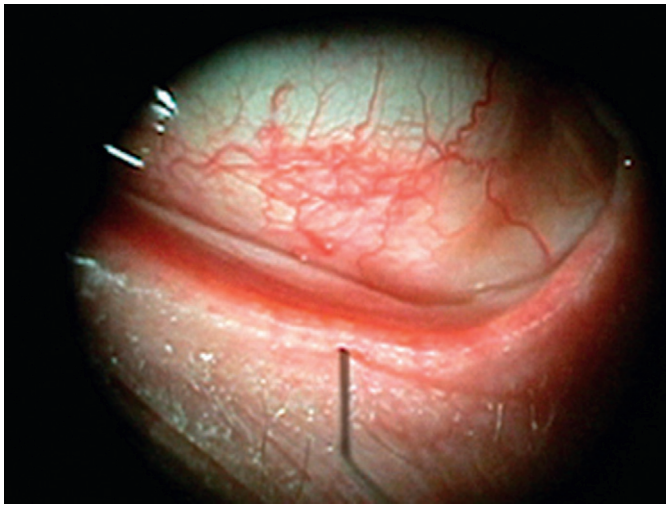


Fig. 7.21 Intra-ductal probing. (Courtesy Steven Maskin, MD.)

SURFACTANT LENS CLEANING

Patients suffering from CL-MGD may experience excessive deposition of abnormal lipids. Symptoms of blurred vision caused by this lipid formation can be alleviated by ensuring that lenses are thoroughly cleaned according to the instructions of the manufacturer. Multi-purpose lens cleaning solutions, which are designed to be compatible with the eye, by necessity contain relatively weak surfactant agents.

In severe cases of CL-MGD, it may be necessary to advise the patient to remove and clean the lenses every 4 hours. This should result in improved vision and comfort during lens wear. More frequent lens replacement (e.g. daily replacement) is unlikely to have any effect as lipid build-up occurs over minutes or hours (not days).

Prognosis

Alghamdi et al.[27] compared the clinical integrity of the meibomian glands of habitual lens wearers versus those of previous lens wearers who had ceased wear for at least 6 months before being examined. Numerous compromises were found in both groups, but there were no significant differences between the two groups. The authors concluded that cessation of wear for up to 6 months does not lead to resolution of CL-MGD.

The findings of Alghamdi et al.[27] suggested that CL-MGD is a chronic disorder with a poor prognosis for recovery; however, the subjects in their study did not receive treatment. By reinforcing good lens hygiene procedures, perhaps in combination with one or more of the other strategies outlined earlier, CL-MGD can be kept under good control and adverse symptoms minimised. Intensive lid hygiene therapy over several weeks may be required to normalise the condition. Once this has been achieved, good comfort and vision are possible by ensuring ongoing attention to lid hygiene and adopting occasional alternative strategies to alleviate acute problems.

Differential diagnosis

There are two aspects relating to the differentiation of CL-MGD from other disorders. First, it is important to be able to differentiate CL-MGD from other possible disorders of the meibomian glands and, indeed, from other glands at the lid margin.

An external hordeolum (stye) is a small swelling at the lid margin associated with a staphylococcal infection and inflammation of a lash follicle and involves the glands of Zeis and Moll. An internal hordeolum is a small abscess associated with a staphylococcal infection and inflammation of a meibomian gland and is observed as a tender swelling of the tarsal plate (Fig. 7.22). Patients suffering from these conditions complain of pain and tenderness; no such pain or tenderness is associated with MGD.

An internal hordeolum (also known as a *meibomian cyst*) is a chronic lipogranulomatous inflammation of a meibomian gland secondary to an obstruction to the gland orifice. Thus, MGD and meibomian cyst formation may be considered to be acute and chronic manifestations, respectively, of the same disease process.

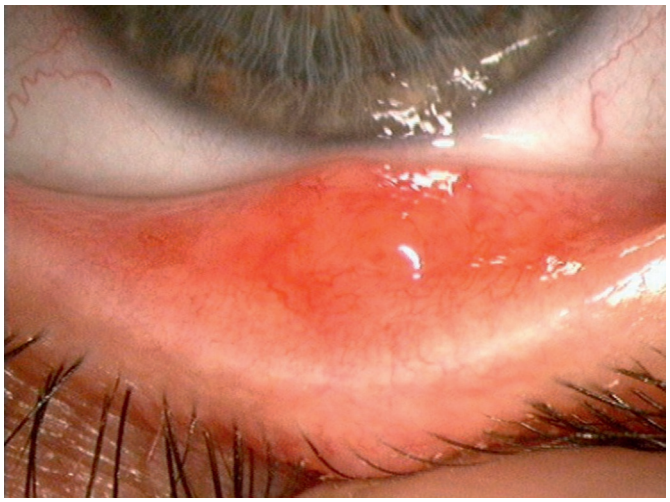


Fig. 7.22 Internal hordeolum in a soft lens wearer; it was surgically treated. (Courtesy Brian Tompkins.)

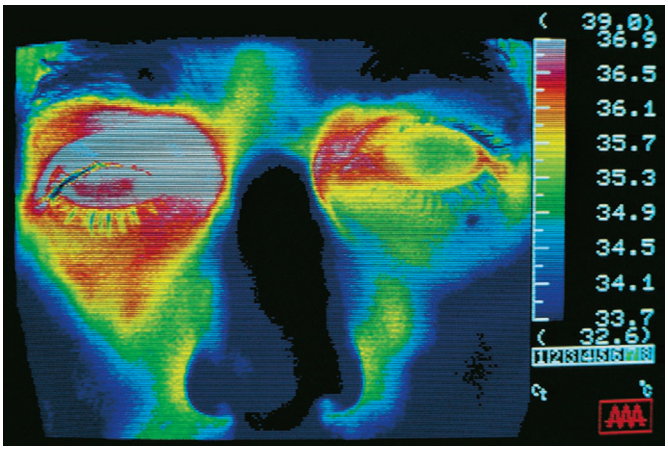


Fig. 7.23 Facial thermogram of a soft lens wearer (the author) suffering from an internal hordeolum of the right eye. (Courtesy Philip Morgan.)

Bron and Mengher[64] reported the unusual case of 16-year-old girl who presented with contact lens intolerance. She was found to have a marked deficiency of the meibomian glands in the upper lids and almost total absence in the lower lids. Evidence of tear film instability was found and attributed to deficient lid oil production. A daily-wear soft contact lens was later fitted and was tolerated by the patient.

Contact lens–associated allergic conjunctivitis is associated with an increase in meibomian gland distortion. Arita et al.[65] pointed out that allergic reaction, rather than contact lens wear, appears to be responsible for the increase in meibomian gland distortion in patients with contact lens–associated allergic conjunctivitis.

In contact lens wearers with CL-MGD, it is sometimes necessary to differentiate the lipid irregularities and associated symptoms of dryness from other causes of tear film dysfunction. In general, this can be achieved by establishing the adequacy of the aqueous phase of the tear film, by applying tests of tear volume (e.g. Schirmer's test or cotton thread test) and lacrimal gland function (e.g. the TearLab Osmolarity Test). Symptoms of dryness and intermittent blurred vision in contact lens wearers in the presence of an adequate tear aqueous component should heighten the suspicion of CL-MGD being the cause of the problem.

Other contact lens–associated meibomian gland disorders

As discussed previously, under 'Differential diagnosis', other disorders of the meibomian gland, such as chalazion and internal hordeolum, may be encountered. Figure 7.23 is a facial thermogram of a soft lens wearer suffering from an internal hordeolum of the right eye. The temperature distribution (red and yellow colours indicating warmer colours) confirms the increased temperature associated with the acute inflammation. In this case, lens wear was discontinued until the condition resolved and the appearance of the tarsal plate returned to normal.

Contact lens wear should be suspended if a patient experiences a chalazion or internal hordeolum and should not be resumed until the condition has resolved. As a prophylactic measure, the importance of greater attention to lid hygiene should be emphasised to patients who have suffered from meibomian gland disease; this strategy could include the prescription of lid scrub kits.

Of the 155 patients found to have MGD in the survey by Hom et al.,[4] 24 had blepharitis, four had chalazia, and one had meibomitis. None of the MGD-negative patients exhibited any of these conditions. Given that there is no difference in prevalence of MGD between contact lens wearers and non–lens wearers, these associated conditions will often be observed in patients wearing contact lenses.

Sebaceous gland carcinomas involving the meibomian glands have also been described. These are the second most common form of malignancy of the eyelid, accounting for 2% to 7% of all eyelid tumours and 1% to 5% of eyelid malignancies. Sebaceous gland carcinomas are observed most commonly in older women and in those of Asian ethnicity. There is no reason to suppose that contact lens wear should be discontinued in patients suffering from such carcinomas, as long as the lenses are comfortable and the carcinoma continues to be monitored.

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8 Eyelash Disorders

Disorders of the eyelashes (cilia) and of the associated structures at the base of the eyelashes such as the eyelash follicles, glands of Zeis and skin of the lid margin, have implications with respect to contact lens wear. Practitioners need to be aware of the possible existence of such conditions in contact lens wearers because it may explain ocular discomfort during lens wear and, in many instances, will be a contraindication for lens wear until the condition is resolved.

Eyelashes typically project from the anterior rounded border of the lid margin in two or three rows. They lie just anterior to the line of Marx – a grey line that indicates the position of the mucocutaneous junction. The superior eyelashes are longer and more numerous than those of the lower lid. Because upper lashes normally curl up and lower lashes normally curl down, lashes do not become tangled on eyelid closure. Eyelashes are typically darker than other hairs of the body, except in such conditions as alopecia areata.[1]

External hordeolum (stye)

An external hordeolum – commonly known as a 'stye' – presents as a discrete inflamed swelling of the anterior lid margin (Fig. 8.1). It is extremely tender to the touch and may occur singly or as multiple small abscesses. A stye is an inflammation of the tissue lining the lash follicle and/or an associated gland of Zeis or gland of Moll. It is typically an acute staphylococcal infection and, as such, commonly presents in patients with staphylococcal blepharitis.

Styes have a typical time course of about 7 days. Sometimes, a stye will discharge spontaneously in an anterior direction. If a patient is in particular discomfort, resolution can be facilitated by removing the eyelash from the infected follicle and applying hot compresses to the affected area.[2]

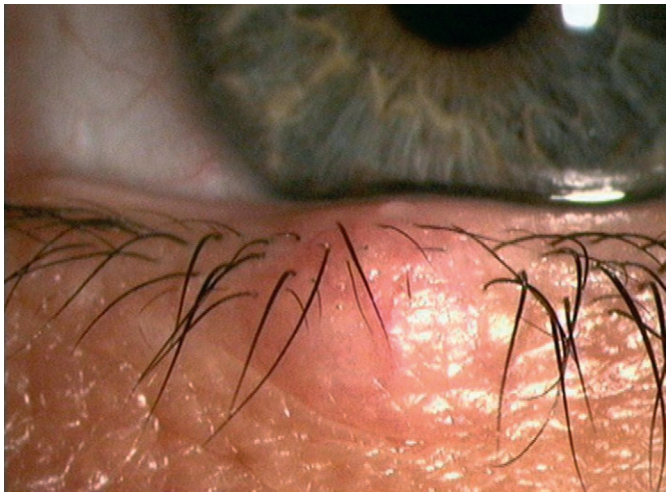


Fig. 8.1 External hordeolum. (Courtesy Brian Tompkins.)

Contact lens wear may add to the discomfort of a stye because of the mechanical effect of the lens. In soft lens wearers, mechanical pressure against the lens between the stye and the globe may effectively grip the lens and result in excessive lens movement during blinking. With a rigid lens fitted interpalpebrally, the lens may bump against the lid margin with each blink, causing considerable discomfort. For these reasons, patients may prefer to discontinue lens wear during the acute phase of the formation of a stye.

Blepharitis

Blepharitis is typically classified as being either anterior or posterior. The condition is sometimes called 'marginal blepharitis' because it is observed along the lid margins. Anterior blepharitis is directly related to infections of the base of the eyelashes and manifests in two forms – staphylococcal blepharitis and seborrheic blepharitis. The severity of blepharitis can be quantified with reference to the grading scale for this condition given in Appendix A.

Recent literature has used the terms 'posterior blepharitis' and 'meibomian gland dysfunction' (MGD) as if they were synonymous, but these terms are not interchangeable.[3] *Posterior blepharitis* describes inflammatory conditions of the posterior lid margin, of which MGD is only one possible cause. In its earliest stages, MGD may not be associated with clinical signs characteristic of posterior blepharitis. At this stage, affected individuals may be symptomatic, but alternatively, they may be asymptomatic and the condition regarded as sub-clinical. As MGD progresses, symptoms develop, and lid margin signs, such as changes in meibum expressibility and quality and lid margin redness, may become more visible. At this point, an MGD-related posterior blepharitis is said to be present[3] (see Chapter 7).

Kabatas et al.[4] reported the prevalence of *Demodex* infestation to be 67% in patients with blepharitis versus 55% in a control group without blepharitis ($p = 0.18$).

STAPHYLOCOCCAL ANTERIOR BLEPHARITIS

This condition is caused by a chronic staphylococcal infection of the eyelash follicles and leads to secondary dermal and epidermal ulceration and tissue destruction. It is often observed in patients with atopic eczema and occurs more frequently in females and in younger patients.

Slit lamp examination of patients suffering from this condition reveals the presence of hyperaemia, telangiectasis and scaling of the anterior lid margins. The scales are brittle (Fig. 8.2) and, when removed, will leave a small bleeding ulcer. The lashes may appear stuck together, and in severe cases, a yellow crust can form as a kind of sleeve that covers the base of the eyelash; these sleeves are called 'cuffs' or 'collarettes' (Fig. 8.3).

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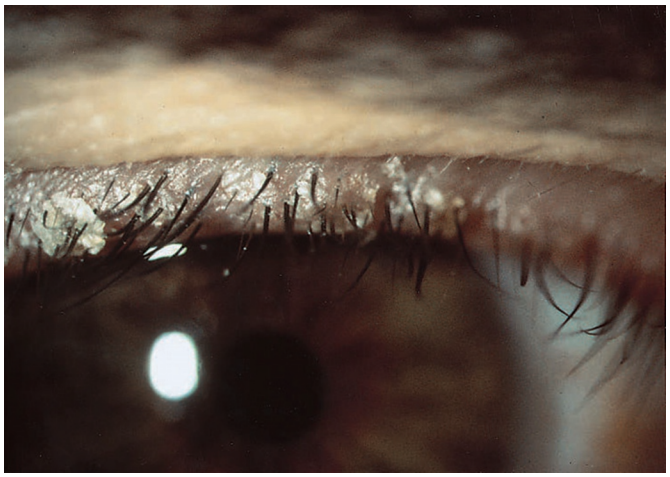


Fig. 8.2 Staphylococcal anterior blepharitis with the lid margin covered in brittle scales. (Courtesy Deborah Jones, British Contact Lens Association Slide Collection.)

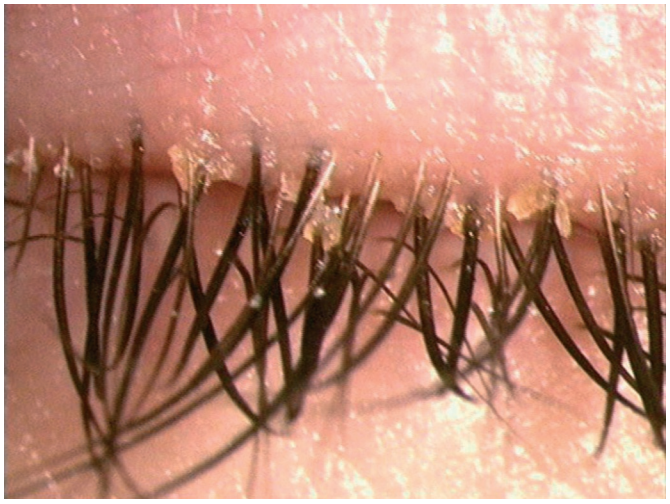


Fig. 8.3 Collarettes in a patient with staphylococcal anterior blepharitis. (Courtesy Brian Tompkins.)

In long-standing cases, there may be a loss of some eyelashes (madarosis), some eyelashes may turn white (poliosis), and the anterior lid margin may become scarred, notched, irregular or hypertrophic (tylosis).

Hypersensitivity to staphylococcal exotoxins may lead to secondary complications, such as low-grade papillary and bulbar conjunctivitis, toxic punctate epitheliopathy involving the inferior third of the cornea and marginal corneal infiltrates.

Patients suffering from staphylococcal anterior blepharitis may complain of burning, itching, foreign body sensations and mild photophobia. Associated tear film instability may also lead to symptoms of dryness. Symptoms are often worse in the morning.

The following management strategies may be employed:

- Antibiotic ointment – after removing crusts, antibiotic ointment is applied, with a clean finger, to the lid margins.
- Promote lid hygiene – crusts and toxic products can be removed by scrubbing the lids twice daily with a commercially available lid scrub. Alternatively, regular washing with a warm, moist face cloth and occasional rubbing with diluted baby shampoo should alleviate the condition.
- Steroids – weak topical steroids may be tried in more severe and protracted cases, especially if the strategies described previously fail.
- Artificial tears – will provide symptomatic relief if the blepharitis is compromising the integrity of the tear film.

The treatment can be tailed off, as appropriate, as the condition improves. However, staphylococcal anterior blepharitis is difficult to treat, and the pattern of recovery is characterised by periods of remission and exacerbation.[2]

SEBORRHEIC ANTERIOR BLEPHARITIS

This condition is caused by a disorder of the gland of Zeis and the gland of Moll, which connect with eyelash follicles. It is frequently associated with seborrheic dermatitis of the scalp, eyebrows, nasolabial folds, retroauricular areas and sternum. The symptoms are similar but less severe than for staphylococcal anterior blepharitis.

The anterior lid margin displays a shiny, waxy appearance with mild erythema and telangiectasis (Fig. 8.4). Soft, yellow greasy scales are observed along the lid margin (Fig. 8.5); unlike



Fig. 8.4 Seborrheic anterior blepharitis, where the eyelashes have become greasy and stuck together. (Courtesy Deborah Jones, British Contact Lens Association Slide Collection.)



Fig. 8.5 Yellow, greasy scales along the lid margin in a patient with staphylococcal anterior blepharitis. (Courtesy Brian Tompkins.)

staphylococcal anterior blepharitis, these scales do not leave a bleeding ulcer when removed. The eyelashes may also become greasy and stuck together.

As with the staphylococcal form, secondary complications of seborrheic anterior blepharitis include mild papillary conjunctivitis and punctate epitheliopathy. The main form of treatment is lid hygiene and artificial tears.[2]

IMPLICATIONS FOR CONTACT LENS WEAR

Contact lens wear is generally contraindicated during the acute phase of anterior blepharitis, especially if the cornea is compromised. If contact lenses are worn during mild staphylococcal anterior blepharitis, attention to lens cleaning is critical to prevent continued re-contamination of the eye. Faherty[5] suggested that contact lens wearers be advised to be careful of cross-contamination occurring among eyes, lenses, lens solutions and/or lens cases and to use cosmetics properly and with care. Daily disposable contact lenses will minimise such problems of cross-contamination.

Keys[6] conducted a 4-month study on 20 contact lens wearers and six non-lens-wearing patients suffering from blepharitis to test the efficacy of various treatment regimens. These regimens were:

- eyelid cleaning with hypoallergenic soap;
- lid scrubbing with dilute baby shampoo; and
- use of a commercial lid scrub.

It was concluded that all three regimens resulted in improvement and that about 85% of patients preferred to use the commercial lid scrub.

Parasite infestation of eyelashes

Infestation of the eyelashes by mites or lice can lead to signs and symptoms that closely resemble blepharitis. Clinicians must therefore be aware of this possibility and must be able to distinguish among the three species of parasite that most commonly infest human eyelashes and associated structures.[7] This is especially important in contact lens practice as failure to identify parasitic eyelash infestation will almost certainly lead to patient drop-out.

MITES

Mite infestation is very common in humans, with a greater prevalence in older persons. In the USA, the prevalence of mites has been reported to be 29% in 0 to 25-year-olds, 53% in 26 to 50-year-olds and 67% in 51 to 90-year-olds.[8] Mite infestation in the eyelashes is ubiquitous and generally sub-clinical, but if present in excessive numbers, adverse signs and symptoms may develop. The mode of transmission of mites between humans is not clear but may arise from intimate contact. Mites are also more abundant in patients with diabetes or AIDS and in patients on long-term corticosteroid therapy, and this suggests that compromised immunity may also influence mite infestation.[7]

Two species of mite (*Demodex*) are found in the human pilosebaceous gland complex – *D. folliculorum* and *D. brevis* (Fig. 8.6). These species are from the family Demodicidae, order Acarina (mites and ticks), class Arachnida (spiders, scorpions, ticks and mites) and phylum Arthropoda. Infestation with *Demodex* species is termed 'demodicosis'.[7]

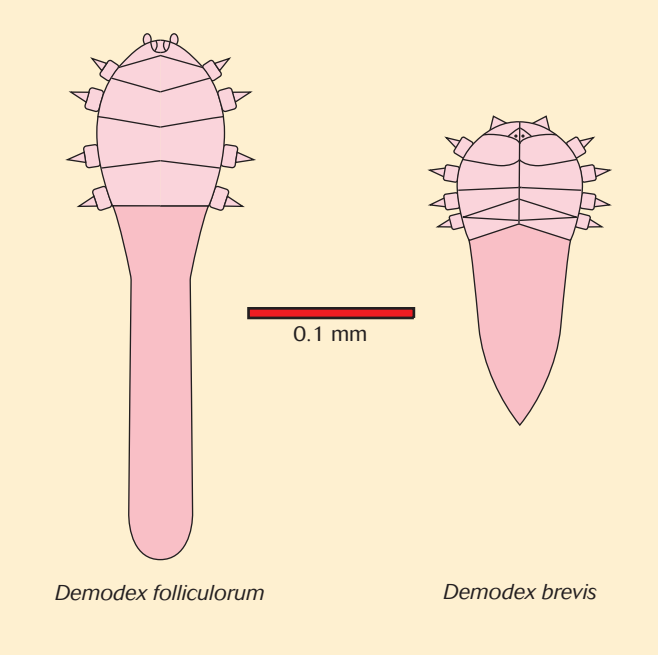


Fig. 8.6 Two sub-species of the *Demodex* found in the human pilosebaceous gland complex.

Demodex folliculorum

This is a cigar-shaped mite. It has four evenly spaced stubby legs on the upper third of its body, which can be clearly seen by using light microscopy (Fig. 8.7) and scanning electron microscopy (Fig. 8.8). This species prefers to live in the space between the eyelash and the follicle wall and will typically exist in small colonies of three to five mites in a single follicle. This species of mite is always located above the level of the gland of Zeis, primarily because of its size.[9]

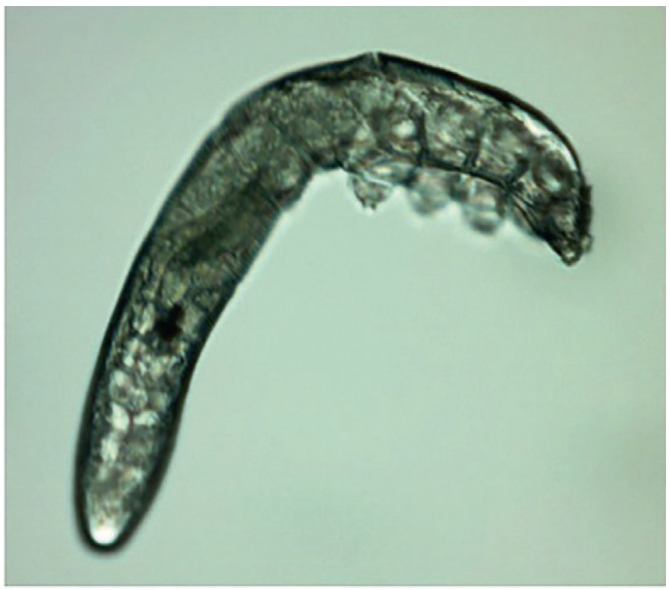


Fig. 8.7 Light micrograph of adult stage of *Demodex folliculorum*. (Reproduced from Tarkowski W, Moneta-Wielgos J, Mlocicki D. *Demodex* spp. as a potential cause of the abandonment of soft contact lenses by their existing users. Biomed Res Int 2015;2015:259109. Reproduced under the Creative Commons Attribution License.)

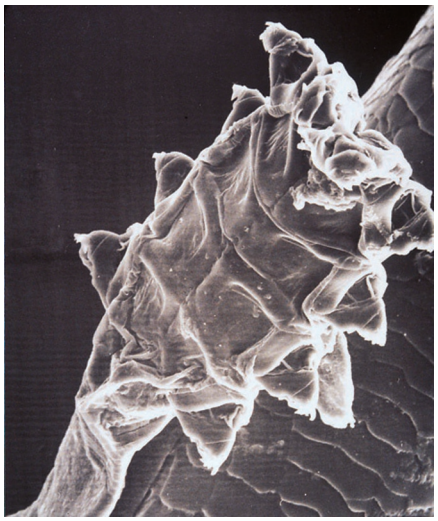


Fig. 8.8 Scanning electron micrograph of a follicle mite, *Demodex folliculorum*, lying on an epilated lash. (Courtesy Patrick Caroline.)

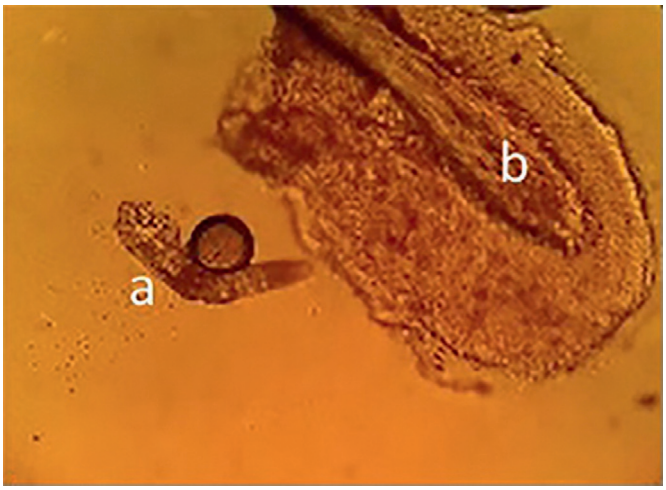


Fig. 8.9 Light micrograph of a lash removed from a soft lens wearer showing a single *Demodex folliculorum* (a) near the base of an eyelash (b). (Courtesy Isabelle Jalbert.)

D. folliculorum mites are much smaller in diameter than the base of the eyelash; the mites bury themselves head first into the follicle and feed off the cytoplasm of follicular epithelium by clawing away at, and puncturing, the epithelial cell walls with sharp mouth-parts. Figure 8.9 is a light micrograph of a lash removed from a soft lens wearer showing a single *Demodex* mite near the base of an eyelash. Figure 8.10 is a laser scanning confocal microscope image showing two *Demodex* mites in situ at the base of an eyelash of the same lens wearer.

The shredded, hyperkeratinised cell material, combined with lipids and sebum, forms clear collarettes (Fig. 8.11) (in cases of staphylococcal anterior blepharitis, the collarettes have more of a creamy-yellow appearance). Extensive mite activity can lead to an aggregation of cuffing material such that the mites are trapped within the hair follicle. This can lead to follicle distension, granulomas, telangiectasis, hyperplasia, erythema, madarosis, hyperaemia, burning and itching, which, of course, must be dealt with clinically.[7]

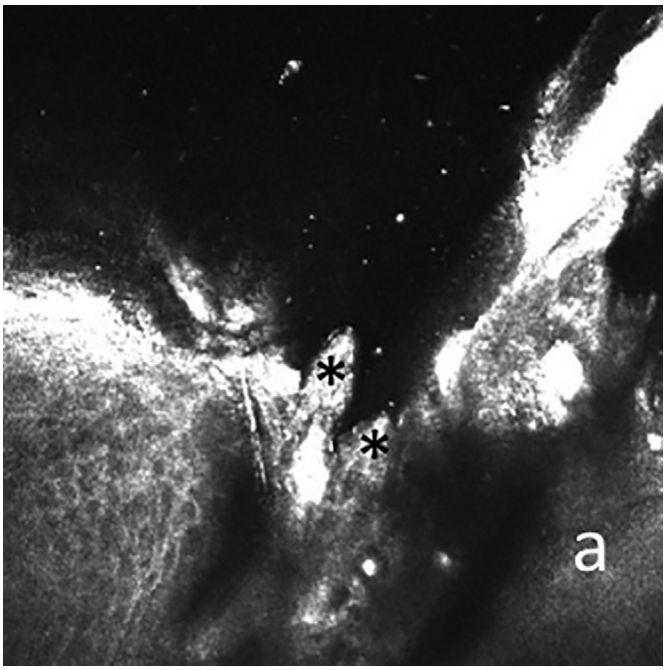


Fig. 8.10 Laser scanning confocal microscope image of two *Demodex folliculorum* mites in situ (asterisks) adjacent to an eyelash (a). (Courtesy Isabelle Jalbert.)



Fig. 8.11 Collarette surrounding an eyelash of a contact lens wearer infested by mites. (Courtesy Lourdes Llobet, Bausch & Lomb Slide Collection.)

Demodex brevis

This mite (Fig. 8.12) is found in human skin rich in sebaceous glands and sebum production. It prefers to infest the gland of Zeis and because of its very small size (0.18 mm long, vs. *D. folliculorum*, which is 0.38 mm long), this mite can easily enter this gland.[8] *D. brevis* has an almost identical structure to *D. folliculorum*, the former being shorter but stubbier (Fig. 8.6). *D. brevis* is often found alone in a single sebaceous gland. In a similar manner to the actions of *D. folliculorum*, *D. brevis* can block the gland of Zeis and, indeed, can block the meibomian glands,



Fig. 8.12 Light micrograph of adult stage of *Demodex brevis*. (Reproduced from Tarkowski W, Moneta-Wielgos J, Mlocicki D. Demodex spp. as a potential cause of the abandonment of soft contact lenses by their existing users. Biomed Res Int 2015;2015:259109. Reproduced under the Creative Commons Attribution License.)

leading to MGD and interference with lipid production, which, in turn, can result in dry eye symptoms.

Because *D. brevis* prefers to live in an oily, sebaceous environment, it tends to thrive in the presence of oily cosmetics and facial preparations. This, in turn, can cause *D. brevis* to proliferate and can lead to the following sequelae of events: meibomian glands, glands of Zeis, and other facial sebaceous glands become blocked; skin becomes dry; the patient applies more oily facial creams; *D. brevis* again proliferates; and the cycle continues.[10]

General characteristics

Demodex species are typically nocturnal, but even during the day, a busy migration of organisms can be observed passing between eyelash follicles. Patient symptoms typically parallel the life cycle of the organisms. Nests of *D. folliculorum* are laid around the base of lashes; they hatch after about 2 to 3 days, and the adult lives for 5 to 14 days.[11]

Although they may be detected at high magnification (×40) on a slit lamp biomicroscope, mites are difficult to observe because they are very small (much narrower than the width of an eyelash), they withdraw back into the follicle in bright light (being nocturnal in nature), and they are translucent. Diagnosis is confirmed by examination of epilated lashes under a light microscope; one or more mites observed on every two lashes are considered indicative of demodicosis.[12] Kojima et al.[13] recently demonstrated that *Demodex* infestation can be diagnosed by using laser scanning confocal microscopy. Their results suggested that this technology not only effectively disclosed the mites embedded in the eyelash bulbs but also provided additional useful information on associated MGD and conjunctival disease, the features of which were acinar dilatation, periglandular inflammation and conjunctival inflammatory infiltrates.[13]

Additional signs of demodicosis include erythema of the lid margins, lid hyperplasia and madarosis (all of which give the impression of blepharitis), conjunctival injection, cuffing around lashes, follicular distension and meibomian gland blockage. Eyelashes are more easily removed during active infestation as a result of damage to the eyelash follicles. Typical symptoms of demodicosis are pruritus, burning, crusting, itching, swelling of the lid margins and loss of lashes. The itching often parallels the 10-day reproductive cycle.[7]

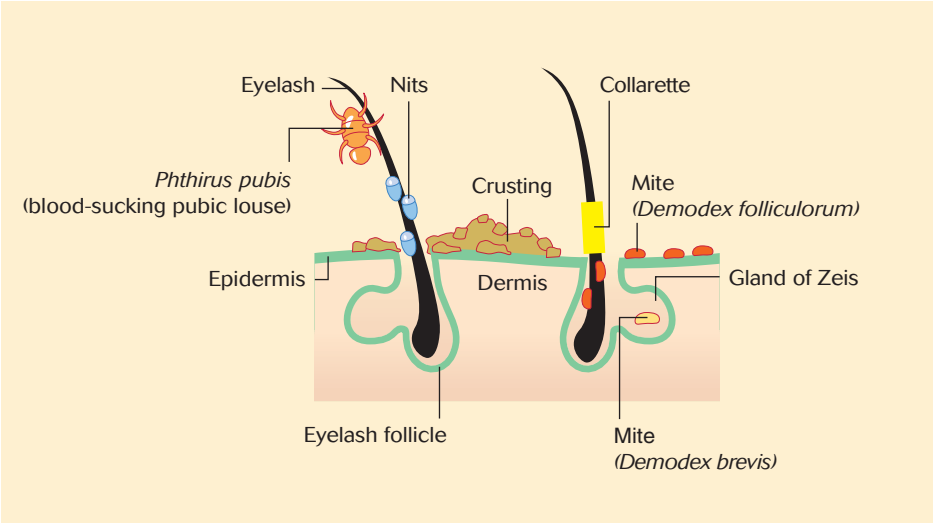
Figure 8.13 is a schematic diagram illustrating the preferred habitat of mites and lice that commonly infest the human pilosebaceous system.

Association with contact lens wear

Siddireddy et al.[14] reported observing greater number of *Demodex* mites in the upper eyelid of symptomatic lens wearers (2 ± 1 mites) compared with asymptomatic lens wearers (0 ± 0 mites) ($p = 0.042$).

Jalbert and Rejab[15] examined 40 Asian female participants (20 non–lens wearers, 20 lens wearers) with a mean (±SD) age of 27 ± 9 years. The number of *Demodex* mites was found to be higher in lens wearers than in non–lens wearers (7.6 ± 5.8 mites vs. 5.0 ± 3.1 mites) ($p = 0.02$). *Demodex* mites were observed in 90% of lens wearers versus 65% of non–lens wearers

Fig. 8.13 Preferred habitat of mites and lice that commonly infest the human pilosebaceous gland complex.



by using confocal microscopy ($p = 0.06$). The detection rate was lower in both groups using conventional light microscopy ($p = 0.003$), where *Demodex* infestation could only be confirmed in 70% and 60% of lens wearers and non–lens wearers, respectively. The number of *Demodex* mites tended to increase with age ($\rho = 0.28$; $p = 0.08$), but *Demodex* did not appear to affect ocular comfort or any clinical signs ($p > 0.05$).

Contrary to the findings of Jalbert and Rejab,[15] no relationship was found by Wesolowska et al.[16] between the use of contact lenses and presence of *Demodex* spp. (positivity in 8 of 20 lens wearers vs. 111 of 269 in non–lens wearers; $\chi^2 = 0.02$; $p = 0.9$).

Tarkowski et al.[17] examined a group of 28 symptomatic and 34 asymptomatic contact lens wearers. A few lashes were removed from each subject and were examined under light microscopy, applying standard parasitological methods for detecting demodicosis. A positive result was assumed if at least one adult stage, larva, protonymph/nymph or egg of *D. folliculorum* and/or *D. brevis* was present. *Demodex* sp. infections were observed in 93% and 6% of symptomatic and asymptomatic wearers, respectively. A positive correlation was observed between the presence of *Demodex* and intolerance lens wear ($p < 0.05$).

LICE

Three species of lice infest the human body:

- head louse (*Pediculus humanus capitis*);
- body louse (*Pediculus humanus corpus*); and
- pubic louse (*Phthirus pubis*) or 'crab' louse.

These species are from the family Pediculidae, order Anoplura (the sucking lice), class Insecta and, like mites, they are classified as belonging to the phylum Arthropoda.[7]

P. capitis typically infests the scalp hair (especially the occipital region). During dense scalp infestation, *P. capitis* can be found in the eyelashes, but this is extremely rare. *P. corpus* inhabits seams and creases in clothing and feeds on the skin of patients. Infestation with these two species is termed 'pediculosis'. The *Pediculus* species are typically 2.5 to 3.5 mm long (Fig. 8.14) and are vectors in humans for serious diseases, such as typhus, relapsing fever and trench fever.[18]



Fig. 8.15 Electron micrograph of a crab louse (*Phthirus pubis*). (Courtesy Patrick Caroline, Bausch & Lomb Slide Collection.)

The crab louse, *P. pubis*, is most commonly found in pubic hair but also in other coarse and widely spaced hair, such as hair on the chest and thighs (Fig. 8.15). Infestation with this species is termed 'phthiriasis'. The crab louse is about 1.0 to 1.5 mm long, which is an ideal size for inhabitation among pubic hairs because these hairs are spaced 2 mm apart, and this corresponds to the anatomical grasping span of the legs of a louse. *P. pubis* can successfully infest eyelashes, which are also approximately 2 mm apart; indeed, of the three species of louse discussed previously, it is the crab louse that is found almost exclusively among human eyelashes.[18] *P. pubis* has two pairs of strong grasping claws on the central and hind legs, allowing it to hold on to eyelashes with considerable tenacity.

Phthiriasis is considered a venereal disease because it is passed on by sexual contact. In adults, genital-to-eye transmission is the most probable cause of eyelash infestation, although infestation from contaminated bedding, towels and bed linen is another possible mode of transfer. The eyelashes of children may be infested through eye-to-eye contact, and eyelashes of infants may be infested from contact with the chest hair of parents or siblings, who themselves are harbouring the lice.[7]

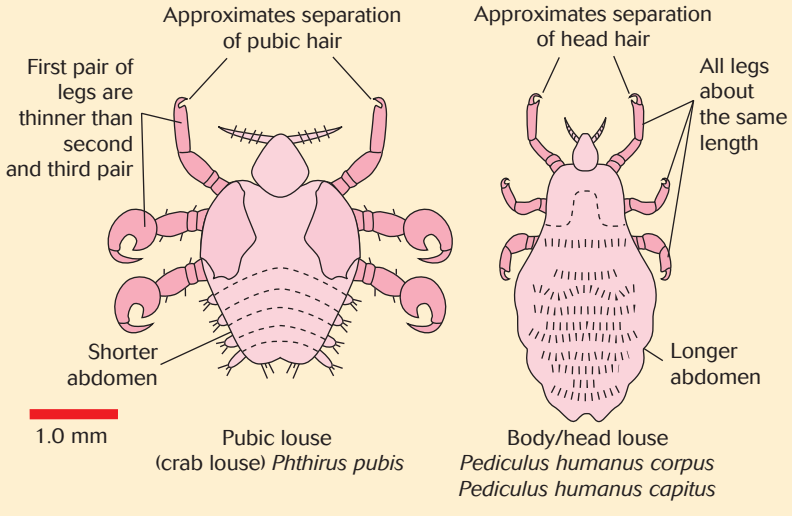


Fig. 8.14 Species of lice that infest the human body.



Fig. 8.16 Electron micrograph of lice eggs, or 'nits', encapsulated in a characteristic cigar-shaped shell. (Courtesy Patrick Caroline.)

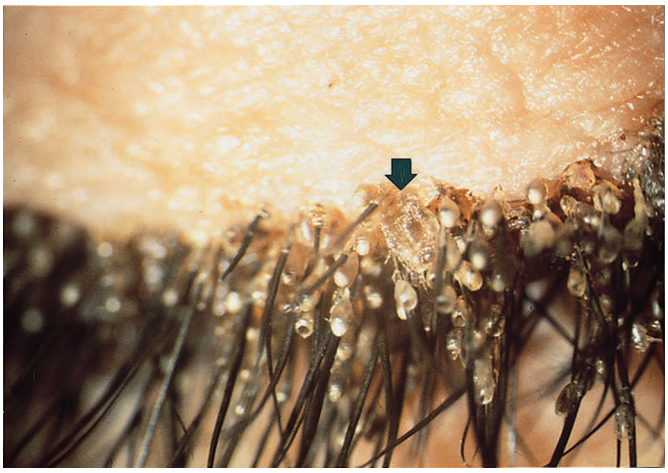


Fig. 8.17 Slit lamp photomicrograph of a nearly transparent louse at the lid margin (arrow) surrounded by a mass of nits encapsulated in shells, and some empty shells that have already hatched open. (Courtesy Patrick Caroline.)

The three species discussed earlier are known as 'sucking lice' because of their mode of feeding, which is by anchoring their mouth hooklets to the skin of the host and to extending a long hollow tube (stylus) into the dermis. Anti-coagulants are secreted to facilitate unimpeded sucking of blood and serum.[7]

All of these lice have internal fertilisation and lay eggs within 2 days of fertilisation. The eggs, or 'nits', are encapsulated in a cigar-shaped shell (Fig. 8.16). Nit shells are cemented to eyelashes about 1 to 2 mm from the base of the lash, and the nits hatch in 7 to 10 days. It takes lice about 1 month to reach adult stage, and the adult lives for a further month. Lice can survive for only 2 days if separated from the host.[7]

Signs of phthiriasis include pruritus of the lid margins, termed 'blepharitis'; marked conjunctival injection; and madarosis. Additional signs include pre-auricular lymphadenopathy and secondary infection along the lid margins at the site of lice bites. The most predominant symptom is intense itching, which is so severe that patients will also report insomnia, irritability and mental depression.[18]

The most obvious sign of phthiriasis is the presence of oval, greyish-white nit shells attached to the base of lashes which can be easily identified by using high magnification (×40) slit lamp biomicroscopy (Fig. 8.17). Adult lice can be difficult to detect because they are almost completely transparent. Reddish-brown deposits at the base of lashes also indicate the presence of lice; these deposits are a combination of blood from the host and faeces from the parasite. Blue spots may also be observed on the lid margins; these are caused by enzymatic reactions from the digestive juices of the lice.[18]

TREATMENT OF MITE INFESTATION

The main aim of treatment is to reduce the level of mite infestation to sub-clinical levels. In treating this condition, it should be assumed that there will be a concurrent bacterial infection. The initial course of action is to attempt to remove as many mites and mite eggs as possible. This can be achieved by applying a topical anaesthetic and swabbing the eyelid margins and eyelashes with a cotton-tipped applicator saturated in a contact lens cleaning solution, taking care to avoid contact with the cornea.[7]

Gao et al.[19] reported the results of a retrospective review of clinical results in 11 patients who had ocular *Demodex* infestation and received weekly lid scrub with 50% tea tree oil combined with daily lid hygiene with tea tree shampoo. This treatment regimen resulted in the *Demodex* mite count dropping to zero at two consecutive visits in less than 4 weeks in 8 of 11 patients. Ten of the 11 patients showed different degrees of symptomatic relief and notable reduction of inflammatory signs. Significant visual improvement in six of 22 eyes was associated with a stable lipid tear film caused by significant reduction of lipid spread time. However, there was notable irritation observed in three patients.

Edmondson et al.[7] recommended advising patients to engage in vigorous lid scrubbing twice daily (morning and evening) with commercially available preparations, diluted baby shampoo, non-allergenic soap or hot flannels. After the evening lid scrub, a viscous ointment should be applied to the upper and lower lid margins. This procedure will result in the following:

- trapping of mites in their follicles;
- smothering and killing of the trapped mites; and
- prevention of mites from migrating and cross-contaminating adjacent follicles.

A lid scrub performed the following morning removes dead lice and associated debris trapped in the ointment. Heavy-metal ointments, such as yellow mercuric oxide, are usually prescribed because of their supplementary anti-microbial efficacy. Pilocarpine gel has been suggested as a more potent alternative. Treatment should be continued for at least 3 weeks, even if early symptomatic relief has been achieved.[7]

Ngo et al.[20] conducted a prospective, randomised, controlled, crossover, open-label study involving 26 non–lens wearers and sought to determine the level of discomfort experienced by patients over time when treated with of various eyelid cleansers with action against *Demodex*. The cleansers used were Biotissue Cliradex (CD), OCuSOFT Lid Scrubs Plus (OP), OCuSOFT OUST Demodex Swabstix (ODS), TheraTears Theralid (TT) and NovaBay Avenova (NA). Bausch + Lomb Sensitive Eyes Plus saline was used as the control. Patients reported significant discomfort when using Biotissue Cliradex, TheraTears Theralid and OCuSOFT OUST Demodex Swabstix. These results may

help clinicians educate patients about what to expect when approaching the topic of eyelid *Demodex* treatment.

If the earlier measures are unsuccessful, more aggressive in-office therapy may need to be adopted. Vigorous scrubs with a cotton-tipped applicator soaked in alcohol or ether, performed weekly for 3 weeks, may bring the condition under control.[7]

Patients experiencing symptoms of dryness as a result of *Demodex* infestation of skin should be cautioned against the use of facial oils and should be advised to wash the affected areas daily with soap.[7]

Practitioners should be alert to the possibility of alarming patients about the existence of 'spider-like' parasites on their body. It should be explained that this is a chronic condition that can be kept under control if the patient complies with the treatment protocol.

TREATMENT OF LICE INFESTATION

The initial course of action is to mechanically remove the lice from the lashes with forceps while visualising the process by using medium to high power on a slit lamp biomicroscope (Fig. 8.18). This may be difficult because the lice typically maintain a tight grasp on the lashes. Heavy infestations are best removed by using cryotherapy (freezing) or argon laser photoablation. The latter technique effectively slices through the lashes; the result is initially unsightly, but the patient should be reassured that the lashes will quickly grow to full length. Lice and nits will also be killed by application of 20% sodium fluorescein.[18]

The patient should be advised to apply yellow mercuric oxide ophthalmic ointment twice daily to the lid margins to smother and kill adult lice. This therapy should be continued for 2 weeks to cover at least one complete life cycle of the louse. Anticholinesterase agents may also be tried. More potent insecticides are seldom used today because of the potential for serious corneal injury. Patients should be warned that symptoms may persist beyond effective eradication of lice because of residual lice-induced hypersensitivity reactions.[18]



Fig. 8.18 Louse on the tip of forceps after having been removed from the eyelash of a patient with phthiriasis. (Courtesy Lisa Howe.)

Patients should be referred for treatment of pubic infestation and other possible sexually transmitted diseases. Sexual partners and family members should also be examined for eyelash infestation and counselled about the possibility of concurrent infestation of pubic hair. More potent pediculicidal ointment can be applied to regions of the body away from the eyes, offering the possibility of rapid and effective treatment.[18]

The home environment should be sanitised to eradicate lice, with heat application being the most effective course of action. Lice will be killed if bed linen, towels, sheets and clothes are washed in boiling water for 30 minutes. Combs, brushes and hair accessories should be soaked in lice-killing products or in boiling water for 10 minutes. Isolation of blankets and other large items from the host for 2 weeks will ensure the death of all lice and nits.[18]

MANAGEMENT IN CONTACT LENS WEARERS

In general, contact lens wearers presenting with parasitic infestation of the eyelids should be treated in the same way as similarly infested non–lens wearers. Paradoxically, contact lenses (soft lenses, in particular) serve a protective function during parasitic eyelash infestation because they prevent the cornea from the mechanical effects of altered lid margins and lashes and prevent toxins and debris from coming into contact with the cornea.[21]

It is advisable to cease lens wear during the treatment period, which, in severe cases, may last up to 1 month. Contact lenses can theoretically serve as a vector for transmission of mites, lice, nits or other potentially toxic or allergenic byproducts of the infestation process. The probability of such vectorial transmission increases if the patient is partially non-compliant by, for example, failing to manually rub their lenses after lens removal. An intense cleaning regimen is important for patients with eyelash infestations. The best strategy of lens wear for patients with recurrent parasitic eyelash infestation is to use daily disposable contact lenses.

Caroline et al.[22] highlighted the sensitive nature of managing crab lice infestation in that it is primarily a sexually transmitted disease. They cautioned that loss to follow-up is to be expected in a significant number of patients, who may be too embarrassed to return to their eye care practitioner for further care of the eyelash infestation or, indeed, for further contact lens management.

Other contact lens–associated eyelash disorders

INSECTS TRAPPED IN EYELASHES

Carcasses of flying insects are occasionally observed on the lid margins, just posterior to the base of the eyelashes. These insects perhaps land on the lid margin quite accidentally; realise that they have found a soft, moist and succulent environment (the conjunctiva and meibomian secretions); and take measures to anchor themselves in position. Another possibility is that they quickly become stuck in the oily lipid secretions of the lid margin. A strong reflex blink or eye rub by the host may then kill or incapacitate the insect and the carcass remains in place until physically dislodged.

Figure 8.19 shows an insect trapped on the upper lid margin of a soft contact lens wearer, who noticed discomfort in her left



Fig. 8.19 Insect stuck on the upper lid margin just posterior to the row of lashes. (Courtesy I DeSchepper, Bausch & Lomb Slide Collection.)

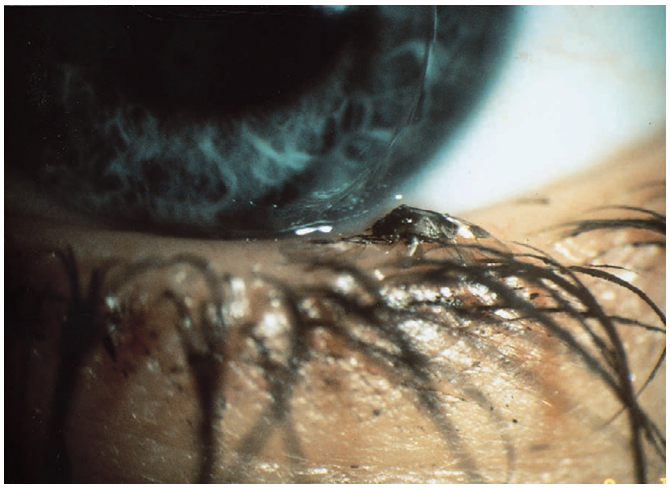


Fig. 8.20 Insect stuck on the lower lid margin just posterior to the row of lashes. (Courtesy J. Prummel, Bausch & Lomb Slide Collection.)

eye while on vacation in Spain. The patient attributed the consequent irritation to a split in her contact lens; upon return home, she went to her eye care practitioner, who detected the insect on slit lamp examination. Figure 8.20 shows a flying insect trapped on the lower lid margin of a rigid lens wearer.

These cases highlight the importance of thoroughly examining the lid margins when trying to find the cause of discomfort that appears to be related to contact lens wear.

SHED EYELASH ENTERING THE EYE

The life cycle of an eyelash is approximately 5 months, and it takes about 2 months for a new eyelash to become fully grown.[1] Thus there are frequent opportunities for a shed eyelash to enter the eye. In non–lens wearers, an eyelash that enters the eye typically elicits an intense foreign body discomfort sensation, causing increased lacrimation and resulting in the lash being flushed out. In contact lens wearers, the lash may become lodged beneath the lens; this is generally very uncomfortable. The patient will remove the lens and will often attempt to remove the eyelash as well, if it can be located. After such an incident

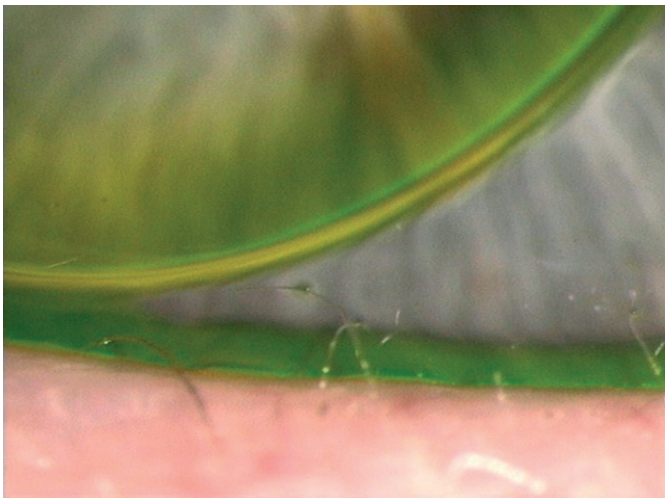


Fig. 8.21 Ingrowing eyelash from the lower lid irritating the ocular surface of a rigid lens wearer. (Courtesy Brian Tompkins.)

has occurred, examination of the eye may reveal evidence of corneal epithelial trauma; if severe, lens wear should be suspended until the epithelium has recovered.

TRICHIASIS

Trichiasis is a condition in which the eyelashes curl inward toward the globe (Fig. 8.21). This can manifest as a primary condition or be secondary to entropion (Fig. 8.22). Whatever the cause, the result can be discomfort and persistent abrasion of the cornea by the eyelashes, and in non–lens wearers, this can lead to significant corneal decompensation in the form of a vascular pannus if left untreated for a significant length of time.[2]

Contact lenses can act as a protective buffer against corneal damage – with soft lenses offering more protection compared with rigid lenses because of the greater corneal coverage of the former. However, the cornea can be damaged when lenses are not being worn, and subsequent lens wear in the presence of epithelial trauma can be problematic because the epithelial breach may cause the eye to be more susceptible to microbial

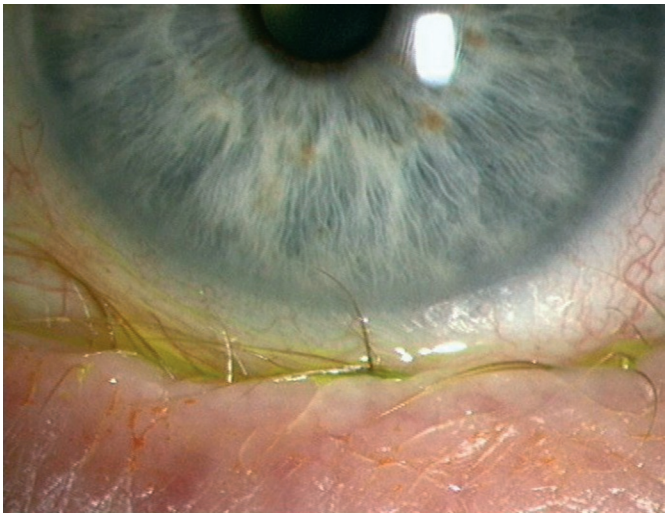


Fig. 8.22 Trichiasis resulting from entropion. (Courtesy Brian Tompkins.)

infection. Inward growing eyelashes should therefore be treated by using one of the following techniques:

- Epilation – eyelashes are mechanically removed with the aid of forceps.
- Electrolysis – the eyelash follicle is destroyed by passing an electrical current through a fine needle inserted into the lash root.
- Cryotherapy – the lash follicle is frozen with a nitrous oxide cryoprobe at −20° C.[2]

DISTICHIASIS

Distichiasis is a condition in which eyelashes emerge from non-typical locations in the lid margin. For example, eyelashes may emerge from between, or even from within, meibomian gland orifices. Distichiasis can be congenital or acquired and typically causes the same problems of irritation and corneal trauma as in trichiasis.[2] The implications with respect to contact lens wear are also similar; the condition is usually treated by using cryotherapy.

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9 Dry Eye

Dry eye in contact lens wearers has been identified as a growing public health problem.[1] Between 2015 and 2017, the Tear Film and Ocular Surface Society (TFOS) convened an international collaboration of over 150 experts in the field of dry eye to appraise, synthesise and summarise current knowledge relating to dry eye disease, in a series of meetings known as the Dry Eye Workshop II (DEWS II).[2] The 'II' designation was to distinguish this effort from the first workshop which reported in 2007.[3]

This process led to the refined TFOS DEWS II global dry eye definition, as follows: 'Dry eye is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyper-osmolarity, ocular surface inflammation and damage and neurosensory abnormalities play aetiological roles.'[4]

An earlier TFOS workshop on contact lens discomfort reported that the primary reasons for contact lens intolerance are discomfort and dryness.[5] In fact, contact lens wearers are 12 times more likely than emmetropes and five times more likely than spectacle wearers to report dry eye symptoms.[6] Contact lens–related dry eye is considered an extrinsic form of evaporative dry eye disease, as indicated in the classification schema for dry eye disease proposed by TFOS DEWS II and shown Figure 9.1. The sections and pathways in this schema that relate to contact lens wear are highlighted by a red border.

The integrity of the tear film is critical for safe and comfortable contact lens wear. If the tear film is of insufficient quantity or quality, a contact lens wearer will generally complain of having a 'dry eye'. Thus, in the contact lens field, the term 'dry eye' is taken as an all-encompassing phrase that encapsulates various aspects of tear film dysfunction relating to contact lens wear. These aspects include, but are not restricted to, patient symptomatology; alterations to the composition, quality, quantity and chemistry of the tear film; lens deposition; and the effect of these changes on tissue integrity, vision and lens performance.

The tear film in contact lens wear differs in many ways from the normal, undisturbed tear film. The most obvious difference from a clinical perspective is a necessary structural re-organisation, whereby the tears are compartmentalised into the pre-lens tear film and post-lens tear film. In addition, the integrity of the tear film remains altered for a short period after ceasing lens wear.

This chapter will consider the key clinically relevant features of the tear film by contrasting the nature of the tear film in the presence and absence of contact lens wear. In the course of this discussion, clinical tests of tear film integrity will be considered, as well as the way in which the results of such tests can be interpreted and applied clinically to solve problems of tear film dysfunction that are invariably reported as 'dry eye'.

Defining dry eye in relation to contact lens wear

A large number of papers have been published on the prevalence of symptoms of dry eye during contact lens wear,[7] with the apparent presumption by many of these authors that they are documenting dry eye disease. However, objective signs also must be demonstrated to confirm the existence of dry eye. Although papers reporting contact lens dryness symptoms in contact lens wear are important to characterise and define the extent of this troubling complaint,[7] they cannot claim to be defining a dry eye condition consistent with the DEWS II definition of dry eye. To provide clarification in this regard, TFOS DEWS II proposed the following two definitions of dryness related to contact lens wear.

CONTACT LENS–INDUCED DRY EYE

Contact lens–induced dry eye (CLIDE) can be defined as the existence of signs and symptoms of dry eye during contact lens wear, whereby such signs and symptoms did not exist before contact lens wear. This definition sets a very high bar for demonstrating CLIDE, which can only be demonstrated in a patient who has not worn contact lenses previously.

Very few studies have demonstrated the presence of CLIDE according to this definition; one example where this has been done is the study of Alzahrani et al.,[8] who reported that, of 60 people free of dry eye disease before lens wear, 25 (42%) developed CLIDE 1 week after commencing wear of daily disposable hydrogel contact lenses.

CONTACT LENS–ASSOCIATED DRY EYE

Contact lens–associated dry eye (CLADE) can be defined as the existence of signs and symptoms of dry eye during contact lens wear. According to this definition, the possibility that the dry eye disease observed in lens wearers is caused by a pre-existing or co-existing dry eye condition cannot be discounted. Unlike the definition for CLIDE, this definition for CLADE sets a relatively low bar.

Two examples of studies that have essentially assessed CLADE are as follows. Pult et al.[9] recruited 20 symptomatic and 13 asymptomatic contact lens wearers (who were not pre-screened for dry eye disease) and assessed symptoms by using the Contact Lens Dry Eye Questionnaire (CLDEQ) and a range of signs over a 4-week period. They concluded that assessment of non-invasive tear break-up time (NITBUT), lid parallel conjunctival folds and the ocular surface disease index could best predict future dry eye symptoms.

Nichols and Sinnott[10] recruited 415 contact lens wearers (who were not pre-screened for dry eye disease) and assessed symptoms and signs in a cross-sectional study. Factors shown to be related to dry eye status in multivariate modelling were

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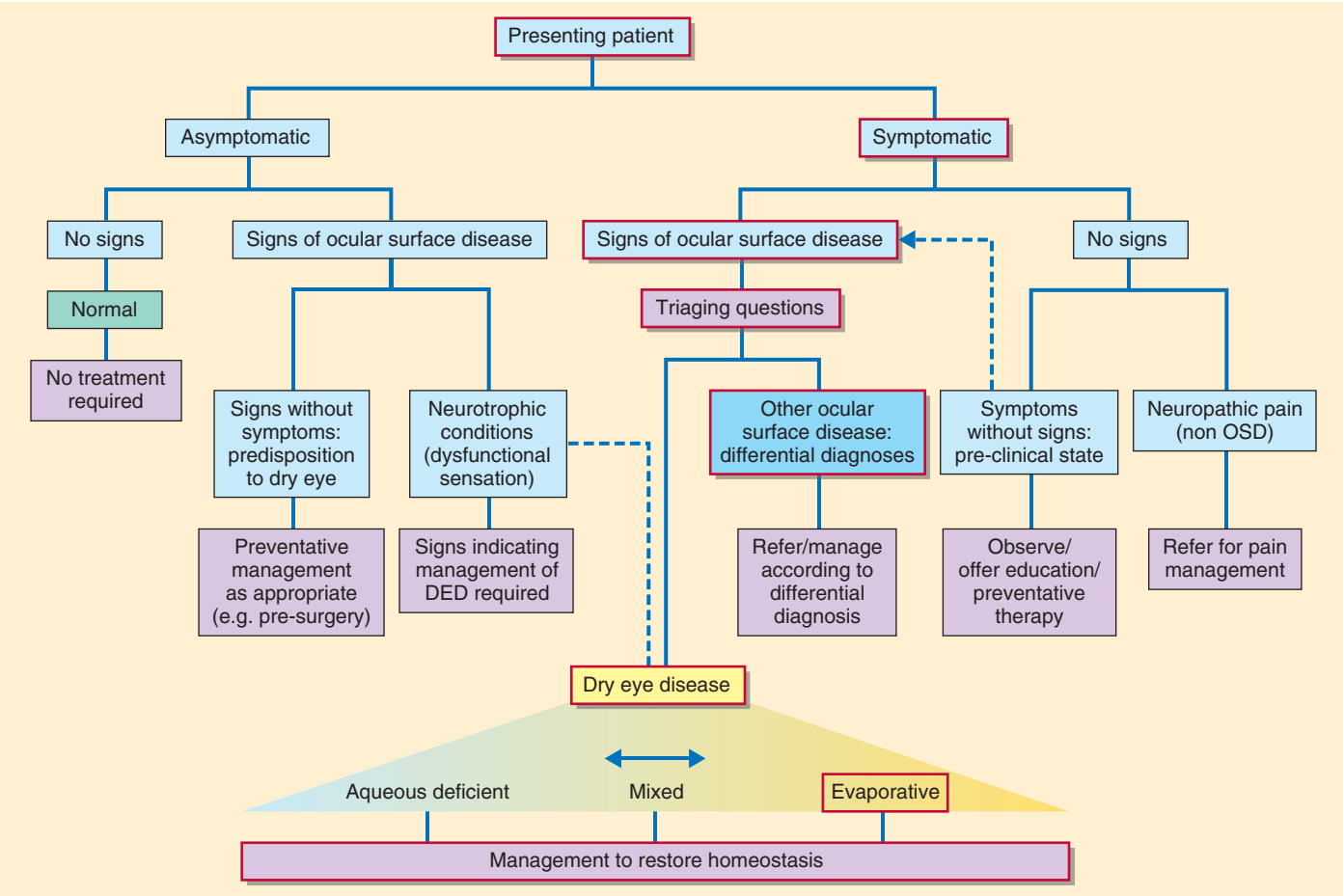


Fig. 9.1 Dry Eye Workshop II (DEWS II) classification schema for dry eye disease, modified to highlight the association between contact lens wear (boxes with red borders) and dry eye disease. The upper portion of the schema represents a clinical decision algorithm, beginning with the assessment of symptoms, followed by review for signs of ocular surface disease. The lower portion of the schema represents the aetiological classification of dry eye disease and highlights the two predominant and non–mutually exclusive categories – aqueous deficient dry eye and evaporative dry eye. (Adapted from Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II report executive summary. Ocul Surf 2017;15:802–12.)

female gender ($p < 0.007$), lenses with higher nominal water content ($p < 0.002$), rapid pre-lens tear film thinning time ($p < 0.008$), frequent usage of over-the-counter pain medication ($p < 0.02$), limbal injection ($p < 0.03$) and increased tear film osmolality ($p < 0.05$).

The normal tear film

STRUCTURE

Appreciation of the structure of the tear film in both the undisturbed and contact lens–wearing eye is confounded by the ongoing uncertainty as to its normal structure. The description of the tear film originally proposed by Wolff,[11] although perhaps somewhat simplistic, is still regarded as providing the most useful, clinically relevant model of tear film structure (Fig. 9.2). According to this model, the tear film is composed of a thin outer lipid layer, a thick intermediate aqueous phase and a thin inner mucus layer.

Subsequent research has suggested refinements of the original Wolff model. Tiffany[12] accepts the basic structure as

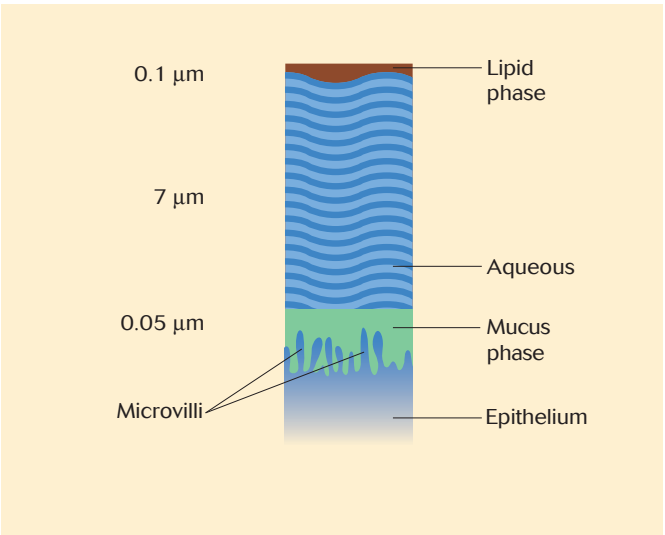


Fig. 9.2 Structure of the pre-corneal tear film (not drawn to scale).

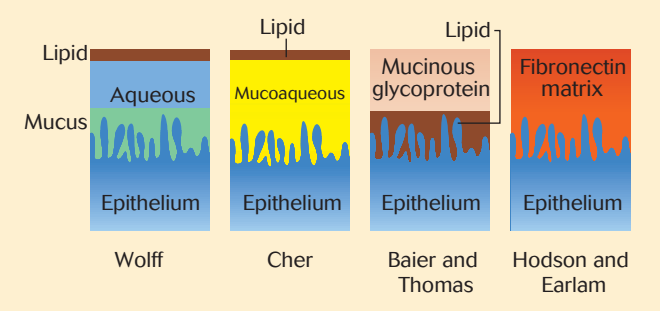


Fig. 9.3 Alternative theories of tear film structure.

outlined by Wolff but argues that the interfaces between air, lipid, aqueous, mucus and epithelium have their own peculiar physico-chemical properties; he concluded that the tear film should technically be considered as being composed of six layers.

Dilly[13] argued that the mucin layer has a decreasing gradient of concentration from the epithelium toward the aqueous layer. Cher[14] argued that the aqueous and mucin layers are a single layer of mucoaqueous gel (referred to as the *mucoaqueous layer*).

Hodson and Earlam[15] suggested that the tear film has no defined structure but instead is composed of a loose fibronectin gel, in which the lipid, mucus and aqueous components are inter-mixed.

Baier and Thomas[16] proposed a more radical model of tear film structure. They argued from a theoretical standpoint (based on the appearance of oil slicks on the ocean as viewed from space) that the structure of the tear film is the reverse of that proposed by Wolff, whereby the outer layer of the tear film is a mucinous glycoprotein gel and an inner lipid layer lines the epithelium.

Alternative models of tear film structure are illustrated in Figure 9.3.

THICKNESS

Wolff[11] originally proposed that the tear film is about 7 μm thick and that the outer lipid layer was approximately 0.1 μm thick, the intermediate aqueous phase was 7 μm thick, and the inner mucus layer was 0.05 μm thick.

Subsequent research has suggested that the tear film is somewhat thinner than originally proposed by Wolff.[11] Evidence from reflection spectra of the pre-corneal tear film suggests the overall tear film has a thickness of approximately 2 to 3 μm.[17] Measurement of tear film thickness by using anterior eye optical coherence tomography has resulted in estimates of tear film thickness ranging from 2.0 to 5.5 μm.[18] Accordingly, a tear film thickness estimate of 4 μm (Fig. 9.2) approximately represents the median value of these more recent estimates.

By using interferometry techniques, the thickness of the lipid layer has been reported to be from 15 to 157 nm, with a mean of 42 nm.[19]

FUNCTION

In the normal, non-lens-wearing eye, the tear film serves six important functions:

- Optical – the tear film maintains an optically uniform interface between air and cornea.
- Mechanical – the tear film acts as a vehicle for the continual blink-mediated removal of intrinsic and extrinsic debris and particulate matter that is constantly entering the eye.
- Lubricant – the tear film ensures a smooth movement of the eyelids over the globe during blinking.
- Bactericidal – the tear film contains defence mechanisms in the form of proteins, antibodies, phagocytic cells and other immunodefence mechanisms that prevent ocular infection.
- Nutritional – the tear film supplies the corneal epithelium with necessary supplies of oxygen, glucose amino acids and vitamins.
- Waste removal – the tear film acts as an intermediate reservoir for the removal of byproducts of metabolism from the cornea, such as carbon dioxide and lactate.

The functions of the tear film during uncomplicated contact lens wear essentially fall into the same categories as those described for the normal tear film but can be restated with subtle differences:

- Optical – the tear film maintains an optically uniform interface between air and the anterior surface of the lens.
- Mechanical – the tear film acts as a vehicle for the continual blink-mediated removal of intrinsic and extrinsic debris and particulate matter from the front of the lens and from beneath the lens.
- Lubricant – the tear film ensures a smooth movement of the eyelids over the front surface of the lens and of the lens over the globe during blinking.
- Bactericidal – the tear film contains defence mechanisms in the form of proteins, antibodies, phagocytic cells and other immunodefence mechanisms that prevent ocular infection.
- Nutritional – the tear film supplies the corneal epithelium with necessary supplies of oxygen, glucose amino acids and vitamins, via the lid-activated tear pump.
- Waste removal – the tear film acts as an intermediate reservoir for the removal of byproducts of metabolism from the cornea, such as carbon dioxide and lactate, that are flushed out from beneath the lens via the lid-activated tear pump.

Signs of tear film dysfunction in contact lens–related dry eye

GENERAL OBSERVATION

The most fundamental test that a clinician can apply when investigating tear film dysfunction in a contact lens wearer is to observe the tears using the slit lamp biomicroscope. Similar techniques that are employed for examining the non-lens-wearing eye can also be applied to the lens-wearing eye. The overall integrity of the tears during lens wear can be assessed by observing the general flow of the tear film over the lens surface after a blink, as indicated by the movement of tear debris. A 'sluggish' movement may indicate an aqueous-deficient, mucus-rich and/or lipid-rich tear film, and the amount of debris provides an indication of the level of contamination of the tears – perhaps, for example, from overuse of cosmetics. A sluggish and/or contaminated tear film is

potentially problematic and could result in increased deposit formation, intermittent blurred vision and discomfort.

REDUCED TEAR VOLUME

The volume of tears in prospective and current contact lens wearers can be assessed by observing the height of the lower lacrimal tear prism (or 'tear meniscus') (Fig. 9.4). Mainstone et al.[20] found that measurements of tear meniscus radius of curvature and height correlated well with cotton thread test results, NITBUT and ocular surface staining scores, demonstrating the value of such an assessment in diagnosing dry eye conditions.

By using optical coherence tomography, Chen et al.[21] demonstrated that tear meniscus volumes in lens wearers with dry eye symptoms are lower than in asymptomatic wearers at baseline and during lens wear. They suggested that these changes directly contribute to the symptom of dryness. Tear volume decreases gradually during the course of lens wear and contributes to ocular discomfort in both symptomatic and asymptomatic wearers.[22]

Tear film volume can be measured in the non-lens-wearing eye by using Schirmer's test or the preferred and less invasive cotton thread tear test. Schirmer's test involves the placement of one end of a strip of filter paper into the lower fornix and measuring the length of paper that becomes wetted over a given period (Fig. 9.5). The greater the length of wetting, the greater is the tear volume. This test is no longer favoured because the strip causes discomfort and reflex stimulation of tears, which can invalidate the test result.

The cotton thread test (also known as the *phenol red thread test*), as adapted by Hamano et al.,[23] involves impregnating fine cotton threads with the pH reactive dye phenolsulphophthalein, which turns the thread yellow in air. A cotton thread is looped over the lower lid margin; one end hangs down over the cheek, and the other end rests in the lower lid cul-de-sac (Fig. 9.6). As a result of a tear-induced shift in pH, the yellow thread turns red as it soaks up the tears. The greater the passage of redness along the thread, the greater is the tear volume (again assuming that there has been no reflex stimulation).

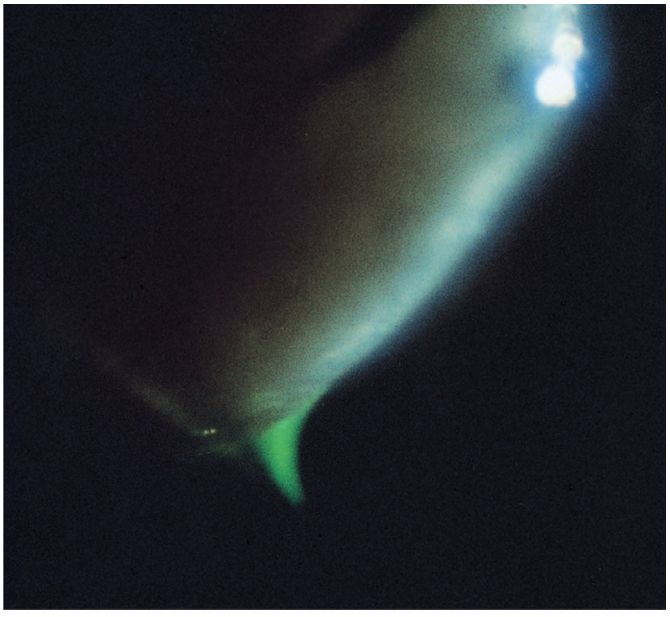


Fig. 9.4 Full inferior tear meniscus stained with fluorescein. (Courtesy Rolf Haberer, Bausch & Lomb Slide Collection.)



Fig. 9.5 Schirmer's test. (Courtesy Timothy Golding.)



Fig. 9.6 Cotton thread tear test. (Courtesy Timothy Golding.)

Hamano et al.[23] applied this test to 1600 asymptomatic polymethyl methacrylate, rigid and soft (hydroxyethyl methacrylate) lens wearers and observed a mean wetting length of 16.9 mm over 15 seconds. This result was no different from that of normal non-lens-wearing subjects, suggesting that from a clinical perspective, contact lenses do not alter tear production in normal subjects. Pult et al.[9] reported that the cotton thread test was not a good discriminator of CLADE in new contact lens wearers.

DISTURBANCES TO TEAR FILM STRUCTURE AND QUALITY

It was established in 1921 that certain structural aspects of the tear film can be assessed clinically by observing the corneal surface in specular reflection.[24] This can be achieved by using the slit lamp biomicroscope by setting the angle of the illumination

arm equal to the angle of the microscope arm (say, 30° to the normal) and observing a thin vertical beam at 30 to ×40 magnification. The limitations of this approach – such as the necessity for using a narrow beam and the generation of heat from the light source – can be overcome by using a wide-field, cold cathode light source, which is available as a hand-held instrument, known as a *tearscope*.[25]

As discussed previously, the component layers of the tear film are extremely thin. The refractive index differences between the air–lipid and lipid–aqueous boundaries cause destructive interference within the lipid layer, resulting in the appearance of coloured fringes, from which the thickness of the lipid layer can be inferred. The aqueous layer of the pre-corneal tear film cannot be observed using this technique because of an insufficient refractive index difference between the aqueous–mucus and mucus–epithelium interfaces.

These coloured fringe patterns, coupled with the general morphological appearance and dynamic characteristics of the lipid layer when viewed in specular reflection, led Guillon and Guillon[26] to devise the following six-category lipid layer classification scheme, with the various appearances ranked in order of increasing lipid layer thickness:

- Open marmoreal ('marble-like') (15–30 nm thickness; observed in 21% of the population) – a static, grey, marble-like appearance with a sparse open meshwork pattern; may represent a contraindication for contact lens wear in some patients because the thin lipid layer may lead to rapid evaporative tear loss (Fig. 9.7).
- Closed marmoreal (30–50 nm; 10%) – a static grey, marble-like appearance with a more compact meshwork pattern; thought to represent a stable lipid layer satisfactory for contact lens wear.
- Flow pattern (50–80 nm; 23%) – also termed 'wave pattern', a dynamic marmoreal appearance, but constantly flowing and changing between blinks; thought to represent a full lipid layer that is generally satisfactory for contact lens wear, although there may be a tendency for excess lipid to accumulate (Fig. 9.8).
- Amorphous pattern (80–90 nm; 24%) – a more or less even pattern with a pale blue appearance; as for flow pattern, the amorphous pattern is thought to represent a full lipid layer that is generally satisfactory for contact lens wear, although there may be a tendency for excess lipid to accumulate.
- First-order colour fringe pattern (90–140nm; 10%) – discrete fringes of brown and blue, superimposed on an amorphous grey background; thought to represent a full lipid layer that may be problematic for contact lens wear (Fig. 9.9).
- Second-order colour fringe pattern (140–180 nm; 5%) – discrete fringes of green and red, superimposed on an amorphous grey background; thought to represent a full lipid layer that will be problematic for contact lens wear

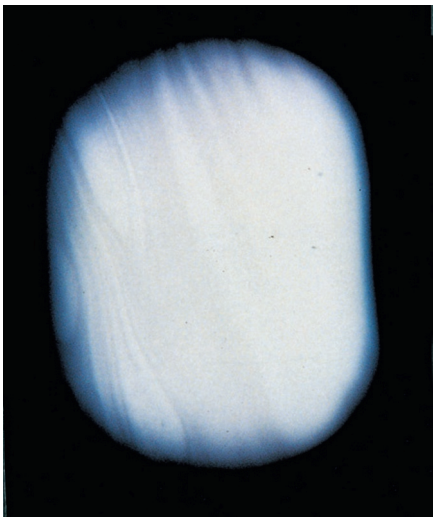


Fig. 9.8 Flow pattern lipid formation viewed in specular reflection. (Courtesy Hilmar Bussaker.)

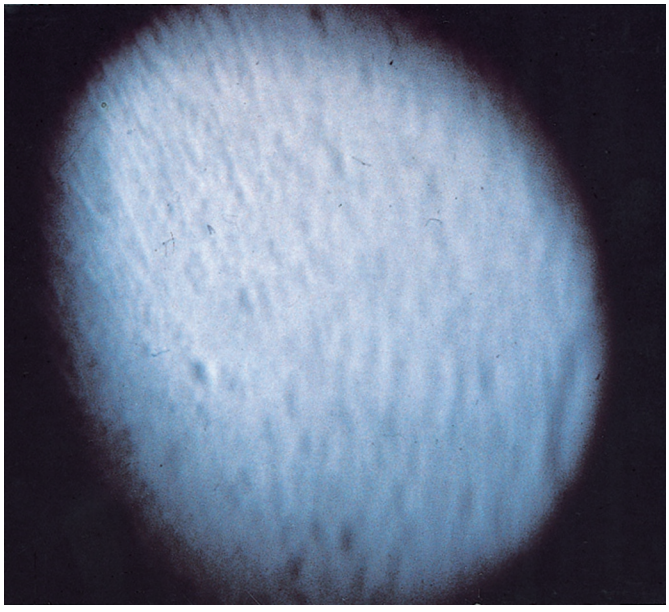


Fig. 9.7 Open marmoreal lipid formation viewed in specular reflection. (Courtesy Hilmar Bussaker.)

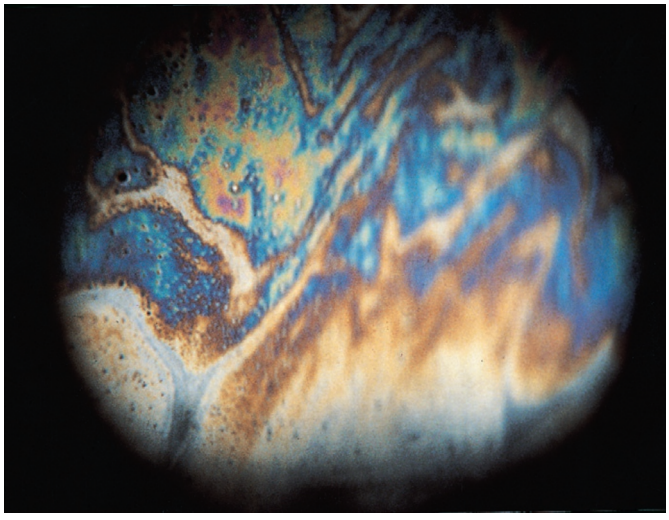


Fig. 9.9 First-order colour fringe lipid pattern viewed in specular reflection. (Courtesy Hilmar Bussaker.)

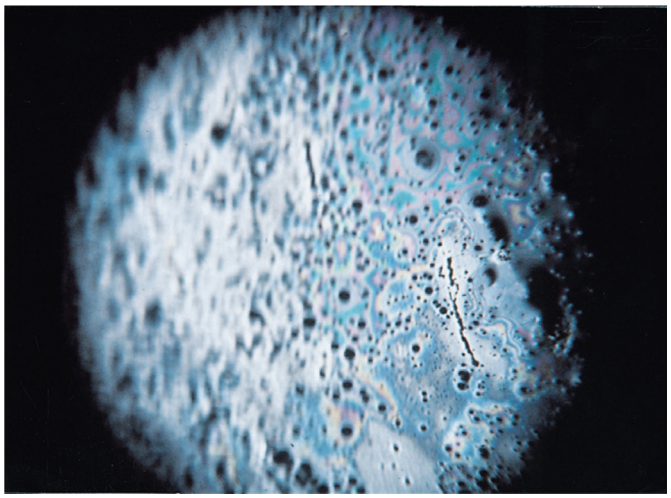


Fig. 9.10 Second-order colour fringe lipid pattern viewed in specular reflection. (Courtesy Hilmar Bussaker.)

because an excess lipid coating on the lens can reduce wettability (Fig. 9.10).

- 'Other' (>180 nm; 7%) – highly variable coloured patterns, sometimes forming as globules or pockets of intense fringe formation (Fig. 9.11), that do not fall comfortably into any of the other categories; probably represent heavy lipid contamination and thus may contraindicate contact lens wear.

The Guillon-Keeler tear film classification system in Appendix B illustrates the appearance of the pre-corneal tear film lipid layer in patients with dark- and light-coloured irides.

Although the aqueous phase of the pre-corneal tear film cannot be observed by using a tearscope, it is often visible on the front surface of a contact lens because the pre-lens lipid layer is generally poorly formed or absent. The thicker the pre-lens lipid layer, the less visible are the aqueous fringes. When aqueous fringes can be observed, it is possible to estimate the thickness of this layer by counting the number of fringes across the field of a tearscope. Fewer than five fringes indicate an aqueous layer thickness of less than 1 μm, and greater than 10 fringes indicate an aqueous layer thickness of 2 μm. An aqueous without fringes is probably more than 3.5 μm thick.

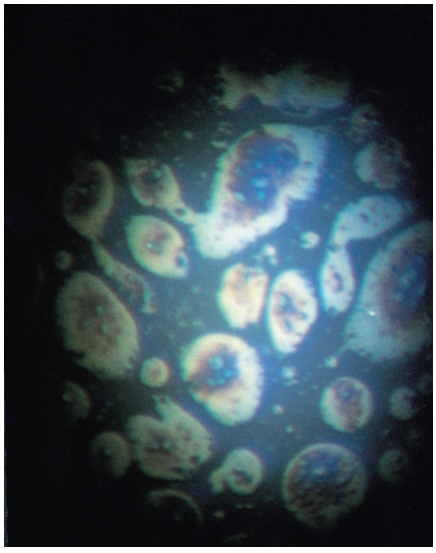


Fig. 9.11 Discrete islands of colour fringes, in the form of lipid globules, viewed in specular reflection. (Courtesy Xavier Llobet, Bausch & Lomb Slide Collection.)

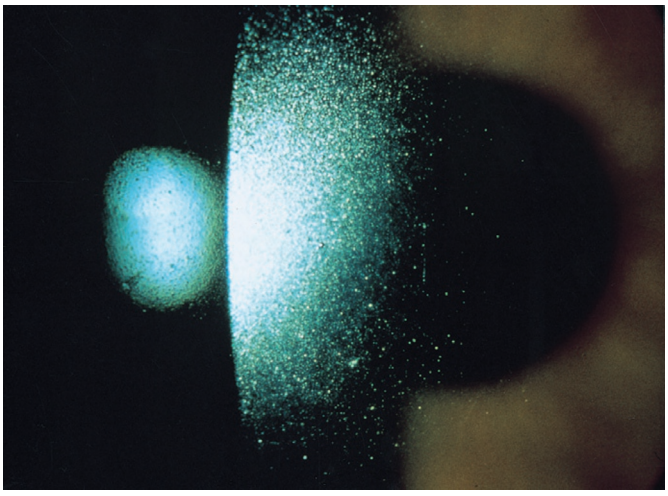


Fig. 9.12 Haze on the surface of a high-Dk rigid lens, observed 4 seconds after a blink. (Courtesy Arthur Back, Bausch & Lomb Slide Collection.)

By using a tearscope, Young and Efron[27] evaluated the structure of the tear film on the surface of a range of hydrogel lenses of various water contents. They observed that the lipid layer was either absent or very thin on all lenses, although there was a tendency for higher-water-content lenses to support a thin lipid layer. The aqueous phase was generally found to be thicker on lenses of higher water content.

As with hydrogel lenses, the lipid layer is extremely thin or absent on the surface of rigid lenses.[28] The aqueous phase over such lenses is also somewhat thin, typically between 2 and 3 μm thick; this variation in thickness is thought to be patient dependent. A poorly wetting hydrophobic surface of a rigid lens takes on a hazy appearance if the surface is allowed to dry (Fig. 9.12). The haziness is thought to be caused by a rapidly drying mucoprotein coating.

The appearance of the tear film on the surface of soft and rigid lenses is shown in Appendix B.

TEAR FILM INSTABILITY

The structural integrity of the pre-lens tear film can be assessed by measuring the elapsed timed from the execution of a normal blink until the tear film breaks up; this is known as the *tear break-up time* (TBUT). The classic method of measuring TBUT by instilling fluorescein into the eye and observing the break-up of the fluorescein pattern cannot be applied to the contact lens–wearing eye because fluorescein will be absorbed into the lens material, thus discolouring (and perhaps destroying) the lens and confounding the estimated time of break-up. In addition, fluorescein is known to destabilise the tear film.

Non-invasive techniques are preferred for measuring break-up of the pre-ocular and pre-lens tear film. This can be achieved by optically projecting a grid pattern on to the cornea and timing how long it takes for the grid to become disrupted. Numerous 'specialist' devices employing this principle have been produced, including the instrument stand-mounted 'NIBUT dome' or 'Mengher's grid'[29] and hand-held devices, such as the keratometer-mounted HIR-CAL grid,[30] the Loveridge's grid[31] and the Tearscope-plus with NIBUT grid attachment.[25]

In the non-lens-wearing eye, the tear film remains stable for at least 30 seconds. In many patients, NITBUT may be considerably greater than this, but such measurements are not possible because few patients can voluntarily refrain from blinking for periods longer than 30 seconds. Young and Efron[27] demonstrated that tear break-up occurs within 3 to 10 seconds on the front surface of hydrogel lenses and that longer pre-lens tear film NITBUTs were generally associated with higher-water-content lenses. This latter finding is consistent with the thicker aqueous layer present on higher-water-content lenses observed by Young and Efron[27] in the same study. The pre-lens tear film NITBUT of rigid lenses typically ranges from 4 to 6 seconds.[32]

Automated techniques for assessing tear film break-up are now available. One example is the Keratograph 5M (OCULUS, Wetzlar, Germany) (Fig. 9.13), which employs an automated tear film scanning process that allows an examiner independent determination of TBUT. The instrument generates a graphic representation of the location on the cornea where tear film break-up occurs; this is referred to as a 'tear map'.[33] Colour coding indicates the regions of break-up: green indicates a stable tear film, yellow indicates a thinning tear film and red indicates tear film regions that are unstable (Fig. 9.14).



Fig. 9.13 Oculus Keratograph 5M. (Courtesy Centre for Ocular Research & Education.)

Optical aberrations created by break-up of the tear film contribute to the decline in image quality observed objectively and psychophysically. Tutt et al.[34] suggested that the decline in image quality that accompanies pre-lens tear break-up may be a direct cause of the blurry vision complaints commonly encountered in patients with lens-induced dry eye.

Reduced NITBUT has been demonstrated to be a good discriminator of contact lens–associated dry eye.[9,35]

OCULAR SURFACE STAINING

Tissue disruption to the surface of the cornea[36] and conjunctiva[37] can occur during contact lens wear as a consequence of disruption of the tear layer. This can be readily detected by instilling fluorescein into the eye and observing the eye in cobalt blue light on a slit lamp biomicroscope. Perhaps the most common manifestation of this problem in patients wearing rigid lenses is 3 & 9 o'clock staining. This is a form of desiccation staining, which may also be observed in association with soft lens wear, particularly in regions where the cornea has become intermittently exposed or in regions of the cornea where the overlying lens has become dehydrated.

Fluorescein staining indicates the presence of disrupted and/or missing superficial cells. Guillon and Maissa[38] reported that lissamine green conjunctival staining could discriminate symptomatic contact lens wearers from asymptomatic wearers. In advanced cases, staining with rose bengal also reveals the presence of devitalised or dead superficial cells. Itoh et al.[39] reported

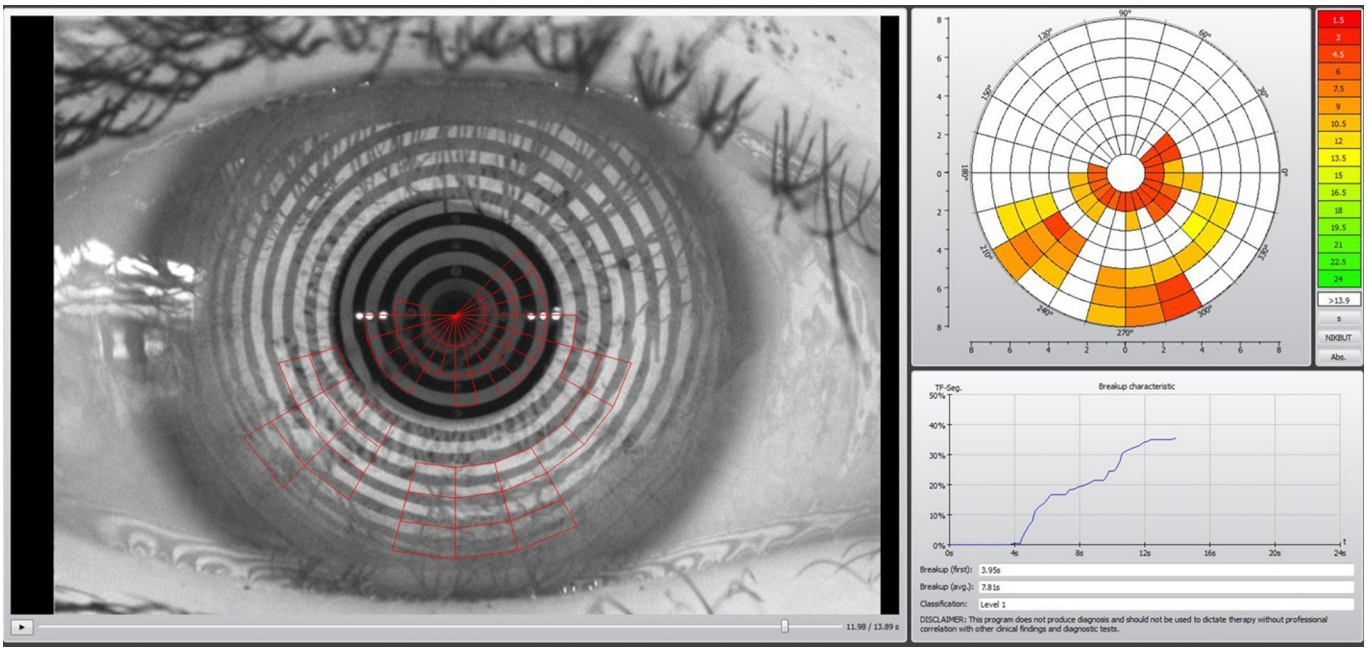


Fig. 9.14 Tear break-up time as measured with the Oculus Keratograph 5M. The heat map on the right identifies the areas of tear break-up as auto-detected by the K5M. The colour coding corresponds to the time until break-up, using a 'traffic light–based' scale from very short (red) to very long (green). The associated sections of break-up on the recorded video (left panel) are shown by the red sections. (Courtesy Centre for Ocular Research & Education.)

that rigid lens–induced tear film instability is associated with damage to the ocular surface epithelium and mucus layer. The topic of ocular surface staining is dealt with in more detail in Chapter 11.

LID-WIPER EPITHELIOPATHY

Constant rubbing of that portion of the upper eyelid in apposition with the lens front surface – the 'lid wiper' – when blinking during lens wear is thought to be a source of discomfort and dry eye sensation. Damage to this tissue is referred to as *lid wiper epitheliopathy*; refer to Chapter 5 for a detailed account of this condition.

LENS DEPOSITS

Numerous factors, many of which are interactive, are involved in the formation of deposits on the front or back surface of contact lenses. These factors include:

- lens wear modality;
- lens replacement frequency;
- bulk chemical composition of the lens material;
- lens water content;
- physico-chemical nature of the lens surface (e.g. ionicity);
- chemical composition of lens maintenance solutions;
- adequacy of lens maintenance procedures (a measure of patient compliance);
- hand contamination;
- proximity to environmental pollutants;
- intrinsic properties of the tears of the patient.

The most common tear-derived components of lens deposits are proteins and lipids.

Visible lens deposits take months or years to form and are, thus, rarely encountered in modern contact lens practice in view of the fact that lenses (in particular soft lenses) are disposed of and replaced regularly – typically daily, weekly, 2-weekly or monthly.

It is clear that proteins and lipids from the tears can deposit on contact lenses within minutes of insertion. Although these rapidly forming deposits cannot be seen and do not generally compromise vision or comfort over this time scale, they can reduce lens surface wettability.[40]

Both tear quality and composition will have a bearing on deposit formation. An excess of a particular tear component, coupled with compromised structural integrity of the tears leading to rapid tear break-up and excessive surface drying, is an intrinsic factor thought to be conducive to deposit formation. Indeed, there is some clinical evidence to support the notion that lens deposition is a particular problem in patients with dry eye wearing contact lenses.[41]

THINNING OF THE POST-LENS TEAR FILM

The tear film between a contact lens and the cornea can also be viewed by specular reflection by using the slit lamp biomicroscope.[42] As for the pre-lens tear film, the thickness of the post-lens tear film can be inferred from the appearance of the specular reflection; an amorphous appearance indicates a relatively thick, aqueous film, and coloured patterns and striated formations (texture without colour) indicate thinner tear films (Fig. 9.15). Patterned appearances occur in 25% of soft lens wearers, irrespective of lens type. Although patterned

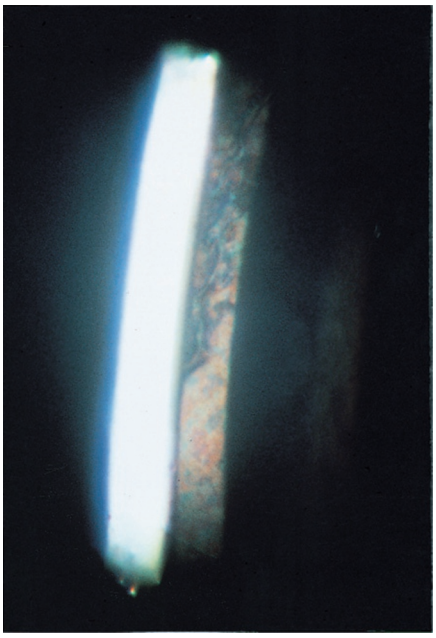


Fig. 9.15 Colour fringe patterns in the post-lens tear film observed in specular reflection. (Courtesy Adrian Bruce, Bausch & Lomb Slide Collection.)

appearances are associated with reduced lens movement, they are unrelated to dryness symptoms.[42]

There are conflicting reports in the literature as to the true thickness of the post-lens tear film. Lin et al.[43] used pachometry to determine post-lens tear film thickness beneath a 58% water content hydrogel lens to be 11 to 12 μm. By using a reflection spectra technique, Nichols and King-Smith[44] found a post-lens tear film thickness of 2 to 3 μm beneath 'traditional' hydrogel lenses and 1 to 2 μm beneath silicone hydrogel lenses. Brennan et al.[45] demonstrated that thinner post-lens tear films are associated with a lower post-lens tear exchange.

Symptoms

Of all the symptoms experienced by contact lens wearers, that of 'dryness' is reported most frequently. This problem, which was first reported in the 1980s,[46,47] persists even today. In one of the earliest surveys of contact lens–associated dryness,[47] only 25% of over 100 contact lens wearers stated that they had never experienced this symptom. Brennan and Efron[47] reported that in a group of contact lens wearers, 100% of females using oral contraceptives reported experiencing 'dryness' at times versus 63% of females not using oral contraceptives and 76% of males; these differences were statistically significant, suggesting possible hormonal influences on contact lens associated dryness symptoms.

More recent studies are reporting similar levels of dryness symptoms. By using a self-administered questionnaire, Young et al.[48] found that 44% of 932 contact lens wearers in the United Kingdom were experiencing dry eye symptoms. Nichols et al.[6] surveyed a mixed population of 893 patients and found that contact lens wearers were most likely to report dry eye disease (52.3%), followed by spectacle wearers (23.9%) and clinical emmetropes (7.1%). Adjustment for age and gender showed that contact lens wearers (adjusted odds ratio = 12.37; 95% confidence interval = 7.55–20.26) and spectacle wearers

(adjusted odds ratio = 2.06, 95% confidence interval = 1.12–3.80) were more likely than emmetropes to report dry eye problems. After adjustment for age and gender, contact lens wearers were shown to be more likely to experience frequent symptoms and an increase in symptoms throughout the day ($F = 51.4$; $p < 0.0001$).

Greiner and Walline[49] observed that paediatric contact lens wearers have fewer complaints about dry eyes compared with adult contact lens wearers, and this may be attributed to improved tear film, differences in reporting of symptoms or modality of contact lens wear.

A major difficulty in assessing the symptom of 'dryness' is that there may be many stimuli that elicit this sensation; that is, it cannot be assumed that the cause of a patient symptom of 'dryness' is necessarily caused by the eye being dry.[5] Additionally, not all contact lens wearers reporting dryness have objective signs of dry eye disease; Young et al.[50] reported that 23% of contact lens wearers with dry eye symptoms did not exhibit typical clinical signs of dryness.

Because there are no specific 'dryness receptors' in human tissue, ocular dryness must be a response to specific coding of afferent neural inputs. Besides an actual dry eye, reports of 'dryness' may arise from the neural misinterpretation of stimuli that are unrelated to dry eye, such as vasodilation induced by mechanical irritation of ocular tissues by the lens. Lowther[51] reported a more rapid tear break-up (lower TBUT) in a group of contact lens wearers with dry eye symptoms versus a group of contact lens wearers without dry eye symptoms, but Bruce et al.[52] failed to demonstrate such an association in a similar experiment. Little and Bruce[42] found no relationship between post-lens tear film morphology and hydrogel lens comfort.

A prudent approach in dealing with a tentative diagnosis of dryness associated with contact lens wear is to apply a questionnaire specifically designed for this condition. Two such questionnaires that have gained considerable traction in recent times are considered here.

CONTACT LENS DRY EYE QUESTIONAIRRE-8

The CLDEQ-8[53] is a validated and shortened version of a previously published longer version.[54] The CLDEQ-8 score is determined based on responses to questions relating to the following symptoms:

- Frequency of dryness.
- Late day intensity of dryness.
- Discomfort.
- Blurry vision.
- Frequency of 'closing eyes to rest them'.
- 'Removing contact lenses to relieve discomfort'.

The sum of CLDEQ-8 scores indicates the severity of symptoms, whereby a higher score represents greater severity, up to a maximum score of 37 points.

Chalmers et al.[55] determined that the cutoff score to identify highly symptomatic soft contact lens wearers is 12 points or greater. A 'clinically important difference' in the CLDEQ-8 score was determined to be ±3 points.

CONTACT LENS USER EXPERIENCE SCALES

The Contact Lens User Experience (CLUE) system[56] has been designed to assess patient evaluations of contact lenses. It was developed using psychometric methods, such as factor analysis and item response theory. The CLUE scales focus around four domains: comfort, vision, handling and packaging. These scales have been found to provide precise and reliable assignment of scores detailing the subjective experiences of those using contact lenses.

Role of ethnicity

Tran et al.[57] explored the relationships between length of contact lens wear, degree of corneal staining and severity of dryness symptoms to determine whether these relationships differ between Asians (n = 180) and non-Asians (n = 215). Asian soft lens wearers reported more severe dryness symptoms and demonstrated more severe corneal staining overall compared with non-Asians. Among non-Asians, dryness symptoms were less severe, on average, with increased years of lens wear and more severe in the presence of corneal staining. Dryness severity was not related to years of lens wear or corneal staining among Asians.

Compliance among patients with CLADE

Ramamoorthy and Nichols[58] sought to determine if compliance factors are associated with CLADE. A compliance survey was administered conducted on 50 subjects with CLADE and 50 without CLADE. The compliance survey queried aspects of lens care, rub and rinse practices, lens and lens case replacement frequency, solution replacement and sleeping with lenses. Overall compliance rates were low for several variables; however, no compliance factors were associated with CLADE status, except that lens care was rated as more difficult by the CLADE group ($p = 0.004$).

Pathology and aetiology

Alterations to tear chemistry, composition and structure may be responsible for various adverse signs and symptoms during contact lens wear. Certain aspects of tear physiology during contact lens wear have been explored through the development and application of existing and experimental methodologies. The results of some of these tests that have more immediate clinical relevance shall be reviewed here. In cases where our understanding of the basis or tear film dysfunction during contact lens wear is poorly understood, various theories have been developed; these shall also be reviewed.

The TFOS DEWS II definition of dry eye highlights tear film instability, hyper-osmolarity, ocular surface inflammation and damage, and neurosensory abnormalities as playing key roles in the aetiology of this condition. These factors will be considered in turn.

TEAR FILM INSTABILITY

Considered broadly, 'tear film instability' can refer to any disturbance to the normal homeostasis of the tear film and can manifest in a variety of ways. Disturbances can be observed in tear composition, turnover, break-up and acid–base balance.

Tear composition

When contact lenses are worn for the first time, the increased reflex lacrimation tends to dilute the concentration of those

components of the tears that are not secreted from the lacrimal gland (i.e. serum-derived components). This phenomenon is particularly evident during adaptation to rigid lenses, which induce a more intense lacrimation response.

Certain components of tears alter during inflammation, metabolic stress and mechanical trauma, and, in many cases, these changes are linked to contact lens wear. For example, Vinding et al.[59] reported decreased tear concentrations of secretory immunoglobulin A in long-tern wearers of daily-wear and extended-wear soft contact lenses, a finding thought to indicate a higher prevalence of sub-clinical corneal and conjunctival inflammation in such patients. Schultz and Kunert[60] reported increased levels of interleukin-6 in basal tears of contact lens wearers versus non–lens wearers.

Fullard and Carney[61] noted an increase in the ratio of lactate dehydrogenase (LDH) to malate dehydrogenase during soft lens wear, and Imayasu et al.[62] observed increased LDH levels in the tears of rabbits fitted with contact lenses of low oxygen transmissibility. Such findings are consistent with the known anaerobic shift in the corneal epithelium as a result of hypoxia during lens wear.

Nichols and Green-Church[63] used variety of proteomic approaches to compare tear samples obtained from subjects with contact lens–related dry eye and a matched control group of asymptomatic contact lens wearers. Beta-2 microglobulin, proline rich 4, lacritin and secretoglobin 1D1 were found to be decreased and secretoglobin 2A2, serum albumin, glycoprotein 340 and prolactin-inducible protein were found to be increased in the dry eye state. These changed tear protein profiles suggest altered tear secretion and may be associated with increased susceptibility to infection.

Mucins are thought to play integral roles in ocular surface lubrication, anchoring of the aqueous, stabilizing the lipid components of the tear film and eliminating foreign bodies and pathogens, with potential involvement in cell cycle mediation and apoptotic activity of ocular surface epithelia.[64] Ocular mucins are of secreted and membrane-associated types. Secreted mucins may be of large gel-forming type or small soluble mucins (e.g. MUC5AC and MUC7). Membrane-associated mucins, such as MUC1 and MUC4, are a major component of the glycocalyx. They are thought to render structural support to the microplicae and mediate epithelial cell cycle and apoptotic activity. Symptomatic contact lens wearers exhibit significantly decreased MUC5AC reactivity.[65] Increased friction might follow from insufficient mucins or an altered composition of the resident mucins at the ocular surface. This, in turn, could contribute to contact lens–associated ocular discomfort.

Levels of nerve growth factor levels in the tear film have been found to be elevated in contact lens–related dry eye, which is thought to occur in response to anti-inflammatory factors, such as transforming growth factor-β_1.[66]

When a small sample of tears is taken from the eye and allowed to dry on a microscope slide, fern-like crystallisation patterns may form and indicate certain characteristics of the tear film, including the salt-to-macromolecule ratio, lipid contamination of mucus and altered tear rheology.[67] A well-structured ferning pattern (Fig. 9.16) represents a good or even excessive supply of mucus, whereas a disrupted pattern with very few or absent ferns (Fig. 9.17) may indicate mucus deficiency. Kogbe and Liotet[68] have recommended that the tear ferning test be used in contact lens practice to diagnose marginal dry eye as the cause of contact lens intolerance.

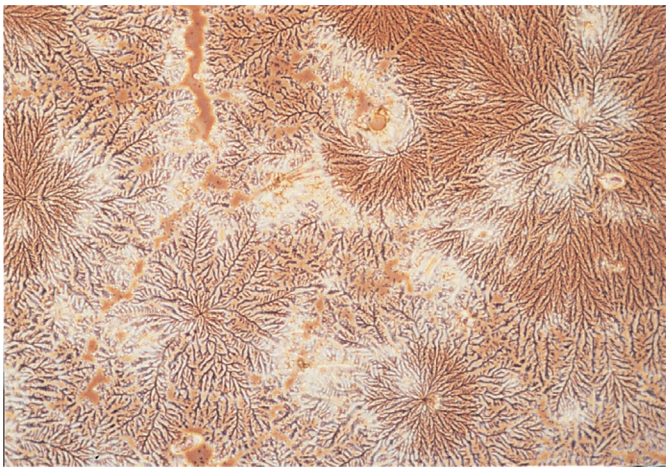


Fig. 9.16 Well-structured tear ferning pattern. (Courtesy Timothy Golding.)

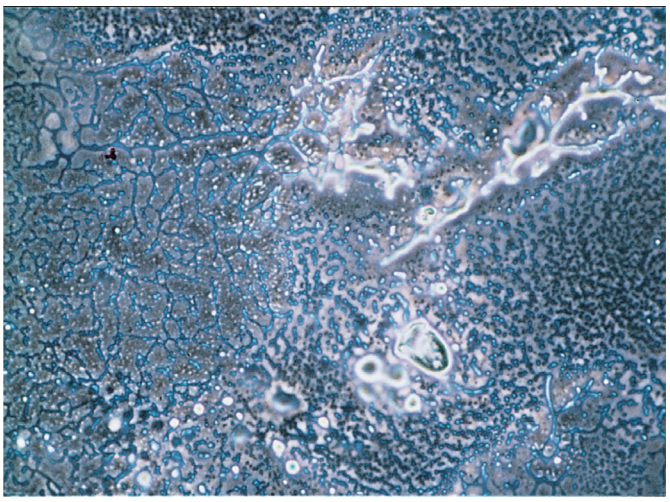


Fig. 9.17 Tear sample displaying an absence of ferning. (Courtesy Timothy Golding.)

Ravazzoni et al.[69] reported that the tear ferning test showed sensitivity of 100%, specificity of 87% and diagnostic precision of 97% when performed after 1 month of contact lens wear, indicating that this test may be useful for predicting contact lens tolerance in a clinical setting. However, Evans et al.[70] reported that tear ferning demonstrates limited sensitivity and specificity for the prediction of ocular surface comfort in both contact lens wearers and non–lens wearers.

Tear turnover

The turnover rate of the tear film is about 16% of the total tear volume per minute.[71] The main determinants of tear turnover are aqueous tear production – primarily from the main lacrimal gland – and tear loss via drainage and/or evaporation. Tear turnover rate can be determined by measuring the decay over time of the fluorescence of tears that have been stained with fluorescein. Such studies have failed to detect any contact lens–induced change in tear production, except during the initial adaptation phase, where increased lacrimation is observed. Tomlinson and Cedarstaff[72] found that tear evaporation is increased during wear of all contact lens types. This is presumably caused by a

compromise of the integrity of the lipid layer of the tear film during lens wear.

Chang and Chang[73] demonstrated that tear clearance in patients with contact lens–associated papillary conjunctivitis is delayed. They proposed that delayed tear clearance might increase the protein and inflammatory mediator concentrations in the tear film and contribute to the pathogenesis or aggravate the severity of contact lens–associated papillary conjunctivitis.

Tear break-up

The precise mechanism leading to tear film break-up is not known. The most popular theory is that advanced by Holly.[74] According to this theory, tear break-up occurs when lipid, which is hydrophobic in nature, migrates down to the mucus layer and compromises the hydrophilicity of the epithelial surface. Tears recede from this region of poor wettability and a dry spot forms. As the tears continue to recede, there is further inter-mixing of lipid and mucus at the receding edge, and the field of hydrophobicity increases, thus increasing the dry area – and the process continues. Alternative theories propose that tear break-up is caused by rupture of the mucus layer[41] or disturbance of the superficial epithelial glycocalyx.[75]

Figure 9.18 is an illustration of the clinical appearance of the thinning and breaking up of the tear film using a projected grid, together with a schematic representation of the process of disruption of the tear film according to the model of Holly.[74]

Gorla and Gorla[76] adopted a theoretical approach in an attempt to determine the reason for pre-corneal tear film break-up. They analysed non-linear thin film rupture by investigating the stability of tear films in response to finite amplitude disturbances. The dynamics of the liquid film was formulated using Navier–Stokes equations, which included a body force term attributable to van der Waals' attractions. They managed to solve the governing equation by using the finite difference method as part of an initial value problem for spatial periodic boundary conditions.

The mechanism of tear break-up on the surface of contact lenses must be different from that on the surface of the eye because of the absence of properly formed lipid or mucus layers on the lens surface. Rapid pre-lens tear break-up times[27] suggest that tear thinning occurs as a result of evaporation[77] and lateral surface tension forces that draw tear fluid from the lens surface into the surrounding tear meniscus at the lens edge. Tear break-up is likely to be expedited by the presence of surface deposition.

Tear acid–base balance (pH)

Theoretically, one might expect an acidic shift in tear pH with contact lens wear as a result of retardation by the lens of the normal carbon dioxide efflux into the atmosphere; the carbon dioxide would then dissolve in the tears and reduce to carbonic acid, inducing an acidic pH shift.

Although Norn[78] reported that all lens types do induce an acidic pH shift during lens wear, other studies have failed to arrive at a consensus on the direction of the pH shift (if any) resulting from contact lens wear. Tapasztó et al.[79] reported an acidic shift during rigid lens wear, but Carney and Hill[80] found no such change. With soft lenses, various authors have reported acidic shifts,[81] alkaline shifts[82] and no shifts in pH.[79] Carney et al.[83] reported that the buffering capacity of tears (i.e. the intrinsic capacity of tears to dampen down pH change) is unaffected by lens wear.

TEAR HYPER-OSMOLARITY

Osmolality is now considered the gold standard diagnostic test,[84,85] in addition to being an aetiological factor, associated with dry eye disease, in general, through proinflammatory mechanisms. Gilbard et al.[86] suggested that 'decreased corneal sensitivity, with a resultant decrease in tear secretory rates, is the most likely cause for increased tear-film osmolality…'. Nichols and Sinnott[87] reported that osmolality was significantly

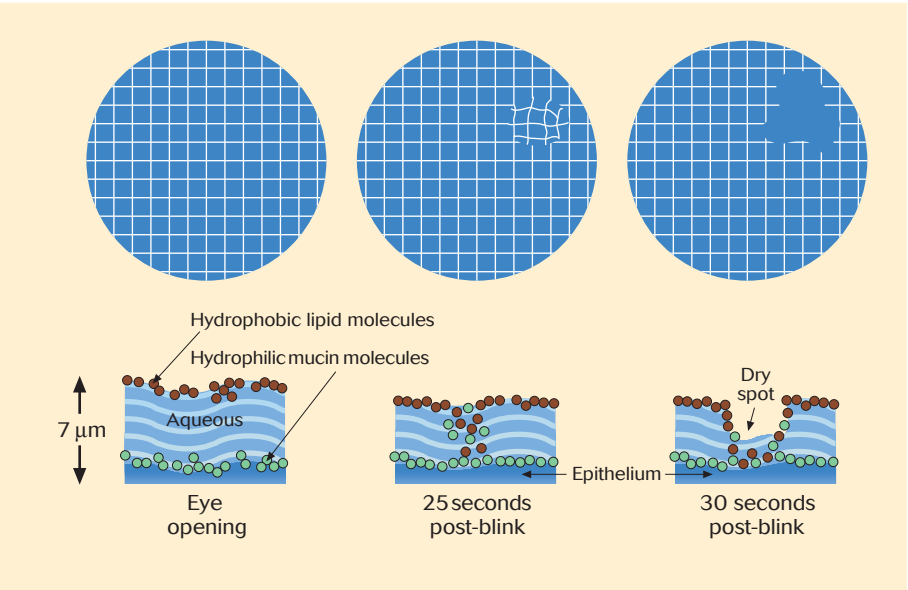


Fig. 9.18 Schematic representation of the intact tear film observed at eye opening (left), followed by tear thinning at 25 seconds (middle) and tear break-up at 30 seconds (right). The top row illustrates this sequence as observed using a projected grid (non-invasive tear break-up time measurement). The bottom row illustrates how a dry spot forms.

related to dry eye status ($p < 0.005$). The average osmolarity in a group of contact lens wearers exhibiting dry eye signs and symptoms was 308 ± 32 mOsM, compared with that in a contact lens–wearing group without dry eye (297 ± 32 mOsM). These authors suggested that a viable explanation for this hyperosmolar shift might be related to tear film evaporation. They observed that contact lens wearers with dry eye signs and symptoms had a reduced tear film lipid layer thickness, rendering them more susceptible to evaporation of the pre-lens tear film than in lens wearers without dry eye. An increase in tear film evaporation may lead to a more concentrated tear film and a resultant increased osmolality.

Until recently, tear osmolarity measurement was a sophisticated laboratory procedure unsuitable for routine clinical use.[88] A new clinical test that is capable of in-office measurement of tear film osmolarity is the TearLab Osmolarity Test[88] (Fig. 9.19). This instrument uses a temperature-corrected impedance measurement to provide an indirect assessment of osmolarity. The tip of the hand-held 'pen' is place in the lower lacrimal river for up to 30 seconds to obtain a reading (Fig. 9.20). After applying a lot-specific calibration curve, osmolarity is calculated and displayed as a quantitative numerical value. However, Khanal and Millar advise that three consecutive readings are required with the TearLab to obtain a reliable measure of tear osmolarity, which is potentially problematic because a separate, expensive, non-reusable measurement chip is required for each reading. The variation in recorded tear osmolarity makes it difficult to use the technique for the diagnosis of mild dry eye.[89]



Fig. 9.19 TearLab Osmolarity test. (Courtesy TearLab Corporation.)

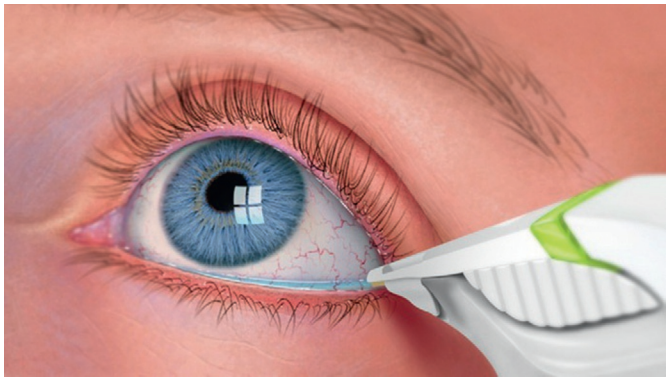


Fig. 9.20 Method of obtaining a reading of tear osmolarity by placing the pen of the TearLab into the lower lacrimal river. (Courtesy TearLab Corporation.)

Immediately after the insertion of either rigid[90] or soft[91] lenses, reflex tearing creates a hypo-osmotic tear film that returns to normal soon thereafter. Martin.[91] observed symmetrical binocular changes in tear osmolarity during monocular lens wear, suggesting that that bilateral reflex lacrimation is responsible for post-lens insertion changes in tear osmolarity.

OCULAR SURFACE INFLAMMATION

Evidence from fundamental physiological research indicates that CLIDE may have an inflammatory basis. Alzahrani et al.[8] investigated longitudinal changes in Langerhans cell density (LCD) in the human cornea and conjunctiva during asymptomatic and symptomatic contact lens wear. Twenty-five participants with CLIDE and 35 without CLIDE (NO-CLIDE), diagnosed using a range of symptom questionnaires and objective tests (tear film break-up, cotton thread tear test and corneal staining), were enrolled. The central cornea and nasal bulbar conjunctiva were examined by using a laser scanning confocal microscope at baseline and after 1, 4 and 24 weeks wear of daily disposable hydrogel contact lenses. Twenty-three non-contact lens-wearing controls were also examined.

In the cornea, mean and standard error of the mean LCD were greater after 1 week of lens wear in CLIDE (55 ± 7 cells/mm^2) versus NO-CLIDE (43 ± 4 cells/mm^2) ($p = 0.041$) and controls (27 ± 4 cells/mm^2) ($p < 0.001$). LCD was also greater in NO-CLIDE versus controls ($p = 0.010$). At week 4, LCD was greater in CLIDE (41 ± 6 cells/mm^2) versus controls (27 ± 4 cells/mm^2) ($p = 0.004$). There were no other significant differences between groups at weeks 4 or 24. In the conjunctiva, LCD was greater after 1 week of lens wear in CLIDE (17 ± 1 cells/mm^2) ($p = 0.003$) and NO-CLIDE (17 ± 3 cells/mm^2) ($p = 0.001$) versus controls (7 ± 1 cells/mm^2). There were no significant differences between groups at weeks 4 or 24. The authors concluded that the initial transient increase in corneal and conjunctival LCD in CLIDE suggests an inflammatory component in the aetiology of this condition[8] (Fig. 9.21).

Alzahrani et al.[92] examined the lid wiper of participants in their study and observed an increase in LCD in those with CLIDE, suggesting that inflammatory changes are also occurring in the eyelids of symptomatic lens wearers.

Dogan et al.[93] also observed an increased LCD in the cornea of patients with CLIDE.

OCULAR SURFACE DAMAGE

There are numerous forms of ocular surface damage resulting from contact lens wear; indeed, this entire book documents such changes. However, one form of ocular surface damage of direct relevance to CLIDE is the effect of lens wear on goblet cell density (GCD), given the role of goblet cells in producing the mucin component to the tear film.

Colorado et al.[94] investigated longitudinal changes in GCD in daily disposable hydrogel contact lens wearers who did develop symptoms of dry eye and those who did not. Sixty healthy individuals fitted with lenses and 23 age-balanced non-lens-wearing controls underwent assessment of symptoms, non-invasive TBUT, ocular surface integrity and tear volume

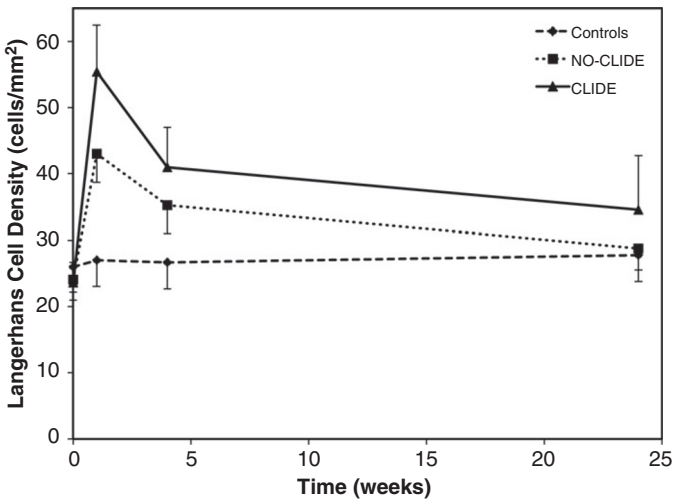


Fig. 9.21 Langerhans cell density in the cornea of patients with contact lens–induced dry eye (CLIDE) and those without CLIDE (NO-CLIDE) and control participants, over 24 weeks. Error bars indicate mean ± standard error. (After Alzahrani Y, Colorado LH, Pritchard N, Efron N. Longitudinal changes in Langerhans cell density of the cornea and conjunctiva in contact lens–induced dry eye. Clin Exp Optom 2017;100:33–40.)

(phenol red thread test). Laser scanning confocal microscopy and conjunctival impression cytology were used to assess GCD at baseline and follow-up visits at 1 week and 1 and 6 months.

After 1 week, all lens wearers were categorised as those who were symptomatic and those who were not. The global mean GCD of the 83 participants at baseline (before lens wear) was 476 ± 41 and 467 ± 52 cells/mm^2 using confocal microscopy and impression cytology, respectively. After 6 months of lens wear, GCD was reduced by approximately 13% and 29% in asymptomatic (N = 29) and symptomatic (N = 17) lens wearers (all $p < 0.001$), respectively, observed with both techniques. The authors concluded that contact lens wear induces a reduction in GCD over 6 months, which is exacerbated in those with dry eye symptoms.

On the basis of a study of 230 patients with CLADE, Kumar et al.[95] suggested that conjunctival impression cytology correlates better than Schirmer's and TBUT with dry eye symptoms and, as such, may be the most appropriate test for the evaluation of dry eye in contact lens wearers.

NEUROSENSORY ABNORMALITIES

The secretory activity of the main lacrimal gland is regulated by autonomic sympathetic and parasympathetic nerves, whose activity is regulated by reflex influences from sensory neurons supplying the ocular surface. Parasympathetic innervation is more extensive. Very little is known about the neural control of accessory lacrimal glands, but it appears to be similar to that of the main lacrimal gland. Although nerves are present around the meibomian glands, there are no studies examining the role of sensory or autonomic nerves and their neurotransmitters in regulating the holocrine secretion of the meibomian gland.[2]

A 'feedback model' has been proposed to explain the pathogenesis of dry eye.[96,97] This theory suggests a link between ocular surface damage and lacrimal gland function. Specifically, it has been proposed that damage to the ocular surface creates a negative feedback loop, which results in damage to the lacrimal gland. One may further surmise that the chronic sub-clinical ocular surface damage caused by contact lens wear sends negative feedback signals to the lacrimal gland, which, in turn, induces or exacerbates dry eye pathology and symptomatology.

Treatment

Most of the strategies that are applied to alleviating signs and symptoms of dryness in the non-lens-wearing eye can also be applied to the eye during contact lens wear. This section will review these strategies, with particular emphasis on their application in contact lens wear.

CHOICE OF CONTACT LENS

The most fundamental choice to make when attempting to solve a contact lens–related dry eye problem is whether to fit soft or rigid lenses. This choice will depend on a number of factors, such as the precise nature of the problem. For example, rigid lens-induced 3 & 9 o'clock staining can be solved by changing the patient from rigid to soft lenses, to prevent epithelial drying at the 3 & 9 o'clock corneal positions.

Efron and Brennan[98] reported that patients wearing hydrogel lenses are more likely to complain of 'dryness' the more the lens has dehydrated; however, other studies[99,100] found that such associations were weak or absent. Notwithstanding these equivocal findings – and uncertainty as to the pathophysiological meaning of the subjective complaint of dryness, as discussed earlier – it is possible that some patients will be most comfortable wearing a hydrogel lens that dehydrates the least. Research, to date, has failed to reveal the material characteristics that determine hydrogel lens dehydration in-eye, so practitioners must rely on comparative date published in the literature.[101]

A number of authors have claimed that refitting hydrogel contact lens wearers with silicone hydrogel contact lenses reduced the frequency and severity of dryness symptoms in many subjects;[102-104] however, Fonn and Dumbleton[105] reported no difference in dryness symptoms between subjects wearing hydrogel and those wearing silicone hydrogel lenses.

Fitting of daily disposable lenses has been claimed to minimise dry eye symptoms. Significantly better end-of-day dryness was reported by Lazon de la Jara et al.[106] for one lens type (senofilcon A) by implementing a daily lens replacement schedule than either (1) 2-week replacement using care systems containing polyhexamethylene biguanide or hydrogen peroxide or (2) 4-week replacement using polyquad-based solutions. This improvement is probably attributable to two factors: (1) avoiding long-term build-up of surface deposits and (2) the elimination of contact lens care solutions. Hickson-Curren et al.[107] reported that the prevalence of dryness symptoms was decreased from 60% to 41% ($p < 0.0001$) after refitting patients wearing reusable contact lenses with daily disposable lenses.

CHOICE OF CONTACT LENS CARE SOLUTIONS

Current generation multipurpose soft lens disinfecting solutions have been formulated to improve comfort, alleviate dryness symptoms, enhance water retention and improve surface

wetting properties of contact lenses. Currently available lens care solutions incorporate different wetting agents, such as a surfactants or ocular demulcents. The most common surfactants found in lens care solutions consist of two distinct groups – poloxamines sold under the trade name 'Tetronic' and poloxamers sold under the trade name 'Pluronic'. Current or previous ocular demulcents found in lens care solutions include hydroxypropyl methylcellulose and propylene glycol.[108] Examples of such lens care systems are provided below.

Opti-Free Replenish (Alcon, Fort Worth, Texas, USA) is designed to enhance lens comfort by retaining moisture on the lens surface. It contains Tetronic 1304, a surfactant that helps lenses retain moisture, and C9-ED3A (nonanoyl ethylenediaminetriacetic acid), a novel surface-active wetting agent. This combination of ingredients forms the proprietary reconditioning system trademarked as 'TearGlyde'. These components apparently work together with natural tears to retain moisture at the lens surface during the course of the day.[108]

Focus (SoloCare) Aqua (Aquify in the USA) (CIBA Vision, Duluth, Georgia, USA) includes dexpanthenol (which acts as a wetting and lubricity-enhancing agent) and sorbitol (which is used to aid lens wetting). Sorbitol, in combination with dexpanthenol, is the basis for the 'hydrolock effect'.

Biotrue (Bausch & Lomb, Rochester, New York, USA) contains hyaluronan (also known as *hyaluronic acid* or *sodium hyaluronate*) as the primary lubricant. Sodium hyaluronate is the sodium salt of hyaluronic acid, which is a naturally occurring disaccharide biopolymer. Hyaluronic acid is a structural polysaccharide composed of repeating units of N-acetylglucosamine and glucuronic acid. It has considerable viscoelastic properties and a high capacity to imbibe water. Sodium hyaluronate solutions strongly adhere to the mucin layer of the tear film, creating a persistent water-retaining layer that resists evaporation.

Hydrogen peroxide solutions are considered the gold standard for disinfecting lenses. However, when residual peroxide is present on the lenses in sufficiently high concentration, it can be toxic to the cornea and can cause discomfort unless neutralised to a concentration of less than 100 parts per million (ppm; the subjective sensitivity threshold range being 50–300 ppm). Nevertheless, when peroxide-based systems are used at the right concentration, studies show that they can provide good comfort in contact lens wearers.

RE-WETTING DROPS

A commonly used strategy in the management of contact lens–related dry eye is to supplement the tear film with viscous substitutes and gels. The most popular form of delivery of these agents is via the periodic instillation of re-wetting drops; alternative delivery systems include ointments and inserts (solid pellets that dissolve slowly over time),[109,110] loading contact lenses (by pre-soaking) with phospholipids[111] or via controllable release of hydroxypropyl methylcellulose[112] or hyaluronic acid[113] by using a molecular imprinting strategy on contact lenses.

Golding et al.[114] found that re-wetting drops improve pre-lens tear film stability for a period of only 5 minutes after instillation and that saline performs no differently from specially formulated products containing viscoelastic lubrication agents. The same authors[115] also found that saline drops provide short-term symptomatic relief that is indistinguishable from that of re-wetting drops. None of these solutions were found to reduce lens dehydration. From these studies, it can be surmised that there is a psychological basis, rather than a physical or physiological basis, for the perception of long-term symptomatic relief (i.e. enhanced comfort for greater than 5 minutes) provided by saline or re-wetting drops.

Caffrey and Josephson[116] evaluated the performance of 10 different commercially available re-wetting drops and found little difference between them, except that non-preserved solutions were preferred to those containing preservatives.

Calvão-Santos et al.[117] compared the efficacy of three different artificial tears – each acting primarily in one of the three tear film layers: lipid, aqueous and mucin – in enhancing tear film quality and symptomatology in patients with dry eye symptoms resulting from external causes. They found that all artificial tear formulations were efficient in improving NITBUT and alleviating symptoms.[117]

Stahl et al.[118] conducted a study to determine whether hypo-osmotic saline drops can improve contact lens–associated discomfort and dryness by decreasing contact lens osmolality. Fifteen symptomatic subjects wore Lotrafilcon A lenses bilaterally for 6 hours on two different days. According to randomisation, hypo-osmotic (280 mmol/kg) or hyper-osmotic (380 mmol/kg) saline drops were applied four times during each day, and ocular symptoms, tear film and contact lens parameters and contact lens osmolality were assessed. Osmolality tended to be lower with the use of hypo-osmotic saline. The authors suggested that hypo-osmotic drops have the potential to decrease contact lens osmolality, which, in turn, may help improve ocular comfort.

SOFT LENS SOAKING

Based upon the observation of Efron and Brennan[98] that lens dehydration leads to complaints of dryness, it stands to reason that brief removal of the lens from the eye and re-hydration in saline solution before re-insertion can redress the problem. This approach was tested by Papas et al.[119] in an experiment in which subjects temporarily removed lenses mid-way through a 10-hour wearing period. Some subjects soaked and then re-inserted the lens, whereas other subjects were given a brand new lens.

The authors observed that there was a brief, transient improvement in comfort when the same lens, a soaked lens, or a new lens was inserted mid-way through the wearing period. However, final comfort was not influenced by reinserting either the same soaked lens or a new lens mid-way through the wearing period. The authors suggested that end-of-day discomfort was more a function of 'eye fatigue' than 'lens fatigue'[119] (Fig. 9.22).

NUTRITIONAL SUPPLEMENTS

Some researchers[120,121] have suggested that systemic malnutrition, and the consequent malnutrition of the tear film and ocular surface, can be the source of dry eye problems. Although it is clear that gross vitamin A deficiency can cause serious disease of the ocular surface, there is no evidence that vitamin A drops or, indeed, other such nutritional supplements can alleviate contact lens–related dry eye problems. Of interest, however, is the claim of Patel et al.[121] that pre-corneal tear film stability can be enhanced by systemic ingestion of vitamin and trace element dietary supplements.

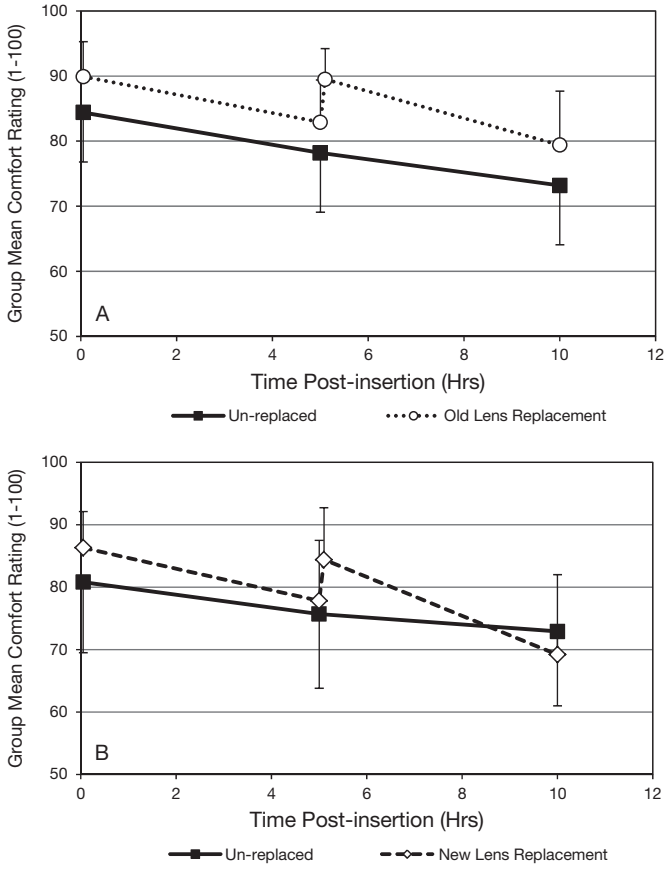


Fig. 9.22 **(A)** Group mean comfort scores at each study time point when hydrogel lenses were either worn continuously for 10 hours or removed after 5 hours and replaced with the same (old) lens. Error bars indicate 95% confidence intervals. **(B)** Group mean comfort scores at each study time point when hydrogel lenses were either worn continuously for 10 hours or removed after 5 hours and replaced with a new lens. Error bars indicate 95% confidence intervals. (From Papas EB, Tilia D, Tomlinson D, Williams J, Chan E, Chan J, Golebiowski B. Consequences of wear interruption for discomfort with contact lenses. Optom Vis Sci 2014;91:24–31.)

OMEGA-3 AND OMEGA-6 FATTY ACIDS

Both omega-3 fatty acids[122] and omega-6 fatty acids[123] have been demonstrated to alleviate signs and symptoms of dryness associated with contact lens wear over a 6-month period. Kokke et al.[123] suggested that these supplements might be useful as a therapeutic adjunct for contact lens–related dry eye.

Wang et al.[124] reported that symptoms of CLADE were attenuated by oral supplement of properly balanced omega-3 and omega-6 fatty acids. Topical cyclosporine treatment provided further relief of symptoms.

AZITHROMYCIN

Azithromycin is a macrolide antibiotic with anti-inflammatory properties. Nichols et al.[125] reported that azithromycin treatment was well tolerated and resulted in a significant improvement in comfortable contact lens wearing time in the patients with CLADE.

REBAMIPIDE

In an uncontrolled experiment, Igarashi et al.[126] examined 40 eyes of 20 soft lens wearers who had dry eye disease and had been using daily disposable lenses for greater than 3 months. Patients were examined before and 4 weeks after starting 2% rebamipide ophthalmic solution four times per day. Rebamipide significantly improved all signs and symptoms.

DIQUAFOSOL

Yamaguchi et al.[127] reported that diquafosol treatment resulted in significant improvement in total symptom score, corneal and conjunctival fluorescein staining score and TBUT in patients with versus without contact lens use. The authors advised that diquafosol can be used effectively and safely as a monotherapy for the treatment of contact lens–wearing patients with dry eye.

ANTIBACTERIAL HONEY

Twenty-four individuals with contact lens–related dry eye were recruited by Wong et al.[128] and randomised to two treatment groups, and 20 of them completed the study. One group used Manuka (*Leptospermum* sp.) honey eye drops (Optimel, Melcare, Australia) twice a day for 2 weeks followed by conventional lubricant (Systane Ultra; Alcon, Fort Worth, Texas, USA) therapy for 2 weeks; the other group completed the treatments in the reverse order. Before and after each treatment, dry eye symptomology, ocular surface inflammation and tear quantity and quality were assessed.

Dry eye symptoms improved significantly after treatment with Optimel. Patients with more severe symptoms at baseline showed a greater improvement in symptoms. No significant differences were observed in the objective signs of dry eye, which the authors attributed to the short duration of treatment.

CONTROL OF EVAPORATION

Wearing contact lenses in normal-humidity conditions (40%) produces a greater evaporation than that experienced by non–contact lens wearers in low humidity (30%).[129] This could explain the higher prevalence of dry eye complaints among contact lens wearers than amongst non–lens wearers.

A number of studies have examined the effect of different ambient environmental conditions on soft lens dehydration and associated symptoms. Morgan et al.[130] had six young adult subjects use hydrogel lenses for 200-minute sessions in arid, temperate and arctic conditions, which were experimentally created in a purpose-built environmental chamber in an aerospace medical facility. Lens dehydration was similar for the three environmental conditions, and no differences were detected with respect to lens comfort among the three environmental conditions. Those authors concluded that soft contact lens dehydration is unaffected by environmental extremes.

Contrary to the findings of Morgan et al.,[130] González-García et al.[131] observed significant adverse changes in comfort among 10 minimally symptomatic contact lens–wearing subjects after 2 hours of exposure to experimentally controlled low-humidity conditions. Furthermore, Maruyama et al.[132] reported that as air temperature and relative humidity decreased, the tear film on the surface of soft contact lenses became thinner, NITBUT became shorter and symptoms of dryness increased. They noticed that dryness was more pronounced in eyes with higher-water-content soft lenses.

Various approaches to reducing tear evaporation in patients suffering from contact lens–related dry eye symptoms can be

adopted in treating this condition. One strategy is to modify the local environment around the eye. This can be achieved by having the patient wear spectacles with tight-fitting side shields. The use of tight-fitting swimming goggles represents more extreme treatment. Clearly, such approaches will be rejected by most contact lens wearers because the very reason they are wearing contact lenses is to avoid wearing spectacles or goggles. Alternatively, the use of a room humidifier may provide some relief.

Patients can be offered the following advice about the environment in which they may be spending a significant amount of time:

- Air conditioners tend to have a dehumidifying effect on the local atmosphere.
- The environment in aeroplanes is generally of low humidity.
- Certain regions of the world have a temperature–humidity relationship that results in a low atmospheric water vapour pressure, which, in turn, is conducive to rapid lens dehydration. To assist practitioners in offering appropriate advice in this regard, Fatt and Rocher[133] tabulated the time of year when patients can be expected to experience dryness problems related to lens dehydration, in various cities throughout the world.

REDUCTION OF TEAR DRAINAGE

Tear volume can be preserved by blocking the puncta with punctal plugs (Fig. 9.23). Lowther and Semes[134] inserted temporary dissolvable collagen plugs into one eye of 32 soft lens–wearing patients with dry eye problems and conducted a 'sham' procedure in the other eye. They found improvement in both the plugged eye and the control eye, demonstrating a powerful placebo effect, and suggested that dissolvable implants were not effective as a provocative test of the efficacy of permanent punctal plugs. Contrary to this finding, Geldis and Nichols[135] reported no treatment effect among 19 contact lens wearers with dry eye symptoms.



Fig. 9.23 Punctal plug in the lower punctum. (Courtesy Brian Tompkins.)

Giovagnoli and Graham[136] reported that symptomatic soft lens patients enjoyed a 35% increase in comfortable wearing time after insertion of permanent punctal plugs into the lower puncta. This finding suggests that punctal plugs are a viable alternative for contact lens patients suffering from discomfort caused by tear insufficiency.

A more radical approach is to surgically close the punctal opening using an argon laser. Djalilian et al.[137] reported the results of a retrospective review of 25 eyes of 13 patients who underwent argon laser punctal stenosis to treat their contact lens intolerance. In 19 eyes, the treatment involved only the lower punctum, whereas in six eyes, it involved both the upper and lower puncta. Eight patients required more than one treatment session (range 2–6). At follow-up after 6 months, 10 (77%) of the 13 patients reported a substantial improvement in their symptoms and contact lens wear time.

TEAR STIMULANTS

Pharmacological stimulation of residual tear function is a relatively new approach for treating dry eye–related problems. A variety of agents that can enhance basal lacrimal secretion, such as pilocarpine, 3-isobutyl-1-methylxanthine, eledoisin and bromhexine, have been investigated for possible commercial development.[138] Some of these substances are administered topically and some systemically. Further research is required to determine whether such an approach (1) can be applied clinically to non-lens-wearing patients with dry eye and (2) will be of benefit to symptomatic contact lens wearers.

MANAGEMENT OF ASSOCIATED DISEASE

It is beyond the scope of this chapter to review all of the possible disease states that can adversely affect the tear film, except to say that practitioners need to be alert to the various possibilities. Perhaps the most common ocular disease state in contact lens wearers associated with lens dryness is meibomian gland dysfunction. Severe blockage of the meibomian gland orifices can result in a lipid deficiency in the tear film, leading to more rapid tear loss. Abnormal lipid may also be secreted from diseased meibomian glands, leading to lipid deposition on lenses that can result in intermittent blurred vision and discomfort. Treatment strategies that can be applied to alleviate this condition are discussed in Chapter 7.

Cyclosporine, which was originally developed as a systemic immunomodulator, has been approved by the US Food and Drug Administration to treat dry eye disease and is available as cyclosporine 0.05% ophthalmic emulsion. This preparation can be used to treat ocular surface disorders that have an immune-based inflammatory component. It has been suggested that this cyclosporine may also be useful for management of contact lens–associated dry eye;[139] however, Willen et al.[140] were unable to demonstrate a positive effect.

Tear secretion is depressed after laser-assisted in situ keratomileusis[141] and photorefractive keratectomy (PRK)[141,142] during the first 6 months after surgery. Ozdamar et al.[143] reported that PRK causes a decrease in tear flow and tear film stability that is probably caused by decreased corneal sensation after PRK. Post-operative dry eye problems are therefore to be expected in patients who need to be fitted with contact lenses after refractive surgery.

BANDAGE LENSES

It may seem paradoxical to be considering the prescription of soft contact lenses for patients with intractable dry eye problems in a review of the problems associated with, or induced by, contact lenses as outlined in this chapter. However, it is clear that patients with severe aqueous deficiency can benefit from bandage lenses. The best type of lens is one with characteristics described previously as being the most suitable for contact lens patients with dry eye problems. It may also be necessary for patients wearing bandage lenses to use re-wetting drops. Rigorous aftercare monitoring of patients wearing bandage lenses is essential in view of the known increase in susceptibility to corneal ulceration in such patients because of the underlying disease state.[144]

REDUCED WEARING TIME OR CESSATION OF LENS WEAR

Symptoms of dryness typically become worse throughout the daytime wearing period[145] to the point where lenses are so uncomfortable that they need to be removed; indeed, discomfort caused by dryness is often the limiting factor in determining maximum lens wearing time. If all other strategies to alleviate extreme dryness fail, then the only advice, albeit unsatisfactory, that can be offered to patients is that the strategy that they have already been forced to adopt – that of reducing lens wearing time – is both the problem itself and the solution to the problem.

The ultimate sanction in the management of intractable contact lens–related tear film dysfunction is to advise the patient to cease lens wear. In such cases, refractive surgery may provide a suitable solution.[146]

CESSATION OF SMOKING AND AVOIDANCE OF PASSIVE EXPOSURE TO CIGARETTE SMOKE

Smoking can adversely affect the lipid layer of pre-corneal tear film, which can lead to increased tear evaporation.[147] This sequence of events may exacerbate symptoms of dryness in contact lens wearers.

Ward et al.[148] reported that brief passive exposure to cigarette smoke is associated with adverse effects on the ocular surface, as evidenced by a decrease in tear stability and damage to the ocular surface epithelia in soft contact lens wearers.

Prognosis

The prognosis for recovery from tear film dysfunction related to contact lens wear will depend on the specific cause of the problem. If the symptoms relate to the wearing of inappropriate lenses or the use of unsuitable solutions, then the prognosis may be good if the right lens and/or solution can be found. Similarly, a good prognosis can be advised if the problem is caused by an associated disease state that can be managed successfully – such as meibomian gland dysfunction. In cases where the underlying cause is difficult to treat – such as aqueous deficiency caused by keratoconjunctivitis sicca – the prognosis is poor, although further research into new strategies, such as the clinical application of tear stimulating agents,[54] do hold promise of a better prognosis for some patients.

An additional consideration of prognostic interest is whether the tear film is disrupted after lens removal and, if so, how long it takes before the tear film returns to normal. This question was addressed by Kline and DeLuca,[149] who documented a 54% decrease in TBUT measured within 10 minutes of removal of a hydrogel lens (compared with pre-fitting estimates of TBUT). Faber et al.[150] made a similar observation and noted that the TBUT had largely returned to normal within 25 minutes of lens removal. Thus, lens-induced disruption to the pre-corneal tear film is short lived after lens removal.

Differential Diagnosis

As has already been discussed, practitioners need to be alert to the myriad of associated disease states that can occur concurrently with contact lens wear so that these can be differentiated from conditions caused by the contact lens alone. Differential diagnosis between contact lens–associated tear film dysfunction versus tear film dysfunction caused by associated disease can be made by having the patient suspend lens wear for 1 month; if problematic signs and symptoms persist for this period, then it is unlikely that contact lenses are the cause of the problem.

Attempts should, of course, be made to treat associated ocular pathology that is identified as a possible cause of dry eye symptoms in a contact lens wearer. Whether or not the associated pathology is cured completely, the practitioner will be in a much better position to devise a viable management plan and to formulate an accurate prognosis of ongoing success of contact lens wear.

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10 Mucin Balls

Various forms of organic and inorganic matter can accumulate in the post-lens tear film. These include intrinsic matter, such as desquamated epithelial cells, inflammatory cells and microorganisms, and extrinsic matter, such as dust particles that may have entered the eye from the atmosphere. Most of this matter is flushed away during daily lens wear because of the blink-activated tear pump. The accumulation of such debris during extended lens wear is potentially more problematic because it can be retained at the corneal surface for longer periods – such as overnight during sleep. An important requirement of extended-wear lenses is that such matter is flushed out from beneath the lens as soon as the patient begins to blink upon awakening in the morning.

A characteristic form of debris known as 'mucin balls' is observed in patients wearing silicone hydrogel contact lenses.[1] Although the appearance of mucin balls was first formally reported in the literature in 2000[2,3] – corresponding to the market release of silicone hydrogel lenses – earlier anecdotal reports suggest that this phenomenon had been observed previously. Other descriptive terms that have been used include lipid plugs,[4] tear microspheres,[5] microdeposits[6] and spherical post-lens debris.[3] Some authors[7,8] have suggested that a small number of mucin balls can be observed in patients using conventional hydrogel lenses on an extended-wear basis.

Signs

Mucin balls are observed within minutes of lens insertion between the posterior lens surface and the corneal epithelium. Observed under direct white light at low illumination, they appear as a mass of discrete grey dots that seem to be fixed in position; that is, they do not move in synchrony with the contact lens after a blink. Observed at higher magnification under direct white light illumination, mucin balls appear as cream-grey, round or ovoid inclusions that may be near-spherical or somewhat flattened (Fig. 10.1).

When viewed by using indirect retro-illumination, mucin balls display reversed illumination, which indicates that the material from which the mucin ball is composed (presumably mucin; see later) is of a higher refractive index than the surrounding medium (tear aqueous). Under these illumination conditions, some mucin balls take on a distinct doughnut-like appearance, with a thick annular rim and membrane across the centre (Fig. 10.2).

Tan et al.[5] and Craig et al.[9] suggested that mucin balls are more commonly observed in the superior cornea, although this characteristic has not been reported by other authors.[2,3,10] Mucin balls can also become embedded in the conjunctival epithelium close to the limbus.

Although the term 'balls' has been used to describe these mucinous features – which implies a round or spherical shape – Grupcheva et al.[11] described mucin balls as being round (70%), oval (28%) or irregular (2%) in shape. Mucin balls were also classified in terms of reflectivity, with 92% classified as being bright (homogeneous) and 8% classified as comprising of dark areas (heterogeneous).

Estimates of the size (diameter) of individual mucin balls vary; Fonn et al.[2] and Dumbleton et al.[3] reported a diameter of 20 to 200 μm, and Craig et al.[9] made a similar estimate of 10 to 200 μm. Bourassa and Benjamin[6] and Tan et al.[5] suggested a smaller diameter, at 40 to 120 μm. Sweeney et al.[8] reported that mucin balls fall into two size categories: small (10–20 μm) and large (20–50 μm).

Matsuzaki et al.[12] reported an atypical case of mucin ball formation in a 25-year-old male wearing extended-wear silicone hydrogel lens (PureVision; balafilcon A (Bausch & Lomb)) for therapeutic use. Mucin balls were found between the cornea and contact lens and stained with rose bengal dye. One of them was atypically larger than usual, and the major axis measured approximately 1.5 mm. Lens wear was stopped, and all mucin balls and corneal staining disappeared within 1 day.

Some authors have used corneal confocal microscopy to measure the size of mucin balls. Ladage et al.[13] measured the size of mucin balls in three patients and reported that the sizes ranged from 33.9 to 78.8 μm (mean 57.9 ± 14 μm). Grupcheva et al.[11] assessed the mean diameter of mucin balls in patients wearing silicone hydrogel lenses for therapeutic and cosmetic reasons and reported these to be 77.4 and 45.8 μm, respectively. These estimates are quite large in comparison with the thickness of the tear film beneath silicone hydrogel lenses (1–2 μm)[14] and the corneal epithelium (about 50–70μm).[15]

Various factors will govern the number of mucin balls present at any given time. In their respective case reports, Bourassa and Benjamin[6] observed 20 to 30 mucin balls, and Pritchard et al.[2] observed up to 50 mucin balls over a number of visits. In clinical trials of patients wearing silicone hydrogel lenses, Fonn et al.[2] reported that 95% of patients displayed fewer than 50 mucin balls over a 3-month period, and Sweeney et al.[8] and Tan et al.[7] reported that the mean number of mucin balls over a 12-month period did not exceed an average of 20. All seven patients wearing silicone hydrogel lenses in the clinical trial performed by Craig et al.[9] demonstrated between 60 and 100 mucin balls within 22 days of commencing lens wear. Sometimes, in excess of 100 mucin balls may be observed.[2,7] Craig et al.[9] reported 230 mucin balls in one subject. Grupcheva et al.[11] observed an average of 15 and 20 mucin balls in patients wearing silicone hydrogel lenses for cosmetic and therapeutic purposes, respectively.

After lens removal, the majority of mucin balls are blinked away, leaving depressions (also termed 'imprints' or 'pits') in the epithelial surface. These depressions fill with tear aqueous and appear as transparent spherical inclusions displaying unreversed illumination when viewed at high magnification with a slit lamp biomicroscope using retro-illumination (Fig. 10.3). Some mucin balls appear to remain lodged in the surface of the epithelium; these continue to display reversed illumination, thus allowing mucin balls to be differentiated from aqueous-filled pits.

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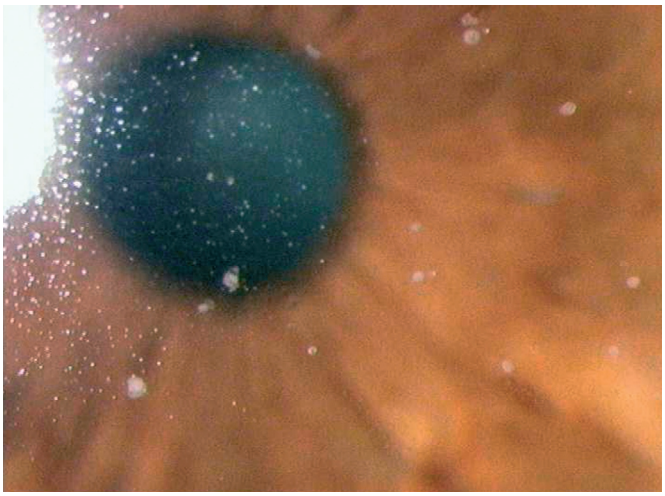


Fig. 10.1 Mucin balls observed under direct illumination at high magnification. (Courtesy Brian Tompkins.)



Fig. 10.2 Mucin balls observed using indirect marginal retro-illumination displaying a flattened doughnut appearance. The mucin balls at the inferior pupil margin display reversed illumination. (Courtesy Brian Tompkins.)

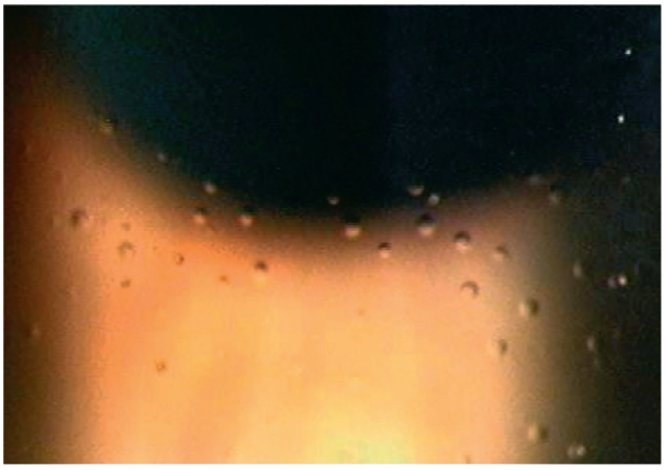


Fig. 10.3 Fluid-filled pits in the epithelium caused by depressions created by large mucin balls, which have since become dislodged. The pits display un-reversed illumination. (Courtesy Brian Tompkins.)

Upon instillation of fluorescein into the eye, both the remaining mucin balls and the aqueous in the epithelial depressions stain with fluorescein, resulting in a pattern of punctate spots over the cornea. In the presence of fluorescein, it is virtually impossible to distinguish between mucin balls and the aqueous-filled epithelial pits; both appear as similar-sized, discrete, solid, fluorescent-green spots when viewed under fluorescent light (Fig. 10.4). Mucin balls do not stain with rose bengal.[8]

TIME COURSE

Sweeney et al.[8] and Tan et al.[7] reported that mucin balls increase in number and size over the initial few months of silicone hydrogel lens extended wear. Morgan and Efron[10] conducted a randomised, crossover clinical trial in which 30 subjects each wore a pair of PureVision (Bausch & Lomb) and Focus Night & Day (CIBA Vision) silicone hydrogel contact lenses for 8 weeks on an extended-wear basis. The percentage of patients presenting with mucin balls increased to 37% and 54% for PureVision and Focus Night & Day, respectively, after 4 weeks and began to decline thereafter (Fig. 10.5). Dumbleton et al.[3] did not detect a change in the mean grade of mucin ball appearance over a 6-month period among 92 patients wearing Focus Night & Day lenses.

PREVALENCE

As stated earlier, Morgan and Efron[10] reported that 37% to 54% of patients wearing silicone hydrogel lenses will display mucin balls after about 4 weeks. Tan et al.[7] observed that the percentage of all subjects wearing silicone hydrogel lenses with mucin balls varied from 37% to 82% during the year. Dumbleton et al.[3] reported that mucin balls were observed in 70% of patients at one or more visits of their clinical trial, and in 29% of subjects at all three visits, while patients were wearing Focus Night & Day lenses. Over half (54.2%) of a group of subjects wearing Focus Night & Day lenses were observed by Szczotka-Flynn et al.[16] to display some presence of mucin balls during at least one visit and about one-third (32.8%) displayed repeated episodes over a 12-month period.

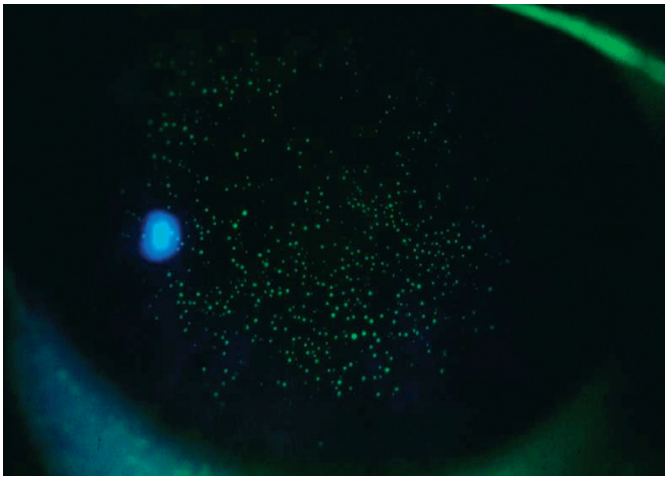


Fig. 10.4 A combination of mucin balls and aqueous-filled epithelial depressions staining with fluorescein (it is not possible to distinguish between these two features when the staining pattern is viewed under fluorescent light). (Courtesy Brian Tompkins.)

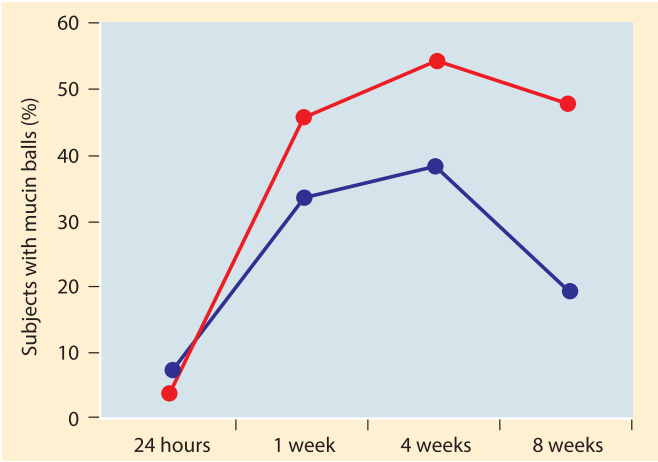


Fig. 10.5 Incidence and time course of mucin ball formation with two types of silicone hydrogel lenses. Red: Focus Night & Day; Blue: PureVision. (Adapted from Morgan PB, Efron N. Comparative clinical performance of two silicone hydrogel contact lenses for continuous wear. Clin Exp Optom 2002;85:183–92.)

ASSOCIATED OBSERVATIONS

Morgan and Efron[10] analysed the results of their clinical trial to see if the presence of mucin balls was related to any other clinical results. Paradoxically, high-contrast visual acuity was demonstrated to be about one letter *better* in the presence of mucin balls[10]; this is consistent with the report of Dumbleton et al.,[3] who showed that subjective appreciation of vision was superior in the presence of mucin balls after 6 months of wear. There was no difference for low contrast visual acuity.[10] It is not clear why vision should be better in the presence of mucin balls.

Some biomicroscopic signs appeared to be related to mucin balls.[10] An unexpected finding in the study by Morgan and Efron[10] was that conjunctival and limbal redness were both reduced and the number of microcysts appeared to increase in subjects exhibiting mucin balls. The apparent association between the appearance of mucin balls and epithelial microcysts, which has also been observed by Tan et al.,[7] may be an observational artefact relating to the difficulty in differentiating mucin balls from microcysts.

An association was revealed between the presence of mucin balls and increased corneal fluorescein staining[10]; this is likely to be caused by the remaining mucin balls and fluid-filled epithelial pits staining with fluorescein. The previously described associations concerning mucin balls contrast with those of other authors[3,5,8] who found no relationship between biomicroscopic signs and mucin balls.

Naduvilath[17] demonstrated an association between the appearance of mucin balls and the development of contact lens–induced peripheral ulcers. Specifically, patients displaying mucin balls have a ×1.6 increased probability of developing contact lens–induced peripheral ulcers compared with patients who do not display mucin balls. Contrary to this, Szczotka-Flynn et al.[16] reported that the presence of mucin balls was significantly associated with a *decreased* incidence of corneal infiltrative events and that the effect was greatest when they occurred repeatedly over time.

Symptoms

Dumbleton et al.[3] found no association between the appearance of mucin balls and overall comfort, waking comfort, waking dryness or end-of-day dryness, although the process of lens removal was reported as being slightly less comfortable in the presence of mucin balls. Other authors[5,8,10] have reported that subjective comfort is unaffected by the presence of mucin balls.

Aetiology

The reason for the formation of mucin balls is unclear and likely to be complex. The prevailing hypothesis is that the low deposition rate of silicone hydrogel materials prevents any significant uptake of deposits (protein, lipid and mucins) onto or into the lens matrix during lens wear. The depletion of aqueous during overnight wear of silicone hydrogel lenses – as evidenced by the very thin post-tear film – results in a viscous, mucin–lipid layer between the lens and epithelial surface. This layer would contain much more mucin than lipid, reflecting the respective proportions of these two entities in the tear film. Silicone hydrogel lenses are thought to induce high inter-facial forces, and this, when coupled with their high modulus of elasticity (greater stiffness), creates a sheering of this viscous, mucin-rich post-lens layer in the course of lens movement induced by normal blinking (daytime wear) and rapid eye movements (during sleep). These sheering forces have the effect of rolling the mucin-rich post-lens layer into spheres, which are observed as mucin balls.

The difference in mucin ball response between the PureVision (Bausch & Lomb) and Focus Night & Day (CIBA Vision) silicone hydrogel contact lenses reported by Morgan and Efron[10] may be related to differences in inter-facial shear forces occurring as a result of the different types of surface treatments applied to each lens. A classic plasma surface modification is used to render the surface of the PureVision lens hydrophilic, whereas a plasma coating is applied to the Focus Night & Day lens to enhance surface wettability. Certainly, the chemical composition and nature of the lens mould used in the manufacture of silicone hydrogel lenses can affect mucin ball formation; for example, Lai and Friends[18] found that the use of polar plastic moulds minimised mucin ball formation.

Dumbleton et al.[3] further postulated that a greater mismatch in shape between the back surface of the lens and the epithelial surface may increase the degree of lens movement over the ocular surface and thus create more sheering and, consequently, more mucin balls. In support of this theory, they demonstrated that subjects who exhibited mucin balls had significantly steeper keratometry readings along the flatter meridian than those who did not develop mucin balls (bearing in mind that all lenses in their experiment had the same back optic zone radius).[3] That is, those with relatively flatter, looser lens fits exhibited a greater number of mucin balls. Szczotka-Flynn et al.[16] also reported that mucin ball scores weakly correlated with corneal curvature ($p < 0.005$); however, other authors who have looked for this association have been unable to confirm this finding.[5,10]

Pathology

STRUCTURE AND COMPOSITION OF MUCIN BALLS

By using a corneal confocal microscope, Craig et al.[9] found that mucin balls display a highly reflective core with a more poorly reflective, apparently translucent, outer layer. The diameter of the central core relative to the outer coating varied among mucin balls. This bilayered appearance of mucin balls was confirmed by the same authors,[9] with the use of phase-contrast

microscopy to examine samples obtained from the back surface of lenses removed from the eye.

The name 'mucin balls' implies that these entities are composed primarily of tear mucins (mucins are the glycoprotein components of mucus and vary greatly in molecular size). To determine if this is the case, Millar et al.[19] collected tears containing mucin balls by using a capillary tube. Histology showed that the mucin balls were periodic acid–Schiff positive, indicating that glycoproteins form a major component. Lipids and bacteria were not detected. Scanning electron microscopy did not show the surface to be smooth but revealed a variation in density across the surface. Elemental analysis was inconclusive. The authors concluded that mucin balls are likely to be made from collapsed mucin and are unlikely to have been formed as a result of pearling around a silicon, lipid or bacterial kernel.[19]

PATHOGENESIS OF MUCIN BALL FORMATION

Within minutes of lens insertion, mucin ball formation begins at the interface of the posterior lens surface and the pre-corneal tear film. Sweeney et al.[8] suggested that mucin balls are more prominent in the superior quadrant of the cornea beneath the resting position of the upper eyelid. The mucinous layer of the tear film, together with some lipid components, is apparently 'rolled up' into discrete elements. At first, the resulting mucin balls are small and appear as an assortment of scattered debris in the form of individual deposits or small clumps of debris. They remain in a static position after a blink, which suggests that mucin balls are somehow fixed to, or partially embedded in, the epithelium.

Figure 10.6 is a schematic diagram illustrating the formation and progressive enlargement of mucin balls in response to sheer forces from the lens. The mucin balls eventually grow large enough to become deeply embedded in epithelium (Fig. 10.7).

Eventually some of the mucin balls dislodge, resulting in an indentation in the surface of the epithelium, which fills with tear fluid. The remaining mucin balls – which are either resting on the surface of the epithelium or embedded to some extent within the epithelium – stain with fluorescein, as do the fluid-filled pits (Fig. 10.8). These formations are indistinguishable when viewed with a broad beam of illumination under white light or under cobalt blue light after fluorescein has been instilled (Fig. 10.9).

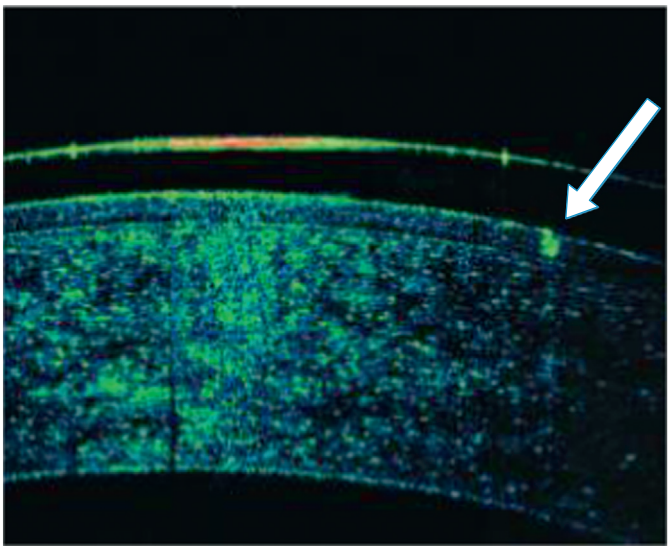


Fig. 10.7 Mucin ball (arrow) embedded deep within the epithelium beneath a silicone hydrogel lens, imaged using optical coherence tomography. (Courtesy Nicholas Rumney.)

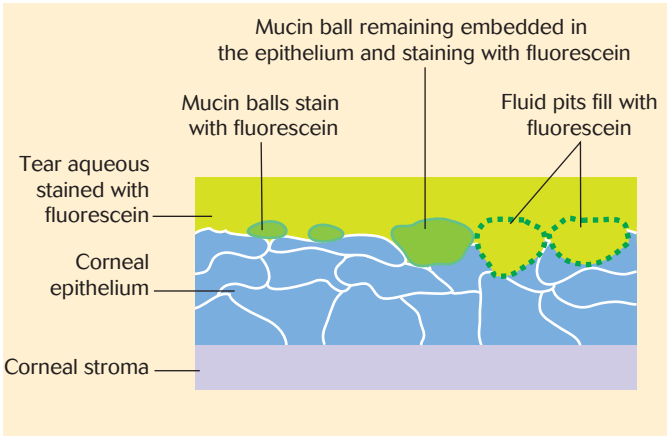


Fig. 10.8 Three separate entities: mucin balls lying on the surface of the epithelium, mucin balls partially embedded within the epithelium and fluid-filled pits.

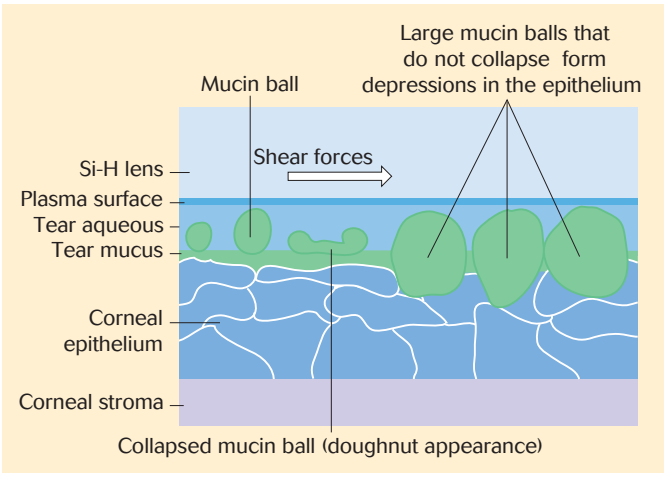


Fig. 10.6 Formation of mucin balls and epithelial depressions.

At this point, slit lamp examination using indirect retroillumination reveals two forms of refractile elements. Those that display reversed illumination are a combination of the mucin balls lying in the aqueous phase of the tear film and those buried deeper in the epithelial surface (see Fig. 10.2). Refractile elements displaying un-reversed illumination are the fluid-filled pits created by mucin balls that subsequently became dislodged as a result of blinking (see Fig. 10.3). These illumination effects are observed both with and without the lens on the eye.

After prolonged periods of lens wear, some of the mucin balls become so large that they cannot maintain their spherical shape and collapse inwards. This results in a doughnut appearance, with a flat centre and tyre-like annulus around the rim.[2] A small circular island of material can sometimes be observed in the centre of the collapsed mucin ball (Fig. 10.10). It is unclear why mucin balls should collapse in this way, rather than the more intuitive scenario of the near-spherical mucin balls simply becoming flattened into a disciform shape.

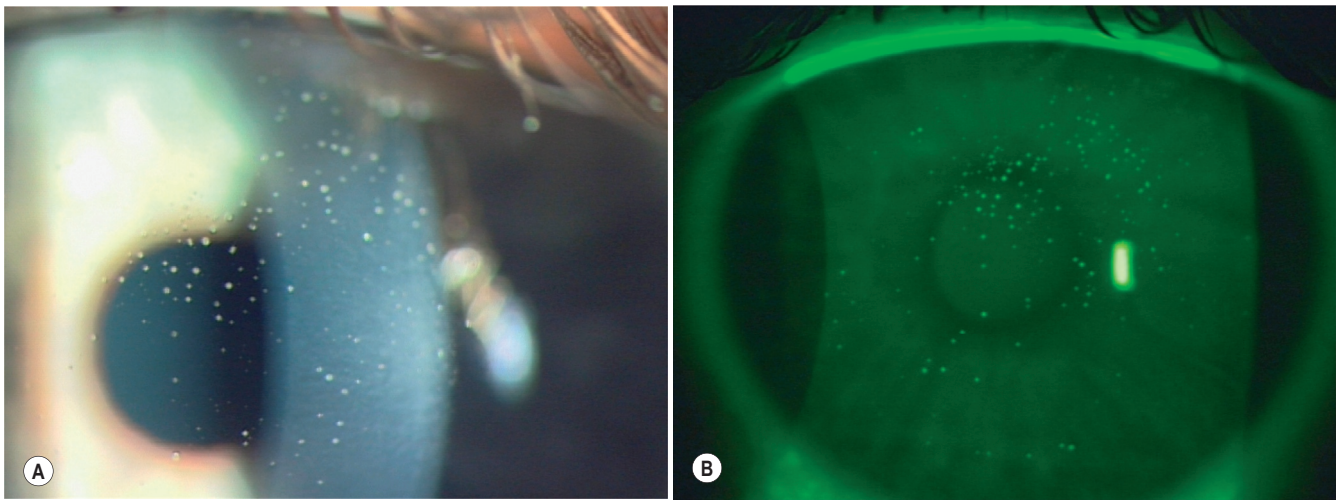


Fig. 10.9 Evidence of staining caused by mucin balls and fluid-filled pits. **(A)** Mucin balls and fluid-filled pits observed behind the lens in white light. **(B)** After lens removal, most of the mucin balls are washed away, and some remain. Fluorescein stains the remaining mucin balls and fills epithelial pits created by the mucin balls that were subsequently washed away. Upon careful inspection, the concordance between the position of the mucin balls and fluid-filled pits observed in white light **(A)** versus the appearance of the same entities stained with fluorescein **(B)** can be seen. (Courtesy Suzanne Efron.)



Fig. 10.10 Large single mucin ball that has collapsed into the form of a doughnut, showing a thin surrounding annulus and a small central island. (Courtesy Suzanne Efron.)

CONSEQUENTIAL PATHOLOGY

Ladage et al.[13] were able to replicate the formation of mucin balls in a rabbit model and observed Ki-67-positive stromal cells immediately beneath indentations that reached the epithelial basement membrane. This indicates that active proliferation of stromal cells has been focally stimulated. These authors also noted a local increase in keratocyte density immediately beneath deep mucin balls. Stromal keratocytes do not divide unless stimulated to do so, leading Ladage et al.[13] to conclude that the Ki-67-positive stromal cells represent either dividing keratocytes or activated fibroblasts.

The corneal confocal microscope observations of Grupcheva et al.[11] also seem to confirm, at least anecdotally, that mucin balls induce transient epithelial alteration and keratocyte 'activation'.

From a theoretical standpoint, clinicians ought to be concerned about the formation of mucin balls inasmuch as they represent a compromise of the mucus phase of the pre-corneal tear film. For example, Fleiszig et al.[20] demonstrated the critical importance of the mucus phase in preventing the attachment of potentially pathogenic bacteria to the corneal surface. In the absence of a properly formed mucus layer, which may occur as a result of extensive mucin ball formation, bacteria are more likely to attach to the cornea and establish an infection.

Szczotka-Flynn et al.[16] initially reported that the presence of mucin balls was associated with a decreased incidence of corneal infiltrative events. However, a subsequent study conducted with 282 participants wearing lotrafilcon A lenses enrolled at three sites in the USA found that repeated mucin ball presence early in their clinical trial significantly increased the rate of corneal infiltrative events at 12-month follow-up by 466% (hazard ratio 4.66; 95% confidence interval 1.10–19.79; $p = 0.0372$).[21] However, repeated, longer-term mucin ball presence during wear of balafilcon A or comfilcon A significantly decreased the rate of corneal infiltrative events by 62% (hazard ratio 0.380; 95% confidence interval 0.145–0.998; $p = 0.0494$). The authors concluded that their initial hypothesis that mucin formation is protective against corneal infiltrative events throughout extended wear was not supported.[21]

Besides the protective function of mucus, potentially pathogenic organisms are more likely to establish an infectious process if there is a breach of the corneal epithelium. Pritchard et al.[2,22] observed that fluorescein does not generally penetrate into the epithelium, and they suggested that this indicates that the epithelial barrier function is not breached as a result of mucin ball formation. However, inspection of images of fluorescein staining in patients who have extensive mucin ball formation (Fig. 10.11) reveals a diffuse halo of staining around some mucin balls, and this is suggestive of an epithelial breach.

Concerns that the factors described could lead to an increased occurrence of infections keratitis among silicone hydrogel contact lens wearers can be allayed because the incidence of sight-threatening corneal ulceration with silicone-hydrogel lenses is low (see Chapter 27).

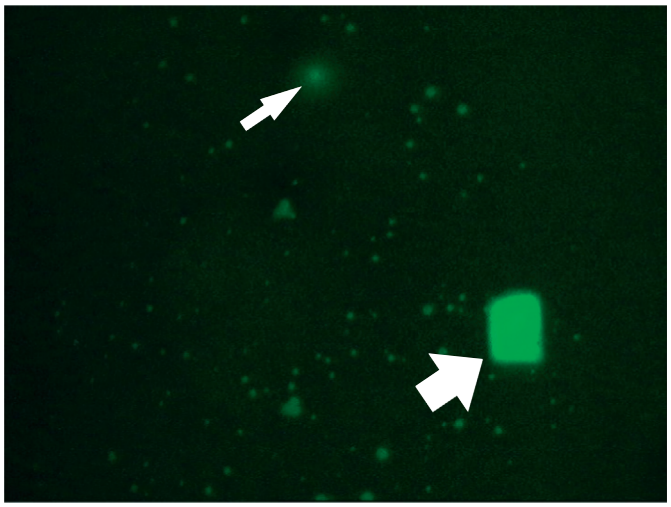


Fig. 10.11 Fluorescein staining caused by mucin balls. Fluorescein diffusion into the surrounding epithelium and possibly also the stroma is evidenced by the diffuse fluorescent haze around one of the punctate stains (thin arrow). The thick arrow indicates the square slit lamp light reflex. (Courtesy Suzanne Efron.)

Pritchard et al.[2,22] presented a case report of a patient demonstrating extensive mucin ball formation. This patient, who was using silicone hydrogel lenses on an extended-wear basis, also presented with an acute red eye reaction, an asymptomatic epithelial defect (with rapid diffusion of fluorescein into the stroma), two further instances of asymptomatic infiltrates and symptoms of dryness, over an 18-month period. These adverse events may have been coincidental to the appearance of mucin balls in this patient.

Mucin balls may cause a slight, though temporary, irregularity in the corneal surface, which could reduce wettability if present as a chronic condition.[3] Besides this, mucin balls do not seem to compromise ocular integrity. As discussed previously, mucin ball formation is not associated with increased corneal inflammation, corneal staining (apart from that staining directly attributable to the mucin balls) or conjunctival redness,[3,8,10] and patients displaying mucin balls experience no discomfort or reduced vision.[3,8,10]

Management

The obvious strategy for preventing mucin ball formation, should this be the aim of the clinician, is to refit the patient with a lens type that is not made from silicone hydrogel materials. This may create a dilemma because silicone hydrogel lenses are the only lens type indicated for extended wear.

In patients wearing silicone hydrogel lenses, mucin ball formation can be minimised by adopting the following strategies:

- Fitting silicone hydrogel lenses made of materials with a low modulus, which might theoretically reduce the sheer forces implicated in their formation. This association has yet to be tested experimentally.
- Optimizing lens fit; flat fitting lenses are thought to exacerbate mucin ball formation.[3,7,10]
- Advising the patient to use lubricating drops after waking and before sleeping.[3,7]
- Advising the patient to adopt a shorter wearing schedule (e.g. removing the lenses once every six nights instead of 30 nights).[3] However, Stern et al.[23] found no difference in mucin ball response in patients wearing monthly replacement silicone hydrogel lenses that were removed every 6 versus 30 nights.
- Advising patients using extended-wear contact lenses to remove lenses daily after waking, clean them with the multi-purpose disinfecting solution and reinsert the lenses.[24]

Prognosis

After lens removal, mucin balls that are not embedded in the epithelium are rapidly blinked away. The residual 'embedded' mucin balls and the fluid-filled pits generally resolve in a matter of hours.[3] In severe cases, embedded mucin balls may remain in the epithelium for up to 7 days.[2] Mucin balls will reform again if silicone hydrogel lens wear is recommenced.

Differential diagnosis

Clinicians need to be able to differentiate mucin balls – and the fluid-filled epithelial pits they cause – from other contact lens–induced phenomena that occur at or near the ocular surface. These include cyst-like inclusions that occur in conditions such as Meesmann's dystrophy bullous keratopathy and Cogan's microcystic dystrophy or phenomena that can be observed in the corneal epithelium, such as vacuoles, microcysts bullae (oedema), infiltrates and dimple veiling.[25]

Microcysts and mucin balls are similar in size. As explained in Chapter 19, microcysts can be observed by using optic section illumination with a slit lamp biomicroscope as being within the epithelium and displaying reversed illumination. Therefore, unlike mucin balls, microcysts do not stain with fluorescein. However, microcysts that break through the epithelial surface do stain with fluorescein and may be indistinguishable from mucin balls.

Epithelial vacuoles reside within the epithelium, display unreversed illumination and do not stain with fluorescein (see Chapter 20). Epithelial bullae are similar to vacuoles but are more oval in shape and have an irregular and indistinct border. Mucin ball–induced fluid-filled epithelial pits also display unreversed illumination, but unlike fluid vacuoles, they do stain with fluorescein.

Contact lens–induced dimple veiling refers to the formation of fluid-filled pits in the epithelial surface caused by pressure from individual air bubbles trapped beneath rigid contact lenses (and to a lesser extent in soft lenses). The epithelial depressions ('dimples') will fill with the aqueous phase of the tear film, stain with fluorescein and display un-reversed illumination; as such, they may be indistinguishable in appearance from mucin ball–induced fluid-filled epithelial pits. Dimple veiling tends to occur in clustered regions corresponding to areas of loose lens fitting that can support the existence of large air bubbles. Thus, the type of lens (i.e. a poorly fitting rigid lens vs. a silicone hydrogel lens) is likely to be a key factor in differentiating these otherwise similar phenomena.

A summary of the features that differentiate conditions described earlier is given in Table 10.1.

TABLE 10.1 Differential diagnosis of intra-epithelial and epithelial surface phenomena

	Size (μm)	Shape	Colour (seen in direct illumination)	Distribution	Refractive index relative to surround	Optical appearance	Staining with fluorescein	Associated contact lenses
Mucin balls	10–200	Spherical or doughnut shaped	Grey	More in superior cornea	Higher	Reversed illumination	Yes	Silicone hydrogel lenses
Epithelial pits (induced by mucin balls)	10–200	Spherical	Clear	More in superior cornea	Lower	Unreversed illumination	Yes	Silicone hydrogel lenses
Epithelial microcysts	5–30	Spherical or irregular	Grey	Pan-corneal	Higher	Reversed illumination	No*	Low oxygen performance lenses
Epithelial vacuoles	5–30	Spherical	Clear	Mid-peripheral cornea	Lower	Unreversed illumination	No	Low oxygen performance lenses
Epithelial bullae	5–30	Irregular (roughly oval)	Clear	Pan-corneal or central	Lower	Unreversed illumination	No	Rigid lenses
Dimple veiling	10–200	Spherical	Clear	Corresponding to large post-lens tear space	Lower	Unreversed illumination	Yes	Flat fitting rigid (or soft) lenses

*Except when breaking through the epithelial surface.

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11 Conjunctival Staining

In the open eye, contact lenses are primarily in physical apposition with the cornea. Well-fitted rigid lenses generally reside almost exclusively on the cornea and only occasionally impinge on the limbus. The situation is different with soft lenses. If the surface area of the cornea[1] is taken to be 132 mm^2, and the surface area of a soft lens – with typical dimensions of 14.5 mm diameter and 8.7 mm back optic zone radius – is 213 mm^2, then 38% of the surface area of a soft lens lies in apposition with the bulbar conjunctiva. It is therefore apparent that changes in the conjunctiva may be seen as a result of the physical presence of soft lenses.

Contact lenses can also affect the conjunctiva via mechanisms that do not involve direct physical contact. Thick rigid lenses can 'bridge' the upper lid away from the conjunctiva, preventing blink-activated wetting and causing drying of the region of corneal and conjunctival tissue adjacent to the lens. Contact lens solutions can cause toxic or immunological reactions of the conjunctiva. Lens-induced changes in the volume and composition of the pre-ocular tear film may also indirectly lead to changes in the conjunctiva.

For the reasons outlined, careful inspection of the bulbar conjunctiva must be considered to constitute an essential part of the external ocular examination of contact lens wearers. An important technique that can be employed to reveal conjunctival tissue damage is to use vital dyes, so this chapter will review the various conjunctival staining techniques that have been proposed.

'Conjunctival staining' is used here as a catch-all phrase that encompasses a wide range of normal and abnormal appearances that are revealed after instillation of a vital dye – typically fluorescein – into the eye.

Use of vital dyes for conjunctival staining

APPROPRIATE STAINING AGENTS

Fluorescein sodium (more commonly referred to as 'fluorescein') is generally adopted as the stain of first choice in ophthalmic diagnosis. It is assumed that fluorescein provides information about the surface quality of the conjunctiva by pooling in natural creases, folds and ridges in the conjunctiva and entering inter-epithelial spaces where an abrasion has occurred.[2] To optimise visualisation of conjunctival staining, a cobalt blue 'excitation' filter, incorporated into the illumination system of the slit lamp biomicroscope, is required to limit illumination to wavelengths of light that maximally absorb fluorescein. When viewing the conjunctiva illuminated in this way, the sclera scatters the incident blue light and desaturates the fluorescent light. (This problem is not encountered when viewing fluorescent staining over a transparent cornea). A yellow 'barrier' filter (Fig. 11.1) interposed within the observation system is therefore essential to limit light transmission back through the eyepieces and maximise contrast between the stained and unstained areas of conjunctiva.

Even with the use of excitation and barrier filters, the blue incident light excites a natural greenish fluorescence in the conjunctiva and sclera, which causes a general background glow that may diminish the contrast of any additional fluorescence present.[3] A similar problem that is encountered is that the contrast of subtle corneal staining can be diminished as a result of the background fluorescent glow emanating from the crystalline lens. An added difficulty with respect to the observation of fluorescein staining of the conjunctiva is that fluorescein is slightly lipid soluble and stains the entire conjunctiva to some extent, further reducing contrast.[3] In view of these limitations of fluorescein, researchers have sought to investigate the utility of other agents for staining the conjunctiva. Sulphorhodamine B, which has an orange fluorescence that can be separated from the green natural fluorescence of the ocular tissues, gives a greater contrast compared with fluorescein.[3]

Lissamine green is a vital stain with dyeing quality similar to that of rose bengal, but causes less discomfort. It stains dead or degenerated epithelial cells green and is used to facilitate the diagnosis of dry eye conditions. It has a molecular weight of 577. Guillon and Maissa[4] demonstrated that lissamine green shows greater specificity for symptomatic subjects, particularly in contact lens wearers. They recommended that the examination of patients complaining of dry eyes – in particular, those wearing contact lenses – should include observation of the conjunctiva stained with lissamine green. Within- and between-grader reliability of lissamine green staining seems to be at least substantial to moderate.[5]

Norn[6] reported that rose bengal stains degenerated epithelial cells and mucus; however, Tseng[7] subsequently disputed this long-held belief by demonstrating that rose bengal also rapidly stains healthy epithelial cells when there is insufficient surface



Fig. 11.1 A yellow barrier filter fitted to the front of the observation system of a slit lamp biomicroscope. (Courtesy Lyndon Jones.)

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mucus. Contrast between rose bengal–stained and unstained areas is usually poor, although the appearance can be enhanced by viewing the stained region in 'red-free' light by interposing a green filter in the illumination system. Patients find this staining agent to be uncomfortable.[8]

Lissamine green has similar properties to rose bengal in that it stains degenerated and dead epithelial cells and mucus. Manning et al.[8] reported that lissamine green is better tolerated by patients compared with rose bengal and is equally as effective as rose bengal in evaluating the ocular surface. However, Emran and Sommer[9] believed that lissamine green is an inadequately sensitive test for practical use.

Numerous other stains, including Congo red,[10] neutral red,[11] trypan blue,[12] bromothymol blue[13] and fluorexon,[14] have been investigated. Foster[15] cited 34 different chemical substances that have been used for ocular surface staining. In addition, the possible benefits of using various mixtures of staining agents, such as fluorescein–rose bengal[16] and tetrazolium–alcian blue,[17] have been examined. The key characteristics of various staining agents that have been applied clinically are outlined in Table 11.1.

Although the usefulness of some of the alternative staining agents described has been demonstrated, the general utility, safety, broad acceptance and ready availability of fluorescein mean that it is the staining agent of first choice for investigating ocular surface compromise. Rose bengal may be used as a supplementary stain to check for degenerated epithelial cells and mucus, and lissamine green may be especially useful in assessing contact lens-related dry eye. Thus, throughout the remainder of this textbook, reference will only be made to the use of fluorescein, rose bengal and lissamine green, which can be considered to be the primary ocular surface staining agents.

STAINING TECHNIQUE

Fluorescein can be administered in liquid form from an eye dropper, but this method is seldom used today because of the propensity of *Pseudomonas aeruginosa* to flourish in liquid fluorescein sodium and hence the high risk for *Pseudomonas* corneal infection. This problem can be overcome by using sterile single-dose units; however, the standard method of introducing fluorescein dye into the eye is via sterile, single-use fluorescein-impregnated paper strips (Fig. 11.2).

The preferred technique is to introduce a small drop of sterile un-preserved saline onto the fluorescein-impregnated tip of the paper strip and then to lightly apply the end of the strip to the surface of the eye. Although the strip should not be applied directly onto the cornea, it can be applied to any part of the bulbar or palpebral conjunctiva. If conjunctival staining is to be assessed, the strip should be applied to a region of the conjunctiva of 'least interest', such as the lower palpebral conjunctiva. This is because a very high fluorescein concentration will usually be deposited at the point of contact of the fluorescein strip (irrespective of how delicately the fluorescein is applied), leaving an intense discrete region of iatrogenic 'pseudo-staining' (Fig. 11.3).

For instillation of fluorescein into the lower lid, the patient should be asked to look up, the lower lid should be gently retracted by a small amount, and the moistened fluorescein strip should be allowed to lightly touch the inner surface (palpebral conjunctiva) of the lower lid. Physical touch may not be required if a sufficient amount of fluorescein in the form of a 'hanging drop' remains suspended from the moistened strip.

TABLE 11.1 Ocular surface staining agents

Stain	Features revealed/highlighted
Fluorescein sodium	'Colours' the tear film. Fills gaps, thus revealing 'missing' cells. Enters and lightly stains living epithelial cells. Enters and reversibly stains hydrogel lenses.
Fluorexon (Calcein)	Essentially high-molecular-weight fluorescein. 'Colours' the tear film. Fills gaps, thus revealing 'missing' cells. Enters and lightly stains living epithelial cells. Does not fluoresce as brightly as fluorescein Cannot enter and stain hydrogel lenses.
Sulphorhodamine B	Essentially fluorescein with different fluorescent characteristics. 'Colours' the tear film. Fills gaps, thus revealing 'missing' cells. Enters and lightly stains living epithelial cells. Does not fluoresce as brightly as fluorescein.
Lissamine green	Stains degenerated and dead cells. Stains mucus. Similar to rose bengal but better tolerated.
Rose bengal	Stains dead cells. Stains mucus (e.g. mucus threads). Reveals absence of surface mucus by staining normal surface tissue unprotected by mucus
Neutral red	Stains epithelial inclusion bodies and granulocytes. Essentially a less efficient version of rose bengal.
Congo red	Stains dead and degenerate cells. Stains mucus. Similar staining effect as rose bengal and lissamine green, but less effective and less intense.
Alcian blue	Only stains mucus. Acts as a counter-stain to rose bengal to help differentiate between dead cells and mucus.
Trypan blue	Stains dead cells. Stains mucus (e.g. mucus threads).
Bromothymol blue	Stains dead cells. Stains degenerate cells. Stains mucus (e.g. mucus threads).
Methylene blue	Stains nerve tissue. Clearly outlines areas of corneal ulceration.
Tetrazolium	Stains degenerate cells, but not live or dead cells. The red stain colouration only appears about 4 minutes after the stain has entered the cell.
Iodonitrotetrazolium	Stains degenerate cells, but not live or dead cells. The red stain colouration only appears about 4 minutes after the stain has entered the cell.

The amount of fluorescein that enters the eye using the described technique will usually provide the correct balance between there being enough fluorescein to effect useful staining but insufficient to 'flood' the eye, which, in the latter case, could reduce contrast and possibly induce false staining. Abdul-Fattah et al.[18] have demonstrated that the amount of fluorescein entering

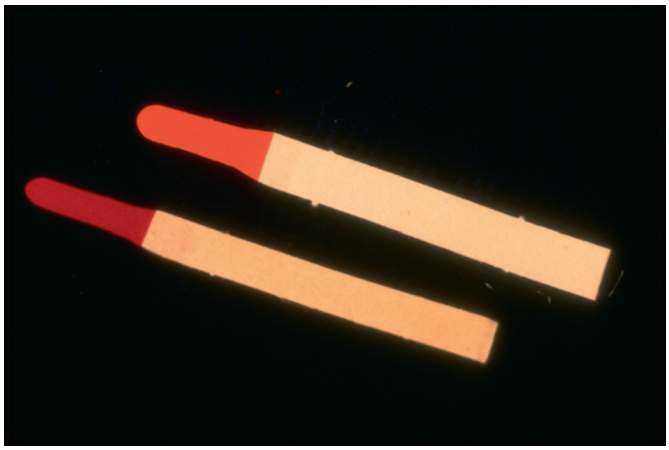


Fig. 11.2 Single-use paper strips with the tips impregnated with sodium fluorescein (top) and rose bengal (bottom). (Courtesy Timothy Golding.)

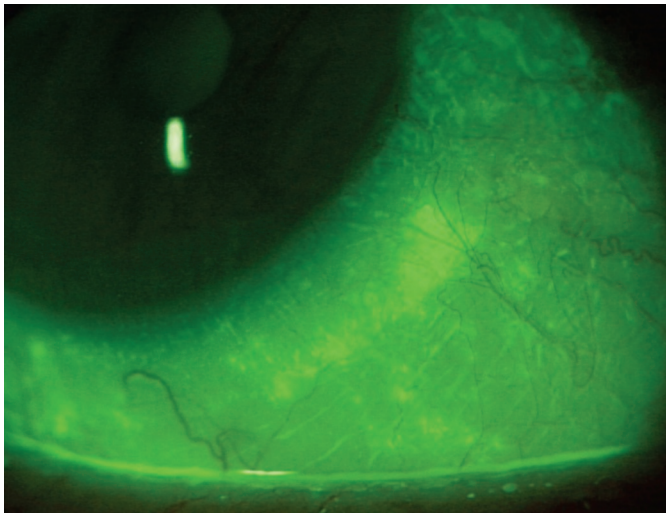


Fig. 11.3 Bright patch of fluorescent 'pseudo-staining' on the conjunctiva corresponding to the location of physical application of a fluorescein-impregnated paper strip to the globe. (Courtesy Suzanne Efron.)

the eye can be controlled by using paper strips in which the fluorescein-impregnated portion varies in area, whereby a smaller area will result in less fluorescein entering the eye. Reduced amounts of fluorescein are usually only required for assessing the tear film in suspected dry eye patients. Korb et al.[19] reported that a specially modified fluorescein strip with a substantially reduced area of fluorescein impregnation (the 'dry eye test') provided a significant reduction in sensation upon application, improved single measurement reliability and enhanced measurement precision, compared with a conventional fluorescent strip.

Signs and symptoms

NORMAL 'FURROW STAINING'

When fluorescein is instilled into a normal eye, patterns of small, thin, curved lines of staining can be observed on the bulbar conjunctiva (Fig. 11.4). The curved lines of staining in regions of conjunctiva close to the cornea are generally concentric with the limbus, whereas they tend to run parallel to the lid margins in regions of the bulbar conjunctiva further away from the cornea. Although the term 'staining' is used to describe these

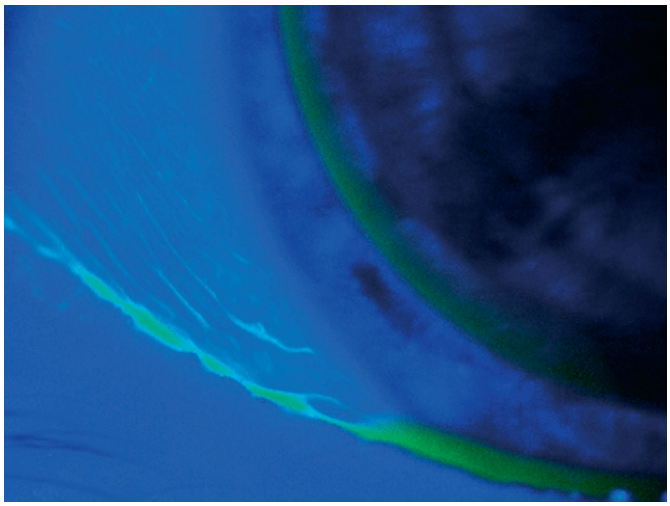


Fig. 11.4 Normal conjunctival furrow staining in a rigid lens wearer. The fine arcuate lines of 'staining' are because of pooling of fluorescein in normal conjunctival folds and are unrelated to lens wear. (Courtesy Brian Tompkins.)

patterns, this is not true staining in that there is no tissue disruption. This appearance is best described as 'normal furrow staining'. What is being observed is pooling of fluorescein in the normal concertina folding or furrows of the conjunctiva.[20] Because the conjunctiva is essentially fixed to the globe at the region of the limbus and to the eyelids, this normal pattern of 'staining' will therefore vary at different gaze directions, as the conjunctiva stretches and folds up in a concertina-like manner to accommodate the position of the globe.

Schwallie et al.[21] have characterised the day-to-day variability in normal conjunctival staining by instilling fluorescein into the eyes of 16 subjects who were monitored for 1 week. All eyes showed some degree of normal conjunctival staining over the week of observation. In total, normal conjunctival staining was noted in 71% of ocular evaluations. Overall, staining ranged from grade 0 to 3, with a mean of 0.5. There was a significant variation in the average grade of staining between subjects. Furthermore, there was a significant variation in the range of grading observed between subjects; the day-to-day range of conjunctival staining varied by 0.5 grading scale units in six subjects, by 1.0 grading scale units in six subjects and by 1.5 grading scale units in four subjects.

A high correlation of staining grade was observed between the two eyes. This finding has important clinical implications in the evaluation of uniocular 'abnormal' conjunctival staining, in that the contralateral (unaffected) eye can be used for comparison with the appearance of the eye that is suspected to have suffered conjunctival compromise.

ABNORMAL STAINING

Stipple staining

A diffuse punctate region of staining (or 'stipple staining') may be observed near the limbus, corresponding to the region of conjunctiva covered by a soft lens (Fig. 11.5). This takes the form of stippling, which refers to a region of numerous, fine, punctate spots. In some areas, these punctate spots tend to coalesce. Confluent areas of staining representing total coalescence, can sometimes be observed in the cornea. Stipple staining is usually only observed in soft lens wearers.

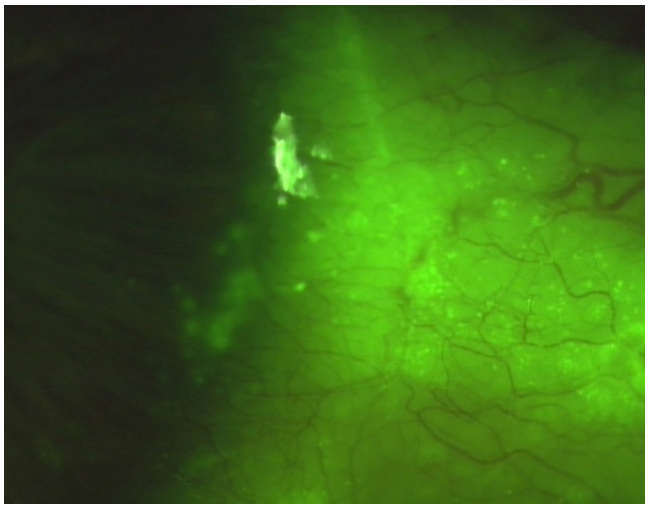


Fig. 11.5 Stipple staining beneath and outside a soft contact lens. The staining in the proximity of the lens edge is more confluent.

Lakkis and Brennan[20] assessed the extent of conjunctival staining in 48 hydrogel lens wearers and 50 non-lens-wearing control subjects. Ignoring the normal furrow staining described previously, these authors observed that only 12% of controls displayed conjunctival staining greater than grade 1.0, whereas 62% of lens wearers had staining above this level. The mean difference in the grade of staining varied between 0.12 and 0.15 for overall conjunctival staining, and contact lens wearers displayed most staining temporally. Neither Lakkis and Brennan[20] nor any of the other authors referred to later specifically described the type of staining they were observing. It is therefore presumed that these authors were observing stipple staining, as defined previously.

Brautaset et al.[22] retrospectively examined the records of 338 adapted hydrogel contact lens wearers and found conjunctival staining to be present in 32.5% of the subjects. Brennan et al.[23] reported an increase in conjunctival staining in patients wearing silicone hydrogel lenses, from baseline grades of 0.39 ± 0.53 and 0.44 ± 0.61 with Acuvue Advance (Johnson & Johnson Vision Care) and Focus Night & Day (CIBA Vision) silicone hydrogel lenses, respectively, to 2-week results of 0.60 ± 0.55 and 0.52 ± 0.69.

Maldonado-Codina et al.[24] investigated the extent of conjunctival staining 2 weeks and 4 weeks after fitting 43 neophytes with one hydrogel lens (Acuvue 2 (Johnson & Johnson Vision Care)) and two silicone hydrogel lenses (Acuvue Advance and Focus Night & Day). Nineteen non-lens-wearing control subjects were also assessed. More conjunctival staining was seen with the silicone hydrogel lenses compared with the conventional hydrogel lenses (Fig. 11.6).

The effect of contact lens preservative system on the ocular surface was investigated by Young et al.[25] They observed that nasal and temporal conjunctival staining was significantly higher after 2 years' use of solutions containing polyhexamethylene biguanide compared with solutions containing polyquaternium-1 ($p < 0.05$).

Zhao et al.[26] reported that in a cohort of patients wearing four different silicone hydrogel lenses and using four different multi-purpose solutions, the amount of protein extracted from lenses was inversely correlated with the extent of conjunctival staining ($R = -0.23$; $p < 0.01$); that is, protein deposition may be protective against conjunctival staining.

Lakkis and Brennan[20] reported that temporal conjunctival staining in soft lens wearers was related to the symptom of dryness and superior conjunctival staining was related more to the symptom of itchiness.

Nichols and Sinnott[27] observed that among 413 contact lens wearers, increased fluorescein corneal staining was associated with increased lissamine green conjunctival staining ($p = 0.002$).

Arcuate staining

An arcuate band of staining corresponding to the lens edge may be seen 2 to 3 mm from the limbus. This may form as a continuous band or as a broken line and can vary from being just visible to being an intense ring of fluorescence up to about 0.5 mm wide. Arcuate conjunctival staining is usually observed in soft lens wearers (Fig. 11.7) but is sometimes seen after overnight wear of rigid lenses that have become decentred during sleep (Fig. 11.8). Covey et al.[28] reported that high levels of conjunctival edge staining occur with silicone hydrogel lenses;

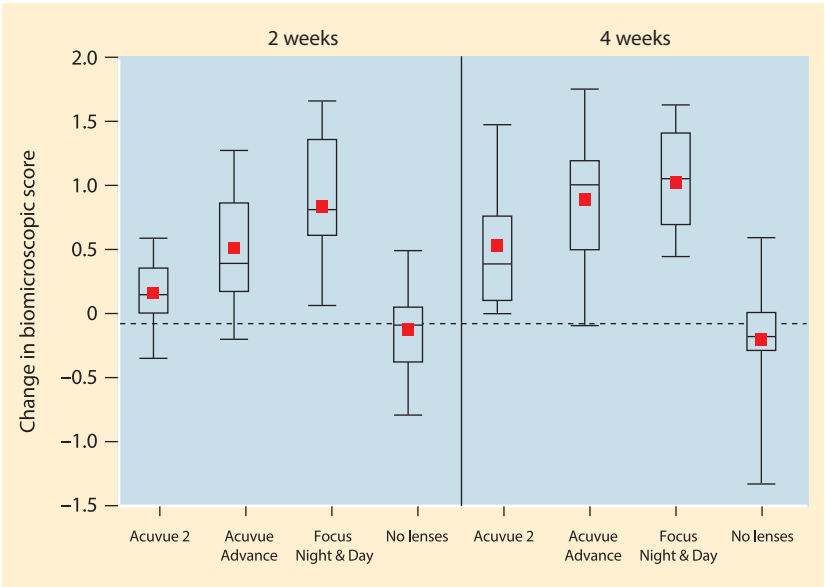


Fig. 11.6 Conjunctival staining. Square, mean; horizontal line, median; box, 25th and 75th centiles; whiskers, extremes of parameters. (Adapted from Maldonado-Codina C, Morgan PB, Schnider CM, Efron N. Short-term physiologic response in neophyte subjects fitted with hydrogel and silicone hydrogel contact lenses. Optom Vis Sci 2004;81:911–21.)

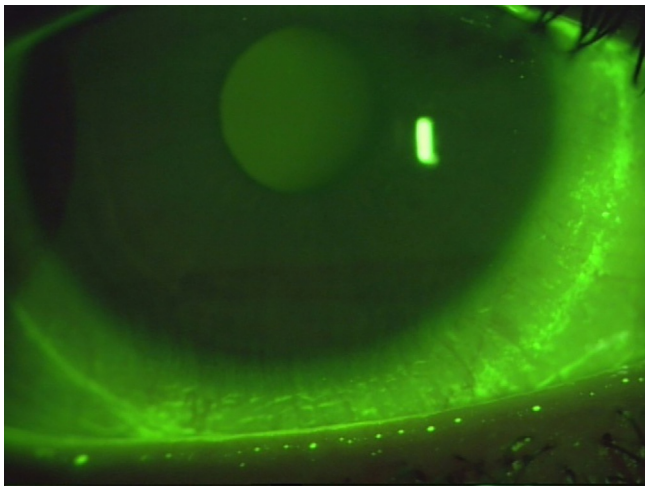


Fig. 11.7 Arcuate band of fluorescein staining corresponding to the edge of an extended-wear silicone hydrogel contact lens.

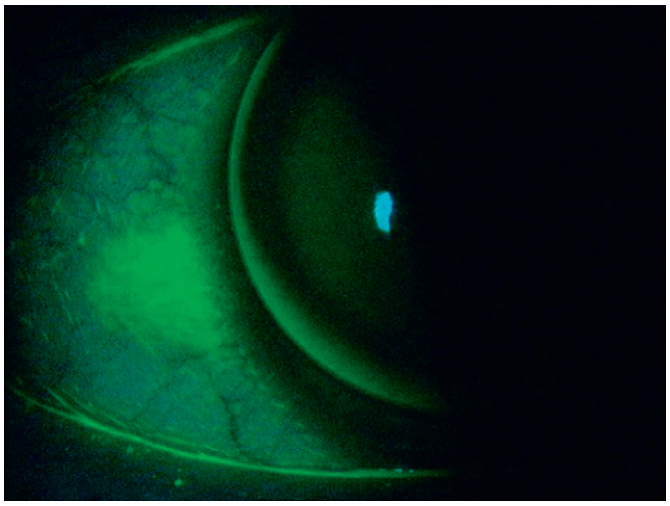


Fig. 11.8 Arcuate band of fluorescein staining corresponding to the edge of a rigid lens, which was bound to the eye upon awakening after overnight lens wear. (Courtesy Suzanne Efron.)

specifically, they reported a mean grade of conjunctival staining of 2.4 ± 0.6 in silicone hydrogel lens wearers versus 0.9 ± 0.7 in non-lens-wearing controls (the latter being 'normal furrow staining').

Maissa et al.[29] assessed arcuate conjunctival staining (using lissamine green) caused by silicone hydrogel contact lenses with different edge designs: Acuvue Oasys (knife edge design), Air Optix, Biofinity (chisel edge–rounded edge combination) and PureVision (rounded edge design), and one hydrogel contact lens, Acuvue 2 (knife edge design). The experiment was conducted on a cohort population of 27 established soft contact lens wearers, with each wearing a different contact lens type, in a random order, for a period of 10 ± 2 days.

The results obtained showed that contact lens edge design was the primary factor in controlling circumlimbal staining for silicone hydrogel lenses: a rounded edge away from the ocular surface produced the lowest staining (average 0.19%) and a knife edge in close apposition to the ocular surface produced the highest staining (average 1.34%). Contact lens material rigidity impacted arcuate staining. An inverse association between arcuate staining and contact lens comfort was demonstrated, with the rounded edge design producing the lowest comfort (72 of 100) and the knife edge design producing the highest (87 of 100). The authors concluded that soft contact lens wear induces arcuate staining, with the level of staining being influenced by the contact lens edge design. However, they observed that high levels of circumlimbal staining were not associated with decreased comfort.[29]

3 & 9 o'clock staining

This is a common form of ocular surface staining observed in association with rigid contact lens wear (Fig. 11.9). Although it is often described in the literature as 3 & 9 o'clock corneal staining, the staining patterns observed usually span the limbus at the temporal and nasal aspects of the cornea and also affect the adjacent conjunctiva.

Conjunctival epithelial flaps

A conjunctival epithelial flap (Fig. 11.10) is a particular form of tissue folding of the bulbar conjunctiva, which has been observed in wearers of silicone hydrogel soft contact lenses.[30,31] It appears as a small tongue-like projection of the conjunctival tissue with irregular free ends and moves with blinking or other

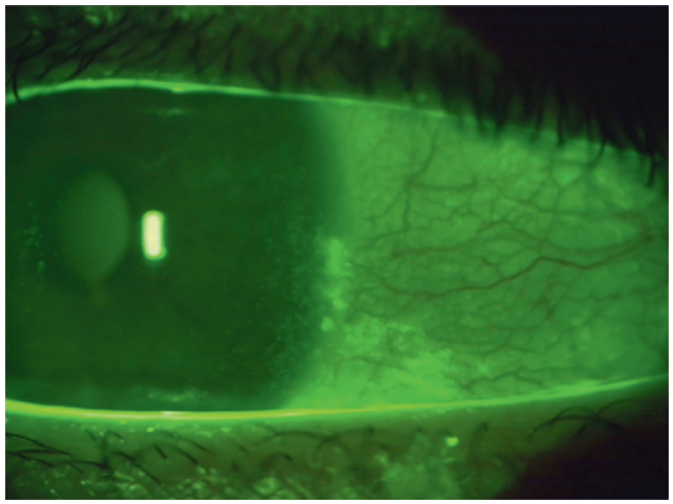


Fig. 11.9 Conjunctival involvement in 3 & 9 o'clock staining in a rigid lens wearer. (Courtesy Carole Maldonado-Codina.)

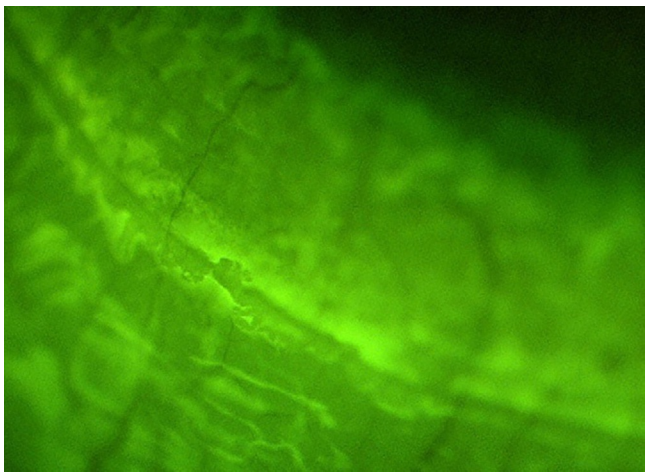


Fig. 11.10 Conjunctival flap. (Courtesy Centre for Ocular Research & Education.)

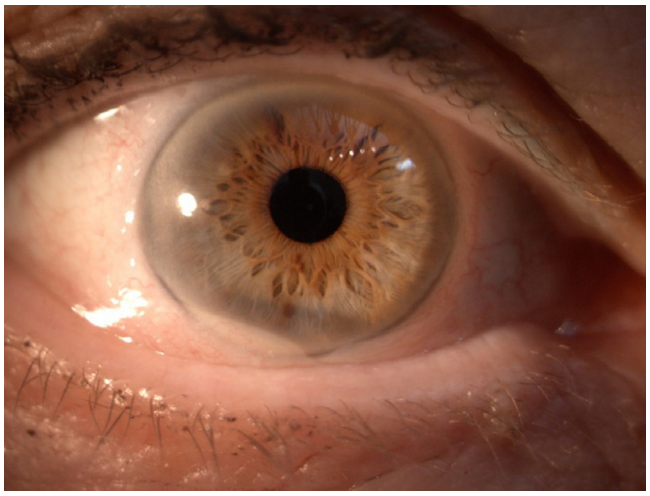


Fig. 11.11 Conjunctivochalasis. (Courtesy Heiko Pult.)

digital manipulation. Typically, there are no associated symptoms or signs.

The flaps are more readily visualised with slit lamp biomicroscopy after instillation of fluorescein. An incidence of 38.7% has been found in 137 silicone hydrogel contact lens wearers during 30-day continuous wear,[30] with a somewhat lower incidence being suggested in daily wear.[31] It has also been found that 39% of cases completely resolve within 1 day of ceasing contact lens wear, 64% resolve within 3 days and 75% resolve within 7 days.[32]

At the first presentation, these features have an average length of 1.4 mm and width of 0.3 mm and are typically located 1.5 mm from the limbus.[32] Although they have been identified in all quadrants of the bulbar conjunctiva, 50% are found superotemporally.[32]

Conjunctivochalasis

Conjunctivochalasis is defined as a redundant, non-oedematous mass of conjunctiva, often in the form of a large fold, which causes a wide variety of symptoms ranging from being completely asymptomatic to causing symptoms of dry eye resulting from a mechanical disruption to tear flow. The condition can be observed clearly in white light under the slit lamp biomicroscope (Fig. 11.11) and can manifest as a prolapse of the conjunctiva over the lower lid margin in temporal, medial or nasal regions.

Mimura et al.[33] assessed the extent of conjunctivochalasis in 94 rigid contact lens wearers, 506 soft contact lens wearers and 579 non-lens-wearing control subjects. The prevalence of conjunctivochalasis increased dramatically with age in all groups. The mean grade of conjunctivochalasis was higher in contact lens wearers than in non–lens wearers ($p < 0.00001$) and was higher in rigid lens wearers than in soft lens wearers ($p < 0.00001$). The authors suggested that contact lens wear is a risk factor for conjunctivochalasis.

Pathology

A variety of techniques have been used to assess the pathological changes occurring in the conjunctiva as a result of contact lens wear.

FLUORESCEIN STAINING

Morgan and Maldonado-Codina[34] pointed out that despite the widespread adoption of use of fluorescein for the assessment of the ocular surface, clinical understanding and interpretation of tissue fluorescence are based on assumption, extrapolation and clinical intuition, rather than solid evidence-based science underpinning the basic causative mechanisms of this phenomenon.

It is currently believed that fluorescein staining is observed when fluorescein fills gaps, as in the case of the 'normal conjunctival staining' resulting from pooling within conjunctival folds. Contrary to previous belief, fluorescein enters sub-populations of healthy, living cells, resulting in mild hyper-fluorescence.[35] Fluorescein does not appear to enter lysed or damaged cells.[35] Lens-induced fluorescein staining may also indicate missing cells or gaps created by compression of the lens edge (see 'Aetiology'). Conjunctival epithelial cells may become damaged or dislodged if there is insufficient lubrication between the lens and conjunctiva, as could occur in a patient with a pre-existing or lens-induced dry eye. Deposits on the back surface of a lens could physically traumatise or dislodge conjunctival cells.

IMPRESSION CYTOLOGY

The integrity of the conjunctiva during contact lens wear has been studied using impression cytology. This is a mildly invasive technique whereby a small disc of filter paper is momentarily pressed onto the anaesthetised conjunctiva and then removed. Superficial conjunctival epithelial and goblet cells adhere to the filter paper, which is fixed to a glass slide, stained and examined under a microscope. Using this technique, Adar et al.[36] reported alterations to conjunctival epithelial cell morphology, a reduction in goblet cell density and the appearance of snake-like chromatin in a group of contact lens wearers, especially those who were symptomatic. Albietz[37] also reported a significant reduction in goblet cell density and a greater expression of ocular surface antigens to the conjunctival inflammatory markers human leucocyte antigen DR and CD 23 in contact lens wearers versus controls. There was an even greater level of conjunctival inflammatory markers in symptomatic lens wearers (principally complaining of 'dry eye').

Two longitudinal studies have documented a decrease in goblet cell density in contact lens wearers over time. By using both conjunctival impression cytology and laser scanning confocal microscopy, Colorado et al.[38] found that contact lens wear induces a reduction in goblet cell density over 6 months, which is exacerbated in those with dry eye symptoms. Simon et al.[39] reported a decrease in goblet cell density after fitting participants with soft and rigid lenses for 6 months. These authors used conjunctival impression cytology and correlated the severity of symptoms with cytological alterations by using a grading system for squamous metaplasia.

In contrast to the findings of other researchers using impression cytology, Connor et al.[40] reported an *increase* in goblet cell count in patients wearing 2-weekly replacement lenses and attributed this to be a beneficial adaptive response to mechanical insult caused by the lens. These authors subsequently reported that daily disposable lens wear does not result in a reduction in goblet cell density, suggesting that this modality of lens wear is less irritating to the ocular surface than lenses which are not replaced daily.[41] The validity of these two studies[40,41] has been

challenged in view of questionable aspects of the methodology adopted by these authors.[38]

Two groups[42,43] have reported that soft contact lens wear can result in cell enlargement (squamous metaplasia) of the bulbar conjunctival cells. With this cell enlargement, the nucleus-to-cytoplasm ratio also changes, but the nucleus size generally increases (rather than decreasing).[43]

CONFOCAL MICROSCOPY

Efron et al.[44] have demonstrated the capabilities of laser scanning confocal microscopy for undertaking qualitative and quantitative investigations of the response of the bulbar conjunctiva to contact lens wear. Specifically, this technique was used to observe and measure morphological characteristics of the bulbar conjunctiva of 11 asymptomatic soft contact lens wearers and 11 healthy volunteer subjects (controls). They found that the thickness of the bulbar conjunctival epithelium of lens wearers (30.9 ± 1.1 μm) was less than that of controls (32.9 ± 1.1 μm) ($p < 0.0001$). Superficial and basal bulbar conjunctival epithelial cell densities in contact lens wearers were 91% and 79% higher, respectively, than that in controls ($p < 0.0001$). No difference was observed in goblet and Langerhans cell density between lens wearers and controls. Conjunctival microcysts were observed in greater numbers and were larger in size in lens wearers compared with controls.

Images of bulbar conjunctival goblet cells obtained using light microscopy, impression cytology and laser scanning confocal microscopy are shown in Figure 11.12.

IN VITRO EXAMINATION OF CONJUNCTIVAL TISSUE

Irrigation

Other techniques have been used for examining the integrity of the conjunctiva, but these produce less satisfactory information. The corneal irrigation chamber[45] is used primarily for collecting tear fluid overlying the cornea; however, the irrigation procedure also results in the collection of loose conjunctival cells (Fig. 11.13). Norn[46] described a method involving cytological examination of conjunctival cells collected in tear fluid from the inferior conjunctival fornix.

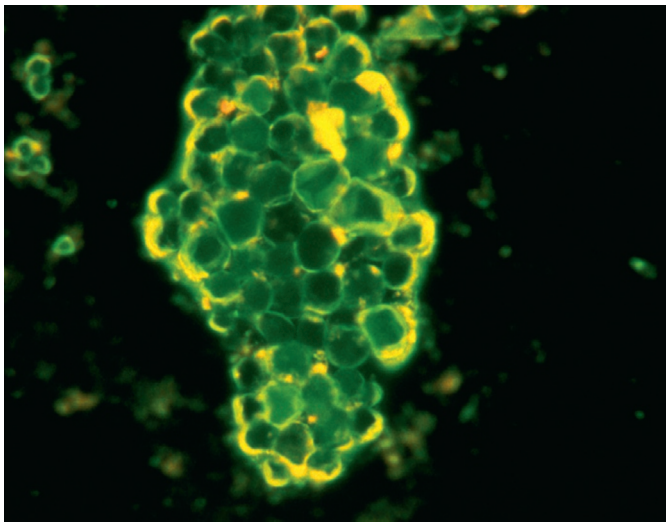


Fig. 11.13 A clump of cuboidal conjunctival cells collected using the irrigation chamber. (Courtesy Shameem Amirbayat.)

Scraping or swabbing

Scraping the anaesthetised conjunctiva with a surgical blade[47] or swabbing with a cotton-tipped applicator[48] is somewhat invasive, and cells are prone to being lost or damaged during transfer.

Biopsy and immunohistochemistry

Conjunctival biopsy (excision of a small tissue sample) preserves the three-dimensional structure of the tissue sample and is highly invasive; therefore, this technique is generally only suitable for scientific investigations.[49]

Colorado et al.[50] examined a single tissue sample obtained from a pterygium that was freshly excised from a 33-year-old male. After observing under a laser scanning confocal microscope what were believed to be goblet cells in the tissue sample, the same sample was observed with laboratory confocal microscopy and immunohistochemistry. Goblet cells were identified by a combination of classic morphological appearance and the use of immunofluorescence to antibodies for mucin 5AC

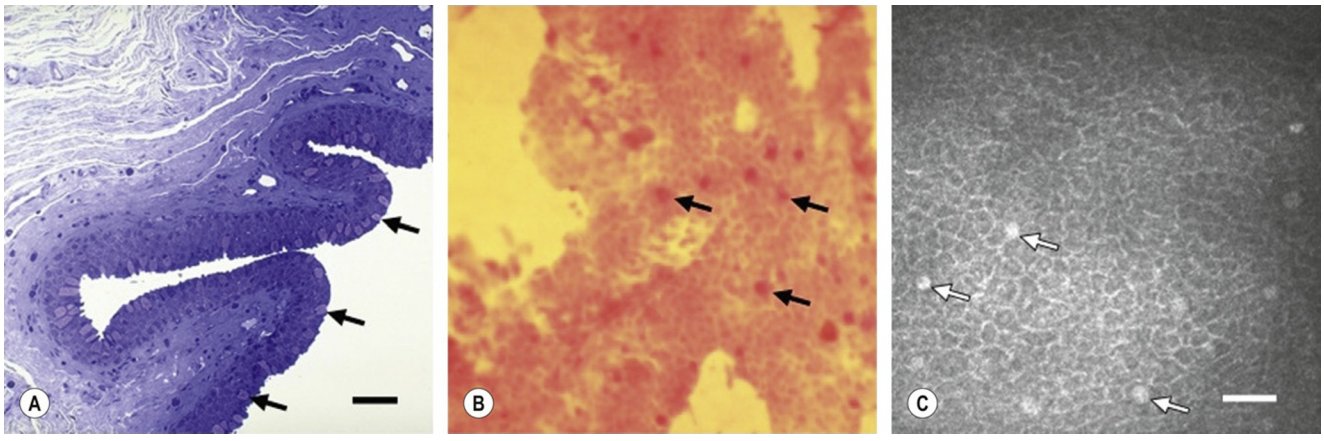


Fig. 11.12 Images of goblet cells obtained using three different techniques. **(A)** Cross-section of conjunctival epithelium imaged by using light microscopy. Stain: 1% toluidine blue. Bar = 50 μm. **(B)** Flat mount of conjunctival sample removed from the ocular surface using impression cytology. **(C)** En face image of basal epithelium imaged with a laser scanning confocal microscope. Bar = 50 μm. In each image, three goblet cells are identified by arrows. (From Efron N, Al-Dossari M, Pritchard N. Confocal microscopy of the bulbar conjunctiva in contact lens wear. Cornea 2010;29:43–52.)

and cytokeratin-7. Using confocal microscopy, goblet cells were observed to be 7 to 41 μm deep, at the level of the superficial basal cells of the tissue sample. Goblet cells were estimated to have a diameter of 35 to 40 μm near the surface and 20 to 30 μm in the deeper layers. A small dark dot was visible in some goblet cells, indicating cell nuclei and/or the opened apical portion of cells representing the site of mucin release. Goblet cells were more reflective and larger than the surrounding cells. Positively stained goblet cells in immunofluorescence showed a similar distribution pattern to those observed with confocal microscopy. The tissue sample stained intensely for goblet cell–specific mucin type 5AC. Colorado et al.[50] concluded that the pattern of discrete, large reflective cells observed by using confocal microscopy is likely to be goblet cells.

Markoulli et al.[32] used histopathological methods to examine tissue samples obtained from the region of conjunctival epithelial flaps of two patients. Analysis of the flap tissue showed even collagen distribution in one subject and a mild focal increase in collagen and mild degeneration of collagen in the other subject, but no increase in elastic tissue and overall normal histology. Bergmanson et al.[51] made similar observations; they reported that conjunctival epithelial flaps appeared to be formed by healthy epithelial and goblet cells that have been dislocated from their normal location along the conjunctival surface by the lens edge. No inflammatory cells were present.

Aetiology

STIPPLE STAINING

In their analysis of contact lens–induced conjunctival stipple staining, Lakkis and Brennan[20] were unable to identify any link between the extent of staining and subject age and sex, contact lens–wearing experience, wearing time per week, wearing time on the day of the examination, lens water content, lens age, lens movement, lens decentration, lens lag in upgaze or lens maintenance system. The only association found was with the symptom of dryness and itchiness. Robboy and Cox[52] suggested that reduced tear film quality in soft lens wearers may be the cause of conjunctival staining whereby a lack of tear fluid leads to conjunctival desiccation and associated tissue disruption.

Stipple or punctate conjunctival staining close to the limbus could be caused by either mechanical irritation of a loosely fitted soft lens (moving to such an extent that the lens edge impinges upon the limbus) or some other property of the peripheral zone of the lens. Deposits on the back surface of a soft lens, close to the lens edge, could theoretically result in abrasion of the conjunctiva.

It is unlikely that conjunctival staining is attributed to lens-induced hypoxia because conjunctiva at the limbal region is supplied with an oxygen-rich vascular supply. Furthermore, there does not appear to be any relationship between conjunctival staining and infection. Norn[2] observed that the conjunctiva did not stain with infectious keratitis, and Lakkis and Brennan[20] demonstrated that most individuals have conjunctival staining in the absence of infection. The findings of Young et al.[25] suggested that long-term use of certain contact lens preservative systems may have a chronic cytotoxic effect that compromised conjunctival epithelial integrity, leading to conjunctival staining. Increased osmolarity of contact lens solutions that may occur during long-term storage can also lead to increased conjunctival staining.[53]

ARCUATE STAINING

It is likely that significant arcuate staining corresponding to the edge of a lens is related to the physical presence of the lens edge. The staining could be attributed to compression into the conjunctiva by a tight-fitting lens, resulting in an indentation in which fluorescein pools. Indirect support for this theory comes from the finding of Robboy and Cox,[52] who described a significant inverse relationship between conjunctival staining and lens movement; that is, the edge of a static, tight-fitting soft lens is more likely to compress the conjunctiva compared with a free-moving lens. Lenses with a high modulus of elasticity (i.e. more stiff), such as early generation silicone hydrogel lenses, are also prone to cause conjunctival indentation and subsequent staining.[28] This probably results from the edge profile of the lens failing to yield sufficiently so as to conform to the surface topography of the globe but instead retaining its edge form and pressing into the conjunctiva. Hydrogel lenses of lower modulus would be more likely to conform to the surface anatomy of the eye.

Lens edge staining, as the name suggests, can be attributed to physical abrasion of the lens edge rubbing against the conjunctiva; certainly, such a mechanism was likely to have occurred in the case of imperfect and or unpolished lens edges in the early days of disposable soft contact lenses.[54-57]

3 & 9 O'CLOCK STAINING

The appearance of rigid lens-induced 3 & 9 o'clock staining is caused by limbal tissue desiccation. The lens bridges the upper lid away from the eye, preventing proper ocular surface wetting by the lid wiper.[58]

CONJUNCTIVAL EPITHELIAL FLAPS

A mechanical hypothesis has been proposed to explain the formation of conjunctival epithelial flaps. Specifically, increased lens–tissue interaction resulting from the higher stiffness and sharper edges of some higher-modulus silicone hydrogels has been hypothesised to be a contributing factor.

Markoulli et al.[32] proposed that contact lens edge pressure, combined with lens motion, creates a conjunctival bleb or blister that eventually ruptures, thus forming the characteristic conjunctival flap with its irregular edge (Fig. 11.14). They suggested that lens stiffness, edge design, fitting relationship, lens design and lens wear schedule could be contributing factors. In view of the appearance of this lesion and the proposed mechanism of formation, Markoulli et al.[32] proposed an alternative term for this condition: contact lens–induced conjunctival schisis.

CONJUNCTIVOCHALASIS

The mechanism by which contact lenses induce or exacerbate conjunctivochalasis is unknown. Mimura et al.[33] propose that wearing contact lenses can cause chronic conjunctival inflammation attributable to hypoxia, mechanical friction, dehydration or incompatibility with the lens material and that these conjunctival inflammatory responses may result in conjunctivochalasis.

The pathogenesis of conjunctivochalasis is thought to involve the degeneration of elastic fibers.[59] The clinical manifestation of redundant bulbar conjunctiva is attributable to

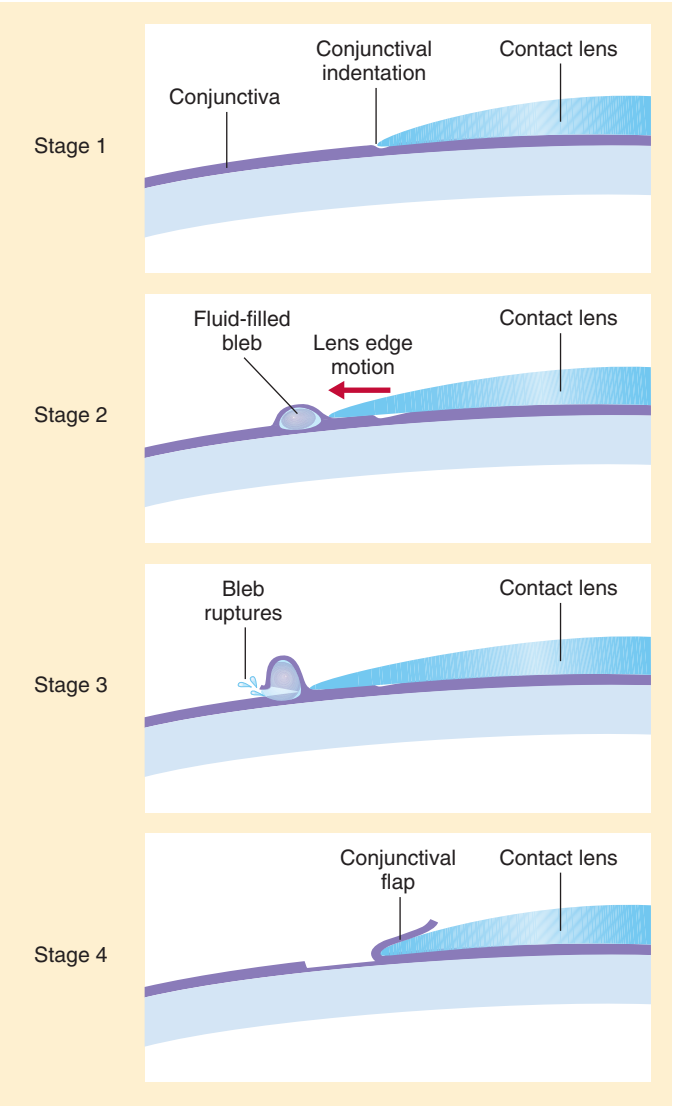


Fig. 11.14 Schematic representation of hypothesised mechanism for conjunctival flap formation. Stage 1: Repeated motion of the contact lens edge against the conjunctiva initially results in indentation. Stage 2: Formation of a bleb at, or near, the lens edge. Stage 3: Continued lens movement causes bleb rupture on side distal to lens. Stage 4: Resulting loose tissue forms the conjunctival flap. Note that the free edge of the flap created is distal to the contact lens edge, consistent with general clinical observation. (Adapted from Markoulli M, Francis IC, Yong J, et al. A histopathological study of bulbar conjunctival flaps occurring in 2 contact lens wearers. Cornea 2011;30:1037–41.)

increased collagenolytic activity, which may contribute to the pathological process of conjunctivochalasis. Watanabe et al.[60] reported that degenerative structural changes of the conjunctiva are involved in the pathogenesis of conjunctivochalasis. Elastotic degeneration may be involved in the pathogenesis of contact lens–induced conjunctivochalasis and age-related conjunctivochalasis.

Treatment

Since mechanical factors are the most likely cause of many of the forms of conjunctival staining described earlier, it follows that removal of the mechanical insult should lead to a resolution of staining. Of course, action only needs to be taken if the severity of staining is deemed to be of clinical significance. A grading scale for conjunctival staining is given in Appendix A. As a general rule, conjunctival staining of less than grade 3 may not require clinical action,[20] although the patient should be monitored carefully. Clinical intervention is required when the conjunctival staining is greater than grade 3 and/or when there is associated pathology, such as venous stasis distal to lens edge compression or excessive conjunctival or limbal redness in the region of the conjunctival insult. The key clinical intervention in such cases is the immediate cessation of lens wear.

In the case of soft lenses, edge staining can be alleviated by changing the lens fit so that the lens edge does not compress the conjunctiva. Two key strategies are indicated. First, the lens should be fitted so as to create a looser fit. This should result in greater lens movement and in that way prevent lens edge bearing in a fixed location. Second, a lens with greater back optic zone radius (flatter fit) should be fitted so that less inward force is brought to bear by the lens edge against the conjunctiva. Of course, fitting a flatter lens will also generally create a looser fit, allowing both strategies to be invoked simultaneously.

The solution to lens edge staining with higher-modulus silicone hydrogel lenses is more problematic. Such staining is attributed to the increased stiffness of the lens material, so fitting a lens made of a lower-modulus material may solve the problem. Changing to a lens with a flatter base curve will also ease off lens pressure against the globe. If the staining still persists and the severity of staining is judged to be clinically significant, then the patient may have to change to hydrogel or rigid lenses.

If the conjunctival staining is thought to be a result of lens edge imperfections, then replacing the lens should solve the problem. If such conjunctival staining persists despite frequent lens replacements, the problem may be related to an inferior product rather than to a 'one-off' problematic lens; in such circumstances, changing to a product of superior edge quality is indicated. Conjunctival staining attributed to direct mechanical abrasion from deposits on the posterior lens surface can be alleviated by tackling the deposit problem by employing one or more of the following strategies: (a) improving the lens cleaning regimen, (b) changing to a lens material that is less prone to deposition or (c) prescribing a lens that is to be replaced more regularly.

Practitioners need to remain mindful of the demonstration by Young et al.[25] – that chronically elevated levels of conjunctival staining may be attributed to long-term use of certain contact preservative solutions. If the use of a particular lens care system is suspected as being the cause of elevated levels of conjunctival staining, patients should be advised to try alternative solutions.

If the observed conjunctival staining is thought to be related to dry eye, then any of the strategies available for alleviating dry eye (see Chapter 9) should help reduce or eliminate staining. Reduced conjunctival staining has been noted in patients treated with 3% diquafosol tetrasodium solution[61] and cyclosporine 0.05% ophthalmic emulsion[62] for contact lens–associated dry eye.

Fahmy et al.[63] demonstrated that symptomatic patients who were replacing lenses every 1 to 4 weeks exhibited significant improvements in conjunctival staining when they changed into daily disposable lenses after 2 weeks ($p = 0.035$) and 4 weeks ($p < 0.008$).

Rigid lenses generally will not physically impinge on the conjunctiva but may adversely affect the limbal conjunctiva by preventing proper wetting of the ocular surface adjacent to the lens edge. The latter case may represent a precursor to 3 & 9 o'clock corneal staining; the various strategies that have been advocated to resolve this problem are outlined in Chapter 18. Lens edge conjunctival staining after overnight wear of rigid lenses is usually associated with overnight lens binding, even though the lens may not appear to be bound when examining the patient later the same day after overnight wear. Strategies for alleviating overnight rigid lens binding will necessarily also resolve conjunctival staining arising from the bound edge of a decentred lens that impinges on the conjunctiva.

Prognosis

The prognosis for recovery from contact lens–induced conjunctival staining is good; Knop and Brewitt[64] reported that contact lens–induced mechanical damage to the conjunctiva reverses after ceasing lens wear. According to Schwallie et al.,[21] the average duration of an episode of conjunctival staining in non–lens wearers is 2.0 ± 2.4 days. From this information, they concluded that most forms of conjunctival staining should resolve within about 4 days of ceasing lens wear; if it does not, then alternative causes of staining need to be investigated.

The prognosis for recovery from contact lens–induced conjunctival staining has not been investigated but is also likely to be within 4 days of cessation of lens wear. Further research is required to confirm this. As a general guide, after cessation of contact lens wear because of excessive conjunctival staining, lens wear should not be recommenced until the severity of staining has subsided to below grade 1.0.

Differential diagnosis

The primary exercise in the differential diagnosis of conjunctival staining is to be able to discern physiological staining from pathological staining. As highlighted by Lakkis and Brennan,[20] the arcuate conjunctival folds or furrows are normal and are observed in all lens wearers and non–lens wearers.

The location of conjunctival staining can be an important clue to the differential diagnosis. The diagnosis of deep continuous arcs or rings of conjunctival staining corresponding to the lens edge is self-evident, although the cause of punctate conjunctival staining is less obvious. Conjunctival staining adjacent to the 3 & 9 o'clock corneal locations is caused by rigid lens edge bridging.

Normal corneal furrow staining may be difficult to distinguish from mild forms of conjunctival epithelial flaps and conjunctivochalasis since all stain with fluorescein and all have linear structural components. Gentle manipulation with a cotton bud under anaesthesia may help reveal the extent of conjunctival flap, or redundant, non-oedematous tissue in the case of conjunctivochalasis.

A bright patch of conjunctival staining may well be iatrogenic and correspond to the location of overzealous application of a fluorescein strip to the eye.

Lid-parallel conjunctival folds, which are considered in detail in Chapter 12, are small folds adjacent and parallel to the inferior lid margin. They can be clearly seen without the aid of fluorescein, being more easily observed in white light.

CONJUNCTIVAL MUCIN BALLS

Small round intense spots of conjunctival staining observed near the limbus may be conjunctival mucin balls (Fig. 11.15). These are balls of mucin embedded in the conjunctival epithelium, and they occur almost exclusively with silicone hydrogel lenses (see Chapter 10). In white light, the mucin balls are clearly visible as spherical refractile elements (like small spherical beads of glass), and they exhibit a pattern of distribution that corresponds with the staining pattern (Fig. 11.16). Thus, silicone hydrogel lens wear is a key factor in differentially diagnosing conjunctival mucin balls from other causes of conjunctival stipple staining.

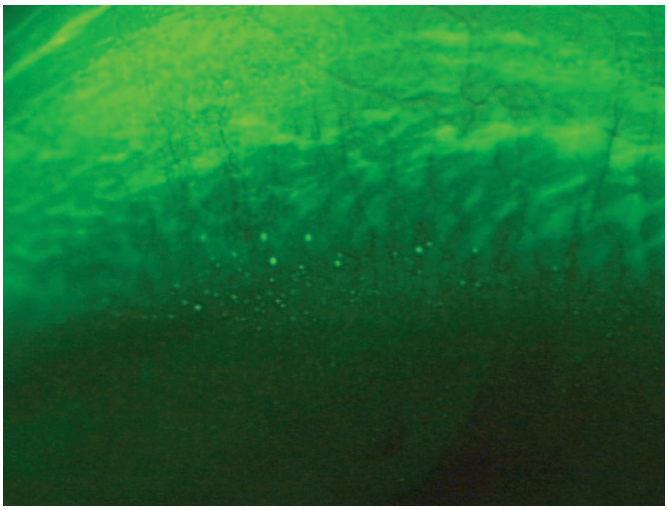


Fig. 11.15 Bright spots of conjunctival staining indicating the presence of mucin balls. (Courtesy Carole Maldonado-Codina.)

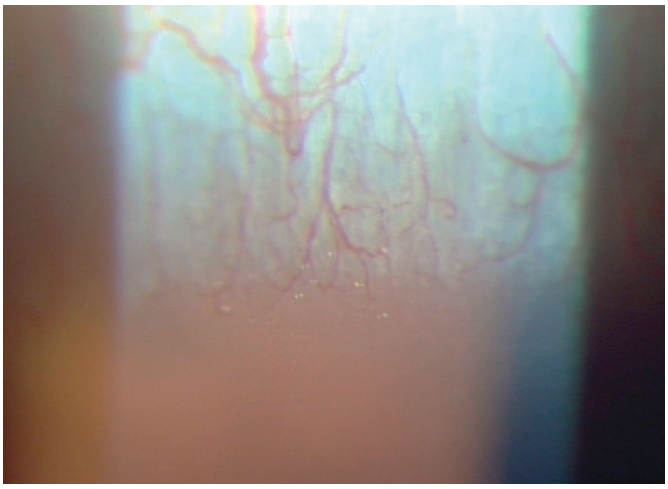


Fig. 11.16 Mucin balls embedded in the conjunctiva, seen here in white light. (Courtesy Carole Maldonado-Codina.)

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12 Lid-Parallel Conjunctival Folds

Lid-parallel conjunctival folds (LIPCOFs) are sub-clinical folds in the lateral, lower quadrant of the bulbar conjunctiva, parallel to the lower lid margin, which are easily observable with the slit lamp biomicroscope (Fig. 12.1). This phenomenon, first described by Hoh et al.[1] in 1995, has received considerable attention in the literature since then. LIPCOFs are not an adverse ocular reaction; rather, it is a sign of dry eye, including contact lens-associated dry eye.

Signs

SLIT LAMP BIOMICROSCOPY

LIPCOFs are assessed at two specific locations where they manifest most clearly.[2] These locations are just above the lower lid margins, at points where an imaginary perpendicular line projects from the nasal and temporal extremities of the cornea. LIPCOFs appear as one or more linear folds which are 3 to 4 mm in length and are parallel to the lid margin and generally parallel to each other.

The preferred observation technique using the slit lamp biomicroscope is as follows. LIPCOFs can be assessed with or without contact lenses being worn. The patient is instructed to gaze straight ahead. Fluorescein or any other dye should not be instilled, as LIPCOFs are best observed in white light. A magnification of around ×25 is selected and, in the first instance, a narrow vertical beam is aligned with the nasal or temporal cornea. LIPCOFs can be observed at the inferior lid margin (Fig. 12.2). The linear folds can be inspected in both direct and indirect illumination (in the latter case, on either side of the beam). The height of the fold, or series of folds, should be recorded in millimetres.

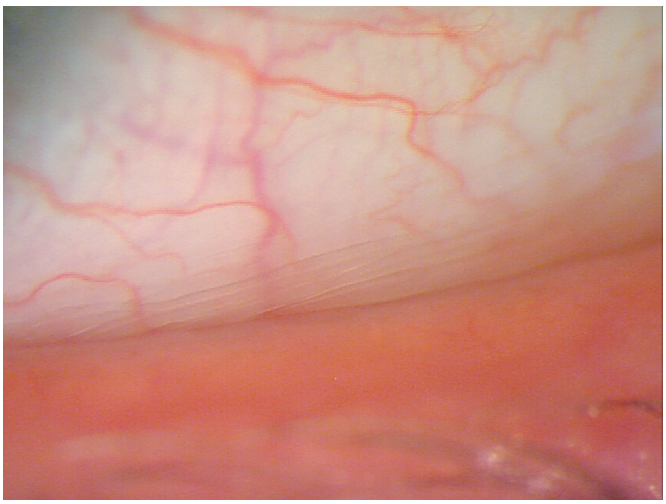


Fig. 12.1 Lid-parallel conjunctival folds. (Courtesy Nancy Kier.)

The observation of folds can be further enhanced by rotating the slit beam so that it is parallel with the folds and the lid margin. The slit beam is positioned above the folds, which can be seen in indirect illumination. Examples of slit lamp illumination techniques for observing LIPCOFs are shown in Fig. 12.3.

The severity of LIPCOFs can be determined by counting the number of folds and assigning a grade accordingly, as shown in Table 12.1. Examples of grades 1 and 2 LIPCOFs are shown in Fig. 12.4. A further combined LIPCOF score (LIPCOF Sum) can be calculated by adding together the nasal and temporal LIPCOF grades.

ANTERIOR SEGMENT OPTICAL COHERENCE TOMOGRAPHY

Anterior segment optical coherence tomography offers a non-invasive, high-resolution method of imaging, evaluating and classifying LIPCOFs. Veres et al.[3] devised three different algorithms to grade LIPCOFs according to tear meniscus height of the covering tear film on the folds, which showed significant correlation with the slit lamp method ($r = 0.470–0.473$, $p < 0.01$). By using this technique, the number of folds can be observed, and various physical dimensions of LIPCOFs can be determined (Fig. 12.5).

Tapaszto et al.[4] used Fourier-domain optical coherence tomography to assess alterations in LIPCOF morphology in the eyes of contact lens wearers; these assessments were repeated after removal of the contact lenses. The presence, height and number of conjunctival folds and the tear meniscus area were evaluated. The authors observed that after removal of the contact lens, the height of the LIPCOF significantly decreased ($p < 0.001$) and the tear meniscus area significantly increased ($p = 0.017$). Although the number of LIPCOFs did not change ($p = 0.971$), LIPCOF coverage by the tear film increased after lens removal.

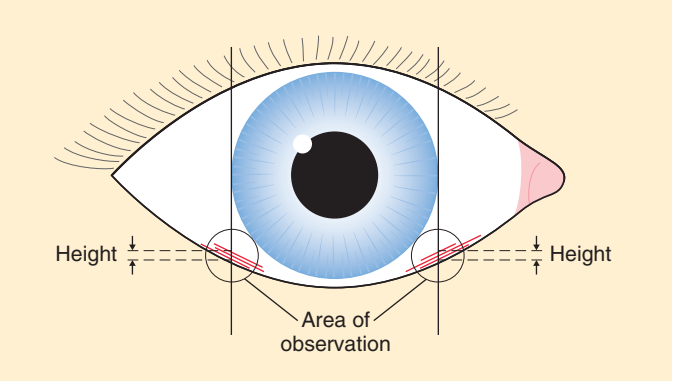


Fig. 12.2 Area of the eye (circles) where LIPCOFs should be observed and graded. (Courtesy Heiko Pult.)

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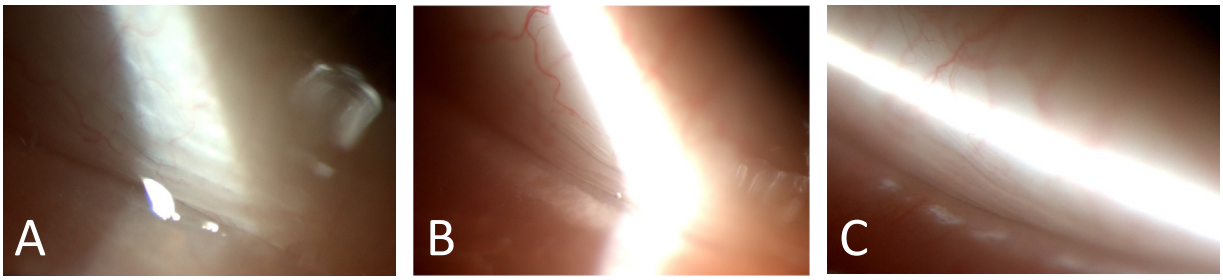


Fig. 12.3 Different illumination techniques for observing LIPCOFs. **(A)** Direct illumination with a vertical beam; LIPCOFs can be seen within the beam. **(B)** Indirect illumination with a vertical beam; LIPCOFs can be seen to the left of the beam. **(C)** Indirect illumination with beam set parallel to the lid margin; LIPCOFs can be seen beneath the beam. (Courtesy Heiko Pult.)

TABLE 12.1 Grading schema for LIPCOF

Description	LIPCOF grade
No conjunctival folds	0
One permanent and clear lid-parallel fold	1
Two permanent and clear lid-parallel folds	2
Three or more permanent and clear lid-parallel folds	3

LIPCOF, Lid-parallel conjunctival folds.

These results suggest that when grading LIPCOFs, the mechanical forces of the lens and the tear meniscus should be taken into account. Thus, repeated measures over time should all be taken using the same protocol (i.e. either all with contact lenses or all without contact lenses).

Symptoms

The clinical significance of LIPCOFs is that their appearance is generally associated with symptoms of dry eye. This association was proposed in the original paper on LIPCOFs by Hoh et al.,[1] who found a negative predictive value (NPV) of 76% and a positive predictive value (PPV) of 93% for the diagnosis of dry eye on the basis of the presence of LIPCOFs.

Pult et al.[5] investigated the value of LIPCOFs in predicting contact lens–associated dry eye by assessing this parameter and other dry eye measures in 38 asymptomatic and 23 symptomatic lens wearers. LIPCOF severity scores were significantly increased in symptomatic patients (U-test, $p < 0.03$), although no significant differences were found between groups for pre-lens tear break-up time, corneal staining or hyperaemia

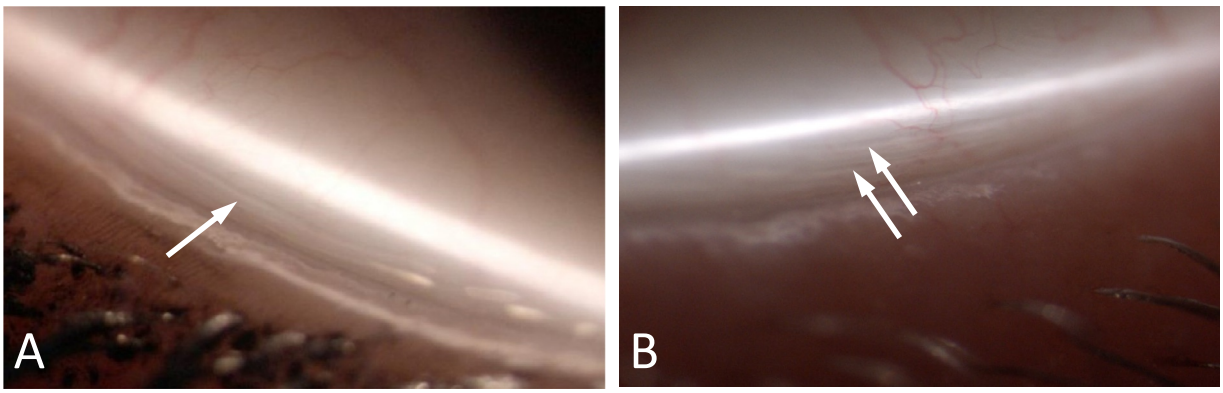


Fig. 12.4 LIPCOF grading. **(A)** A single fold can be seen (arrow), indicating LIPCOF grade 1. **(B)** Two folds can be seen (arrows), indicating LIPCOF grade 2. (Courtesy Heiko Pult.)

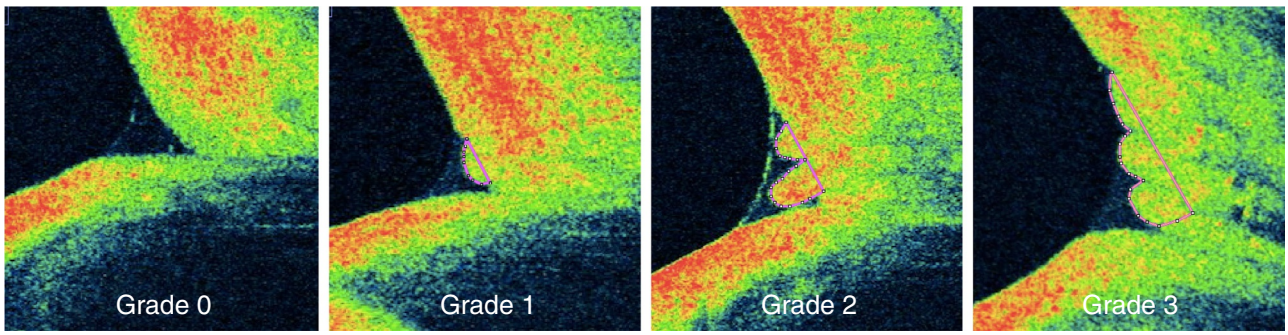


Fig. 12.5 LIPCOF grading using anterior segment optical coherence tomography. The number of folds (outlined) can be clearly seen, with one, two and three folds evident in grades 1, 2 and 3, respectively. (Courtesy Bandlitz S, Purslow C, Murphy PJ, Pult H. The usefulness of optical coherence tomography in LIPCOF grading. Poster presented at the Annual Meeting of the British Contact Lens Association, Liverpool, UK. June 2017.)

($0.29 < p < 0.88$). The predictive value of temporal LIPCOF was positive in 56.9% and negative in 77.1%, with a cutoff value of ≥ 2 (PPV/NPV/cutoff value), of nasal LIPCOF 70.7%/75.0%/$\geq$1 and of LIPCOF Sum 79.8%/86.5%/$\geq$2.

Pult et al.[6] subsequently investigated whether LIPCOF scores, combined with scores of other anterior eye parameters, could better predict dry eye symptoms in new contact lens wearers. They found that the best test combination to predict contact lens–associated dry eye was LIPCOF Sum plus non-invasive break-up time and the Ocular Surface Disease Index (PPV = 87% and accuracy = 91%).

Berry et al.[7] investigated whether alterations of mucins were detectable in symptomatic soft contact lens wearers. The authors examined 31 asymptomatic and 19 symptomatic lens wearers and found that LIPCOFs were significantly increased ($p < 0.035$) and MUC5AC reactivity was significantly decreased in symptomatic subjects ($p = 0.050$). MUC4 correlated to temporal LIPCOF ($r = -0.47$; $p < 0.01$).

The usefulness of LIPCOFs for diagnosing dry eye has been challenged by Miller et al.,[8] who could find little difference in LIPCOF grades between patients with dry eye disease and those without.

Pathology

The essential structural change that leads to the appearance of LIPCOFs appears to be a concertina-like folding of the conjunctival tissue adjacent to the lid margin. Fig. 12.6 is a schematic illustration of the structural construct of LIPCOF.

The morphology of LIPCOF has not been investigated, but may share some similarities with other structural alterations of the conjunctiva – such as conjunctival flaps and conjunctivochalasis – which involve tissue folding caused by mechanical lid-mediated friction forces.

The pathogenesis of conjunctivochalasis is thought to involve the degeneration of elastic fibres.[9] The clinical manifestation of redundant bulbar conjunctiva is attributable to increased collagenolytic activity, which may contribute to the pathological process of conjunctivochalasis. Watanabe et al.[10] reported that elastotic degenerative structural changes of the conjunctiva are involved in the pathogenesis of conjunctivochalasis.

The conjunctiva of one of two patients with conjunctival flaps was observed by Markoulli et al.[11] to display even collagen distribution and overall normal histology. The conjunctival flap of the second subject displayed a mild focal increase in collagen and mild degeneration of collagen, but no increase in elastic tissue. Conjunctival epithelium was normal in both cases.

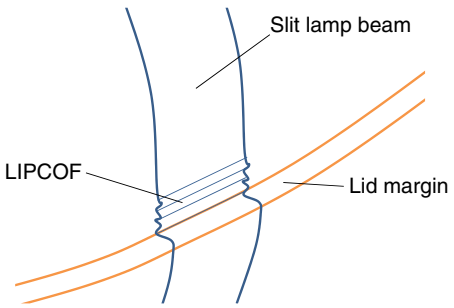


Fig. 12.6 Structural formation of LIPCOFs. (Courtesy Heiko Pult.)

Histological studies conducted on biopsy samples of LIPCOFs would be required to confirm a common pathological basis of LIPCOFs, conjunctival flaps and conjunctivochalasis.

Aetiology

The significant correlation between lid wiper epitheliopathy and LIPCOF suggests that the two conditions might share a similar aetiology – that is, they are both induced by friction during blinking. In both cases, there is direct contact of the affected tissues with the ocular surface. As negative correlations between LIPCOFs and non-invasive tear break-up time or tear meniscus height have been reported,[12,13] this friction may result from deficient tear film stability or volume. Tear volume may be reduced in cases with LIPCOFs, or the tear film may be partly bound in the folds. Improvements in tear film stability have been accompanied by a reduction in LIPCOF when phospholipid liposome eye sprays have been used in patients with dry eye,[14] suggesting that tear stability is a factor. Furthermore, insertion of a contact lens reduces tear film stability.

The mechanical influence of the lens edge may also be involved in the formation of conjunctival folds. The relationships between LIPCOFs and tear film stability, tear volume and lid wiper epitheliopathy in contact lens wearers points to LIPCOFs being a result of mechanical forces during blinking: the bulbar conjunctiva will be stretched, rubbed and massaged during the blink, which, in turn, may result in an overexpansion or/and lymphatic dilation that is visible as bulbar conjunctival folds. The resulting friction may also present as staining of the lid wiper.

If this theory is correct and there is a surface frictional component in the aetiology of LIPCOFs, then an association of this condition with abnormal blinking might be expected. Pult et al.[15] investigated the relationship among blink action, dry eye symptoms and LIPCOFs in 30 subjects. The authors observed that the percentage of 'almost complete' blinks was significantly correlated to LIPCOF Sum (nasal + temporal) and Ocular Surface Disease Index scores ($r > 0.570$; $p < 0.001$). The percentage of 'incomplete blinks' was significantly correlated to LIPCOF Sum ($r = -0.541$; $p < 0.001$) but not to Ocular Surface Disease Index scores. The authors concluded that the frequency and type of blinking may have an effect on dry eye symptoms and LIPCOF severity.

Treatment

Although there is no requirement to treat LIPCOFs as a 'standalone' tissue change in contact lens wearers, it would be expected that a reduction in LIPCOFs would be observed in patients who were successfully treated for contact lens–associated dry eye. As described earlier (see 'Symptoms'), more LIPCOFs are observed in symptomatic versus asymptomatic contact lens wearers.

In patients with dry eye (without contact lens wear), treatment for evaporative dry eye with hyaluronate artificial tears (Vismed Light) and phospholipid-liposome eye spray (Tears Again) resulted in a significant reduction in LIPCOF grade.[16]

Kiss and Nemeth[17] reported that regular use of glycerol/hyaluronate artificial tears for 3 months resulted in a significant improvement in mean LIPCOF grade, from 2.9 ± 0.4 before treatment to 1.4 ± 0.6 after treatment ($p < 0.001$).

Essa et al.[18] assessed dry eye treatment with four preservative-free dry eye artificial tear treatments – Clinitas

Soothe, Hyabak, Tears Again and TheraTears artificial tears. The trial was conducted on 50 symptomatic patients with dry eye, aged 60.8 ± 14.2 years. The authors observed that LIPCOFs had significantly improved after 4 weeks ($p = 0.014$) and that the effect of each dry eye treatment on ocular symptoms and signs was similar.

Prognosis

It seems that LIPCOFs resolve when dry eye disease is successfully treated, and it can be presumed that the time course of resolution of LIPCOFs is commensurate with the time course of resolution of the dry eye.

Differential diagnosis

Three conditions involve conjunctival folding – LIPCOFs, conjunctival flaps and conjunctivochalasis (see Chapter 11). Although these conditions may have similar aetiologies, the distinguishing feature of LIPCOFs is that they are observed adjacent to the lower lid margin, whereas conjunctival flaps and conjunctivochalasis can occur anywhere on the bulbar conjunctiva. Staining does not assist in differential diagnosis, as all three conditions can be observed with and without fluorescein.

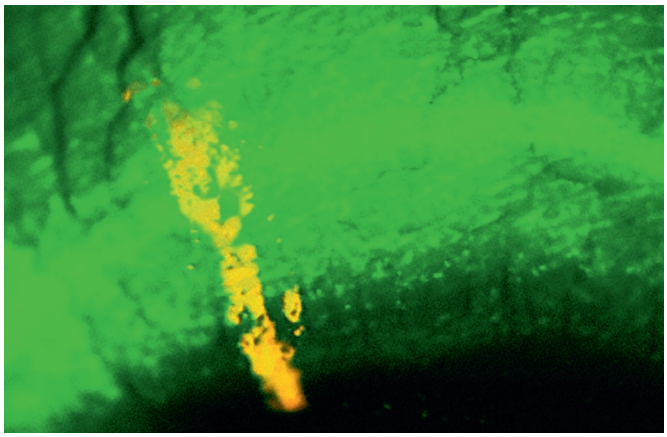


Fig. 12.7 Conjunctival furrows seen in a contact lens wearer. Also seen in this image is conjunctival staining from the lens edge. (Courtesy the Centre for Ocular Research & Education.)

LIPCOFs do need to be differentiated from normal conjunctival furrows (Fig. 12.7). Normal furrowing of the conjunctiva can only be seen with fluorescein staining and can appear at various orientations, although they are generally parallel to the corneal margin. Conjunctival furrows are shorter in length and tend to have a 'dots and dashes' appearance.

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13 Conjunctival Redness

Increased conjunctival redness in response to contact lens wear is so easily recognised that it serves as a fundamental indicator to clinicians of the physiological status of the contact lens–wearing eye. It is not surprising that the first two clinical reports of contact lens wearing trials on humans – conducted independently in the late 1880s by Adolf Fick[1] and August Müller[2] – used conjunctival redness as a measure of the severity of reaction to, and time course of recovery from, lens wear.

Conjunctival redness is so obvious and easily recognizable that it is perhaps the only tissue reaction to contact lens wear that is also reported as a symptom by patients (Fig. 13.1). Indeed, excessive eye redness is cosmetically unsightly and is often perceived as a disadvantage of wearing contact lenses.

It is generally recognised in eye care that the clinical presentation of a 'red eye' can be one of the most difficult cases to solve because of the numerous possible causes that are known. This problem may be even more complex in a contact lens wearer because there are also many other contact lens–related causes of red eye.

Definitions

Throughout the literature, the terms 'hyperaemia', 'injection', 'erythema', 'vascularity' and 'redness' are used as synonyms. These terms are defined as follows:

Hyperaemia – increased blood in a part, resulting in distension of the blood vessels[3]

Erythema – a redness of the skin occurring in patches of variable size or shape[3]

Injection – a state of hyperaemia[3]

Vascularity – the quality of vessels[3]

Redness – of or approaching the colour seen at the least-refracted end of the spectrum, of shades varying from crimson to bright brown and orange[4]

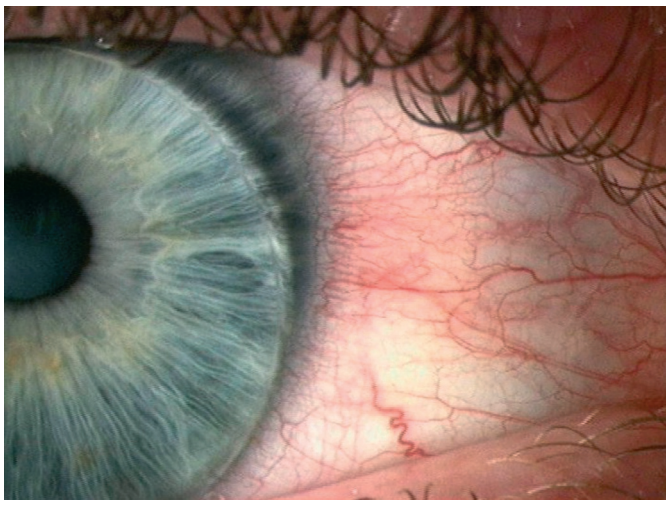


Fig. 13.1 Conjunctival redness (grade 2.7). (Courtesy Brian Tompkins.)

Strictly speaking, 'hyperaemia' or 'injection' is the cause, and 'redness' is the effect. That is, an increased volume of blood in the conjunctival vessels (hyperaemia or injection) causes an increased appearance of redness. The term 'erythema' refers to redness of skin; thus, the use of this term to describe conjunctival redness is acceptable in the broad context of considering the conjunctiva to be a specially adapted form of skin (technically it is a mucus membrane). The term 'vascularity' is somewhat ambiguous and could represent both the cause and the effect. Since this book is primarily structured in terms of considering clinical signs, the expression 'conjunctival redness' will be used here.

Prevalence

Most contact lens wearers will have experienced an episode of eye redness, no matter how mild, that may or may not have been related to lens wear. Reports of the prevalence of contact lens–associated eye redness vary dramatically, from 2.4%[5] to 77%[6] of lens wearers. This large variance in reported prevalence of conjunctival redness results from differences in methodological and reporting protocols. Some studies record if redness was the primary presenting complaint or one of a number of problems. Some studies are conducted retrospectively, and some prospectively. In reality, virtually all patients who present to their eye care practitioner complaining of ocular discomfort with contact lenses will have associated eye redness.

Signs and symptoms

The term 'conjunctival redness' is potentially confusing because it may not be clear whether this refers to redness of the bulbar, limbal or tarsal conjunctiva. Indeed, in his 1888 thesis on contact lenses, Müller[2] clearly differentiated among the extent of bulbar conjunctival redness, bulbar episcleral redness and limbal redness, and he used the degree of redness in these three tissue types as the basis of his analysis of the likely pathophysiological effects of lens wear. This chapter will concentrate on bulbar conjunctival redness. Tarsal conjunctival redness is considered in Chapter 14, and limbal redness is the topic of Chapter 15.

As with all adverse reactions that can involve a wide expanse of tissue, there may be significant regional variations in the extent of redness with respect to a given conjunctival structure. Figure 13.2 illustrates severe bulbar conjunctival redness limited to the 3 & 9 o'clock positions, associated with circumlimbal redness, in a patient wearing rigid lenses. The limbal engorgement suggests corneal involvement, which is consistent with the fact that this patient also displayed 3 & 9 o'clock staining.

There is also considerable variation in the magnitude of a hyperaemic response among individuals, as noted by Fick[1] in his 1888 article. He observed: 'The degree of injection … varies greatly…'. Fick[1] also used the conjunctival hyperaemic response to discover that the eye adapts to lens wear; he observed: 'The degree of injection … is apt to be absent entirely

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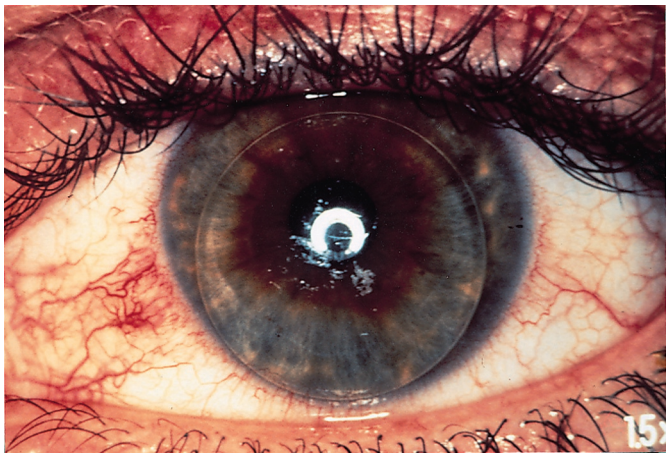


Fig. 13.2 Localised 3 & 9 o'clock bulbar conjunctival redness and circumlimbal redness in a rigid lens wearer. (Courtesy Leon Davids, Bausch & Lomb Slide Collection.)

in those … eyes … which have already been utilised in a long series of experiments. Apparently, therefore, a sort of toleration is established very soon.' Interestingly, Papas[7] suggested that subjective judgments of erythema made by human observers do not rely primarily on colour but can be closely approximated by a univariate, linear model involving only the proportion of the scene occupied by vessels (i.e. erythema can be judged equally well from black-and-white images vs. colour images).

Conjunctival redness is generally asymptomatic, but patients may complain of itchiness, congestion, non-specific mild irritation or a warm or cold feeling. The existence of pain usually indicates corneal involvement (e.g. keratitis) or other tissue pathology (e.g. uveitis or scleritis).

Inferior bulbar conjunctival redness was assessed in asymptomatic contact lens wearers by McMonnies and Chapman-Davies.[8,9] The mean grading of redness was as follows: No lenses, 0.8; rigid lenses, 1.0; hydrogel lenses used in the absence of preservative-based care systems, 1.5; and hydrogel lenses used in conjunction with preservative-based care systems, 2.1. Murphy et al.[10] reported a higher grade of bulbar conjunctival redness in normal eyes of 1.9 on the BHVI grading scales. They suggested that this difference could be attributed, in part, to the different grading scales used.

Silicone hydrogel lenses seem to induce much lower levels of conjunctival redness. Numerous authors[11-13] have reported that silicone hydrogel lenses worn on an extended-wear basis induced significantly lower grades of conjunctival redness compared with that observed with hydrogel extended-wear lenses. Morgan and Efron[14] also demonstrated that silicone hydrogel lenses worn on an extended-wear basis induce relatively low grades of conjunctival redness (0.4–0.6). Covey et al.[15] were unable to detect any difference in the grades of conjunctival redness between patients wearing silicone hydrogel lenses on an extended-wear basis (2.4 ± 0.4) and that in patients who did not wear lenses (2.3 ± 0.4).

As well as being statistically significant, these differences are undoubtedly clinically meaningful. Greater redness with hydrogel lenses, compared with no lens wear or rigid lens wear, is plausible because hydrogel lenses impinge on the limbus and conjunctiva, whereas rigid lenses generally do not. It should be noted that the study of McMonnies and Chapman-Davies[8,9] was conducted in the mid-1980s – at a time when relatively unsophisticated and potentially toxic preservatives (thimerosal and chlorhexidine) were included in contact lens solutions. The use of current generation preservatives is less likely to be associated with increased conjunctival redness.[16]

The increasing availability of video-capture technology, which can be interfaced with sophisticated computer-based image analysis systems, has led a number of researchers to develop objective techniques for measuring the level of conjunctival redness in response to contact lens wear.[17-20] Owen et al.[19] used such a system to demonstrate that over a 4-month period, rigid lens wear was associated with an increase in conjunctival redness, whereas soft lens wear was not associated with increased redness. These results do not necessarily conflict with those of McMonnies and Chapman-Davies,[8,9] who examined the conjunctivae of *adapted* lens wearers. The data of Owen et al.[19] probably reflect the general ocular irritation experienced during the initial adaptive phase of rigid lens wear.

Holden et al.[21] measured the extent of general conjunctival redness and limbal redness in a group of patients who had worn a high-water-content hydrogel lens on an extended-wear basis for an average of 5 years. General conjunctival redness was graded as 0.9 (vs. 0.7 in non-lens-wearing control eyes) and limbal redness was graded as 1.1 (vs. 0.3 in non-lens-wearing control eyes). From these data, it can be inferred that extended-wear of soft lenses have a much greater effect on limbal redness compared with general conjunctival redness.

Guillon and Shah[20] used a computer-based video-capture system to objectively monitor diurnal changes in conjunctival redness in patients wearing soft lenses on a daily-wear basis and on an extended-wear basis. Non–lens wearers displayed similar levels of redness in the morning and evening, but less redness during the day. With daily-wear lenses, conjunctival redness was greatest in the evening, whereas extended wear of soft lenses was associated with the greatest levels of redness upon waking.

Sorbara et al.[22] compared measures of bulbar redness obtained objectively by using a photometric method with standard grading methods. They concluded that the photometric method has great potential to replace subjective grading scales, especially with multi-centre studies, where variability between investigators occurs. They also reported that the photometric method may also detect smaller changes between visits or between eyes.

Functional slit lamp biomicroscopy allows for assessment of the conjunctival microvascular responses to contact lens wear. This approach can be used to generate non-invasive bulbar conjunctival microvascular perfusion maps and to assess bulbar conjunctival morphometry and haemodynamics. A digital camera is attached to a traditional slit lamp biomicroscope to image the bulbar conjunctiva. Perfusion maps are generated and are used to measure venular blood flow haemodynamics. By using this technique, Jiang et al.[23] found that bulbar conjunctival vessel diameter increased from 18.8 ± 2.7 μm at baseline to 19.6 ± 2.4 μm after 6 hours of soft contact lens wear ($p = 0.020$). The blood flow velocity was increased from 0.60 ± 0.12 mm/s to 0.88 ± 0.21 mm/s ($p = 0.001$). Significant increases in fractal dimensions were found after 6 hours of lens wear ($p < 0.05$).

Pathology

The bulbar conjunctiva contains a rich plexus of arterioles. Unlike arteries, arteriolar walls contain little elastic connective tissue. They do, however, contain a thick layer of smooth muscle that is richly enervated with sympathetic nerve fibres. The

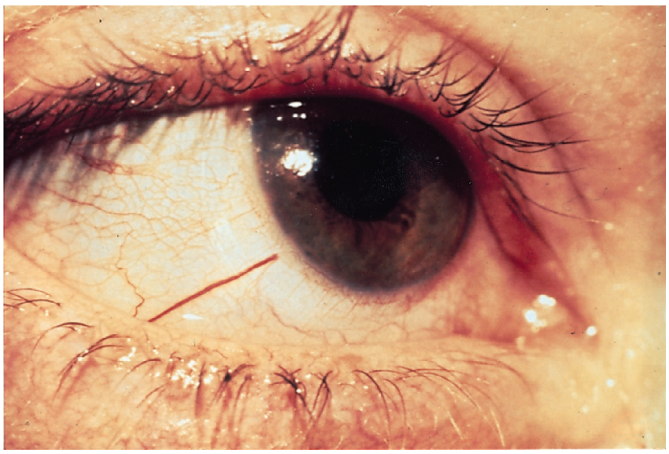


Fig. 13.3 Single distended conjunctival vessel presumed to be caused by blockage at the limbus. (Courtesy MF Pettigrew, Bausch & Lomb Slide Collection.)

smooth muscle, as well as being under central autonomic control, can be influenced by numerous local changes.

Vasodilation refers to enlargement in the circumference of a vessel resulting from relaxation of its smooth muscle layer, which leads to decreased resistance and increased blood flow through the vessel.[24] This is known as *active hyperaemia*. Since blood vessels can be observed directly through the transparent conjunctiva, this leads to an appearance of increased redness (less white sclera is visible).

Vasodilation can also occur as a result of passive mechanisms, such as vessel blockages. Fig. 13.3 shows a distended arteriole, possibly caused by a blockage near the limbus.

Arteriolar muscle normally displays a state of constriction known as *vascular tone*. This ongoing tonic activity is attributed to two factors: (a) intrinsic myogenic activity resulting from fluctuating membrane potentials and (b) norepinephrine release from sympathetic fibres enervating the arterioles. Vessel circumference can thus be either increased or decreased by altering one or both of the above mechanisms.[24] This can be achieved by local control mechanisms or intrinsic controls; the latter mechanism relates more to blood pressure regulation and has relatively little influence on conjunctival redness.

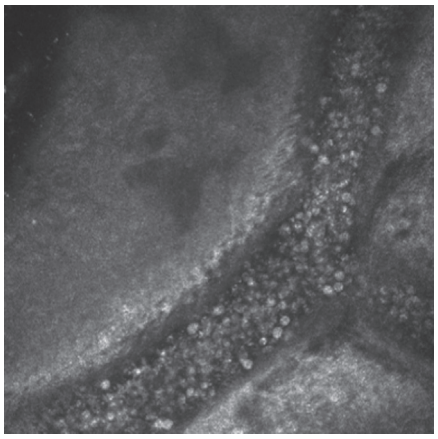


Fig. 13.4 Conjunctival blood vessel imaged using laser scanning confocal microscopy. The leucocytes can be imaged within the vessel. 'Rolling' versus 'sticking' leucocytes can be distinguished when these images are viewed as part of a movie sequence.

Insights into the inflammatory status of the conjunctiva can be examined by observing leucocytes within conjunctival vessels (Fig. 13.4). Leucocyte rolling and sticking (hallmarks of the inflammatory process) was recorded using confocal microscopy by Nguyen et al.[25] from conjunctival vessels in 55 contact lens wearers and 22 non-lens-wearing control subjects. The authors noted the presence of more rolling cells in the conjunctival vessels of those wearing low-Dk/t contact lenses than in those wearing higher-Dk/t lenses or controls. The authors suggested that their data validate a novel approach for the identification of a critical, sub-clinical component of inflammation.

Aetiology

Eye redness, to a varying degree, is a sign and symptom of virtually every adverse response to contact lens wear. As a physical entity that comes into direct contact with the conjunctiva, a contact lens can have a local mechanical effect on the conjunctiva, resulting in increased redness. As a device that (a) can interfere with normal metabolic processes of the cornea and conjunctiva and (b) is used in association with various solutions, a contact lens can also affect the level of conjunctival redness via a local chemical or toxic effect. Local infection and inflammation can also cause eye redness. Each of these influences shall be considered in turn.

METABOLIC INFLUENCES

Conjunctival arterioles are exposed to the various chemical components of the interstitial fluid in the tissue. During metabolic activity, the concentration of these chemical components can change, leading to vessel dilation and an increase in blood flow. The following metabolic influences relax arteriolar smooth muscle:

- hypoxia – caused by the lens; lenses of lower oxygen transmissibility (Dk/t) induce greater levels of hypoxia;[15]
- hypercapnia – caused by the lens; lenses of lower carbon dioxide transmissibility (Dk/t) induce greater levels of hypercapnia;
- acidic shift – caused by accumulation of lactic and carbonic acid as a consequence of hypoxia and hypercapnia, respectively;
- increased osmolarity – caused by an increased metabolic production of osmotically active particles;
- increased potassium – caused by repeated action potentials that cause a flood of potassium that cannot be removed by the sodium–potassium pump.

CHEMICAL INFLUENCES

Non-toxic chemicals introduced into the eye either directly or indirectly (with contact lens insertion) can lead to conjunctival redness for the following reasons:

- acidic shift – caused by the introduction into the eye of a solution of different pH to that of conjunctival tissue;
- increased osmolarity – caused by the introduction into the eye of a hypertonic contact lens solution.

TOXIC REACTION

A toxic reaction can occur as a result of exposure to noxious preservatives, buffers, enzymes, chelating agents or other chemical agents that are incorporated into contact lens solutions.[26] Paugh

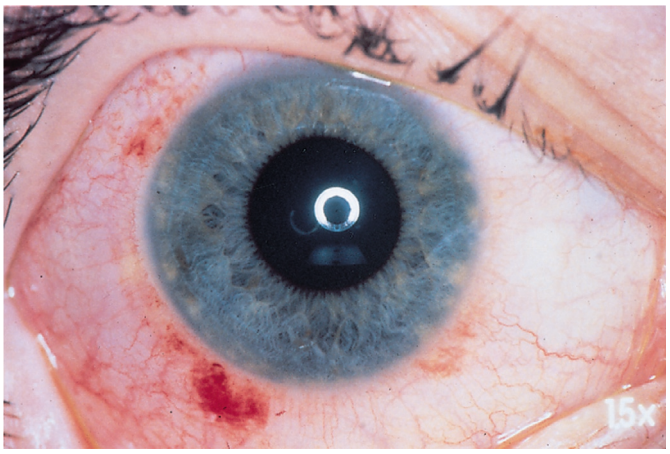


Fig. 13.5 Circumlimbal toxic response to an experimental contact lens disinfecting solution. (Courtesy Charline Gauthier, Bausch & Lomb Slide Collection.)

et al.[27] demonstrated an association between the concentration of hydrogen peroxide solution introduced into the eye and the degree of conjunctival redness, with a concentration of 800 parts per million (ppm; the highest concentration tested), causing a degree of redness of grade 2.7. Fig. 13.5 displays an acute circumlimbal toxic response to an experimental contact lens disinfecting solution; note the associated conjunctival haemorrhaging.

ALLERGIC REACTION

The fact that the conjunctiva supports and reflects immunological activity is evidenced clinically by atopic patients who display variations in conjunctival redness that coincide with seasonal fluctuations in the concentration of airborne antigens such as pollen. Allergic reactions may also be triggered by chemicals in contact lens solutions or deposits on contact lenses.[26]

Corneal confocal microscopy is providing new insights into the immunological status of the conjunctiva during lens wear. This is possible because Langerhans cells, which modulate the immune response of the eye, can be directly observed with this techique.[28] Immature Langerhans cells, which are small cells that lack dendritic processes, are equipped to capture antigens. Mature forms, which have long dendritic processes (Fig. 13.6), are able to sensitise native T cells through major histocompatibility complex molecules and secretion of interleukin-12 and co-stimulatory molecules and thus represent an integral part of the immune system.

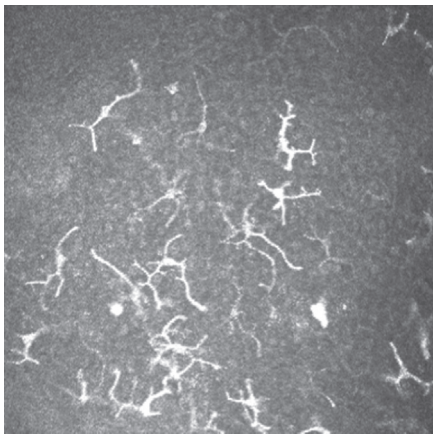


Fig. 13.6 Langerhans cells in the bulbar conjunctiva of a contact lens wearer.

NEURAL CONTROL

The rich sympathetic enervation of conjunctival arterioles can exert an overall influence on conjunctival redness. Thus, pharmacological agents that modulate sympathetic enervation will affect eye redness. Such agents are generally not used in conjunction with contact lens care systems. The arteriolar system of the body, in general, is under sympathetic control for the regulation of blood pressure; however, variations in conjunctival redness as a result of this central control mechanism are likely to be minimal.

INFLAMMATION

Inflammation, which is the reaction of tissue to injury, is characterised by heat, swelling, redness, pain and loss of function. Efron[29] argued that all five of these signs can be demonstrated in uncomplicated contact lens wear, leading to the conclusion that contact lens wear is intrinsically inflammatory. The small amount of conjunctival redness evident in virtually all contact lens wearers is consistent with this theory.

In the conjunctiva, the association between heat and redness has been demonstrated by Efron et al.,[30] who showed that a change of one grade of conjunctival redness corresponds to a change in conjunctival temperature of 0.15 °C. Fig. 13.7 is a graphic example of the association between ocular inflammation (primarily involving the cornea and conjunctiva – but also the surrounding facial tissues) and ocular temperature in a patient suffering from *Acanthamoeba* keratitis. This image, obtained by using ocular thermography,[31,32] demonstrates how this technique can be used to monitor contact lens–related ocular inflammation in terms of the heat generated from a hyperaemic eye.

Alzahrani et al.[33] studied longitudinal changes in Langerhans cell density (LCD) in the conjunctiva during asymptomatic and symptomatic contact lens wear. Twenty-five participants with contact lens–induced dry eye (CLIDE) and 35 without CLIDE

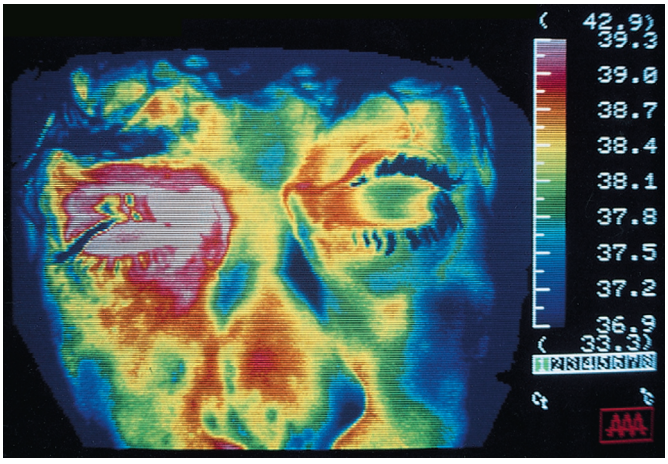


Fig. 13.7 Ocular thermogram of patient suffering from *Acanthamoeba* keratitis, indicating increased temperature of the inflamed right eye. (Courtesy Meng Poey Soh.)

(NO-CLIDE), diagnosed with the use of a range of symptom questionnaires and objective tests (tear film break-up, cotton thread tear test and corneal staining) were enrolled. The nasal bulbar conjunctiva was examined using a Heidelberg laser scanning confocal microscope at baseline and after 1, 4 and 24 weeks of wear of daily disposable hydrogel contact lenses. Twenty-three non-contact lens–wearing controls were also examined. The authors[33] observed that conjunctival LCD was greater after 1 week of lens wear in CLIDE (17 ± 1 cells/mm^2) ($p = 0.003$) and NO-CLIDE (17 ± 3 cells/mm^2) ($p = 0.001$) versus controls (7 ± 1 cells/mm^2). There were no significant differences between groups at weeks 4 or 24. The initial transient increase in conjunctival LCD in both CLIDE and NO-CLIDE suggests an inflammatory component in both asymptomatic and symptomatic contact lens wearers.

'CONTACT LENS ACUTE RED EYE' SYNDROME

A syndrome known as the 'contact lens acute red eye' (CLARE) is observed from time to time in patients wearing extended-wear contact lenses.[34] This is an inflammatory response, in which the patient wakes in the morning with unilateral bulbar conjunctival and limbal redness, discomfort, lacrimation and photophobia (Fig. 13.8). The severity of these signs and symptoms can vary from being mild to severe. On slit lamp examination, anterior stromal infiltrates are usually observed near the limbus, but, by definition, there is no overlying epithelial staining or underlying erosion of stromal tissue (ulceration).

This syndrome is generally attributed to the pathological effects of proteases released by Gram-negative bacteria,[35-37] which, for example, may be adherent to the contact lens or may enter the eye via lens solutions during lens insertion and removal. Other factors which may be of significance in the aetiology of CLARE include the following:

- an immobile lens;
- direct or indirect effects of hypoxia/hypercapnia (e.g. respiratory distress) in lenses of low Dk/t;
- toxicity or inflammation because of trapped post-lens debris;
- the mechanical effect of the lens;

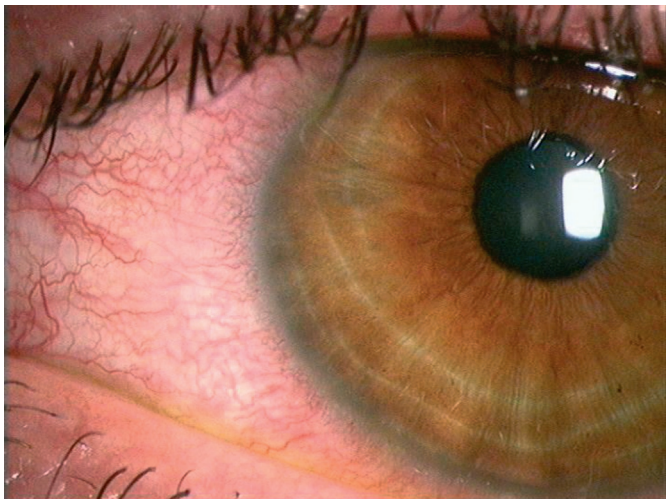


Fig. 13.8 Contact lens acute red eye (CLARE). (Courtesy Brian Tompkins.)

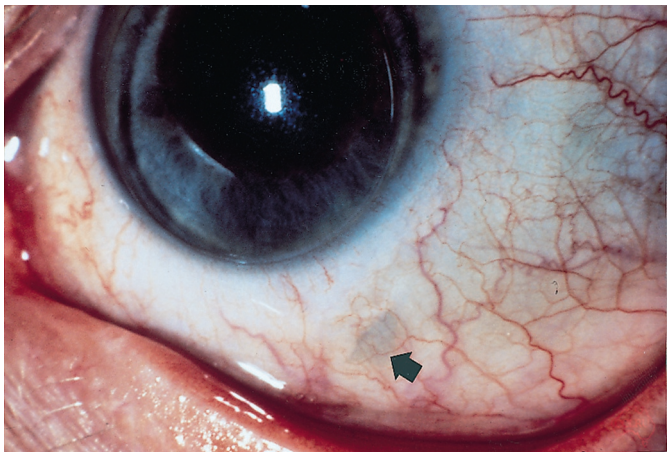


Fig. 13.9 Moderate chronic conjunctival hyperaemia caused by a fragment of a rigid lens having become embedded in the conjunctiva (arrow) after traumatic injury. (Courtesy HJ Rutten, Bausch & Lomb Slide Collection.)

- toxic, inflammatory, immunological or mechanical effects of lens deposits;
- tear film thinning;
- hypersensitivity or toxicity to preservatives re-released back into the eye from high water content lenses;[34]
- increased temperature beneath the lens.

MECHANICAL INFLUENCES

Contact lenses can come into direct contact with the conjunctiva and cause mechanical damage.[38] Trauma is known to cause mast cell degranulation, which results in histamine release. Histamine is the major cause of vasodilation in an injured area and can also lead to conjunctival chemosis (swelling). Young and Coleman[39] have demonstrated that physical irritation from a loosely fitting lens can induce significant conjunctival redness.

Figure 13.9 shows the eye of a 35-year-old female who suffered a traumatic injury to this eye while wearing a rigid lens. The lens broke into many pieces and a small fragment became embedded in her conjunctiva (arrow), causing mild redness. The patient was asymptomatic and refused surgical treatment to remove the lens fragment. This case illustrates that chronic mechanical irritation, albeit asymptomatic, can induce conjunctival redness.

Many of the reactions described are mediated by intrinsic substances in the body, such as prostaglandins, which are described as 'local hormones' in that they are synthesised locally, they have short half-lives, they exert a rapid and often profound effect, and they are finally metabolised to a biologically inactive form. Figure 13.10 is an illustration of a possible mechanism of prostaglandin-mediated vasodilation caused by lens-induced hypoxia, as proposed by Efron et al.[40] Other intrinsic substances, such as neutrophil chemotactic factor, are released in traumatised tissue, which help establish an inflammatory reaction.

Observation and grading

The extent of conjunctival redness can be graded using the grading scales provided in Appendix A. Although illustrative grading scales are not as accurate as objective photometric or

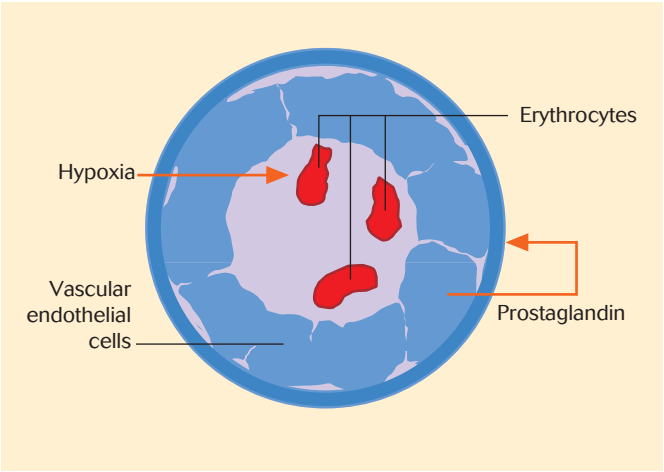


Fig. 13.10 Possible mechanism of prostaglandin-mediated vasodilation caused by lens-induced hypoxia.

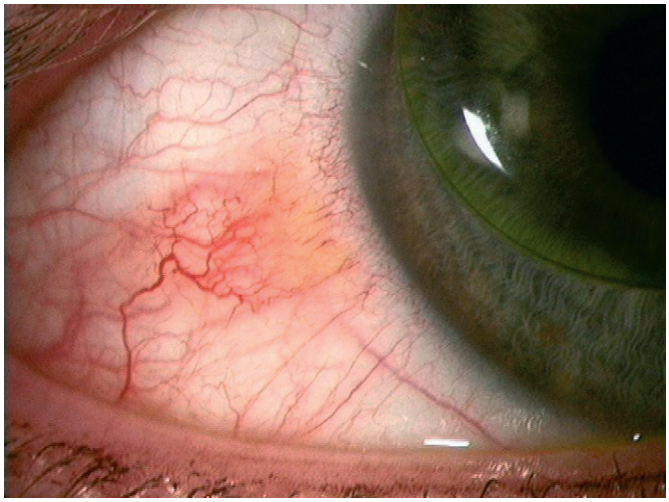


Fig. 13.11 Increased eye redness, which is particularly intense at the 8 o'clock location. (Courtesy Timothy Golding.)

computer-based image analysis systems, grading scales do offer sufficient sensitivity for general clinical use if clinicians are willing to estimate the grade of redness to the nearest 0.1 grade unit.

Because conjunctival redness typically displays regional variations, it is important to indicate on the record card the area of conjunctiva being graded. This can be achieved by designating the general zone, such as superior, inferior, temporal or nasal, or a more specific region, by specifying the 'time' with reference to the cornea being the 'clock face' (e.g. 8 o'clock in Fig. 13.11). It may also be worth noting the time of day that the observation is made in view of the normal diurnal variation in conjunctival redness.[20]

Treatment

As described earlier, numerous factors may result in a red eye, and the key factor in a given patient is rarely obvious. In some cases, a variety of actions may need to be taken, either sequentially or simultaneously.

Eye redness may be acute or chronic. Most acute reactions, including CLARE syndrome,[34] are transient and self-limiting, and in many cases, the eye redness would have resolved before the patient decided to seek the advice of a practitioner. Thus, eye redness as a key presenting complaint from a contact lens patient will often suggest a chronic problem requiring active intervention.

Treatment options fall into four broad categories: (a) alterations to the type, design and modality of lens wear, (b) alterations to care systems, (c) improving ocular hygiene or (d) prescription of pharmaceutical agents. Each of these shall be considered in turn.

ALTERATION TO THE LENS

All soft lenses – including daily disposable lenses – develop deposits over the lifetime of the lens. Most of deposits that form on reusable lenses can be removed by daily surfactant cleaning, but some deposits, such as protein, gradually build up regardless.[41] Protein removal systems may slow the rate of protein build-up, but they do not prevent it. Furthermore, it is the *quality* of protein deposition, rather than the *quantity*, that will govern biocompatibility.[42] For example, with type IV (ionic high water) lenses, the physiological compatibility of the protein is preserved, whereas type I lenses (non-ionic low water) lenses attract protein which readily denatures and is therefore more likely to be antigenic to the eye.

If it is true that bacteria adherent to protein deposits are the trigger for eye redness, then the quantity of protein may be more important – less protein should mean less bacterial attachment.

Assuming protein accumulation to be one cause of red eye in patients wearing soft lenses, effective lens-related strategies would include changing to the following:

- A lens material that deposits a protein film that is physiologically compatible with the eye.
- A lens material that deposits less protein.
- A greater lens replacement frequency, with daily disposability being the ultimate modality in this regard.[43]

Alterations to soft lens design may alleviate eye redness if this has the effect of minimizing the mechanical effect of the lens on the eye. Thus, the fitting of good-quality thin lenses with restricted movement may be beneficial. Rigid lenses with smooth edges and adequate edge lift are most likely to alleviate bulbar conjunctival redness because the lens will not usually come into physical contact with the bulbar conjunctiva.

As discussed previously, silicone hydrogel lenses induce minimal amounts of conjunctival redness.[11-13]

ALTERATION TO CARE SYSTEMS

In the first instance, it is necessary to establish that the patient is being fully compliant with the prescribed care regimes, which for reusable soft lenses would include surfactant cleaning, rinsing, disinfection and possibly periodic protein removal treatment. Any deficiencies in this regard would need to be rectified.

Strategies aimed at reducing deposit build-up may alleviate chronic eye redness. An increase in frequency of lens replacement may be beneficial for both soft and rigid lens wearers.

If preservatives in contact lens solutions are thought to be of aetiological significance in a particular patient, then the employment of preservative-free systems may alleviate the condition (some hydrogen peroxide solutions fall into this category).

IMPROVING OCULAR HYGIENE

Improvements to ocular hygiene begin with improvements to personal hygiene. Thus, routine and thorough hand washing before lens handling and regular face washing have a role in reducing eye redness. Some authors[44] have recommended the additional step of conjunctival irrigation with sterile unpreserved saline before and after lens insertion, and periodically during the day, as a means of diluting or removing antigens and generally enhancing patient comfort. Although this procedure was advocated for alleviating contact lens–induced papillary conjunctivitis, the principle can also be applied to the management of chronic red eye.

Attention to lid hygiene could also be of benefit. Encouraging the patient to employ such strategies as lid scrubbing, warm compresses and expression could alleviate eye redness if lid involvement is suspected as being wholly or partially responsible for eye redness.

PHARMACEUTICAL AGENTS

In certain cases, consideration can be given to prescribing ocular decongestants.[45] These drugs all contain vasoconstrictor agents that serve the dual purpose of reducing eye redness and alleviating symptoms. Of course, ocular disease and all other possible lens-related causes of eye redness must be ruled out before prescribing decongestants because they could end up exacerbating the problem by masking and prolonging the real cause of eye redness.

'Over-the-counter' ocular decongestants include the following:

- Phenylephrine 0.12% (e.g. P Isopto Frin).
- Naphazoline 0.01% combined with witch-hazel 12% (e.g. P Eye Dew).
- Naphazoline 0.01%–0.1% combined with antazoline (e.g. P Murine).
- Xylometazoline 0.05% combined with antazoline (e.g. P Otrivine-Antistin).
- Levocabastine 0.05% (e.g. P Livostin Direct).[45]

Phenylephrine in concentrations of 0.12% is insufficient to cause pupil dilation. However, the side effects of phenylephrine include reactive hyperaemia – an uncomfortable red eye that can occur after prolonged use, allergic reactions and soft lens discolouration.

Naphazoline is more stable and longer acting and is less likely to cause an allergic reaction or rebound congestion, compared with phenylephrine. However, some patients – especially children – have apparently experienced a sedation effect after prolonged use.

In conclusion, ocular decongestants should generally be avoided, and maximum effort should be directed towards identifying and rectifying the primary cause of the problem. When all possible causes of eye redness have been ruled out, then decongestants can be prescribed for intermittent use with the primary cosmetic objective of alleviating an unsightly red eye appearance. Patients using decongestants should be monitored more frequently than normal (say, every 3 months).

Prognosis

Recovery from acute lens-induced conjunctival redness is extremely rapid. In his early writings, Fick[1] recognised this and noted: 'The injection of the eyeball disappears with extraordinary rapidity after removal of the (haptic lens)', and '… any possible injection of the conjunctiva will disappear within half an hour…'. Contemporary research has confirmed the observations of Fick that acute redness dissipates rapidly. For example, Paugh et al.[27] demonstrated that after instillation of 800 ppm hydrogen peroxide into the eye, it only took 5 minutes to improve eye redness grading from 2.7 down to a normal grading of 0.4.

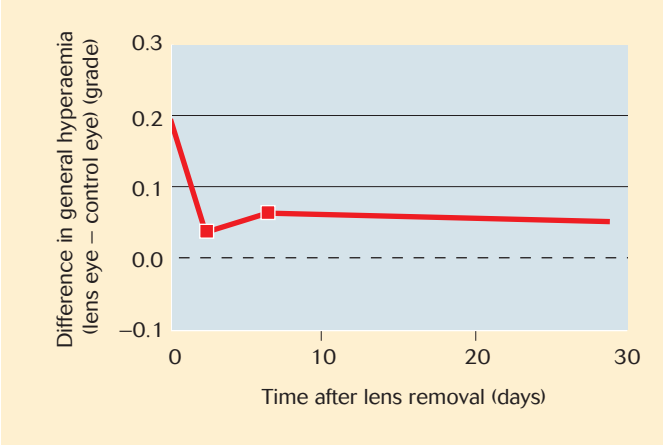


Fig. 13.12 Time course of resolution of general conjunctival redness after 5 years of extended wear of a high-water-content hydrogel lens in one eye only, relative to non-lens-wearing control eye. (Adapted from Covey M, Sweeney DF, Terry R, Sankaridurg PR, Holden BA. Hypoxic effects on the anterior eye of high-Dk soft contact lens wearers are negligible. Optom Vis Sci 2001;78:95–9.)

In general, removal of any acute noxious stimulus, including a contact lens, will lead to a very rapid recovery of eye redness to normal levels.

The prognosis for recovery from chronic contact lens–induced red eye after removal of lenses and cessation of wear is also reasonably rapid. Holden et al.[21] found that after approximately 5 years of hydrogel extended lens wear, general conjunctival redness resolved within 2 days of ceasing lens wear (Fig. 13.12).

Differential diagnosis

When a contact lens–wearing patient presents with a red eye as a primary complaint, the initial diagnostic step is to determine whether or not the problem is related to lens wear. This can often be simply solved by removing the lens, and eye redness should dissipate rapidly if the problem is purely lens related. However, the possibility that the lens was somehow exacerbating a complication unrelated to lens wear itself should not be discounted.

Another differential diagnosis that may be necessary when presented with an extremely red eye is to determine the extent to which the redness is a result of conjunctival injection or ciliary flush. Two simple tests can be applied. A sterile cotton bud can be applied to the bulbar conjunctiva in the region of redness and gently moved from side to side. The conjunctival vessels move but the ciliary vessels will remain in a fixed position. It can therefore be determined whether the redness relates primarily to the 'moving' vessels (indicating conjunctival involvement) or the 'static' vessels (indicating ciliary involvement).

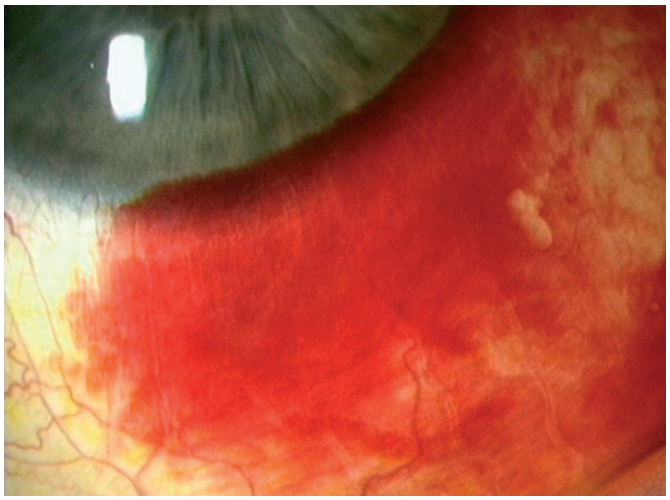


Fig. 13.13 Sub-conjunctival ecchymosis. (Courtesy Brian Tompkins.)

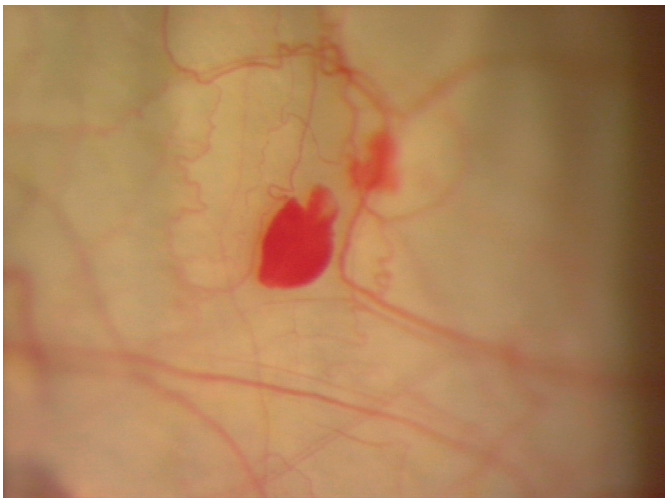


Fig. 13.14 Localised conjunctival haemorrhages in a soft lens wearer. (Courtesy Suzanne Efron.)

An alternative test is to instil a decongestant into the eye. The effect of a decongestant is limited to the superficial conjunctival vessels; these drugs have no effect on the deeper ciliary vessels. Thus, if the instillation of a decongestant alleviates eye redness, the condition is primarily conjunctival. If the decongestant has no effect on eye redness, then the redness can be attributed to excessive ciliary flush.

A sub-conjunctival haemorrhage can be easily differentiated from conjunctival and/or ciliary redness because of the stark appearance of an intensely 'blood red' eye (Fig. 13.13). Repeated clumsy insertion and removal of contact lenses by a patient new to contact lens wear – in particular rigid lens wear – can lead to the formation of a sub-conjunctival haemorrhage. Although this condition is benign and self-limiting, its appearance will be startling to an uninformed lens wearer and may undermine the confidence that such a patient has in contact lens wear despite assurances to the contrary. Small haemorrhages of individual conjunctival vessels can cause a localised increase in conjunctival redness (Fig. 13.14), but again these are self-evident and differential diagnosis from vascular engorgement is clear.

Assuming that a given case of eye redness is lens related, it is necessary to determine whether the source of problem is the cornea or the conjunctiva. Conjunctival redness associated with a quiet limbus and absence of pain indicates a primary conjunctival problem. Conjunctival redness associated with an injected limbus and corneal pain indicates corneal involvement or, indeed, a problem that is related *exclusively* to the cornea. Careful slit lamp examination of the anterior ocular structures, and inspection of the lens at high magnification, will generally reveal the cause of the problem. It may also be necessary to prescribe different care systems and differentially diagnose the effects of various solutions over time.

If the red eye is deemed to be unrelated to lens wear, then all other possible causes of red eye must be investigated. This may involve a full ocular examination involving the use of direct and indirect ophthalmoscopy, tonometry and so on. A full account of the differential diagnosis of the red eye in a general ophthalmic context is beyond the scope of this book.

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14 Papillary Conjunctivitis

Australian ophthalmologist Tom Spring is widely credited as being the first to observe an allergic-like reaction of the upper tarsal conjunctiva, which was later to become known as 'giant papillary conjunctivitis'. In his 1974 letter to the editor of the *Medical Journal of Australia*, Spring reported observing the presence of large tarsal papillae, accompanied by discomfort and excessive mucus production in 43% of patients wearing soft lenses.[1]

The term 'giant papillary conjunctivitis' was coined by Allansmith et al.[2] to describe papillary changes on the tarsal conjunctiva that were likened to a cobblestone formation (Fig. 14.1). However, this condition can take on a variety of different appearances, depending on the level of severity and whether it relates to soft or rigid lens wear. In its mild form, this condition has been termed 'lid roughness' and 'papillary hypertrophy'. Even in advanced stages, the papillary formations may be extensive but not necessarily 'giant'. Thus, a more appropriate term that encompasses all of the possible manifestations of the same condition is 'contact lens–induced papillary conjunctivitis' (CLPC).

Prevalence

In soft lens wearers, CLPC may take as little as 3 weeks to develop or as long as 4 years to manifest. In rigid lens wearers, CLPC typically appears after about 12 months.

It is difficult to characterise the prevalence of a condition that (a) has a variable time of onset, (b) varies in severity throughout the seasons of the year (because of its allergic nature) and (c) varies over the years as different lens care regimens and lens wear modalities come into and go out of vogue. It is also apparent that the definition of CLPC has changed over time, with the earlier literature (say, pre-1985) focusing on the appearance of very large papillae (consistent with the notion of 'giant' papillae) and the subsequent literature paying more attention to CLPC in its more subtle variants.

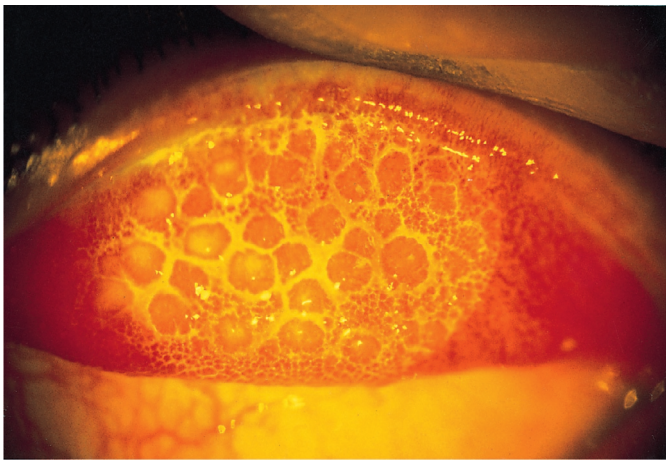


Fig. 14.1 'Giant' papillae in a patient wearing soft lenses on a daily-wear basis, observed with fluorescein under white light. (Courtesy Russell Lowe, Bausch & Lomb Slide Collection.)

In his original article, Spring[1] reported a prevalence of CLPC in 43% in hydrogel lens wearers; however, this was during the days when patients were using thermally disinfected hydroxyethyl methacrylate (HEMA) lenses. Before the introduction of disposable contact lenses, the prevalence of overt CLPC in those using hydrogel lenses on a daily-wear basis was reported to be 2% to 18%.[3-5]

Grant[6] reported a CLPC prevalence of 19% in patients using non-planned replacement extended-wear hydrogel lenses versus 3% with disposable hydrogel extended-wear lenses. However, Poggio and Abelson[3] found no difference in CLPC between patients wearing those lens types (1.9% and 2%, respectively). Other authors reported somewhat higher incidence figures of 6.4%,[7] 6.7%,[8] and 6% to 12%[9] for disposable hydrogel extended-wear lenses.

Reviewing chart records of subjects participating in clinical trials of various silicone hydrogel/care solution combinations, Carnt et al.[10] reported CLPC occurrence at a rate of 0.4 cases per 100 participant-months. There was no difference in this response rate between among brands of silicone hydrogel lenses, although solution type had a small effect.

Radford et al.[11] did not find a significant difference in the frequency of CLPC among users of silicone hydrogel lenses versus hydrogel lenses. However, Maldonado-Codina et al.[12] reported increased grades of papillary conjunctivitis among patients wearing silicone hydrogel lenses of high modulus (Focus Night & Day) versus those of low modulus (Acuvue Advance). Santodomingo-Rubido et al.[13] reported the following number of adverse events in 53 subjects followed up for 18 months: Focus Night & Day daily wear – 2, extended wear – 5; Pure Vision daily wear – 2, extended wear – 4. This represents an overall response rate of CLPC of 16% per year.

Alemany and Redal[5] found a lower incidence of overt CLPC in patients wearing daily-wear rigid lenses compared with conventional daily-wear soft lenses. Grant et al.[9] reported that the incidence of CLPC in patients wearing rigid lenses on an extended-wear basis was 2%, versus 6% to 12% for soft disposable extended wear. Fonn et al.[14] reported the results of a 4-month clinical trial in which 6 (33%) of 18 patients wearing silicone hydrogel lenses on an extended-wear basis developed CLPC; two of these cases were removed from the study because of the severity of their conditions.

Tagliaferri et al.[15] observed that 25% of subjects fitted with lotrafilcon A silicone hydrogel lenses for up to 30 days of continuous wear developed CLPC after 12 months.

Surveys of contact lens wearers presenting to hospital clinics have revealed the following prevalence figures for CLPC: China – 5%[16]; India – 6%[17]; Singapore – 16%[18]; Nepal – 37%[19]; and United States – 58%.[20]

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Normal tarsal conjunctiva

The normal tarsal conjunctiva can take on a variety of forms, which may be categorised in different ways. Allansmith[21] described three forms of normal tarsal conjunctival appearance: (a) satin or smooth (14%); (b) small, uniformly sized 'micropapillae', which are less than 0.3 mm in diameter (85%); and (c) non-uniform papillae (<1%), where some papillae can be as large as 0.5 mm in diameter.

An alternative model for classifying the normal tarsal conjunctiva was proposed by Potvin et al.,[22] who conducted a computer-assisted morphometric examination of photographic images of the fluorescein-stained tarsal conjunctiva of eight asymptomatic non–lens wearers. The eight subjects were classified into two distinct groups: (a) those displaying 'small feature' tarsal plates (with a modal feature area of 25,000 to 35,000 μm^2 and a restricted range of areas); and (b) those displaying 'large feature' tarsal plates (with a modal feature area of 50,000 to 70,000 μm^2 and a wide range of areas). The cells generally appear to be pentagonal or hexagonal in shape.

The three-category model of Allansmith[21] is of more immediate relevance to clinicians because it is based on the appearance of the tarsal conjunctiva under low magnification with the use of the slit lamp biomicroscope.

Signs and symptoms

It is important that an assessment is made only of the central region of the tarsal plate, for the following reasons: (a) there is often increased 'roughness' of the conjunctiva at the lateral extremities of the everted lid that is unrelated to lens-induced pathology; (b) the process of lid eversion causes the conjunctiva to artificially appear distorted and irregular along the margin of the lid eversion fold (i.e. anatomically superior to the tarsal plate, but paradoxically 'inferior' as the everted lid is viewed); and (c) the conjunctiva just inside the lid margin (i.e. anatomically inferior to the tarsal plate) is rarely affected by lens wear.

Allansmith[21] noted that the appearance of CLPC was different in soft lens wearers versus rigid lens wearers. In soft lens wearers, papillae are more numerous and are located more towards the upper tarsal plate (i.e. closer to the fold of the everted lid); and the apex of the papillae take on a rounded flatter form (Fig. 14.1). In rigid lens wearers, papillae take on a crater-like form and are located more towards the lash margin, with few papillae being present on the upper tarsal plate (Fig. 14.2). Skotnitsky et al.[23] suggested that patients wearing silicone hydrogel lenses for extended periods are more predisposed to developing localised CLPC as a result of the stiffer modulus of these lenses interacting with the superior palpebral conjunctiva.

In the early stages of development, the tarsal conjunctiva in patients suffering from CLPC may be indistinguishable from the normal tarsal conjunctiva. An important early distinguishing feature is increased redness of the tarsal conjunctiva (Fig. 14.3). This change can be detected with reference to the lower palpebral conjunctiva, which is usually unaffected and can therefore act as a 'baseline' against which any change is measured.

In advanced cases, papillae can exceed 1 mm in diameter and often take on a bright red/orange hue. Evidence of papillae often appears in the form of irregular light reflexes (Fig. 14.4). The hexagonal/pentagonal shape may be lost in favour of a more



Fig. 14.2 Contact lens–induced papillary conjunctivitis (CLPC) in a rigid-lens wearer, with more papillae observed (arrow) towards the lash margin. (Courtesy Brien Holden, Brien Holden Vision Institute.)



Fig. 14.3 Gross redness of tarsal conjunctiva with mucus formation (arrow) in contact lens–induced papillary conjunctivitis (CLPC). (Courtesy A. Gustafsson.)

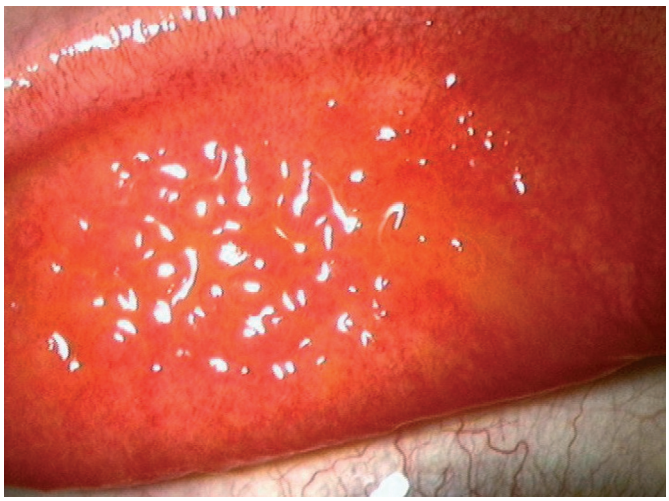


Fig. 14.4 Irregular light reflexes in contact lens–induced papillary conjunctivitis. (Courtesy Brian Tompkins.)

rounded appearance. The pattern of distribution of papillae may reflect the underlying anatomy of the tarsus; for example, Fig. 14.5 is a non-uniform CLPC that has developed in a soft lens wearer. Three-dimensionally, giant papillae can be said to take on a 'mushroom' form, with a flattened or even slightly depressed apex or tip.

Because the conjunctiva is thickened, oedematous and often hyperaemic, fine vessels which can normally be observed to traverse the conjunctival surface are obscured, although deep vessels remain visible over the tarsal plate. A tuft of convoluted capillary vessels is often observed at the apex of papillae; this vascular tuft will generally stain with fluorescein.

Other signs that can be observed in severe manifestations of CLPC include conjunctival oedema and excessive mucus (Fig. 14.3), which usually forms into strands that lie in the valleys between papillae. Excess mucus will also accumulate at the inner and outer canthi at night and can sometimes be observed as clumps or strands floating across the cornea or on the lens surface (Fig. 14.6). Prolonged oedema may result in a mild ptosis, which is often asymmetrical.

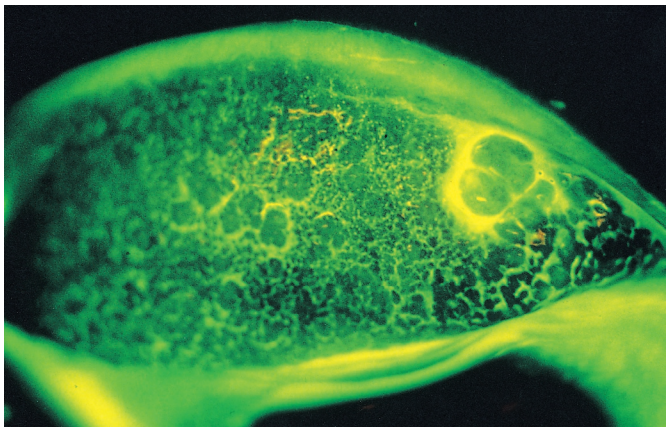


Fig. 14.5 Non-uniform contact lens–induced papillary conjunctivitis in a soft lens wearer, observed with fluorescein under cobalt blue light. (Courtesy Robert Terry, Bausch & Lomb Slide Collection.)

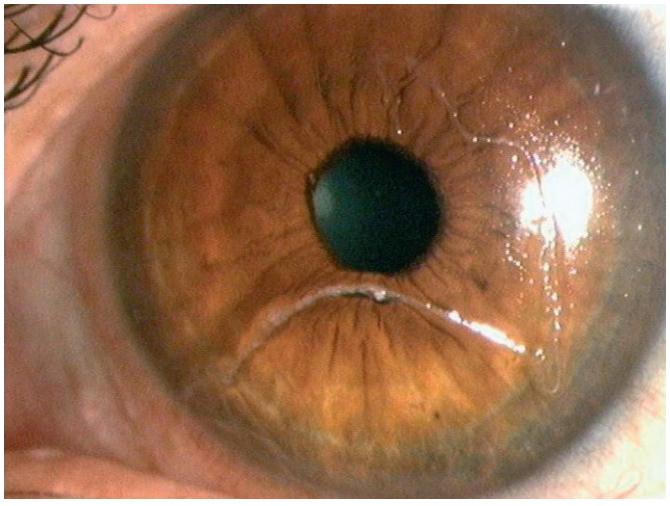


Fig. 14.6 Strand of mucus on the surface of a soft lens in a patient with contact lens–induced papillary conjunctivitis. (Courtesy Brian Tompkins.)

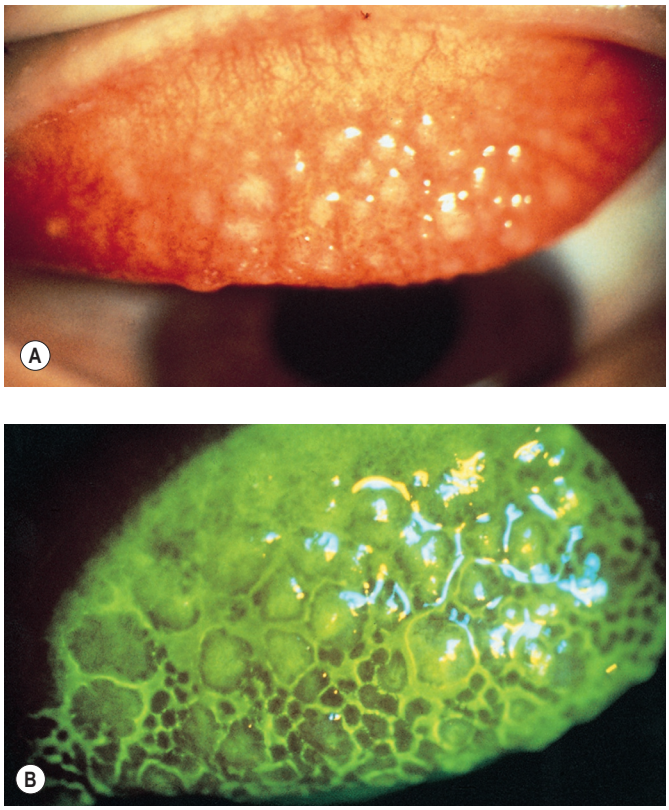


Fig. 14.7 Scarring at the apex of papillae, seen here **(A)** in white light and **(B)** cobalt blue light (right). (Courtesy C.D. Euwijk, Bausch & Lomb Slide Collection.)

Giant papillae can display infiltrates, and if the condition persists for some time, the conjunctival surface at the apex of the papillae can become scarred and appear cream/white in colour (Fig. 14.7). The cornea may be compromised and display superficial punctate staining and infiltrates superiorly. Injection of the superior limbus may also be apparent.

There is general concordance between the severity of signs and symptoms. In the early stages of CLPC, patients may complain of discomfort towards the end of the wearing period and slight itching. Patients may report an increase in mucus production upon awakening. Intermittent blurring is sometimes noted; this results from mucus being periodically smeared across the lens surface. A slight but non-variable vision loss is attributable to more tenacious lens deposits, such as protein, which is of aetiological significance in this condition (see later).

In more severe cases, the itching and discomfort can become so marked that the patient is forced to remove the lens. Excessive lens movement and decentration can result from a combination of (a) the large papillae creating greater contact and friction with the coated lens surface, and (b) excess mucus acting as an 'adhesive' between the tarsal conjunctival and lens surfaces.

The signs and symptoms of CLPC, as they manifest with different grades of severity, are summarised in Table 14.1.

Pathology

It has been possible to thoroughly document pathological changes that take place in patients with CLPC because it is a relatively simple matter to biopsy tissue from the tarsal conjunctiva. However, contact lens–induced corneal pathology is

TABLE 14.1 Signs and symptoms of papillary conjunctivitis

Grade	Signs	Symptoms
0	• Normal tarsal conjunctiva: Smooth, uniform micropapillae; non-uniform micropapillae	• None
1	• Slight redness of upper tarsus	• Occasional itching
2	• Slight papillary roughness • Slight redness of upper tarsus • Slight increase in lens movement	• Mild itching • Mild awareness of lens
3	• Moderate papillary roughness • Small papillae along lid fold • Moderate redness of upper tarsus • Infiltrates in vascular tuft • Moderate lens movement • Moderate lens decentration • Fine mucus strands on tarsus • Some mucus in tears • Slight coating apparent • Vision variable	• Moderate itching • Moderate lens awareness • Wearing time reduced • Some mucus noted • Awareness of moderate lens movement • Awareness of moderate lens decentration • Slight intermittent blur with lens
4	• Severe papillary roughness • Large papillae extending over tarsus • Severe redness of upper tarsus • Infiltrates may mask vascular tuft • Central scarring of papillae • Excessive lens movement • Excessive lens decentration • Mucus pooling between papillae • Mucus strands on cornea • Mucus strands and clumps in tears • Heavy lens coating • Vision variable • Vision slightly reduced • Superficial limbal redness • Superficial corneal staining • Superficial corneal infiltrates	• Severe itching • Severe lens awareness • Wearing time minimal • Excess mucus noted • Awareness of excessive lens movement • Awareness of excessive lens decentration • Frequent intermittent blur with lens • Slight vision loss with lens

often poorly understood because researchers rarely biopsy tissue specimens from the living human cornea.

The conjunctiva becomes thicker in CLPC (0.2 mm in CLPC vs. 0.05 mm in normals). Greiner et al.[24] observed dramatic ultrastructural changes in the conjunctival surface in patients with CLPC. Conjunctival surface area is increased by two-fold and epithelial cells are enlarged and distorted, becoming elongated in shape. The microvilli are reduced in number and become distorted, forming aggregated tufts on the surface of papillae. Normally present crypts of Henle are not observed. The number of mucus-secreting non-goblet cells is increased. More dark cells are observed at the apices of the papillae.

CLPC is associated with a dramatic redistribution of inflammatory cells between the epithelium and the stroma of the conjunctiva. Mast cells, eosinophils and basophils are found in the epithelium (they do not normally reside there), and there is an increase in the number of neutrophils and lymphocytes in the epithelium. Eosinophils and basophils are found in the stroma, with an increase in the number of mast cells, plasma cells and neutrophils.

Zhong at al.[25] have demonstrated that membranous epithelial cells (M cells) play a key role in the pathogenesis of CLPC for the binding and translocation of antigen and pathogen.

Fig. 14.8 is a schematic diagram of tissue and cellular pathological changes that characterise a papilla.

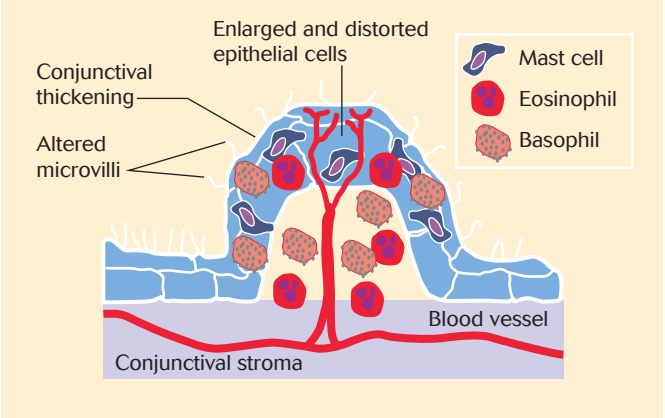


Fig. 14.8 Pathological changes that characterise a papilla.

Aetiology

A number of factors have been suggested as playing a role in the aetiology of CLPC, and it is unlikely that any one causative factor can account for all cases. These factors are summarised in the following.

MECHANICAL TRAUMA

Papillary conjunctivitis of an apparently identical form to that induced by contact lenses has been observed in patients who do not wear contact lenses but whose tarsal conjunctivae have been exposed to various types of mechanical trauma, such as:

- plastic ocular prostheses[26];
- extruded scleral buckle[27];
- excessive cyanoacrylate glue used to close a perforated cornea[28];
- protruding nylon sutures[29];
- rigid contact lens imbedded in upper fornix[30];
- elevated corneal deposits[31]; and
- epithelialised corneal foreign body.[32]

In many of these cases, the papillary conjunctivitis resolved and patient symptoms were alleviated upon removal of the trauma. The reports of Dunn et al.[31] and Greiner[32] are particularly noteworthy because, unlike the other cases which involve trauma induced by man-made materials, the papillary conjunctivitis was induced by trauma from inert epithelial irregularities.

Trauma is known to cause mast cell degranulation, so the presence of large numbers of degranulated mast cells in the conjunctival epithelium and stroma of patients with CLPC[33] is consistent with trauma being a factor of aetiological significance in this condition. The conjunctivae of patients with CLPC have significantly higher levels of neutrophil chemotactic factor[34] – a substance which is generally released in traumatised tissue. The decay-accelerating factor (DAF), a membrane-associated complement regulatory protein which inhibits the central C3 amplification of the cascade, is present on both the ocular surface and in tears. Szczotka et al.[35] reported that DAF concentrations were significantly reduced in patients with CLPC compared with normal non–contact lens wearing controls. This reduction may be associated with enhanced complement activation contributing to the pathogeneses of CLPC.

IMMEDIATE HYPERSENSITIVITY

This anaphylactic reaction is mediated by immunoglobulin type E (IgE) antibodies which proliferate when the conjunctiva is exposed to certain antigens. The IgE antibodies set off a chain reaction leading to mast cell degranulation and the release of inflammatory mediators and other substances that can affect tissue damage and repair. Patients with CLPC exhibit large numbers of degranulated mast cells in the conjunctival epithelium[36] and elevated levels of IgE in tears.[37]

Protein deposition on the lens has been implicated as the antigenic stimulant to IgE production. More specifically, deposits that form on the anterior lens surface are likely to be more significant in that this surface lies in direct apposition with the tarsal conjunctiva. In support of this lens deposition theory, Ballow et al.[38] demonstrated that when contact lenses from patients suffering from CLPC were placed in the eyes of monkeys, a frank papillary conjunctivitis ensued, with elevated IgE levels. These changes did not occur when new lenses or lenses from patients without CLPC were placed in the eyes of monkeys.

A critical issue in formulating strategies to treat or prevent CLPC is to determine the specific causative antigens. Protein deposition on the lens surface is the most popular candidate; however, protein on lenses of patients with CLPC is indistinguishable from protein on lenses of patients without CLPC. The antigenic stimulus could also be one of a number of other potential lens contaminants, such as lipids, calcium, mucus and albumin.[39] Microorganisms such as bacteria (and bacterial endotoxins) may also trigger CLPC.

The type of plastic used to fabricate the contact lens could theoretically have an antigenic role; however, this is difficult to prove.[40] The success or otherwise of various polymers in alleviating or preventing CLPC probably relates more to the propensity of different materials to become deposited and/or the frequency of lens replacement, rather than any real differences in their intrinsic antigenic potency.

Early-generation preservatives, such as thimerosal and benzalkonium chloride, are known to have a causative role in the development of CLPC.[41] Certainly, treatment is more likely to succeed if lens care systems are free of such preservatives.[42]

DELAYED HYPERSENSITIVITY

In their initial writings, Allansmith et al.[2] likened CLPC to vernal conjunctivitis in view of the similar inflammatory cell profiles of the two conditions; this view still holds today.[43] The unusual presence of large numbers of basophils led Allansmith et al.[2] to suggest that these diseases were of the cutaneous basophilic type. This is a classic skin reaction which has a delayed time course and is mediated by sensitised T lymphocytes and antibodies. In support of this proposed aetiology, Hann et al.[44] induced a CLPC-type reaction in guinea pigs after injection of various antigens into the tarsal plate.

Despite the evidence cited earlier, the proportion of basophils to the total pool of inflammatory cells in CLPC is significantly less than that observed in a typical cutaneous basophilic hypersensitivity reaction. In view of this, Begley[45] suggested that CLPC may better reflect the classic tuberculin type of delayed hypersensitivity reaction in which variable numbers of basophils can be present.

The antigens discussed in the previous section on the immediate hypersensitivity reaction are likely to be the same as those that mediate the delayed hypersensitivity reaction.

INDIVIDUAL SUSCEPTIBILITY

There is disagreement in the literature as to whether atopic individuals are more susceptible to developing CLPC. Some authors have found no connection between atopy and CLPC,[2,36] whereas others have reported an increased prevalence of allergies in patients exhibiting CLPC.[46] Buckley[47] found elevated serum IgE levels in patients suffering from CLPC, suggesting the presence of an IgE-mediated atopy in these patients.

Indirect evidence of the association of atopy with CLPC comes from the work of Begley et al.,[48] who reported that the onset of this condition was seasonal in a population of 68 patients. The condition peaked during the 'allergy seasons' in mid-western USA, where the study was conducted. These patients reported significantly more overall allergies, in addition to CLPC, compared with a control group.

MEIBOMIAN GLAND DYSFUNCTION

Some researchers have suggested an association between CLPC and meibomian gland dysfunction (MGD).[49,50] Martin et al.[49] found that 42 consecutively presenting patients with CLPC were also suffering from MGD and that the severity of the conditions were positively correlated. After treating the MGD and refitting new lenses to 32 patients, 28 were deemed to be successful 21 months later.

Fig. 14.9 is a schematic illustration describing the various factors thought to be of aetiological significance in CLPC.

Observation and grading

As CLPC manifests in the superior palpebral conjunctiva, it is necessary to evert the lid to detect this condition. This is best performed with the patient positioned in the head and brow rest of a slit lamp biomicroscope so that the everted lid can be readily observed at low magnification (×10–×15) and high illumination. The extent of tarsal redness and oedema, and the general position and distribution of papillae, should be noted. High magnification can then be employed to examine the

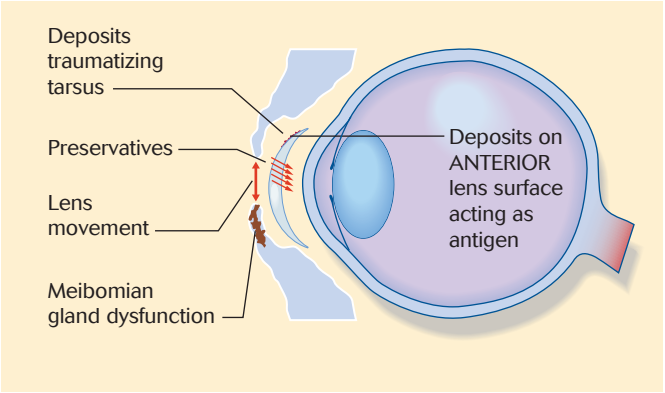
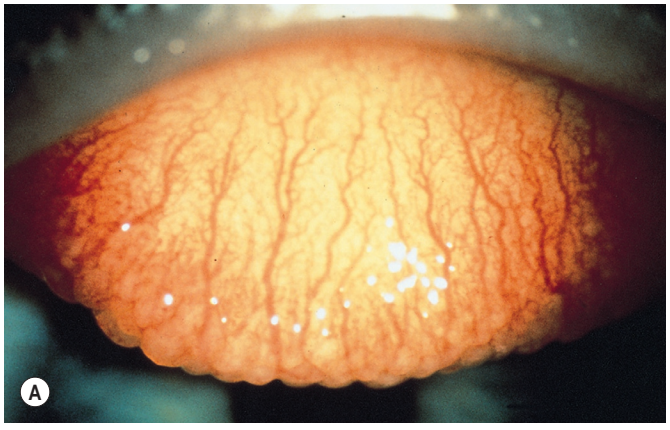


Fig. 14.9 Factors of aetiological significance in contact lens–induced papillary conjunctivitis (CLPC).

conjunctival surface, with particular attention to the distribution of vessels over the surface of the papillae.

After observing the tarsal conjunctiva in white light, the lid should be reverted back to its normal form and fluorescein instilled. After a few blinks, the lid should be everted once again and observed under white light (Fig. 14.10A) and then cobalt blue light (Fig. 14.10B). Fluorescein pools at the base of the papillae, allowing individual papillae to be resolved and the overall pattern of papillary formation to be more readily appreciated. The reason for recommending viewing of the fluorescein-stained conjunctiva in white light and blue light is that the 'white light with fluorescein' view represents an intermediate step or 'link' that allows reconciliation of the 'white light without fluorescein' and 'blue light with fluorescein' views. The severity of CLPC can be assessed with reference to the grading scales presented in Appendix A.

The lower lid should be everted by simply pulling downwards on the skin just beneath the lashes on the lower eyelid. The exposed lower palpebral conjunctiva will generally be clear and forms a useful baseline reference for assessing the level of tarsal redness and oedema of the superior palpebral conjunctiva. However, a mild CLPC will very occasionally be observed in the lower lid (Fig. 14.11). It is also important to carefully examine the superior cornea as CLPC can be associated with superior limbal redness, corneal staining, corneal infiltrates and excess tear mucus.



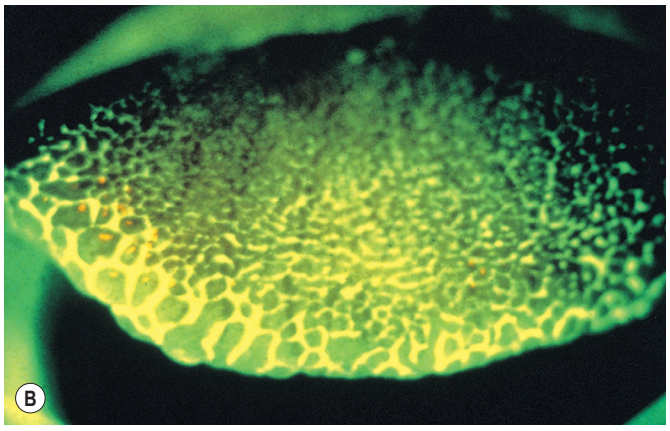


Fig. 14.10 Contact lens–induced papillary conjunctivitis observed under **(A)** white light and **(B)** cobalt blue light. Observation with cobalt blue reveals a more extensive pattern of papillae. (Courtesy Eric Papas, Bausch & Lomb Slide Collection.)

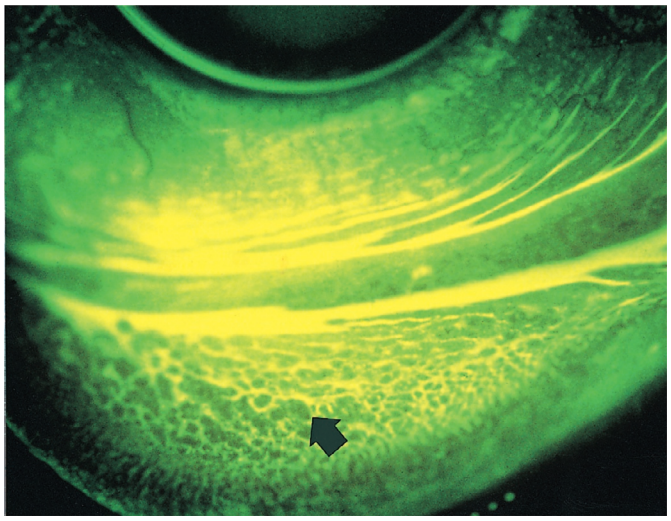


Fig. 14.11 An unusual case of contact lens–induced papillary conjunctivitis of the lower palpebral conjunctiva (arrow) in response to rigid lens wear, observed with fluorescein under cobalt blue light. (Courtesy Martina Alt, Bausch & Lomb Slide Collection.)

Treatment

Because there are many possible factors involved in the aetiology of CLPC – and the key factor in a given patient is rarely obvious – a variety of treatment options may need to be employed, either sequentially or simultaneously. As a general rule, the earlier the condition is detected and treated, the better is the prognosis for an effective and speedy cure.

In many respects, CLPC is a condition that is best managed with reference to patient symptoms rather than signs. Many patients will be motivated to continue lens wear even in the presence of low-grade CLPC (grades 1 and 2), and they should be allowed to do so. Subtle non-intrusive strategies should be introduced in an attempt to alleviate the condition while maintaining patient motivation. The tarsal plate of patients who are largely asymptomatic should be monitored carefully to detect the development of chronic tissue compromise.

Treatment options fall into four broad categories: (a) alterations to the type, design and modality of lens wear; (b) alterations to care systems; (c) improving ocular hygiene; and (d) prescribing pharmaceutical agents. Each of these shall be considered in turn.

ALTERATION TO THE LENS

All soft lenses develop deposits over time. Most of these deposits can be removed by daily surfactant cleaning, but some, such as protein, gradually build up regardless. Protein removal systems may slow the rate of protein build-up, but they do not prevent it. Furthermore, it is the *quality* of protein deposition, rather than the *quantity*, that will govern biocompatibility. For example, Sack[51] demonstrated that although type IV (ionic high water) lenses attract significant amounts of protein, the conformational integrity (i.e. physiological compatibility) of the protein is preserved. Type I lenses (non-ionic low water) attract much less protein, but the protein is denatured and therefore more likely to be antigenic to the eye.

If it is true that bacteria adherent to protein deposits are the trigger for CLPC, then the quantity of protein may

be more important – less protein should mean less bacterial attachment.

Assuming protein accumulation to be one cause of CLPC in soft lens patients, effective lens-related strategies would include:

- changing to a lens material that deposits a protein film that is physiologically compatible with the eye;
- changing to a lens material that deposits less protein;
- changing to a rigid lens material; or
- replacing lenses more frequently.

Alterations to soft lens design may alleviate CLPC if the mechanical effect of the lens is minimised. Thus, the fitting of good-quality thin soft lenses with restricted movement may be beneficial.

The ophthalmic literature is devoid of descriptions of properly controlled studies that prove the efficacy of the various treatments described earlier. Even the ultimate form of regular lens replacement – daily disposable lenses – will not necessarily solve the problem. For example, daily disposable lenses made from type IV materials deposit significant levels of protein within 15 minutes of insertion.[52] The success or otherwise of such lenses in the prevention or cure of CLPC will depend on the physiological compatibility of the protein that rapidly accumulates and/or the rate of attachment of bacteria to the protein.

Cessation of lens wear will certainly result in a complete cure, but such an option is generally met with little enthusiasm by patients. In severe cases (grade 3 or 4), ceasing lens wear for a brief period of, say, 2 to 4 weeks will enhance the prospect of success of subsequent treatment strategies. Similarly, a reduction in wearing time in the early phase of treatment will optimise the prospect for recovery.

Certain rigid lenses may attract deposits in such a way that is less antigenic to the patient (e.g. a lesser amount of protein and/or more physiologically compatible protein). However, rigid lenses potentially have a greater physical effect on the eye, which could exacerbate CLPC. Woods and Efron[53] were unable to demonstrate a difference in the tarsal response in a group of rigid lens wearers who replaced their lenses frequently versus a matched group of rigid lens wearers who did not frequently replace their lenses; this suggests that the mechanical effect of the lenses is the primary determinant of tarsal changes in rigid lens wearers. Lenses with thin inter-palpebral designs, smooth edges and restricted movement are most likely to yield a successful outcome. Douglas et al.[54] reported that the onset of CLPC could be delayed or prevented by fitting lenses of higher oxygen transmissibility, although the success of this strategy may relate more to the surface effects of the lens materials rather than the enhanced oxygen performance of these lenses.

Shimamoto et al.[55] demonstrated that membership in a contact lens supply system, which promoted better compliance in terms of lens usage and replacement, was associated with a reduced incidence of papillary conjunctivitis, compared with those who were not members.

ALTERATION TO CARE SYSTEMS

In the first instance, it is necessary to establish that the patient is being fully compliant with the prescribed care regimes, which for soft lenses would include digital cleaning, rinsing and disinfection.

If preservatives in contact lens solutions are thought to be of aetiological significance in a particular patient, then the employment of preservative-free systems (some hydrogen peroxide solutions fall into this category) may alleviate the condition.

IMPROVING OCULAR HYGIENE

Improvements to ocular hygiene begin with improvements to personal hygiene. Thus, routine and thorough hand washing before lens handling and regular face washing should mitigate against development of CLPC. Some authors[42,56] have recommended the additional step of conjunctival irrigation with sterile unpreserved saline before and after lens insertion, and periodically during the day, as a means of diluting or removing antigens to CLPC and generally enhancing patient comfort.

If one accepts the association between CLPC and MGD described earlier,[49,50] then attention to lid hygiene should be of benefit. Encouraging the patient to employ such strategies as lid scrubbing, warm compresses and expression will help alleviate MGD and presumably have some positive outcome with respect to the CLPC.

PHARMACEUTICAL AGENTS

Prescription of any drug is generally used to supplement alternative strategies, such as those described previously. A variety of medications have been advocated for the treatment of CLPC and the provision of symptomatic relief, as discussed in the following.

Mast cell stabilisers

The first agent to receive attention as a viable treatment for CLPC was ocular cromolyn sodium, which acts by stabilizing mast cell membranes, thus preventing the release of inflammatory mediators, such as histamine. An initial dosage of 2% or 4% cromolyn sodium four times a day, tapering off to once a day as the condition improves, has been advocated by various authors.[57,58] The preservative-free form of this drug should be used if there is a poor initial response. Mast-cell stabilisers are best used regularly as it takes a little time for their effect to build up; these drugs serve as a preventative measure against further inflammation.

Figure 14.12 shows the tarsal conjunctiva of an atopic individual who presented with a request for contact lenses. She had never worn lenses previously, and she had been using cromolyn sodium daily for over 10 years. The scarring and abnormal vascular changes present may reflect a combination of long-term ocular compromise and drug-induced alterations to the normal inflammatory and tissue repair processes.

Other mast-cell stabilisers include nedocromil sodium (Rapitil) and lodoxamide trometamol (Lomide). Forty-five patients with CLPC were studied by Bailey and Buckley[59] in a 6-week double-masked group comparative study of unpreserved 2% nedocromil sodium eye drops and placebo. There was significantly less itching in the nedocromil sodium group compared with the placebo group during weeks 1 to 3 of the study, but not during weeks 4 to 6. Biomicroscopic assessment showed a significant difference in mucus found on the upper tarsal surface in favour of nedocromil sodium by the end of the study. However, during the study, 21 patients experienced adverse events, such as an unpleasant taste and/or stinging on insertion of the drops.

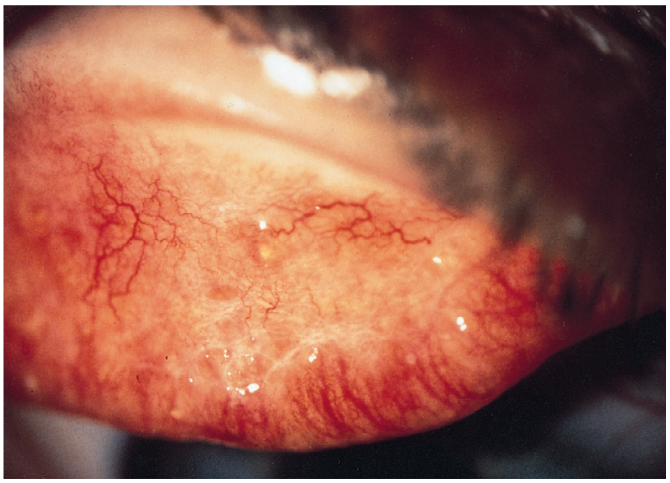


Fig. 14.12 Deformities in the tarsal plate of an atopic individual who had never worn contact lenses and had used cromolyn sodium for over 10 years. (Courtesy Lyndon Jones, British Contact Lens Association Slide Collection.)

Corticosteroids

Steroidal agents can be very effective in more severe cases of CLPC (grade 3–4); however, in view of the risks of cataract formation, increased intra-ocular pressure and corneal infection, their use is generally only for a short duration. Fluorometholone is an example of a corticosteroid that is used to reduce inflammation of the palpebral and bulbar conjunctiva. It inhibits the inflammatory response to inciting agents of a mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called *lipocortins*. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation, such as prostaglandins and leukotrienes, by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipase A2. Although fluorometholone can produce a rise in intra-ocular pressure, it has a lower propensity to do so compared with dexamethasone.

Loteprednol etabonate (a chemical analogue of prednisolone), a 'soft steroid', has been found to be as effective as conventional steroids in treating CLPC, but without the untoward side effects of the latter. Specifically, Asbell and Howes[60] found that this drug resulted in a significant reduction both in the size of papillae and the extent of itching and lens intolerance in patients with CLPC.

Non-steroidal anti-inflammatory agents

Suprofen is a non-steroidal anti-inflammatory drug (NSAID) which has been used to treat CLPC. This drug, which inhibits prostaglandin synthesis, was found by Wood et al.[61] to have a significant effect on signs and symptoms of CLPC after 2 to 3 weeks. Patients instilled two drops of 1% suprofen solution four times daily. Ketorolac is another NSAID which has been used in the treatment of allergic conjunctivitis generally. Although it was found to be more effective than placebo in alleviating the signs and symptoms of allergic conjunctivitis, olopatadine was found to be significantly better at reducing ocular itching compared with ketorolac.[62]

Antihistamines

Oral antihistamines may be used when attempting to control multiple allergic symptoms in the eyes, nose and pharynx; however, they often give rise to unwanted side effects of drowsiness and dry mouth. When symptoms are confined to the eye, as in CLPC, a topical antihistamine is likely to be more efficacious as the therapy is more focused. Some topical treatments are 'pure' antihistamines, such as levocabastine. Others are multi-action histamine H(1) receptor agonists, such as olopatadine, ketotifen, azelastine and epinastine. These are suggested to combine anti-histaminic effect, mast cell stabilization and anti-inflammatory action. This pharmaceutical class is therefore rapidly becoming the first choice for prevention and treatment for allergic conjunctivitis.[63] Olopatadine 0.1% and ketotifen 0.025% are used twice daily.

Vasoconstrictors

Topical vasoconstrictor agents provide rapid relief, especially for redness; however, the relief is often short-lived, and overuse of vasoconstrictors may lead to rebound hyperaemia and irritation. Their use is to be discouraged in contact lens wearers.

Combination therapy

Khurana et al.[64] studied the use of olopatadine (a mast cell stabiliser) and fluorometholone (a corticosteroid) separately and in conjunction. They concluded that most effect was obtained when both olopatadine and fluorometholone were used for papillary conjunctivitis followed by olopatadine monotherapy and then fluorometholone monotherapy. These authors concluded that corticosteroids or modified corticosteroids will be very useful in the initial management of CLPC, with either mast-cell stabilisers or multi-action antihistamines being used over a more prolonged period.

Tacrolimus

Diao et al.[65] reported that tacrolimus 0.05% may be a safe and effective treatment for mild to moderate CLPC and is comparable with fluorometholone 0.1% in efficacy. Tacrolimus inhibits the production of interleukin-2, a molecule that promotes the development and proliferation of T cells, which are vital to the adaptive immune response.

Prognosis

The prognosis for recovery from CLPC after removal of lenses and cessation of wear is good. Even in the most severe conditions (grade 4), symptoms will disappear within 5 days to 2 weeks of lens removal[2,61] and tarsal redness and excess mucus will resolve over a similar time course. Resolution of papillae takes place over a much longer time course – typically many weeks and as long as 6 months. The more severe the condition, the longer the recovery period.

In the longer term, however, the prognosis is not so good. The condition can recur, especially in atopic patients, who appear to have a propensity for developing the condition. Fortunately, such patients will have a lower threshold for noticing the early 'warning signs' and will typically seek prompt attention, which will, in turn, enhance the probability of successful treatment.

Differential diagnosis

A key issue in the accurate diagnosis of CLPC is the capacity to differentiate between papillae and follicles (Fig. 14.13). Papillae

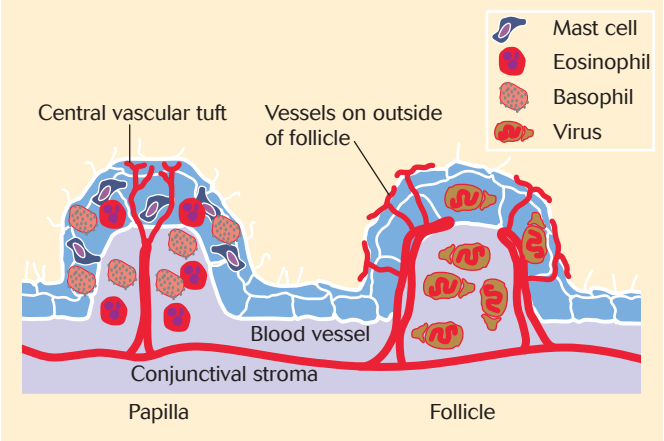


Fig. 14.13 Pathological changes that characterise a papilla (left) and follicle (right).



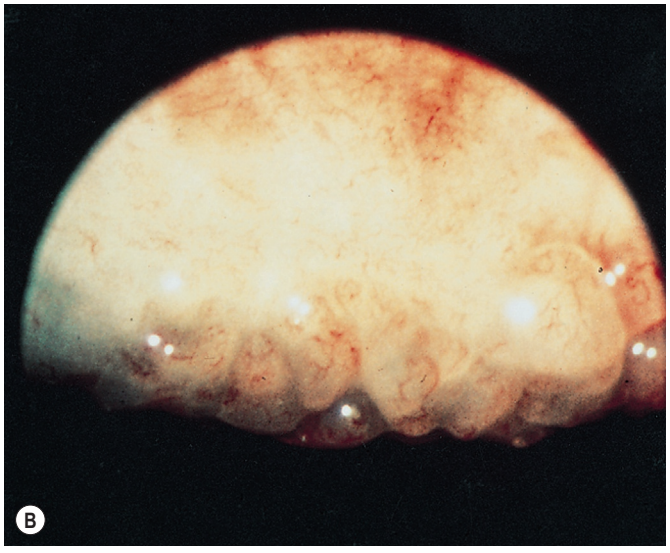


Fig. 14.14 Magnified view of **(A)** papillae and **(B)** follicles. Note the presence of vascular tufts (arrow) at the apex of papillae. (A, Courtesy Maki Shiobara, Bausch & Lomb Slide Collection. B, Courtesy Brien Holden, Brien Holden Vision Institute.)

are observed in allergic diseases, such as CLPC and vernal conjunctivitis, whereas follicles are indicative of viral or chlamydial conjunctival infections. There is generally little to distinguish between the two conditions, and careful history taking will provide the most important diagnostic clues.

The appearance of papillae has been described in detail previously in this chapter. According to Allansmith et al.,[42] the side walls of papillae may be perpendicular to the plane of the tarsal plate and not pyramidal like follicles (Fig. 14.14). Other key distinguishing features are as follows: Some deep vessels can be observed traversing the surface of papillae, whereas vessels may be more obvious on the surface of follicles; papillae often display a rich plexus of convoluted vessels (vascular tuft) at the apex, whereas follicles generally do not display this feature. Follicles tend to be paler in colour.

In the advanced stages of CLPC, the apex of papillae may fill with infiltrates, thus masking the vascular tuft and taking on a whitish centre. Subsequent scarring also tends to be whitish in appearance, making it easy to distinguish papillae from follicles, which usually do not display scar-like areas.

In vernal conjunctivitis that is unrelated to lens wear, the papillae can be truly gigantic (Fig. 14.15) and thus differentiated from CLPC. Other distinguishing features of vernal conjunctivitis are the characteristic thick yellow discharge which consists of mucus, epithelial cells, neutrophils and eosinophils. The



Fig. 14.15 Advanced vernal conjunctivitis with characteristic thick yellow discharge. (Courtesy VK Dada, Bausch & Lomb Slide Collection.)

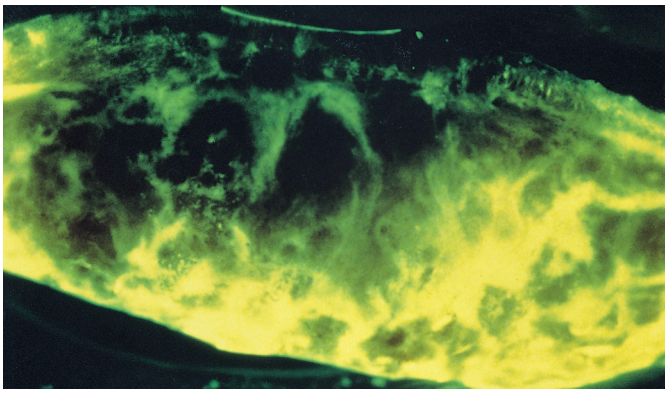


Fig. 14.16 Long-standing vernal conjunctivitis with distorted papillae and disorganised scarring, observed with fluorescein under cobalt blue light. (Courtesy Desmond Fonn, Bausch & Lomb Slide Collection.)

condition is usually bilateral, and bilateral ptosis may be present. Long-standing vernal conjunctivitis may result in distorted papillae and disorganised scarring (Fig. 14.16).

Other pathologies of the tarsal conjunctiva will present from time to time, but these are easily distinguishable from the classic cobblestone appearance of multiple papillae formations.

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15 Limbal Redness

'Limbus' is the Latin word for 'border'. When the eye is viewed macroscopically from a social viewing distance of, say, 50 cm, the limbus appears as a reasonably clear circle that forms the outer limit (or 'border') of the visible iris. However, defining the exact position of the limbus is more problematic from both a clinical and a histological perspective. When the limbus is viewed under magnification with a slit lamp biomicroscope, the transition zone between the cornea and conjunctiva is gradual and occurs over a span of about 0.2 to 0.4 mm, generally being slightly greater in the vertical meridian.[1]

From a histological perspective, defining the location of the limbus is even more problematic. The limbus is formally defined as being about 1.5 mm wide.[2] This is because various histological features that define the limbal region start and finish at different locations, and some changes are abrupt and some are gradual; a 1.5-mm zone encompasses all these features. Specifically, changes that take place in the transition from the cornea to the conjunctiva and sclera include

- abrupt termination of Bowman's layer,
- gradual thickening of the epithelium,
- introduction of loose connective tissue underlying the conjunctival epithelium,
- increasing irregularity of anterior stromal lamellae, and
- appearance of blood vessels in the stroma.[1] (Fig. 15.1)

It is the last of these features that is the topic of this chapter, and for the purposes of discussion of the limbal redness response to contact lens wear, it is convenient to regard the limbus as the region within which the vascular network of the conjunctiva gives way to the avascularity of the cornea.[3]

Signs and symptoms

ANATOMICAL CONSIDERATIONS

The fact that the limbus displays a distinct response to contact lens wear was first recognised by Müller over a century ago.[4]

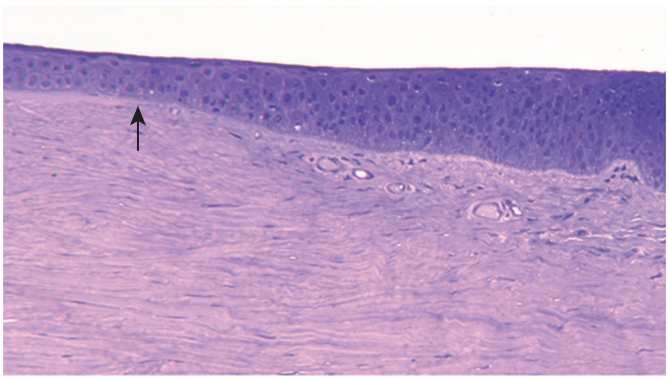


Fig. 15.1 Light micrograph of a radial section through the corneoscleral transition in the vertical meridian. The cornea is to the left. The arrow marks the termination of Bowman's layer (it is visible to the left of the arrow). (Courtesy John Lawrenson.)

Careful inspection of the superficial blood vessels at the limbus reveals the presence of 'anterior limbal loops' (Fig. 15.2). In some patients, a series of two or three layers of anterior limbal loops can be observed to build on top of each other as the limbal vascular plexus extends towards the cornea, with the vessels constituting each successive inwardly progressing loop becoming finer and finer. The innermost series of loops are termed 'terminal arcades'.

When the limbus has been physically and/or physiologically stressed – for example, by some types of contact lens – the limbal vessels dilate and two types of vascular features connected to the terminal arcades can be readily visualised – 'recurrent limbal vessels' and 'spike vessels'. On casual inspection with the slit lamp biomicroscope, a recurrent limbal vessel may appear as a single vessel, with an accompanying shadow, that connects tangentially from a terminal arcade. On closer inspection, however, it can be seen that two vessels of different calibre are present – a thicker arteriole and a much thinner venule (the 'shadow') (Fig. 15.3).

Vessel spikes look similar to recurrent limbal vessels, the distinction being that the vessel spike is a single arteriole that does not have a returning venule. The lumen of vessel spikes and recurrent limbal vessels can become so narrow that only clear serum (not red blood corpuscles) can pass through. This raises the question as to whether a vessel spike really only represents the visible arteriolar component of a recurrent limbal vessel, with the venular component being too narrow to allow red blood cells to pass through (and thus remaining invisible). However, electron microscopic evidence (Fig. 15.4) has confirmed the structure of vessel spikes as single arterioles.[1]

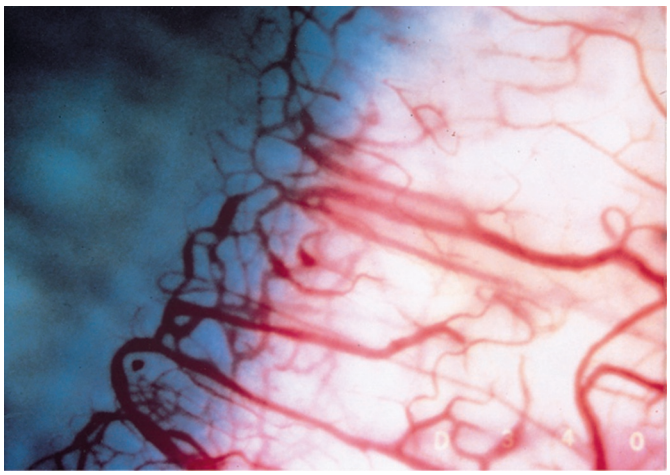


Fig. 15.2 Engorged conjunctival and limbal vessels and possible slight neovascularisation. The anterior limbal loops are clearly visible at the termination of the vessels in the peripheral cornea.

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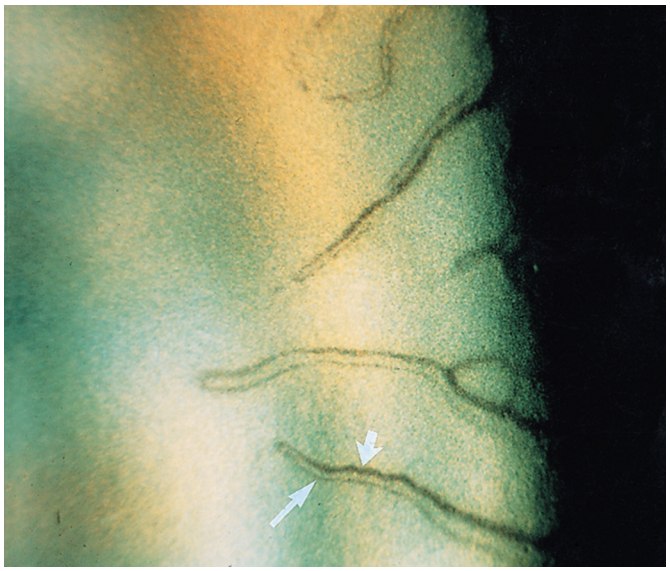


Fig. 15.3 High-magnification view (×100) of a thick arteriolar component (thick arrow) and thin venular component (thin arrow) of a recurrent limbal vessel.

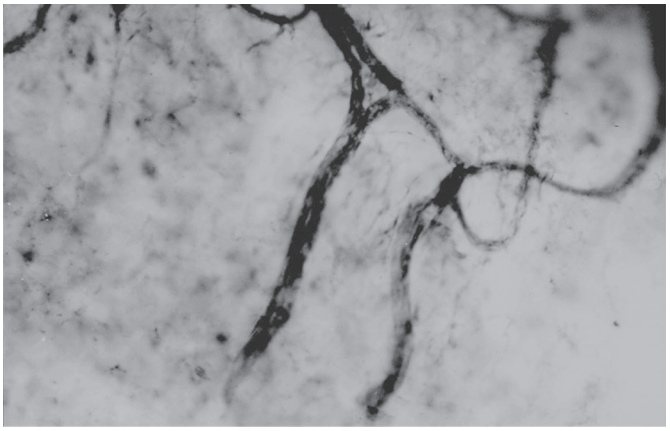


Fig. 15.4 Whole-mount gold chloride preparation of anterior limbal vessels showing two vessel spike formations. (Courtesy John Lawrenson.)

CLINICAL OBSERVATIONS

Holden et al.[5] measured the extent of bulbar conjunctival and limbal redness in a group of patients who had worn a conventional (low-Dk) high-water-content soft lens on an extended-wear basis in one eye only (the other eye being emmetropic or amblyopic) for an average of 5 years. Bulbar conjunctival redness was graded as 0.9 (vs. 0.7 in non-lens-wearing control eyes) and limbal redness was graded as 1.1 (vs. 0.3 in the non-lens-wearing control eyes). From these data, it can be inferred that extended wear of conventional soft lenses has a much greater effect on limbal redness than on bulbar conjunctival redness.

The time course of development of limbal redness in response to conventional hydrogel lenses and silicone hydrogel (Si-H) (high-Dk) lenses during open and closed eye wear has been investigated by Papas et al.[6] Subjects were first monitored without lenses. They then wore a conventional hydrogel lens in one eye and a Si-H lens in the other eye and were observed after 4 and 16 hours. When not wearing lenses, limbal redness changes averaged 0.2 ± 0.2 and 0.4 ± 0.2 grades at 4 and 16 hours, respectively (inferior quadrant). The corresponding values for conventional hydrogel lens wear were 1.0 ± 0.6 and 1.1 ± 0.6, whereas for Si-H lens wear, they were 0.2 ± 0.4 and 0.5 ± 0.5, respectively (Fig. 15.5). Both for the non-lens-wearing eyes and eyes wearing Si-H lenses, increases in limbal redness were significant only during eye closure. During conventional hydrogel lens wear, significant and larger limbal redness increases were seen after 4 hours open-eye wear, with only relatively small further changes being observed over the next 12 hours. Papas et al.[6] concluded that (a) conventional hydrogel lens wear induces a marked increase in limbal redness during open-eye wear, which is not seen either in the no-lens situation or when Si-H lenses are worn, and (b) the pattern of limbal redness for both the open and closed eyes during Si-H lens wear is very similar to that for the no-lens situation.

A similar study to that of Papas et al.[6] was conducted by Dumbleton et al.,[7] and the subjects were monitored over a 9-month period rather than a few hours. On a 0-to-100 scale, extended wear of conventional hydrogel lenses resulted in a 16-point increase in limbal redness; no significant change occurred with the Si-H lenses (Fig. 15.6). Interestingly, the difference was greatest for subjects wearing conventional hydrogel lenses initially presenting with lower levels of redness. There was

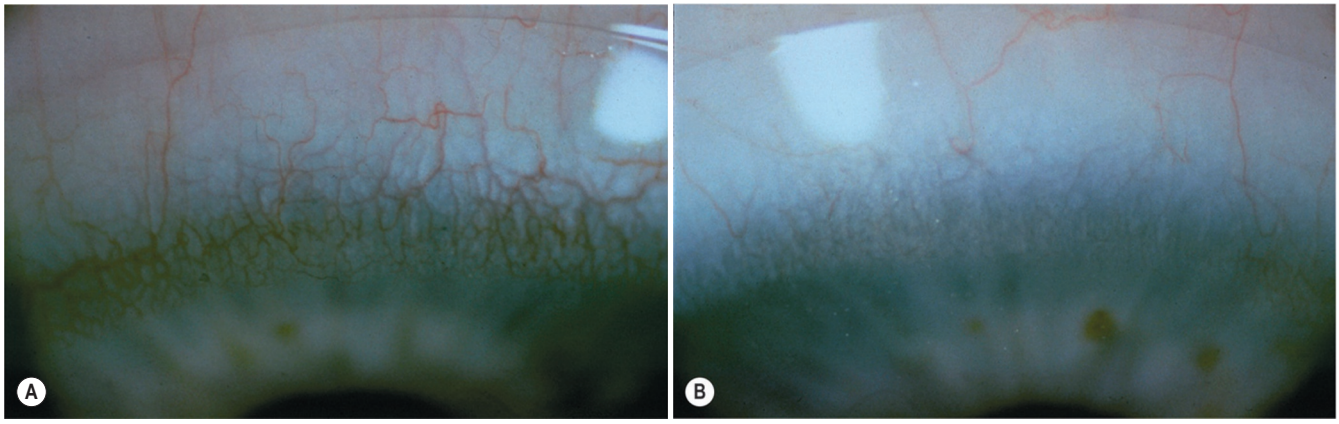


Fig. 15.5 Demonstration of the effect of hypoxia on limbal redness. **(A)** Grade 2.2 limbal redness is evident in this patient wearing a conventional hydrogel (38% water content hydroxyethyl methacrylate (HEMA)) contact lens in one eye. **(B)** The same patient is wearing a silicone hydrogel contact lens in the other eye; the extent of limbal redness (grade 1) is much less than that in the eye wearing the HEMA lens. (Courtesy Eric Papas, In: Efron N, editor. Contact Lens Practice. 2nd ed. Oxford, UK: Butterworth-Heinemann; 2010.)

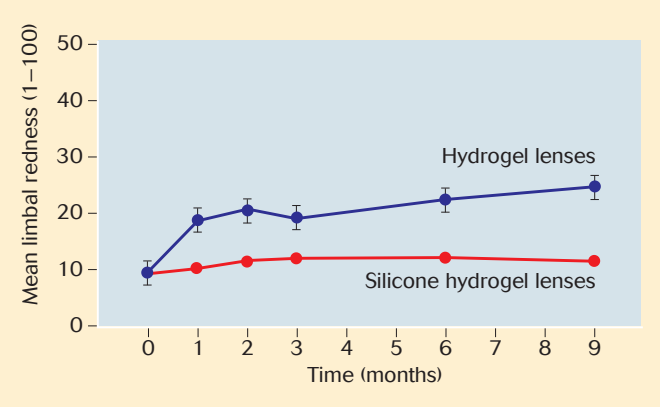


Fig. 15.6 Mean change in limbal redness grade over time for silicone hydrogel lenses (red line) and conventional hydrogel lenses (blue line). (Approximate scale: 0 = trace redness; 100 = extreme redness). (Adapted from Dumbleton KA, Chalmers RL, Richter DB, Fonn D. Vascular response to extended wear of hydrogel lenses with high and low oxygen permeability. Optom Vis Sci 2001;78:147–51.)

a slight resolution of redness in participants who initially presented with higher levels of redness after wearing the Si-H lenses.

Covey et al.[8] were unable to detect any difference in the grade of limbal redness between patients wearing Si-H lenses (2.6 ± 0.3) on an extended-wear basis versus patients who wore no lenses (2.4 ± 0.4), over a 9-month period.

Numerous other studies have confirmed that silicone hydrogel lenses result in significantly reduced levels of limbal redness compared with hydrogel lenses, for both daily and extended lens wear.[9-17] This is not just a short-term effect; reductions in limbal redness are still evident after 3 years of silicone hydrogel lens wear.[18] Improved limbal redness with silicone hydrogel lenses is equally evident in Caucasian and Asian eyes.[19]

Szczotka-Flynn et al.[20] also confirmed that two silicone hydrogel lens types – lotrafilcon B (Air Optix Aqua) and comfilcon A (Biofinity) – induce less limbal redness (0.10 and 0.18 grade difference, respectively) than a mid-water hydrogel lens (etafilcon A; Acuvue 2). However, they deemed these differences to be clinically inconsequential and suggested that etafilcon A was 'non-inferior' to lotrafilcon B and comfilcon A in this regard.

The development of limbal redness is not thought to be associated with any subjective symptoms, although patients with severe contact lens–induced complications may coincidentally have limbal redness and be suffering from discomfort or pain. None of the short-term or long-term studies referred to earlier reported any symptoms relating to limbal redness during uncomplicated lens wear.

Pathology

Throughout the vascular system, blood flow is constantly adjusted to meet the local tissue needs. This is achieved via four basic regulatory mechanisms:

- Neural control – the calibre of vessels is controlled by balancing the input of parasympathetic and sympathetic innervation to vascular smooth muscle in the vessel wall.
- Myogenic control – vessel diameter is altered in response to changes in blood pressure within the vessel. Thus, distension of the vessel wall with increased pressure will cause smooth muscle contraction. In the limbus, this mechanism dampens the tendency for increased fluid filtration to cause interstitial oedema during periods of raised blood pressure.
- Metabolic control – the accumulation of waste products, such as carbon dioxide and lactic acid surrounding the vessels, causes the vessels to dilate, increasing blood flow and removing the metabolic waste. Local hypoxia has a similar effect.
- Humoral control – agents circulating in blood, such as epinephrine, norepinephrine, histamine, serotonin, angiotensin, bradykinin and vasopressin.

However, because microcirculatory fields, such as the limbus, are devoid of direct neural control and lack smooth muscle in the vessel walls, alternative mechanisms must come into play to control blood flow. Two mechanisms are thought to be involved. First, it is thought that a system of precapillary sphincters – defined as the last (most peripheral) smooth muscle cell along any branch of a terminal arteriole – control blood flow into the limbal plexus in a co-ordinated manner. This implies that capillary flow is not continuous but will start and stop according to local needs and conditions. Second, small cells which surround capillary vessels, known as *pericytes*, and vascular endothelial cells appear to have contractile properties that allow them to alter the calibre of limbal vessels.[3]

When fine terminal vessels – comprising either vessel spikes or recurrent limbal vessels – are viewed with the electron microscope, they are found to display the usual features of normal limbal capillaries.[1] They are non-fenestrated, with thick endothelial walls surrounded by pericytes and their processes, and connective tissue cells. Although many vessels possess an open lumen capable of allowing the passage of formed elements of blood (Fig. 15.7), many others are observed in which the calibre is reduced so as to prevent the passage of these elements, and in extreme cases, the lumen is completely closed (Fig. 15.8).[1] These observations highlight the dynamic growth patterns of capillaries.

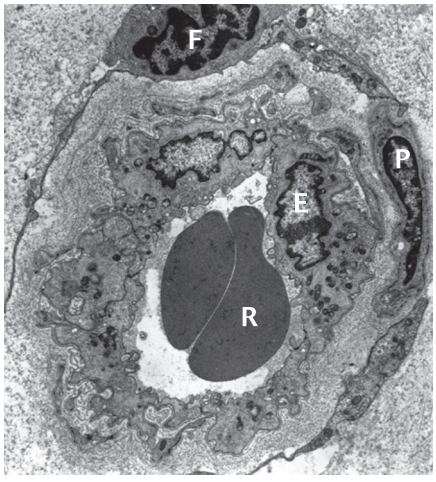


Fig. 15.7 Electron micrograph of a non-fenestrated capillary from the limbal conjunctiva, close to the termination of Bowman's membrane. R, red blood cells; E, vascular endothelium; F, fibroblast; P, pericyte. (Courtesy John Lawrenson.)

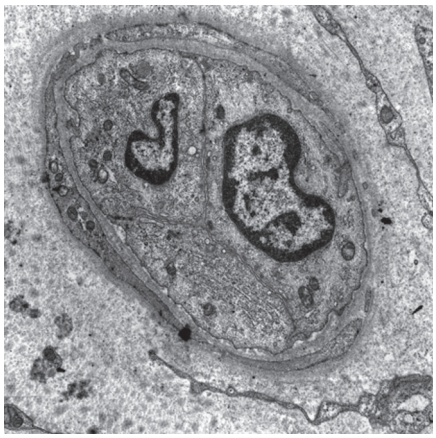


Fig. 15.8 Electron micrograph of a limbal conjunctival capillary displaying a closed lumen. (Courtesy John Lawrenson.)

Aetiology

A number of factors may be of aetiological significance in the development of limbal redness in contact lens wear.

HYPOXIA

Convincing evidence of the role of hypoxia in causing limbal redness has been provided by Papas,[21] who demonstrated a strong inverse relationship between the oxygen transmissibility of contact lenses in the region of the limbus (i.e. the lens periphery) and limbal redness; that is, the lower the local lens oxygen transmissibility, the greater is the limbal redness. Since other properties of the lens may have contributed to the limbal redness response, such as lens-induced hypercapnia (carbon dioxide build-up) and lens stiffness, Papas[22] conducted a supplementary experiment in which the eyes of subjects were exposed to atmospheric anoxia in a gas goggle (i.e. no lens wear); these eyes displayed significantly greater levels of limbal redness, providing evidence that reducing the oxygen concentration at the ocular surface induces more blood flow in limbal vessels.

The precise mechanism by which hypoxia causes increased redness is still unclear; however, Papas[22] has proposed the following sequence of events. Hypoxia may exert an effect on the vascular endothelium, causing the release of nitrous oxide. This local mediator diffuses towards the smooth muscle cells comprising the adjacent precapillary sphincters, which are induced to relax, resulting in increased blood flow to the hypoxic region. Direct influence of hypoxia on the vascular pericytes, as described previously, is another possibility.

INFECTION

Infection of the cornea leads to a cascade of inflammatory events that induces limbal redness. Increased perfusion of the capillary vessels in the limbus is mediated by the release of vasodilating agents, such as nitrous oxide, histamine and various prostaglandins. This increased blood flow allows immune system cells, such as polymorphonuclear leucocytes (PMNs), to rapidly approach the site of the infection. Chemical mediators, such as cytokines, are involved in the mediation of this process; the cytokines stimulate the release of adhesion molecules that act to hold the PMNs at the site of the injury for maximal effect. This is followed by extravasation, whereby the distended limbal vessel walls increase in permeability and cells and fluid pass out of the vessel into the surrounding tissue. This can sometimes be observed clinically as a milky haze surrounding engorged limbal vessels[22] (Fig. 15.9).

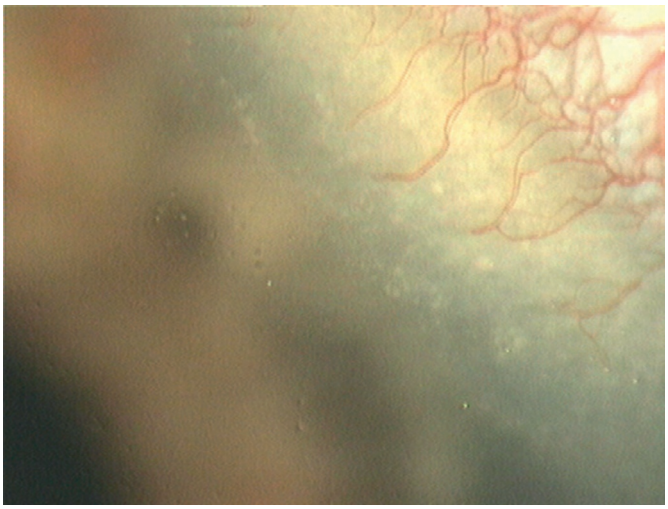


Fig. 15.9 Recurrent limbal vessel surrounded by extravascular fluid, seen here as a mottled milky haze. (Courtesy Brian Tompkins.)

INFLAMMATION

There is an increase in the inflammatory cell population in the conjunctival sac overnight,[23] which may explain why our eyes sometimes appear a little red upon awakening. It is also recognised that contact lenses can alter the concentrations of inflammatory mediators in the tear film.[24] These mild inflammatory effects, taken together, may explain why patients who wear contact lenses on an extended wear basis are more prone to conditions, such as contact lens–associated red eye. That is, the mild inflammatory situation present with closed-eye lens wear may predispose the eye to develop more overt inflammatory episodes.

TRAUMA

Soft contact lenses rest in direct apposition to the limbus. This constant physical presence may cause the direct release of inflammatory mediators and result in increased limbal redness. Clinical observations of local limbal redness in the proximity of a traumatic source, such as a damaged lens edge, supports the notion of direct trauma being of aetiological significance in limbal redness (see Fig. 15.7). However, the possibility of more subtle physical influences on limbal redness, such as variations in soft lens modulus (stiffness), has been discounted by Dumbleton et al.[7] As discussed previously, these authors observed that silicone hydrogel lenses cause less limbal redness than conventional soft lenses, the latter having much lower oxygen transmissibility (which should reduce redness) and lower modulus (which should theoretically tend to increase redness). They concluded that the effects of lens oxygen performance far outweigh the effects of lens modulus on limbal redness.[7]

SOLUTION TOXICITY OR HYPERSENSITIVITY

The preservatives present in various contact lens care solutions may affect limbal redness. The more noxious forms of

preservatives used in early generation systems, such as thimerosal and chlorhexidine, were clearly associated with increased levels of eye redness.[25] Willcox et al.[26] and Santodomingo-Rubido[27] failed to observe differences in the limbal response when silicone hydrogel contact lenses were used in combination with lens care product containing either Polyquad/Aldox or polyhexamethylene biguanide.

However, Soni et al.[28] reported different levels of limbal redness in response to three different lens care systems over an 18-month period, which was likely to be more of a delayed hypersensitivity type of response. The preservatives may act directly as a stimulus on either the precapillary sphincters or the vessel walls, causing vessel distension (and limbal redness) to facilitate either an immediate toxic or immediate hypersensitivity reaction or a more long-term immune response.

LENS DEPOSITS

Fahmy et al.[29] reported alleviation of limbal redness after 4 weeks in patients who changed from reusable lenses (replaced at intervals between 1 and 4 weeks) to daily disposable lenses. This suggests that deposits that build up on the surface of reusable lenses over days or weeks can contribute to the limbal redness response.

Management

As ought to be clear from the preceding discussion, the management strategy for the removal or alleviation of limbal redness will involve elimination or modification of the causative agent. This raises two questions: (a) What is the acceptable threshold level of limbal redness? (b)What is the causative agent in a given patient?

Increased limbal redness in itself is harmless in the immediate sense and does not cause any discomfort for the lens wearer; however, it is an important sign of ocular distress and an indicator that action needs to be taken. The severity of limbal redness can be determined with reference to the grading scales for this tissue change provided in Appendix A. According to Pult et al.,[30] a level of limbal redness of greater than about grade 2.5 may be considered as being abnormal. Fonn et al.[31] plotted the frequency of eyes wearing Si-H lenses with limbal redness greater than grade 2, implying that they considered this to be the approximate threshold for clinical significance. It is likely that increased limbal redness, if allowed to persist, is a precursor for corneal neovascularization.

Szczotka-Flynn et al.[32] reported that limbal redness may predict the subsequent development of an infiltrative event among patients wearing contact lenses continuously.

A useful framework for the adoption of possible management strategies to eliminate or alleviate limbal redness is to consider whether the case is (a) acute or chronic or (b) local or circumlimbal. An example of a possible cause and management strategy with respect to these various scenarios is given here:

- Acute local limbal redness – keratitis in a region of the cornea near the local redness. Aggressive anti-infectious and anti-inflammatory treatment may be indicated (management of such conditions is dealt with in Chapter 27).
- Chronic local limbal redness – defect in the edge of a rigid lens designed for lens orientation (e.g. truncated design). Replace the damaged lens.

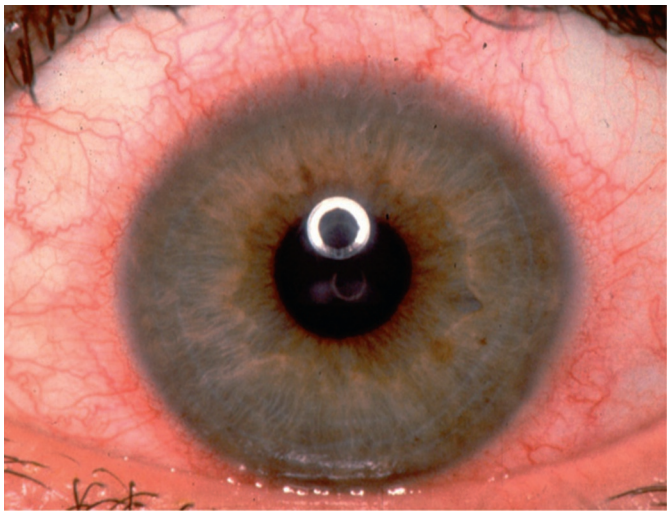


Fig. 15.10 Severe circumlimbal redness (grade 4).

- Acute circumlimbal redness – contact lens solution immediate hypersensitivity or toxicity reaction. Change lens solutions and change contact lens. A daily disposable lens would solve this problem.
- Chronic circumlimbal redness – caused by contact lens–induced hypoxia or lens deposits. Figure 15.10 shows grade 4 circumlimbal redness caused by long-term use of a low-permeability soft lens used on an extended-wear basis.

Chalmers et al.[10] demonstrated that a reduction in limbal redness can be achieved by refitting patients from conventional hydrogel lenses into silicone hydrogel lenses. Limbal redness in patients wearing reusable contact lenses can be reduced by refitting with daily disposable lenses,[29] especially those supplied with enhanced lubricating agents.[29, 33]

Prognosis

The prognosis for recovery from chronic contact lens–induced limbal redness after removal of lenses and cessation of wear is good. Holden et al.[34] found that after approximately 5 years of extended wear of conventional hydrogel lenses, general conjunctival redness resolved within 2 days and limbal redness had a slightly longer time course, taking about 7 days to resolve fully (Fig 15.11).

du Toit et al.[35] measured the limbal vascular response after 8 hours of eye closure while wearing Si-H and conventional hydrogel lenses compared with control eyes without lenses. They found that upon waking and after lens removal, there were no differences in hyperaemia between eyes wearing Si-H and conventional hydrogel lenses; however, the reduction in redness over time of the Si-H lens–wearing eyes was more rapid compared with the conventional hydrogel lens–wearing eyes. du Toit et al. suggested that the faster recovery from redness in the eyes wearing the Si-H lenses may be a result of the increased oxygen transmissibility of these lenses.

Differential diagnosis

A primary consideration in differential diagnosis of limbal redness is to determine whether simple increased vascular engorgement or neovascularisation is being observed. In the case of

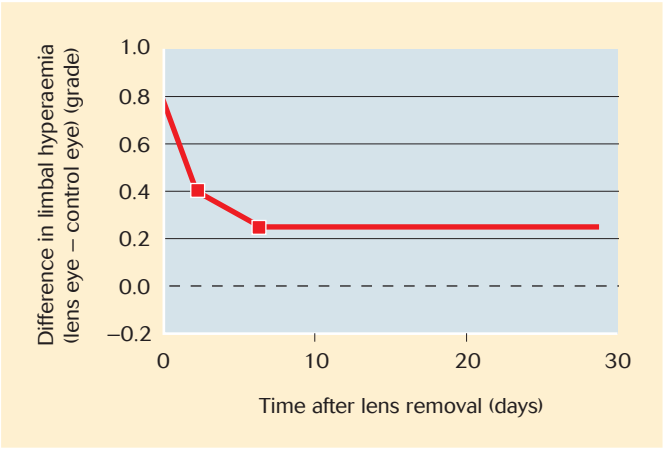


Fig. 15.11 Time course of resolution of limbal redness after 5 years extended wear of a high-water-content hydrogel lens in one eye only, relative to a non-lens-wearing control eye. (Adapted from Holden BA, Sweeney DF, Swarbrick HA, et al. The vascular response to long-term extended contact lens wear. Clin Exp Optom 1986;69:112–9.)

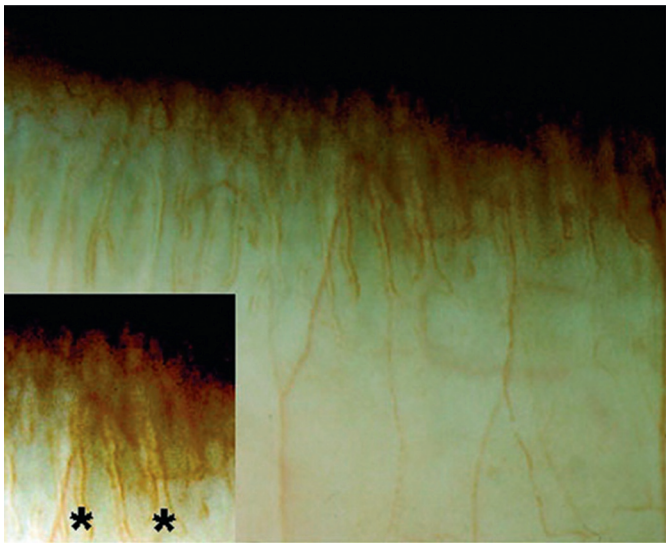


Fig. 15.12 High-power slit lamp view of the palisades of Vogt at the lower limbus. Inset: Asterisks highlight two palisades. (Courtesy John Lawrenson.)

increased limbal redness, more blood is flowing through vessels that have become thicker, but the limbal vascular plexus has not become more extensive and/or vessels have not become longer. Neovascularisation implies vessel growth into the normal avascular cornea (see Chapter 25). Although the normal level of vascular encroachment into a healthy cornea is about 0.2 mm in a non–lens wearer, uncomplicated contact lens wear can induce low levels of vascular encroachment that may still be considered 'normal' within certain limits. The only real way of determining if active re-vascularisation is beginning to occur is to carefully monitor the limbal vasculature over time and measure the degree of vessel penetration into the cornea.

An early sign of contact lens–induced superior limbal keratoconjunctivitis or Theodore's superior limbal keratoconjunctivitis (the latter being a condition unrelated to contact lens wear; see Chapter 17 for a discussion of both these conditions) is increased redness of the superior limbus. Thus, detection of increased limbal redness superiorly should raise suspicion that the patient could be suffering from one of these conditions. The observation of associated signs and symptoms of irritation suggests early contact lens–induced superior limbal keratoconjunctivitis or Theodore's superior limbal keratoconjunctivitis.

Some patients display prominent palisades of Vogt, which, upon first inspection, give the appearance of a prominent plexus of limbal vessels. Palisades of Vogt consist of an array of connective tissue ridges that commence in the peripheral corneal epithelium and extend into the limbus as spoke-like radiations arranged at right angles to the peripheral cornea[2] (Fig. 15.12). They measure about 0.5 mm wide and vary in length among individuals, ranging from 2 to 4 mm. Palisades of Vogt are more prominent at the inferior limbus, and in darker-skinned races, they are more heavily pigmented and thus easier to see. Limbal vessels have a similar appearance and typically run in parallel to the palisades of Vogt. On careful slit lamp examination, differential diagnosis between the dark brown palisades of Vogt and red limbal vessels should be clear.

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16 Vascularised Limbal Keratitis

The limbus is prone to pathological changes for a variety of reasons. A rich capillary plexus is embedded in the limbus and these vessels may become engorged (see Chapter 15) or may constitute the platform from which vessels may penetrate into the cornea (see Chapter 25). The limbus is the site of the corneal stem cells, which are the primary source for the differentiation and proliferation of the corneal epithelium. A deficiency in limbal stem cells may lead to a plethora of corneal complications.[1] A sharp transition in the topography of the anterior eye occurs at the limbus, whereby there is a pronounced flattening from the corneal surface to the conjunctival surface, forming a physical 'ridge'.[2] These three limbal features – the capillary plexus, stem cells and the limbal ridge – render the limbus susceptible to metabolic, immunological, toxic and physical insult, and all of these challenges may be induced or exacerbated by contact lenses.

It has long been recognised that the integrity of the limbus is more likely to be compromised by soft lenses because they rest in physical proximity to that tissue.[3] The limbus is less likely to be insulted by rigid lenses that are smaller than the corneal diameter and only intermittently impinge on the limbus. Vascularised limbal keratitis (VLK) is an unusual complication of rigid contact lens wear, which, as the name suggests, is characterised in its most severe manifestation as an inflammation of the limbus in association with a process of vascularisation.[4]

The condition is usually associated with extended rigid lens wear and has been demonstrated to occur with both low-oxygen permeable lenses[4] and super-permeable rigid lenses[5] – in the latter case with an incidence of only 0.8% of patients per year. VLK has also been observed in patients wearing rigid lenses on a daily-wear basis. It is always observed at the 3 & 9 o'clock corneal locations.

Signs and symptoms

According to Grohe and Lebow,[4] VLK can be characterised as a condition that develops in four grades, representing stages of increasing severity; these grades are outlined in the next subsections. This condition typically develops over a period of up to 6 months, but the time course can be more protracted, taking up to 24 months for the condition to become severe.

GRADE 1

The patient is asymptomatic. The epithelium adjacent to the limbus appears disrupted as evidenced by superficial punctate staining. An apparent 'heaping' or accumulation of hyperplastic corneal and/or limbal epithelial tissue can be observed. This appears as an elevated, opaque or whitish elevated mass at the 3 & 9 o'clock corneal locations, with a diffuse, ill-defined border. The mass typically appears to bridge from the conjunctiva, over the limbus, on to the cornea, although it can form almost exclusively on the cornea or the conjunctiva, but always immediately adjacent to the limbus. The tear film meniscus at the edge of the rigid lens is absent or disrupted (Fig. 16.1).

GRADE 2

The patient will typically complain of mild ocular discomfort and increased lens awareness and may be aware that the eyes are red. Corneal infiltrates may be present, as well as mild overlying staining (grade 2) and mild conjunctival redness (grade 2) (Fig. 16.2).

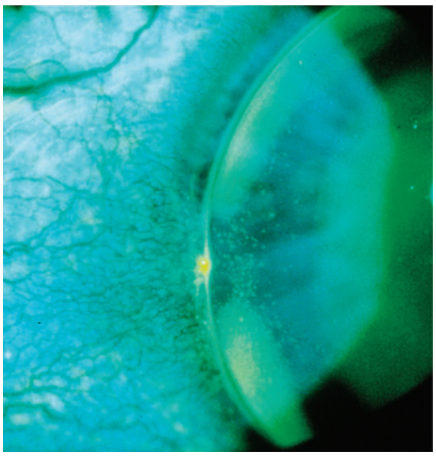


Fig. 16.1 Grade 1 vascularised limbal keratitis viewed in cobalt blue light with fluorescein instilled. (Courtesy Robert Grohe.)

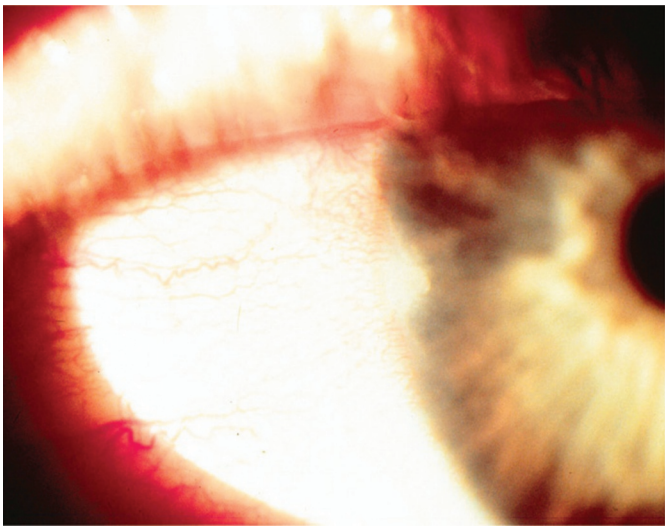


Fig. 16.2 Grade 2 vascularised limbal keratitis (VLK). (Courtesy Robert Grohe.)

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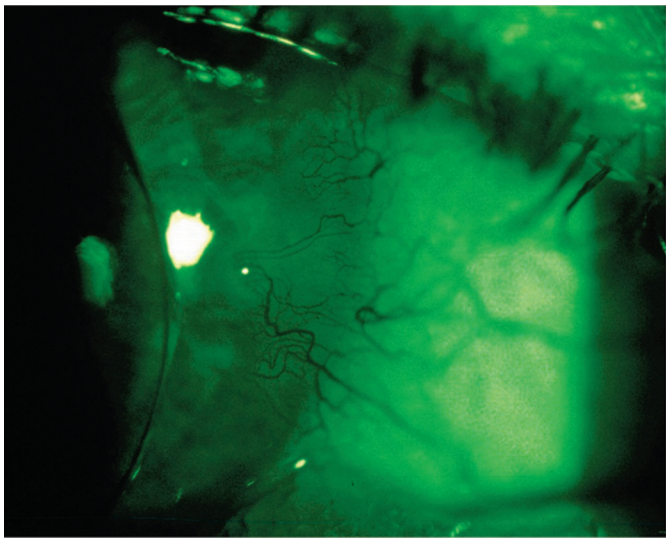


Fig. 16.3 Grade 3 vascularised limbal keratitis (VLK) viewed in red-free (green) light. (Courtesy Robert Grohe.)

GRADE 3

The patient will complain of mild to moderate discomfort and may report reduced lens wearing time. Moderate conjunctival redness (grade 3), more extensive corneal epithelial staining and mild limbal and conjunctival staining are observed. There may also be a greater infiltrative response. The conjunctiva and limbus may appear to be slightly oedematous. A vascular leash, emanating from the conjunctiva and across the limbus, encroaches on the hyperplastic epithelial mass (Fig. 16.3).

GRADE 4

Patients will report considerable discomfort and photophobia. Pain is experienced when the lens edge impinges on the affected region, making lens wear almost intolerable. Significant conjunctival redness and staining are apparent, often associated with an erosion of the elevated hyperplastic epithelial mass. Superficial and deep vascularization may be present. The patient will be aware of the hyperplastic epithelial mass and may refer to this as a 'lump' on the eye (Fig. 16.4).

Pathology

The precise pathological changes that are occurring at a cellular level are unknown because studies to this effect have not been reported in the literature. However, it can be deduced from the clinical observations outlined earlier that there is a syndrome of concurrent tissue pathologies, including epithelial cell hyperplasia (Fig. 16.5), vessel engorgement and progression, tissue erosion, tissue oedema and corneal infiltrates.

Aetiology

The aetiology of VLK is unknown, but Grohe and Lebow[4] hypothesised that this condition is caused by an interruption to the normal tear film dynamics at the limbus induced by rigid lenses of inappropriate design. Specifically, they propose that design faults, such as a low lens edge lift, create abnormal fluid dynamics at the edge of the lens. This could, in turn, compromise the normally full tear meniscus at the lens, resulting in a

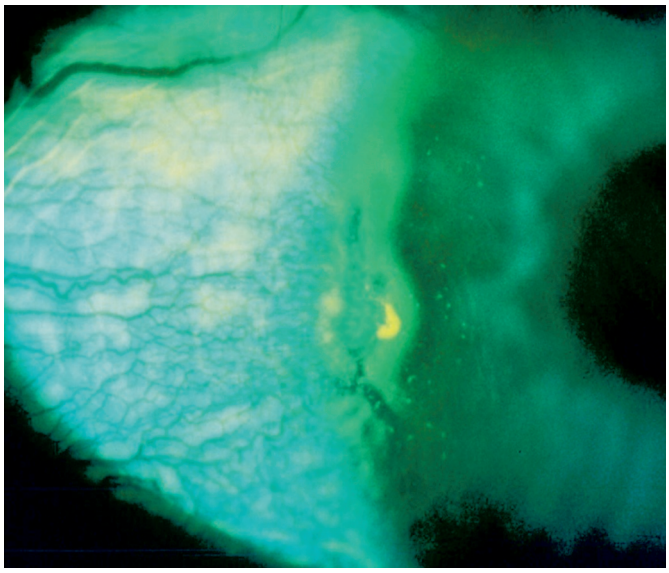


Fig. 16.4 Grade 4 vascularised limbal keratitis (VLK) viewed in cobalt blue light with fluorescein instilled. (Courtesy Robert Grohe.)

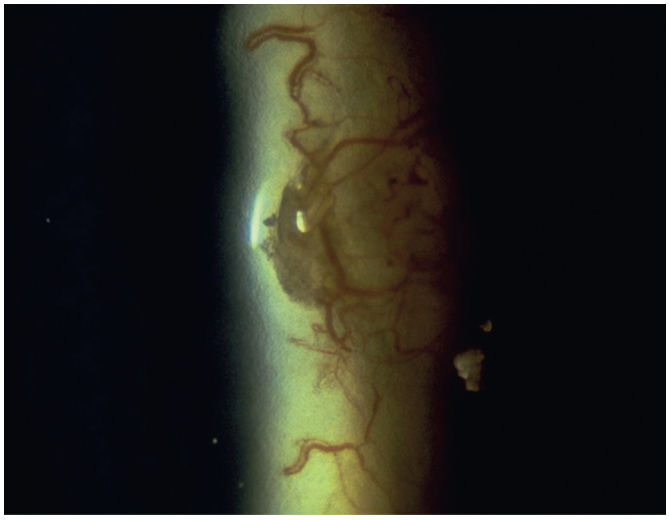


Fig. 16.5 Vascularised epithelial mass in vascularised limbal keratitis (VLK). (Courtesy Robert Grohe.)

desiccation effect and consequent interruption to surface wetting in the region of the limbus. Constant ongoing physical irritation of the poorly lubricated ocular surface by a combination of the eyelids and lens causes a low-grade inflammatory reaction, which, if left unchecked, progresses through the various grades of VLK, as described previously. In a case report, Miller[6] found that VLK was caused by surface crazing on a rigid lens.

The theory as to the cause of VLK, as outlined previously, and the clinical description of this condition strongly suggest that VLK represents a severe clinical sequel of 3 & 9 o'clock staining, albeit uncommon. Indeed, Grohe and Lebow[4] admitted that five of the eight patients with VLK they described had previously been fitted because of unacceptable peripheral 3 & 9 o'clock corneal staining with rigid lenses, and the patient described by Miller[6] also has a previous case history of 3 & 9 o'clock corneal staining. If this is the case, considerable clinical significance ought to be attached to the early detection and management of 3 & 9 o'clock staining in rigid contact lens wearers.

Treatment

Treatment of VLK can be outlined with respect to the four grades of severity of the condition.[4]

GRADE 1

The patient should be instructed to change from extended-wear to daily-wear lens. If already in daily wear, wearing time should be reduced from all-day wear to 6 to 8 hours per day. The lens should be redesigned such that the peripheral curve configuration is flattened to create greater edge lift and improved fluid dynamics at the lens edge. Lubricating drops used throughout the day may provide symptomatic relief and assist in improving lens dynamics.

GRADE 2

Lens wear should be discontinued for 5 days, and ocular decongestants may be prescribed to alleviate lens redness. The lens should be redesigned as for grade 1, as well as possibly reducing the lens diameter and/or flattening the lens base curve. Efforts should be made to eliminate mechanical bearing at the peripheral cornea. Daily lens wear can be recommenced initially, and if the eye remains quiet in due course, extended wear may be resumed.

GRADE 3

Lens wear should be discontinued for 5 days, and tissue scrapings should be taken and sent for analysis to differentiate from possible infectious causes (see 'Differential Diagnosis'). Topical corticosteroids may be required if the infiltrative response is severe. The lens should be redesigned utilizing the principles for grade 2, as outlined earlier. Daily lens wear can be recommenced initially, but extended wear should only be resumed if there has been full recovery and there is a pressing need.

GRADE 4

Lens wear should be discontinued for 3 weeks. Tissue scrapings should be taken and the eye should be treated with an antibiotic steroid combination. Topical corticosteroids may be required if the infiltrative response is severe. The lens should be redesigned utilising the principles for grade 2, as outlined earlier. Daily lens wear can be recommenced initially, but future extended wear is generally contraindicated.

Miller[6] was able to manage a case of VLK by prescribing a new set of lenses of a different material to replace the lenses that had suffered surface crazing. The parameters of the replaced lenses were not altered. Thus, changing lens material is a possible alternative strategy to altering lens parameters in the management of VLK.

Cressey et al.[7] reported successfully treating a 58-year-old white woman with advanced keratoconus and VLK by fitting her with a custom-designed scleral lens. VLK was present in both eyes and was associated with vascularisation and lipid keratopathy. Corneal scarring projected into the central cornea of both eyes, but more so in the left eye. After lens fitting, the patient demonstrated initial improvements in both comfort and vision, from 6/9 to 6/7.5 in the right eye and from 6/12 to 6/6 in the left eye. After 2 years, the patient reported excellent vision and comfort. Acuities were R 6/7.5^{+2} and L 6/6. There was normalization of the corneal surface with reduced staining and epithelial irregularity and substantial regression of corneal neovascularization and opacity, particularly in the left eye.

Prognosis

If a patient recommences lens wear prematurely after lens wear has been suspended because of VLK, a 'rebound' phenomenon may occur, whereby the condition flares up once again and rapidly progresses to the equivalent level of severity at the time of cessation. This situation typically occurs in cases when the patient recommences wearing the original offending lens (i.e. the lens design has remained unaltered). This phenomenon strongly suggests a lens design aetiology.

The prognosis for recovery from VLK is generally very good; even severe cases can recover within days[4] or a few weeks.[6] As an illustration of this rapid time course of resolution of this condition, consider the following case: a patient presented 3 months after being fitted with 9.2 mm diameter fluorosilicone acrylate rigid lenses for extended wear; these lenses were worn continuously for up to 7 days at a time. The patient was diagnosed with grade 3 VLK. Objective findings included a raised limbal epithelial mass with fluorescein staining and a prominent vascular leash. The lens edge can be seen impinging against the raised mass in Figure 16.6. With the aid of fluorescein, the tear film meniscus at the lens edge can be seen to thin out and virtually disappear in the proximity of the raised mass (Fig. 16.7).

The lens diameter was subsequently reduced to 8 mm; as can be seen in Figure 16.8, the lens no longer impinges on the epithelial mass. By comparing Figure 16.8 with Figure 16.6, it can be seen that this strategy has resulted in a slight reduction in the size of the epithelial mass, and the vascularisation has subsided. In a further attempt to resolve the condition, the wearing schedule was restricted of to a maximum of 3 days of extended wear at a time; this resulted in further resolution, but not elimination, of the raised mass and vascular leash. Lens wear was then suspended for 5 days, resulting in almost complete resolution of the raised mass (Fig. 16.9) and vascular leash (Fig. 16.10).



Fig. 16.6 Grade 3 vascularised limbal keratitis in a patient wearing a 9.2 mm diameter rigid lens. (Courtesy Robert Grohe.)

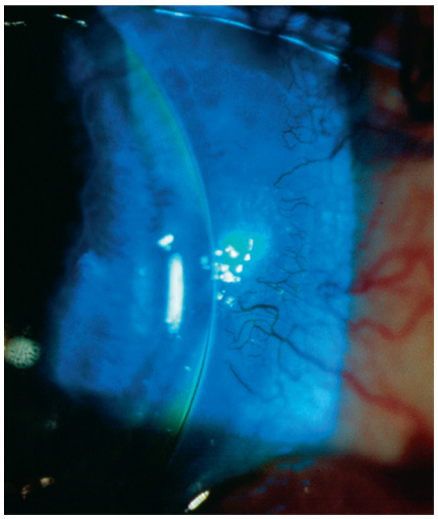


Fig. 16.7 Same eye as in Figure 16.6 after instillation of fluorescein and viewed with a cobalt blue light. The tear film meniscus at the lens edge is virtually absent at the point of contact between the raised epithelial mass and the lens. (Courtesy Robert Grohe.)

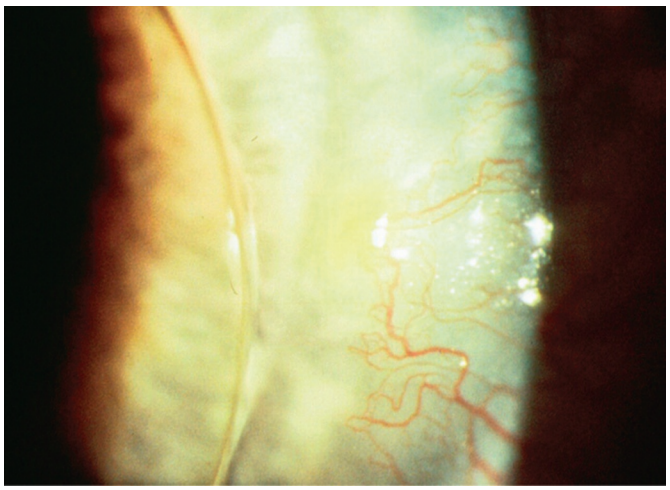


Fig. 16.8 Same eye as in Figure 16.6, but the patient has been refitted with an 8-mm-diameter rigid lens, which is now not impinging on the raised epithelial mass. (Courtesy Robert Grohe.)

The patient was subsequently able to resume extended wear for 2 days at a time, and the VLK did not recur.

Differential diagnosis

The key conditions that need to be differentially diagnosed from VLK are phlyctenulosis, peripheral corneal ulceration, pterygium, pseudo-pterygium and pinguecula.

Phlyctenulosis is an inflammatory disorder involving the conjunctiva, limbus and/or cornea.[8] It is usually bilateral and primarily affects young children and young adults. Phlyctenules are pinkish-white nodules that vary in size from pinpoint to several millimetres. They may be solitary or multiple. The limbus is generally affected first, but there may be isolated involvement of

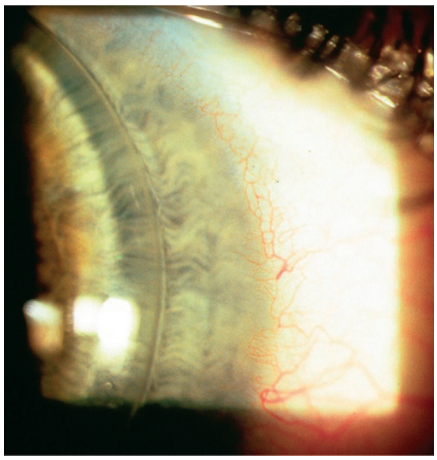


Fig. 16.9 Same eye as in Figure 16.6 but the wearing schedule was restricted to a maximum of 3 days of extended wear at a time, followed by a cessation of lens wear for 5 days. The raised mass has now almost completely resolved. (Courtesy Robert Grohe.)

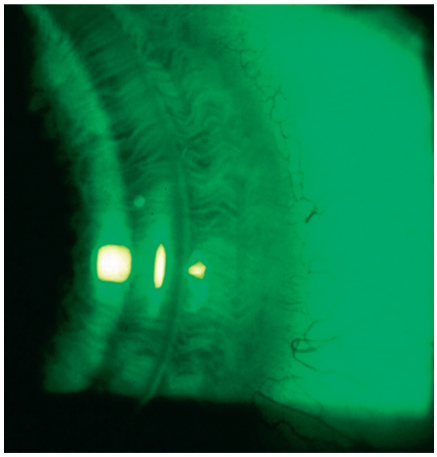


Fig. 16.10 Same eye and lens as in Figure 16.6 viewed with a red-free (green) light, confirming the absence of vascular leashing. (Courtesy Robert Grohe.)

the bulbar conjunctiva or cornea. The condition is generally self-limiting, whereby the phlyctenule progressively becomes greyish, ulcerates and heals completely within 10 to 15 days to leave residual scarring and vascularisation. Symptoms include a foreign body sensation and the reporting of eye redness. The patient will report severe photophobia if the cornea is affected. The pathogenesis of this condition is believed to be a local immunological reaction of the ocular surface to bacteria-elaborated antigens; the most commonly associated microbial agent is *Staphylococcus aureus*. It can also potentially occur secondary to antigens from a variety of different organisms, such as mycobacteria and intestinal worms.[9] The condition may be associated with blepharitis. Differential diagnosis between VLK and phlyctenulosis is achieved by culturing the eyelid margins and conjunctiva; a positive culture for *Staphylococcus* and the presence of residual pathology after the active phase of the condition has resolved should heighten suspicion of phlyctenulosis. Furthermore, phlyctenules can present at any location

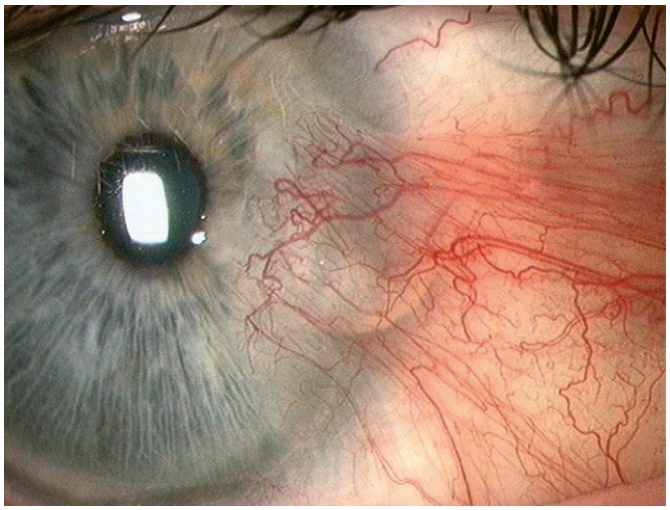


Fig. 16.11 Pterygium. (Courtesy Brian Tompkins.)

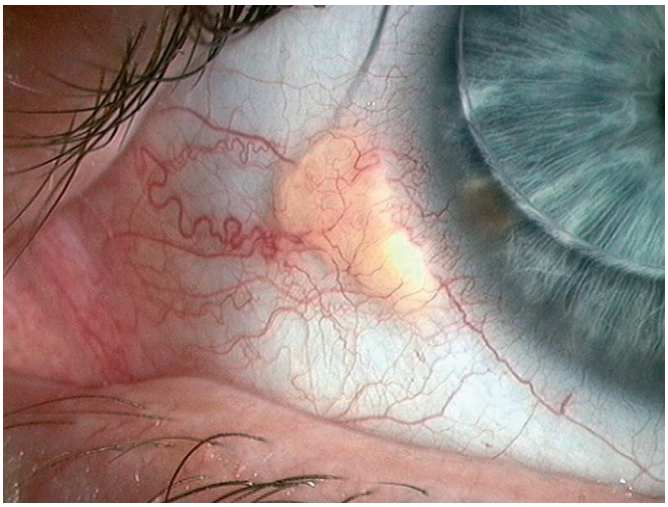


Fig. 16.12 Pinguecula, with the raised epithelial mass separated from the limbus by about 1 mm. (Courtesy Brian Tompkins.)

around the limbus, whereas VLK only presents at the 3 & 9 o'clock positions.

Peripheral corneal ulcers will be considered in detail in Chapters 26 and 27. A microbial peripheral ulcer is extremely painful, and a sterile peripheral ulcer may be asymptomatic; the discomfort occurring as a result of VLK probably falls equally between the two. The term 'ulcer' implies an erosion of tissue, which is the opposite of a raised tissue mass seen in VLK; however, in the active stages of a microbial peripheral ulcer, the edges of the ulcer may be uneven and slightly raised at certain points, making differential diagnosis difficult. As is the case with phlyctenulosis, peripheral corneal ulcers can present at any location around the limbus, whereas VLK only presents at the 3 & 9 o'clock positions. Vascularisation of peripheral ulcers usually only occurs when the condition is advanced.

A pterygium is a triangular growth of fibrovascular tissue into the cornea (Fig. 16.11). It can be differentiated from VLK because of its chronic time course (thought to be caused by chronic exposure to ultraviolet light), classic triangular shape and extensive corneal encroachment in its late stage. Furthermore, pterygium is asymptomatic. Excision and adjunctive treatment with mitomycin C or conjunctival autograft are the most acceptable and most popular modes of treating both primary and recurrent pterygium. Outcomes seem to have been further improved with adjuvant combination therapy.[10]

A pseudo-pterygium is a conjunctival adherence to the cornea caused by limbal or corneal inflammation or trauma. It may have an atypical shape or position, giving a similar appearance to VLK. Differential diagnosis between pseudo-pterygium and VLK can be achieved by determining whether a probe can be passed behind the lesion; this is likely to occur in the case of pseudo-pterygium because of its lack of adherence to the limbus.[8]

Pinguecula is a horizontal, triangular or oval, elevated milky-yellow area of bulbar conjunctival thickening in the palpebral fissure adjacent to the limbus.[8] It may encroach the limbus, but when the cornea is involved, it becomes a pterygium. The aetiology of pinguecula is uncertain but may be the same as that of pterygium. Mimura et al.[11] suggested that contact lens wear – and especially rigid lens wear – is a risk factor for the development of pinguecula.

A pinguecula that lies close to the limbus can give the appearance of VLK, but these conditions can be differentiated because the raised tissue mass of the pinguecula, by definition, does not fully encroach onto the limbus. The difficulty in differentially diagnosing pinguecula from VLK can be illustrated by comparing the pinguecula in Figure 16.12 with the VLK in Figure 16.13. Certain features, such as the yellow colour and the extensive vascularity of the tissue mass, are almost identical. However, differential diagnosis can be made by noting that the base of the pinguecula is separated by about 1 mm from the limbus, whereas the raised mass in the VLK – although being located primarily on the conjunctiva – clearly impinges on the limbus.

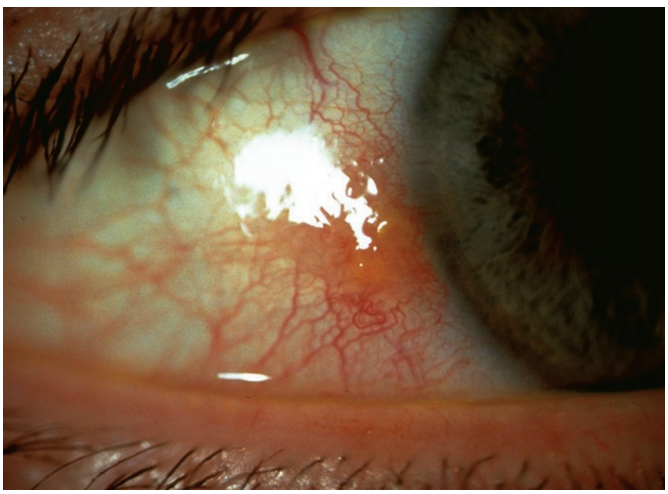


Fig. 16.13 Vascularised limbal keratitis, with the raised epithelial mass impinging on the limbus. (Courtesy Debbie Jones.)

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17 Superior Limbic Keratoconjunctivitis

Contact lens–induced superior limbic keratoconjunctivitis (CLSLK) is a syndrome comprising a combination of tissue pathologies. Tissues affected include the corneal epithelium and stroma, the limbus and the bulbar and tarsal conjunctivae. Although this condition was first fully described in the literature in the early 1980s,[1-11] a similar syndrome unrelated to contact lens wear known as Theodore's superior limbic keratoconjunctivitis (or 'Theodore's SLK') had been described about 20 years before this.[12]

Because of the strong association between the development of CLSLK and the use of contact lens care solutions containing thimerosal, this condition has also been called 'thimerosal keratoconjunctivitis'[1] or 'thimerosal keratopathy'.[13]

In its mild form, CLSLK is easily overlooked (Fig. 17.1). The condition is confined to the superior limbal area and, as such, is hidden by the upper lid in primary gaze. The proper procedure for observing this condition is to lift the upper lid while the patient gazes down. Such an examination technique should be part of the routine procedure during every contact lens aftercare examination.

Prevalence

For reasons explained later in this chapter, the prevalence of CLSLK in the general population at the present time is extremely low. Previous studies have documented the prevalence of this condition among symptomatic contact lens wearers at a time when thimerosal preservatives were used in contact lens care systems. In 1989, Wilson-Holt and Dart[1] reported the results of a retrospective evaluation of the record cards of 312 patients with contact lens-related complications presenting consecutively to an eye clinic. They found that 42 patients (13.5%) presented with a typical CLSLK and 13 (4.1%) presented with an atypical CLSLK. Thus, a total of 55 patients (17.6%) were afflicted with this condition.

In 1992, Stapleton et al.[14] reported that of 1,104 patients with contact lens–related disorders presenting to an eye clinic, only five (0.5%) displayed classic CLSLK; however, 67 patients (6%) displayed what was described as 'thimerosal keratopathy/conjunctivitis'. These authors' description of the pathological changes at the superior limbus that characterised this latter condition indicated that they were observing an atypical form of CLSLK.[14] Thus, combining these figures gives a prevalence rate of CLSLK-associated disease among symptomatic contact lens wearers during the 1980s and early 1990s of about 6.5%. None of the extensive 21st century hospital-based surveys of contact lens complications – carried out in China,[15] India,[16] Nepal,[17] Singapore,[18] the USA[19] or UK[20] – record any presenting cases of CLSLK.

Thimerosal was commonly used as a preservative in contact lens solutions up until the mid-1980s; its use declined thereafter as a result of practitioners and industry taking note of the increasing number of reports linking thimerosal to CLSLK. This may explain why the prevalence of this condition declined from 17.6%[1] to 6.5%[14] between 1989 and 1992. The prevalence of CLSLK has reduced even further since the introduction in the late 1980s of solutions that do not contain preservatives that could be toxic or allergenic to the cornea, such as thimerosal. Instead, these solutions contain safe chlorhexidine-based preservatives, such as alexidine, myristamidopropyl dimethylamine, polyhexamethylene biguanide and polyquaternium-1 (Table 17.1). Such products, together with hydrogen peroxide-based disinfecting systems, now dominate the market.[21] It appears that all contact lens manufacturers have ceased using noxious preservatives, such as thimerosal, in contact lens

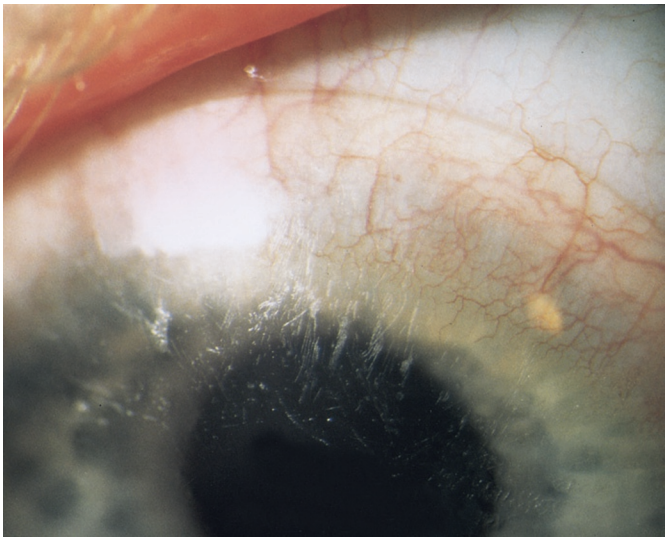


Fig. 17.1 Contact lens–induced superior limbic keratoconjunctivitis in a patient wearing soft lenses (grade 2). (Courtesy AJ Elder Smith, British Contact Lens Association Slide Collection.)

TABLE 17.1 Preservatives used in contact lens care solutions

Multi-purpose solution	Preservative
AQuify*	PHMB
Biotrue†	PHMB, PQ-1
Complete Easy Rub‡	PHMB
Opti-Free Evermoist (UK) Puremoist (USA) *	PQ-1, MAPD
Opti-Free Express*	PQ-1, MAPD
Opti-Free RepleniSH*	PQ-1, MAPD
Renu fresh†	PHMB
Renu sensitive†	PHMB
Revitalens OcuTec‡	Alexidine, PQ-1

MAPD, myristamidopropyl dimethylamine; PHMB, polyhexamethylene biguanide; PQ-1, polyquaternium-1. Trademark of *Alcon, †Bausch & Lomb, Inc., and ‡Johnson & Johnson Vision Care.

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care products.[22] A literature search failed to reveal any case reports of CLSLK among patients using these modern disinfection systems in the 21st century.

Signs and symptoms

Symptoms of CLSLK include increased lens awareness, lens intolerance, foreign body sensation, burning, itching, photophobia, redness and increased lacrimation. Although an occasional slight mucus secretion might be observed, there is no heavy discharge, such as that seen in bacterial conjunctivitis. Some loss of vision (by three or more lines of Snellen acuity[1,3]) has been reported in advanced cases, such as with extensive pannus formation.

A myriad of signs is observed in patients with CLSLK, including:

- punctate epithelial fluorescein staining (Fig. 17.2) – typically in the upper third to half of the cornea, which can be course in some patients, and sometimes in a swirled pattern[2];
- epithelial rose bengal staining of the superior cornea;
- intra-epithelial opacities;
- sub-epithelial haze in the superior cornea – extending in a V-shaped pattern towards the pupil;
- epithelial dulling of the superior cornea;
- epithelial microcysts of the superior cornea;
- epithelial infiltrates in the superior cornea (Fig. 17.3);
- epithelial irregularity of the superior cornea;
- stromal opacification;
- fibrovascular micro-pannus – a plexus of vessels advancing from the superior cornea in the form of a V-shape, with the apex towards the pupil and an even linear leading edge parallel with the upper lid margin; (Fig. 17.1 and Fig. 17.4)
- fine sub-epithelial linear opacities at the periphery of the superior cornea – aligned with the general direction of blood vessels in the pannus;
- superior limbal oedema;
- superior limbal hypertrophy;
- superior limbal fluorescein staining;
- superior limbal vascular injection;
- poor wetting of the superior bulbar conjunctiva;
- superior bulbar conjunctival punctate staining;
- superior bulbar conjunctival redness;

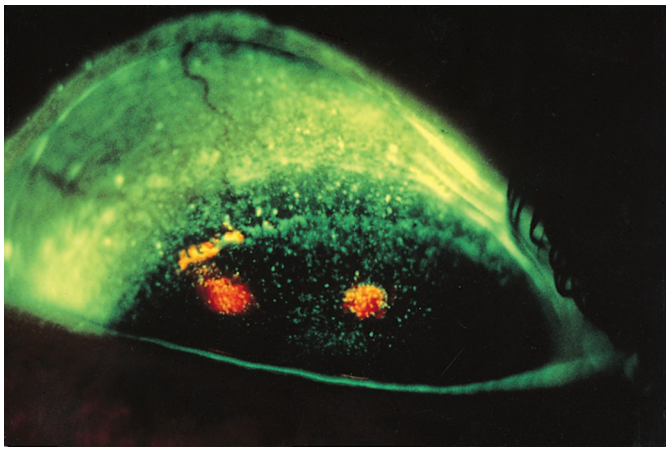


Fig. 17.2 Corneal, limbal and conjunctival fluorescein staining in contact lens–induced superior limbic keratoconjunctivitis in a patient wearing hydrogel bifocal contact lenses (grade 3). (Courtesy Mee Sing Chong, Bausch & Lomb Slide Collection.)

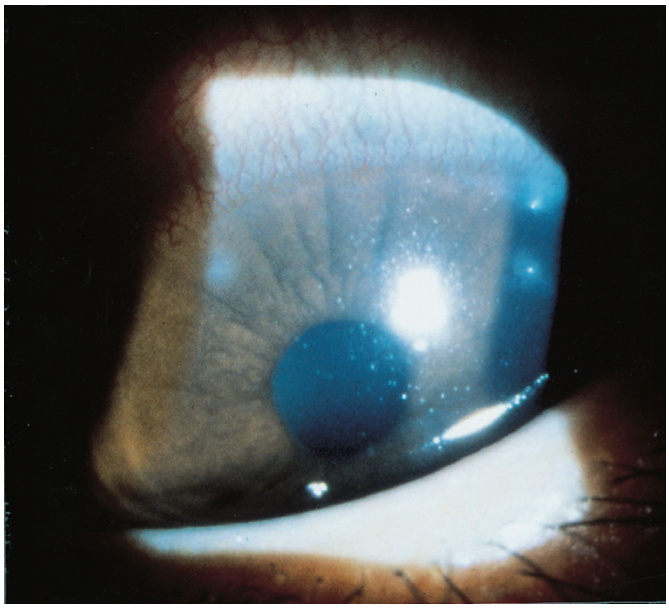


Fig. 17.3 Contact lens–induced superior limbic keratoconjunctivitis in a soft lens–wearing patient displaying superior limbal redness, focal infiltrates and increased lacrimation. The hazy corneal reflex indicates an uneven epithelium (grade 1.5).

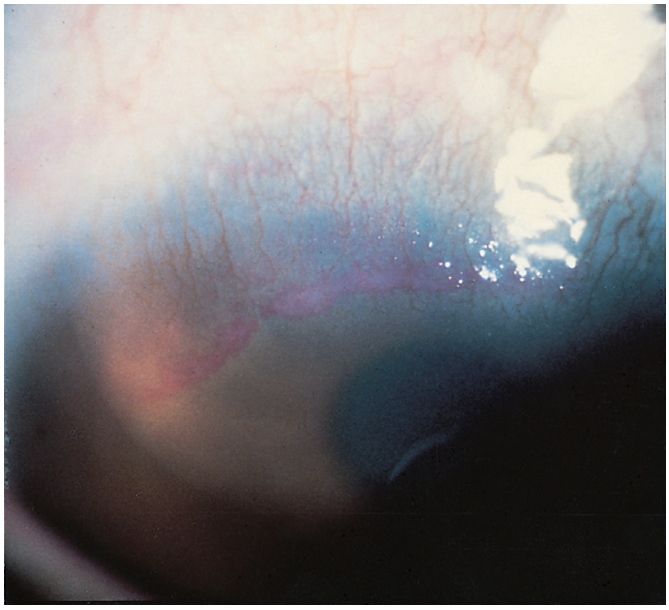


Fig. 17.4 Fibrovascular pannus in contact lens–induced superior limbic keratoconjunctivitis, stained with rose bengal (grade 1.5). (Courtesy Brien Holden, Brien Holden Vision Institute.)

- superior bulbar conjunctival chemosis – described as a 'boggy apron' of bulbar conjunctiva that forms redundant folds over the superior limbus[3];
- irregular thickening and redundancy of the superior bulbar conjunctiva;
- papillary hypertrophy of the upper tarsal conjunctiva – in 25% of cases[3];
- follicular hypertrophy of the upper tarsal conjunctiva;
- redness of the upper tarsal conjunctiva;
- scattered petechiae on the upper tarsal conjunctiva;
- corneal filaments – said to be present in 13% of patients suffering from CLSLK;[3]

TABLE 17.2 Comparison of Theodore's SLK and CLSLK

Feature	Theodore's SLK	Contact lens–induced SLK
Age	• Usually middle-aged (over 40 years)	• Younger (under 40 years)
Gender	• More common in females	• Equal male/female distribution
Associated factors	• Linked to thyroid disease	• Usually soft contact lens wear • Increased lens movement • Soiled lenses • Thimerosal in lens solutions
Symptoms	• Mild to severe irritation without lenses • Vision rarely affected	• Mild to severe irritation with lenses • Vision can be reduced
Signs	• Mild superior corneal staining • Superior bulbar conjunctival redness • Superior bulbar conjunctival chemosis • Limbal redness • Grade 3 papillary hypertrophy • Corneal filaments frequently observed	• Severe superior corneal staining • Superior bulbar conjunctival redness • Superior bulbar conjunctival chemosis • Limbal redness • Grade 1 papillary hypertrophy • Corneal filaments rarely observed
Staining	• Superior corneal fluorescein staining	• Superior corneal rose bengal staining
Pathology	• Epithelial keratinization • Nuclear degeneration	• Epithelial keratinization • Neutrophilic response • Reduced number of goblet cells
Management	• Lubricants • Silver nitrate application • Bandage lens therapy • Pressure patching • Conjunctival resection • Conjunctival cauterization • Systemic management of thyroid disease	• Temporary cessation of lens wear • Interim steroids • Interim lubricants • Interim prostaglandin inhibitors • Change lens design • Use non-thimerosal regimen • Regular lens replacement • Daily disposable lenses

CLSLK, contact lens–induced superior limbic keratoconjunctivitis; SLK, superior limbic keratoconjunctivitis.

- corneal warpage;
- corneal astigmatism; and
- pseudo-dendrites — bilateral dendritic corneal lesions that lack the terminal bulbs characteristic of herpetic disease.

CLSLK is almost always bilateral, and the specific signs often display symmetry between the eyes. There is considerable variability in the time course of onset of the condition; signs usually become manifest between 2 months and 2 years of commencement of lens wear.[3,5] The approximate sequence of manifestation of signs of increasing severity is shown in the grading scales in Appendix A.

It is interesting to compare the clinical presentation of CLSLK with that of Theodore's SLK, which also occurs in non–contact lens wearers. Table 17.2 is a summary of the similarities and differences between the two conditions.

There have been a few reports of CLSLK in patients wearing rigid contact lenses. Wilson-Holt and Dart[1] report two cases in which the patients were using a wetting solution containing thimerosal. One patient had previously worn soft lenses. Both patients suffered from lens intolerance and red eyes, although the overall signs and symptoms were less severe compared with those observed in patients wearing soft lenses.

Pathology

Sendele et al.[3] used light microscopy to examine biopsy material from the superior bulbar conjunctiva of five patients suffering from CLSLK and of five normal control subjects. The following observations were made of the affected specimens:

- Epithelial keratinization (two patients)
- Intra-cellular epithelial oedema (three patients)
- Acanthosis (three patients)
- Pseudo-epitheliomatous hyperplasia (three patients)
- Acute inflammatory cells in the epithelium (three patients)
- Acute inflammatory cells in the stroma (three patients)
- Plasma cells in stroma (indicating chronic inflammation) (five patients)
- Mononuclear cells in stroma (indicating chronic inflammation) (five patients)
- Absence of goblet cells (four patients)

Transmission electron microscopy of the same tissue samples confirmed light microscopic observations and revealed the following additional pathological changes:

- flattening of surface microvilli;
- accumulation of intra-cytoplasmic keratin filaments;
- condensed cytoplasm;
- fibrillogranular inclusions (probably lipoproteinaceous); and
- epithelial infiltration of polymorphonuclear leucocytes.

Sendele et al.[3] pointed out that although their findings provided evidence of acute and chronic inflammation typical of Theodore's SLK, they did not observe marked epithelial keratinization, nuclear degeneration or glycogen accumulation – which have been reported by other researchers to be representative of Theodore's SLK. However, Stenson[5] observed prekeratinised epithelial cells and a neutrophilic response in conjunctival and corneal scrapings of patients with CLSLK.

Figure 17.5 is a schematic diagram highlighting the differences between the normal bulbar conjunctiva and the bulbar conjunctiva of a patient suffering from CLSLK.

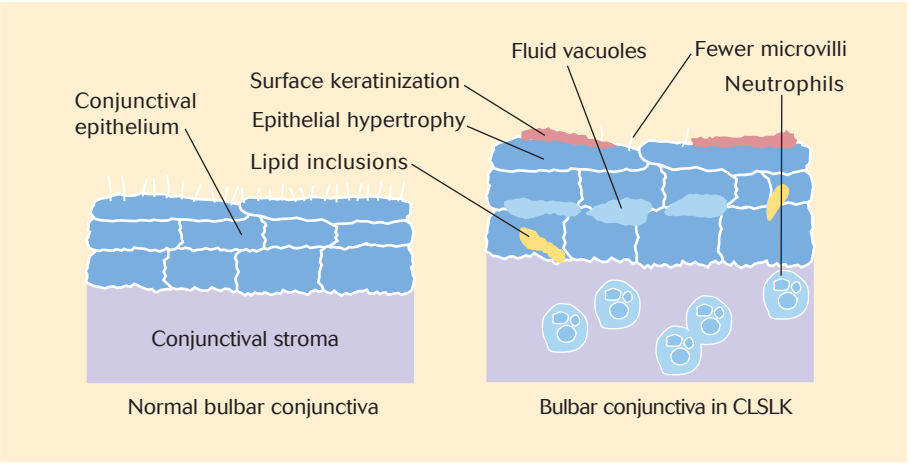


Fig. 17.5 The normal bulbar conjunctiva and the bulbar conjunctiva in contact lens–induced superior limbic keratoconjunctivitis.

Aetiology

The primary aetiological factor in the development of CLSLK is thimerosal hypersensitivity. Provocative tests in thimerosal-sensitised patients result in general conjunctival redness[1,3] (not just confined to the superior limbus) – that is, contact lens wear has impacted the clinical presentation. Therefore, other factors perhaps play a minor role by initiating, modulating or exacerbating this condition. Evidence relating to the significance of these aetiological factors shall be considered in turn here.

THIMEROSAL HYPERSENSITIVITY

Thimerosal is an organic mercury compound that interacts with living tissue (e.g. bacteria or corneal epithelial cells) by binding to sulphydryl groups of enzymes and other proteins. Compared with other traditional preservatives, such as chlorhexidine, thimerosal has relatively inferior anti-bacterial potency but superior anti-fungal potency.[23]

There is some confusion in the literature because two spellings – 'thimerosal' and 'thiomersal' – are used in the same context. These are, in fact, different products – thimerosal being the American formulation and thiomersal (or thiomersolate) being the British formulation.[24] Because the American formulation is used almost universally in solutions, 'thimerosal' is the preferred spelling (and is thus used here).

The key evidence linking thimerosal to CLSLK comes from clinical studies that have sought to identify a common causative factor in patients presenting with this condition. Wright and Mackie[6] observed that all 61 patients suffering from CLSLK in their sample were using solutions containing thimerosal. All of 10 patients subjected to a provocative test (a challenge dose of 0.005% thimerosal (in normal saline) applied topically) showed a rapid adverse response. Sendele et al.[3] reported 40 cases of CLSLK; in every case, patients were using thimerosal-preserved care solutions. In all 40 CLSLK patients of Sendele et al.,[3] all six CLSLK patients of Miller et al.,[7] all 15 CLSLK patients of Fuerst et al.[8] and all 31 CLSLK patients of Wilson et al.,[9] thimerosal was a component of the care solutions used.

Other evidence implicating thimerosal in the aetiology of CLSLK includes:

- the condition is always bilateral;
- signs and symptoms resolve when the patient ceases using thimerosal-preserved solutions[1,3];
- the syndrome recurs if thimerosal is re-introduced into the care regimen; and
- the syndrome does not recur if thimerosal-free solutions are used.

The results of 'patch testing' have confounded the thimerosal argument. For example, Sendele et al.[3] applied the following three challenge tests to patients suffering from CLSLK: (a) two drops of 0.001% and 0.01% thimerosal (the latter being 10 times the concentration normally used in contact lens solution formulations), balanced in saline, instilled into the eyes of 15 patients every hour during waking hours; (b) an occlusive skin patch test soaked in 0.001% thimerosal applied to the forearm; and (c) 0.1 mL of 0.001% thimerosal injected into the forearm. Only five of the 15 patients tested (and none of the control subjects) developed a reaction to the thimerosal within 72 hours. Similarly, Miller et al.[7] noted a positive skin test reaction to thimerosal in only one of six patients examined.

Wilson-Holt and Dart[1] adopted a different approach to provocative testing. They instilled one drop of a saline solution containing 0.005% thimerosal into the eye, four times each day. Conjunctival redness was observed in all patients – usually within 12 hours but sometimes taking up to 72 hours to develop. The inconclusive nature of patch testing results may result from the thimerosal molecule being too small for skin testing of an antibody mediated response.[2]

There have been reports of patients who have recovered from CLSLK but have suffered a recurrence when lens wear has been resumed in the *absence* of thimerosal.[8] Such reports are inconclusive because in many cases, the same lens was reused. Despite thorough cleaning, not all of the offending antigen may have been completely purged from the lens.

Of the four patients in the study of Stenson,[5] three experienced a resolution of signs of CLSLK after lens removal and were able to resume a limited wearing schedule with thinner lenses, presumably while still using thimerosal-preserved solutions. However, the fact that it was necessary to restrict wearing time suggests that the condition was not fully resolved. A shorter wearing schedule would have minimised the time of contact of thimerosal with the ocular surface, thus reducing the severity of the condition. Any additional strategy to minimise the overall physiological challenge of lens wear, such as the use of silicone hydrogel lenses (of necessarily superior oxygen performance), would be expected to have a general beneficial effect on ocular

signs and symptoms (e.g. eye redness) independently of any direct effect in curing CLSLK.

Thimerosal has long been known to cause an intense delayed hypersensitivity reaction. The mechanism of a delayed hypersensitivity reaction requires that affected patients have been previously sensitised to an offending antigen and are then re-exposed to that antigen for a prolonged period before the condition flares up. Likely mechanisms for presensitisation that involve thimerosal include previous vaccine injections (e.g. those for diphtheria and tetanus), topical antiseptics and ophthalmic preparations.

Once a patient has been sensitised to thimerosal, re-exposure of minute concentrations later in life results in the onset of symptoms and signs over a period of weeks or months. This is typical of a hypersensitivity reaction, as distinct from a toxicity reaction which is dose dependent and immediate. Furthermore, Langerhans cells are present in the limbus and adjacent tissues; such cells are known to mediate cutaneous hypersensitivity reactions to a variety of chemicals.[13] Patch testing studies have revealed that the incidence of skin hypersensitivity to thimerosal is about 7% in the USA[25] and 25% in Sweden.[26]

Mackie[13] argued that CLSLK can present as a type I (immediate) or type IV (delayed) hypersensitivity reaction, primarily based on clinical evidence that some patients display an immediate reaction and some display a delayed response.

The precise mechanism by which thimerosal induces a hypersensitivity reaction in CLSLK is not known. Wilson-Holt and Dart[1] advanced the following theory: soft lenses absorb thimerosal (which is highly water soluble) during the disinfection procedure, and the thimerosal is slowly re-released back into the eye during lens wear. This prolonged ocular contact with thimerosal induces a local delayed hypersensitivity reaction initiated by sensitised T lymphocytes.

THIMEROSAL TOXICITY

Thimerosal is only mildly cytotoxic, but to a degree that is much less than other preservative systems.[27] A true toxicity reaction would affect the entire ocular surface and would not be restricted to the superior cornea and conjunctiva as occurs in CLSLK. It is for these reasons that CLSLK is not considered a toxic reaction. Despite this, Nguyen et al.[28] suggested that CLSLK is a toxic reaction resulting from thimerosal-induced limbal stem cell failure.

MECHANICAL EFFECTS

Evidence that there is a significant mechanical component to the aetiology of CLSLK is weak and largely anecdotal. Stenson[5] noted that some of her patients with CLSLK displayed excessive lens movement. Abel et al.[10] noted excessive lens movement in the majority of their patients; this indicates a poor fit and may be associated with increased mechanical influences.

Stenson[5] also reported that refitting with thinner lenses resulted in some alleviation of CLSLK; however, as explained earlier, the reason for this improvement may be more physiological (increased oxygen) than physical (mechanical).

Abel et al.[10] reported one case where a patient had apparently been successfully wearing spin-cast hydrogel lenses cared for with thimerosal-based preservatives. CLSLK developed after switching to lenses with a lathe-cut design. These authors surmised that the new lenses may have created a mechanical heaping of the superior bulbar conjunctiva, resulting in poor wetting of the superior cornea and eventual epithelial pathology.

The fact that CLSLK occurs at the site of the superior limbus lends some support to the theory of mechanical aetiology because the physical bearing of the upper lid against the lens would exacerbate any ocular irritation caused, for example, by lens surface deposits. Certainly, blink-induced 'micro-trauma' is thought to be a cause of superior limbic keratoconjunctivitis in the absence of contact lens wear.[29]

Ocular lubricants provide some symptomatic relief,[10] suggesting that mechanical irritation is a component of CLSLK syndrome.

LENS DEPOSITS

Lens deposits, such as protein, are of potential significance in the aetiology of adverse ocular reactions to lens wear because these deposits can (a) support bacterial colonization and (b) absorb or attract extraneous contaminants, such as metal ions, preservatives and other components of care systems. It is thought that the latter mechanism, in particular, may be relevant to CLSLK because of possible absorption of the mercuric component of thimerosal into lens surface deposits and subsequent release onto the ocular surface during wear.

To examine the role of lens deposition in CLSLK, Barr et al.[30] conducted a thorough protein and elemental analysis of contact lenses worn by 12 patients suffering from this condition. Apart from one case in which high levels of mercury were found in a lens, no clear association between deposit type and the genesis of CLSLK could be demonstrated. Thus, the role of lens spoilage in the aetiology of CLSLK remains unclear. This is of minimal relevance to current day optometric practice because virtually all soft lenses are replaced monthly or daily.

HYPOXIA BENEATH UPPER LID

The fact that the ocular response in CLSLK is confined to the region of the superior limbus suggests that upper lid–induced hypoxia may be a contributing factor to the aetiology of this condition.[31] The upper lid normally covers the superior third of the cornea. The oxygen supply to the superior limbus during normal open-eye lens wear comes from the capillary plexus of the superior palpebral conjunctiva. The partial pressure of oxygen at the lens surface beneath the upper eyelid is 55 mmHg[32] versus 155 mmHg in the open eye.

Of course, lid-induced hypoxia cannot be the sole or primary cause of CLSLK, otherwise all contact lens wearers would be affected. Nevertheless, partial oxygen deprivation may be an exacerbating factor that compromises the physiological status of the superior cornea and limbus, and thus, this region is more prone to immunological challenge. Holden et al.[33] provided evidence for this by demonstrating that lens-induced hypoxia inhibits respiration and growth of the corneal epithelium and stroma.

Figure 17.6 is a schematic diagram illustrating the various aetiological factors that are thought to lead to the development of CLSLK.

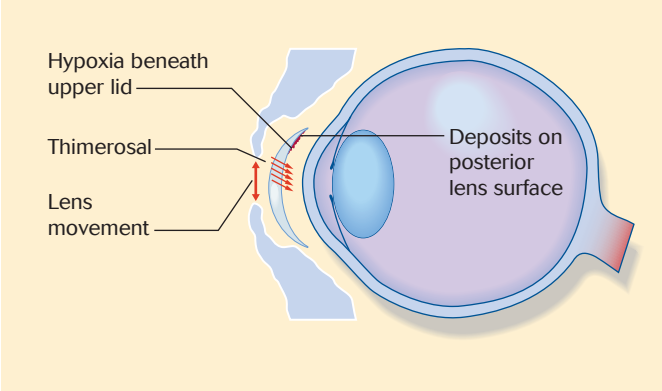


Fig. 17.6 Factors of aetiological significance in contact lens–induced superior limbic keratoconjunctivitis.

Treatment

The accumulated clinical evidence implicating thimerosal as the prime cause of CLSLK provides an excellent focus for treating this condition.

SUSPENSION OF LENS WEAR

After suspension of lens wear, the signs and symptoms of CLSLK will immediately begin to resolve because the ocular surface will no longer be in contact with thimerosal. The recommended period of cessation of lens wear is related to the severity of the condition. Patients suffering from CLSLK may be advised to cease lens wear for 2 to 4 weeks in mild cases and up to 3 months in severe cases. The time course of resolution is discussed under 'Prognosis'.

Boruchoff and Bajart[34] suggested the following criterion for resumption of lens wear: There must no longer be any epithelial haze, surface irregularity or peripheral revascularization. These criteria may be a little too stringent. Certainly, it would be prudent to wait until corneal haze has largely resolved and the corneal surface is smooth; however, a vascular pannus may be permanent. Lens wear can be resumed in the presence of a vascular pannus as long as the patient is monitored closely to check for the absence of further vascular encroachment.

ELIMINATION OF THIMEROSAL

In the unlikely event that a patient is using a contact lens care product containing thimerosal (this preservative is no longer used in contact lens care systems), then total elimination of thimerosal will almost certainly cure CLSLK, and the patient should be cautioned against using any form of contact lens care solution containing thimerosal in the future. The patient should also be carefully interrogated as to whether he or she uses any other topical ocular medications – even those not related to contact lens wear. If thimerosal is an ingredient of any product being used, the patient should be advised to cease using them. In cases where the patient is using a prescription product containing thimerosal, the prescribing practitioner should be notified and advised to alter the medication. Patients should be specifically warned of their allergy to thimerosal and should be told to always check that thimerosal is not an ingredient of any product to be applied to the eye in the future.

ALTERATION TO THE LENS

Any lens that has been worn by a patient suffering from CLSLK – soft or rigid – should be discarded because no matter how thoroughly such a lens is cleaned, it only takes a trace amount of residual thimerosal to induce a reaction.

Assuming that subsequent lens wear is prescribed in the absence of thimerosal-preserved solutions, there are no constraints on the design of the replacement lenses or the modality of lens wear. However, for patients who are re-commencing lens wear before completely recovering from CLSLK, it would be advisable to prescribe a lens of minimum thickness profile, low modulus and high surface lubricity so as to reduce the potential for mechanical irritation. Silicone hydrogel lenses should be prescribed if hypoxia is thought to be related to the development of the condition. Daily disposable lenses may be beneficial if protein or elemental deposition is thought to be related to the problem. Daily disposable lenses also obviate any problems that could potentially be due to solutions. Changing over to rigid lenses is unlikely to be of any additional benefit because CLSLK can also occur in patients wearing such lenses.[9]

PHARMACEUTICAL AGENTS

Because there is no infectious component to CLSLK, there is no benefit in prescribing antibiotics or anti-viral agents during the active phase of the condition. Opinion is divided as to the value of prescribing corticosteroids to dampen the immunological response. Abel et al.[10] found that corticosteroids helped in severe cases, whereas others[3,9,13] found that such drugs had no beneficial effect. Wilson-Holt and Dart[9] did not attempt to use any other therapeutic agents in the management of their CLSLK cases.

For patients whose eyes are particularly red and uncomfortable, Mackie[13] recommended the prescription of oxytetracycline 250 mg twice daily or oral doxycycline 100 mg on alternate days for the anti-inflammatory effect of these agents on the conjunctiva. In severe cases, the cornea can be treated with silver nitrate to remove affected cells and to promote re-growth of a new healthy epithelium.

Ocular lubricants in the form of hydroxypropyl cellulose ophthalmic inserts,[35] drops or ointments may provide symptomatic relief during the recovery phase[10] and a positive placebo effect in patients prone to be anxious.

BANDAGE LENSES AND PRESSURE PATCHING

Paradoxically, bandage lenses have been advocated for patients suffering from Theodore's SLK.[36-40] Adapting this approach to CLSLK would mean rapid resumption of lens wear in the absence of thimerosal-preserved lens care systems. The main beneficiary of such an approach would be a patient who is suffering from concurrent tarsal hypertrophy and whose limbus would be protected from mechanical insult resulting from the roughened tarsus. Similarly, pressure patches provide symptomatic relief by limiting eye movement and consequent mechanical irritation.[38] In addition to using a bandage lens for the treatment of SLK, Chun and Kim[37] injected botulinum toxin A to Riolan's muscle to further alleviate pressure from the upper lid.

SURGERY

Sendele et al.[3] removed the involved superior corneal epithelium in two patients with CLSLK as well as an incapacitating reduction

of vision attributed to corneal epithelial irregularity. This was achieved by mechanical scraping with a scalpel blade. They reported that although this procedure may have hastened visual recovery, it did not seem to otherwise affect the clinical course.

Kenyon and Tseng[41] described three severe cases of CLSLK, in which two free grafts of limbal tissue were transplanted from the most affected to the least affected eye, the latter having been prepared by limited conjunctival resection and superficial dissection of the fibrovascular pannus. Subsequent impression cytology confirmed restoration of the corneal epithelium. It is curious that this procedure is possible in view of the perfect symmetry that is encountered in virtually all cases of CLSLK.[13] With the absence of thimerosal in contact lens care solutions and the virtual elimination of severe cases of CLSLK, such radical surgical procedures are unlikely to be necessary in the future.

Prognosis

In the 42 patients examined by Wilson-Holt and Dart,[9] the time of resolution of clinical signs of CLSLK after cessation of lens wear took 3 weeks to 9 months (mean 4.2 months). Sendele et al.[3] reported a similar time course of resolution, as did Abel et al.,[10] who noted that recovery took 5 days to 10 months in the eight patients they monitored. In these patients, oedema and redness subsided first, followed by clearing of the epitheliopathy. Papillary changes took the longest to resolve and persisted for months in several cases. Sendele et al.[3] reported that one patient took 2 years to recover in the absence of lens wear; fortunately, such a prolonged period of recovery is rare.

Recovery of visual acuity after severe cases of CLSLK was reported by Sendele et al.[3] to be 'gradual'. These authors inferred that visual acuity had only recovered to 6/9 in some subjects, even after several months.

Differential diagnosis

In the early stages, CLSLK may be mistaken for increased redness of the superior conjunctiva or limbus, or neovascularisation of the superior cornea – conditions that could be caused by a variety of insults. For example, Figure 17.7 depicts superior limbal redness in a 24-year-old asymptomatic male wearing rigid lenses. The edge of the lens was chipped, leading to irritation of the superior limbus between the 8 & 12 o'clock positions. A case of conjunctivitis affecting the superior globe is shown in Figure 17.8. Soft lens–induced neovascularisation of the superior cornea is shown in Figure 17.9. All of these conditions display pathology in common with certain features of CLSLK.

Wilson-Holt and Dart[9] reported that they had misdiagnosed two patients with CLSLK as having bacterial conjunctivitis; these patients were unfortunately treated with thimerosal-preserved topical antibiotics, which exacerbated the condition.

CLSLK can also be mistaken for infiltrative keratitis. A culture-positive scraping would provide verification of an infectious keratitis. True CLSLK should be suspected if thimerosal-preserved care solutions were being used by the patient.

The key difference between CLSLK and Theodore's SLK is that the latter generally occurs in the absence of lens wear. Theoretically, a contact lens wearer can coincidentally develop

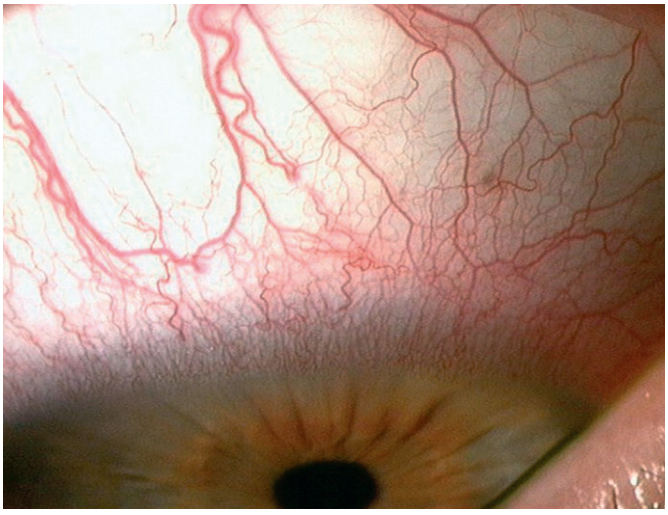


Fig. 17.8 Conjunctivitis affecting the superior globe, which takes on a similar appearance to contact lens–induced superior limbic keratoconjunctivitis. (Courtesy Brian Tompkins.)

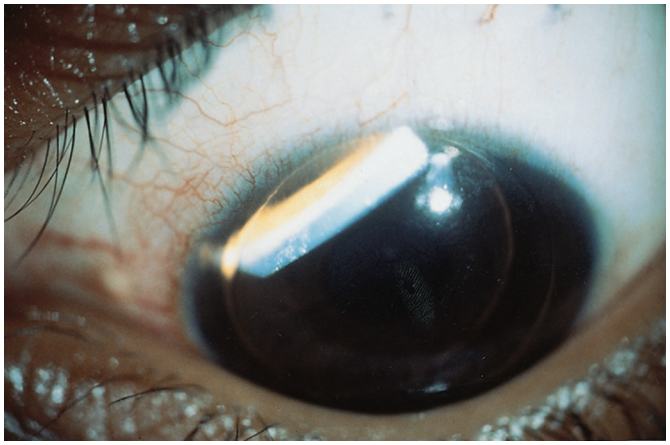


Fig. 17.7 Increased redness of the superior limbus caused by irritation from the edge of a chipped rigid lens, which takes on a similar appearance to contact lens–induced superior limbic keratoconjunctivitis. (Courtesy Padmaja Sankaridurg, Bausch & Lomb Slide Collection.)

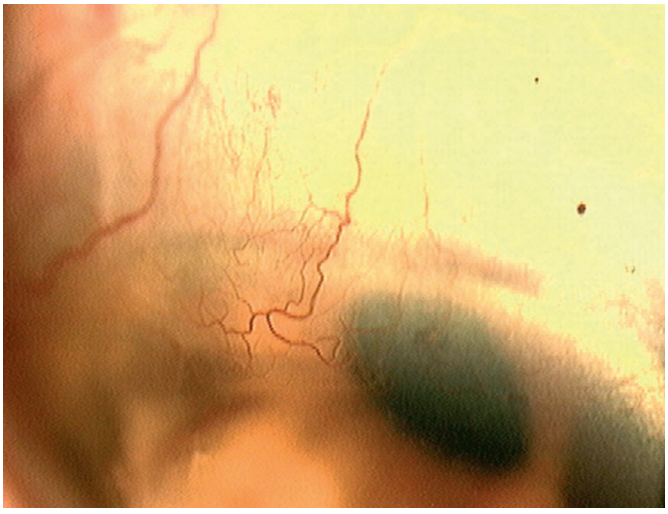


Fig. 17.9 Soft lens-induced neovascularisation of the superior cornea, which takes on an appearance similar to that of contact lens–induced superior limbic keratoconjunctivitis. (Courtesy Michael Hare.)

Theodore's SLK with or without the use of thimerosal-preserved care systems. The distinguishing features between these two conditions are outlined in Table 17.2.

In general, the clinical presentation of a severe case of CLSLK is unambiguous, with a host of corneal, limbal and conjunctival pathologies confined to the region of the superior limbus.

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18 Corneal Staining

The use of fluorescein in the examination of corneal integrity was introduced by Pflüger[1] in 1882, just 6 years before the first fitting of contact lenses to humans was reported by Fick.[2] However, it is only in the past 50 years that fluorescein has been used routinely by clinicians for this purpose.[3]

Corneal staining is probably the most familiar of all potential contact lens complications since its clinical importance is well established and it is easily observed.[4] Strictly speaking, corneal staining is not a condition in itself – rather, it is a general term that refers to the appearance of tissue disruption and other pathophysiological changes in the anterior eye as seen with the aid of one or more of a number of dyes, such as fluorescein, rose bengal and lissamine green. These dyes are sometimes referred to as 'vital stains', suggesting that they stain living things; however, this is a misleading term because such stains can be taken up by inorganic material.[5]

It has become a convention among clinicians to use the term 'corneal staining' to describe the appearance of bright areas of fluorescence in the epithelium after instillation of the dye fluorescein and illumination with cobalt blue light (Fig. 18.1). Throughout this chapter, it is to be assumed that corneal staining refers to staining with *fluorescein*, unless otherwise stated.

Prevalence

NON–LENS WEARERS

Before considering corneal staining in contact lens wearers, the extent of staining in the normal population should be noted. Schwallie et al.[6] evaluated corneal fluorescein staining in 16 normal, non-lens-wearing subjects over a 2-week period. The average duration for an episode of staining above the group median (grade 0.5) was found to be 1.2 ± 0.4 days. For both eyes, the most prevalent location of staining was the inferior region (50%), followed by the nasal region (20%). Overall, a mean staining grade of 0.5 to 0.6 was found. In a similar study, Dundas et al.[7] found some degree of corneal staining on 79% of the corneas of 102 normal subjects they examined.

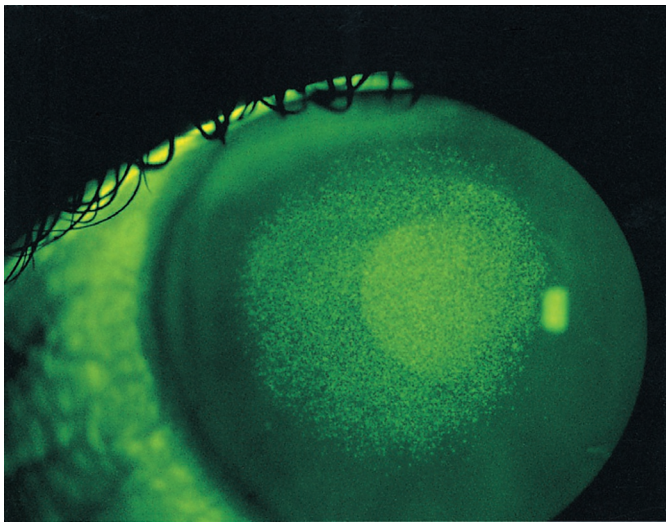


Fig. 18.1 Punctate staining of the central cornea. (Courtesy Gary Orsborn, Bausch & Lomb Slide Collection.)

LENS WEARERS

The prevalence of corneal staining of any degree of severity in a population of contact lens wearers is thought to be as high as 60%,[8] but often staining is of a low level and generally clinically insignificant. Indeed, as noted earlier, corneal staining is frequently observed in non–lens wearers.[8,9] Brautaset et al.[10] reported an incidence of 19.5% corneal staining among 338 adapted hydrogel lens wearers, with no subjects displaying staining greater than grade 2.

Begley et al.[11] found that the average overall staining grade for both eyes of 98 asymptomatic soft contact lens wearers was 0.5. Corneal staining between the two eyes was positively and significantly correlated. One-third of the subjects who participated in the study had notable corneal staining. Jalbert et al.[12] measured levels of corneal staining over a 2-year period in those successfully using daily-wear and extended-wear disposable hydrogel contact lenses. Their results were similar to those of Begley et al.[11]; overall levels of corneal staining were low, with median values below or equal to grade 0.5 in all groups. There was no difference in the extent, depth or geographical distribution of corneal staining between the daily-wear and extended-wear groups. Staining was more frequently recorded in the superior and inferior areas of the cornea than in the central, nasal or temporal regions.

In perhaps the largest survey ever undertaken of the ocular response to contact lens wear (66,218 patients), Hamano et al.[13] determined the prevalence of clinically significant staining (corneal erosion or superficial punctate keratitis greater than grade 2; see further in the chapter) to be 0.9% in soft lens wearers, 0.5% in rigid lens wearers and 1.3% in polymethyl methacrylate lens wearers.

Among symptomatic contact lens wearers presenting to hospital clinics around the world between 2009 and 2018, the reported incidence of corneal staining ranged from 2% to 87% (Table 18.1).[14-19]

Signs and symptoms

VITAL STAINS

A variety of vital stains can be used to highlight various aspects of surface tissue pathology, and a review of the types of stains and their application for staining the conjunctival surface is discussed in detail in Chapter 11. Following is a brief overview of

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TABLE 18.1 Prevalence of corneal staining among hospital-presenting contact lens wearers

Author	Country	Year	Population size studied	Retrospective or prospective	Prevalence
Li et al.[14]	China	2018	141	Retrospective	2.1%
Sapkota et al.[15]	Nepal	2013	4064	Retrospective	2%
Lee et al.[16]	USA	2012	1369	Prospective	87%
Teo et al.[17]	Singapore	2011	953	Prospective	24%
Nagachandrika et al.[18]	India	2011	1255	Retrospective	4.8%
Radford et al.[19]	UK	2009	877	Prospective	21.3%

the use of the three main stains used in contact lens practice to investigate various abnormalities and pathology of the corneal surface.

Fluorescein

Fluorescein is combined with sodium salt to make it more soluble in water.[20] Although it is available as a 2% solution, fluorescein is rarely used in this form because it supports the growth of bacteria which are potentially pathogenic to the eye, such as *Pseudomonas aeruginosa*.[21] Therefore, paper strips impregnated with fluorescein are preferred; these strips have an orange-yellow colour. Fluorescein can be instilled by wetting the strip with two drops of sterile unpreserved saline, having the patient look up and briefly and gently touching the strip, or preferably by letting a large drop fall from the paper, on the inferior bulbar conjunctiva.

When examining a fluorescein-stained eye, it is important to prompt the patient to blink frequently. If the patient blinks infrequently, the tear film will break up, leaving large dark areas of non-fluorescence which could (a) mask true staining or (b) be misinterpreted as non-staining background fluorescence. Fluorescein break-up in the absence of blinking is the basis of an important test of tear film stability (see Chapter 9).[22]

Because fluorescein has a molecular weight of 376, it is smaller than the pore size of many hydrogels and can be absorbed into the lens, resulting in a yellow stain. Therefore, as a precaution, the eye should be irrigated with sterile saline before inserting a soft lens after examination of the eye with fluorescein. If a reusable lens does become stained with fluorescein, it usually washes out after the next disinfection cycle.

Fluorescein is generally considered inert and safe; however, Kaimbo[23] reported a rare case of syncope and anaphylactic shock in a patient who received topical fluorescein to a corneal abrasion caused by a fingernail.

High-molecular-weight fluorescein, known as *fluorexon*,[24,25] (molecular weight 710) is available but not used widely because it has relatively low fluorescent properties and causes discomfort and stinging in some patients.[26]

Sequential fluorescein staining

Sequential staining refers to the repeated application of fluorescein over a period of minutes followed by observation with the slit lamp biomicroscope in the usual way.[27] This has been suggested as a more sensitive technique which is predictive of epithelial complications of contact lens wear, although this link has not been proven. It is likely that sequential staining merely results in high concentrations of fluorescein in the eye that causes a toxic epithelial response. The value of this technique is therefore questionable.

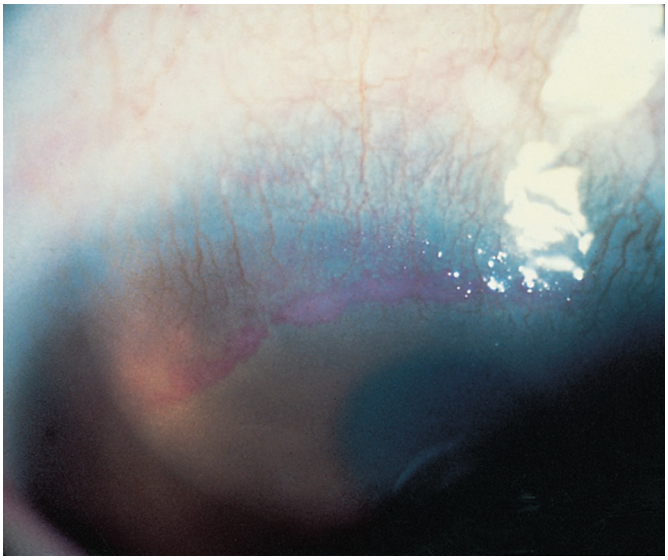


Fig. 18.2 Rose bengal staining the leading edge of a fibrovascular pannus. (Courtesy Brien Holden, Brien Holden Vision Institute.)

Rose bengal

Rose bengal is a mildly toxic bright red stain which is adsorbed to and absorbed by compromised epithelial cells, mucus and fibrous tissue (Fig. 18.2).[5] It is available as a 1% solution or as impregnated filter strips. Davis and Lebow[26] suggested that much better results are obtained if the solution form is used. After instillation, the eye is observed in white light.

In the absence of a complete tear film – and especially in the case of mucus deficiency – rose bengal is taken up by healthy epithelial cells.[5] Accordingly, this stain is especially useful for investigating dry eye conditions; that is, a dry eye may display extensive staining with rose bengal, especially if there is a mucus deficiency.

Lissamine green

An alternative stain with similar properties to rose bengal is lissamine green; both agents stain degenerated and dead epithelial cells and mucus.[28] The stained regions appear as a vivid green colour (Fig. 18.3). Lissamine green is better tolerated by patients compared with rose bengal and is as effective as rose bengal in evaluating the surface of the eye. However, Emran and Sommer[29] believed that lissamine green is an inadequately sensitive test for practical use.

SLIT LAMP BIOMICROSCOPE APPEARANCE

Fluorescein staining should be considered a routine procedure to be performed as part of the contact lens aftercare examination.

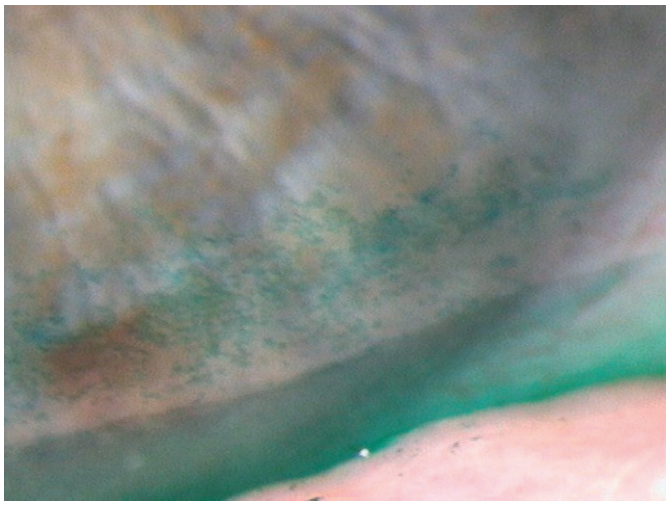


Fig. 18.3 Diffuse lissamine green staining of the inferior cornea. (Courtesy Brian Tompkins.)

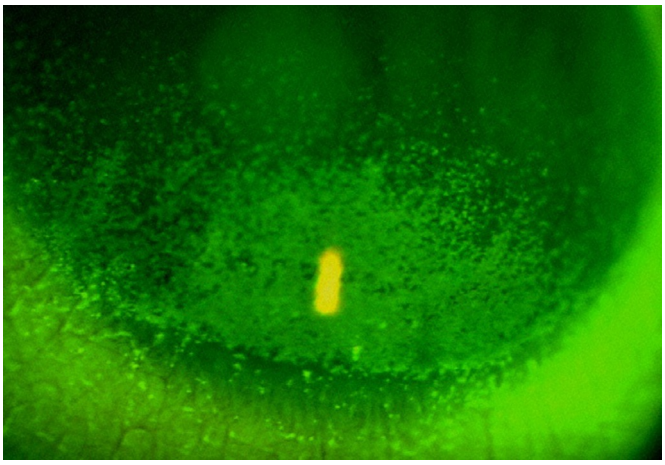


Fig. 18.4 Diffuse staining of the superior cornea. (Courtesy the Centre for Ocular Research & Education.)

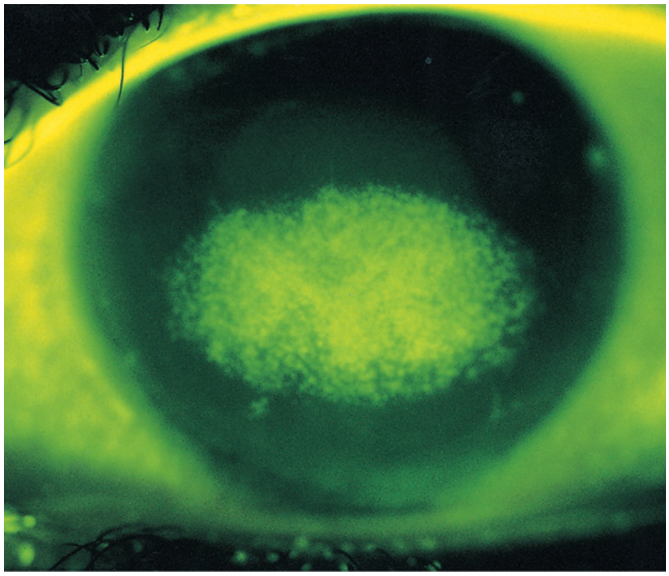


Fig. 18.5 Coalescent superficial corneal staining. (Courtesy Luigina Sorbara, Bausch & Lomb Slide Collection.)

Although corneal staining has received extensive interest amongst the academic community, most practitioners in Europe do not routinely use fluorescein at aftercare visits.[30]

Corneal staining after instillation of fluorescein is observed as a bright green fluorescence and may present in an infinite combination of shapes, locations, depths and intensities. The position is generally noted as superior, inferior, temporal, nasal or central. The depth of staining is noted as deep or superficial. A large number of terms has been used to describe the various forms of appearance of staining. Some of these have assumed the status of 'syndromes' based on frequently observed characteristic patterns of tissue damage. These various appearances are considered briefly in the next sub-sections.

The lack of a standard nomenclature for labelling various appearances of corneal staining has resulted in practitioners adopting different terms to describe the same condition.[31] Accurate record keeping, including grading, making careful sketches or attaching slit lamp photographs to record files, is therefore paramount.

Punctate staining

Perhaps the most often noted form of disturbance is punctate staining, whereby small superficial discrete dots are observed on the corneal surface (Fig. 18.1). This is also referred to as *micropunctate staining*, *superficial punctate erosion* (SPE) or *superficial punctate keratitis* (SPK). Intense punctate staining is sometimes called 'stipple staining'.

Diffuse staining

A vast array of closely separated punctate spots gives rise to a 'diffuse' appearance. The terms SPE and SPK are also used to describe this appearance (Fig. 18.4).

Coalescent staining

The overall pattern of fluorescence may be so diffuse as to obscure the constituent elements of staining, resulting in an appearance described as confluent or coalescent staining (Fig. 18.5).

3 & 9 o'clock staining

The classic form of staining in rigid lens wearers is known as *3 & 9 o'clock staining*, which refers to a triangular area of staining (apex away from the central cornea) at the nasal and temporal cornea outside the lens periphery (Fig. 18.6).[32] Although this condition may, in part, be caused by incomplete or infrequent blinking, it occurs primarily as a result of corneal non-wetting caused by the lids being bridged away from the cornea by the lens edge.[33]

Dimple-veil 'staining'

Dimple-veil 'staining' is not true staining in that fluorescein is not taken up by the corneal tissue; instead, fluorescein pools in indentations in the epithelial surface. This condition is caused by air bubbles becoming trapped between the back surface of the lens and the corneal epithelium (Fig. 18.7A) and is caused by a poor lens–cornea fitting relationship. Dimple-veil 'staining' is usually observed centrally in steep-fitting rigid lenses or in peripheral regions where the lens stands off the cornea, such as in with-the-rule astigmatism (Fig. 18.7B). Patients are asymptomatic, and the indentations in the corneal epithelium are similar in appearance to the stippled surface of a golf ball. Improving the fitting relationship will immediately eliminate the signs.[34]

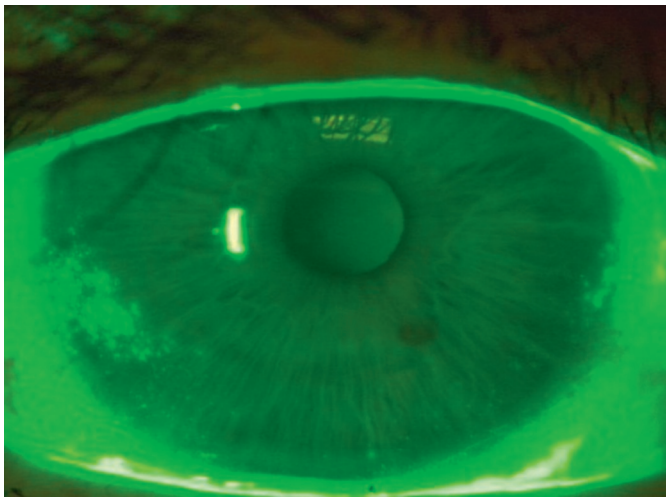


Fig. 18.6 3 & 9 o'clock corneal staining caused by rigid lens wear. (Courtesy Suzanne Efron.)

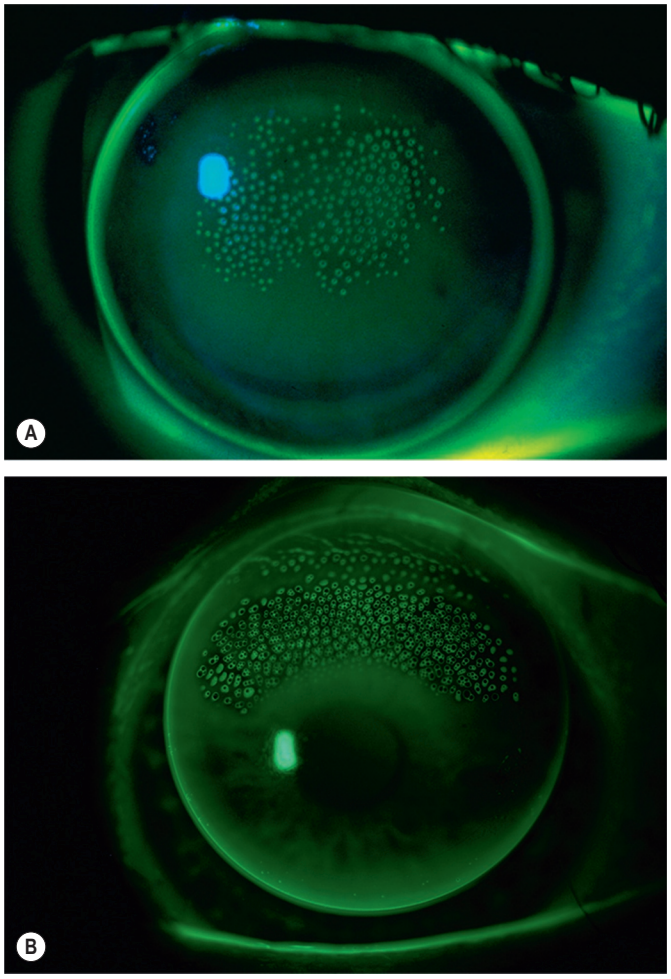


Fig. 18.7 **(A)** Dimple-veil 'staining' caused by rigid lens wear. **(B)** Superior dimple staining beneath a rigid lens in a region of lens stand-off. (A, Courtesy Kathy Dumbleton, Bausch & Lomb Slide Collection. B, Courtesy H. Kloes, British Contact Lens Association Slide Collection.)

Inferior epithelial arcuate lesion ('smile stain')

In 1975, Kline and DeLuca[35] reported a study in which 46% of 72 eyes fitted with soft lenses displayed superficial epithelial arcuate staining located in an area between the 4 and 8 o'clock locations on the cornea. This pattern of staining has come to be known as an 'inferior epithelial arcuate lesion', or 'smile stain'.[36] Zadnik and Mutti described this condition as an arcuate band of coarse, white, punctate epithelial disruption (Fig. 18.8). Many authors[36-38] subsequently reported this finding in soft lens wearers, and all believed that the condition is a metabolic/desiccation mechanism relating to a combination of factors, such as an insufficient post-lens tear film, lens adherence and/or lens dehydration. Watanabe and Hamano[38] observed inferior epithelial arcuate lesions in 3.3% of disposable-lens wearers.

Superior epithelial arcuate lesion

Superior epithelial arcuate lesions (SEALs) are an infrequent and often asymptomatic complication of conventional soft contact lens wear.[39,40] The characteristic arcuate pattern of the full-thickness corneal epithelial lesion usually occurs in the area covered by the upper eyelid, within 2 to 3 mm of the superior limbus in the 10 and 2 o'clock region.[40] (Fig. 18.9) The reported

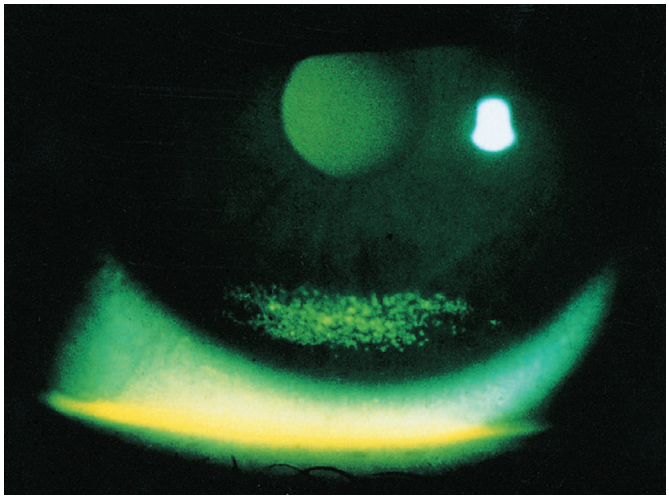


Fig. 18.8 Inferior epithelial arcuate lesion, or 'smile stain'. (Courtesy Lyndon Jones, Bausch & Lomb Slide Collection.)

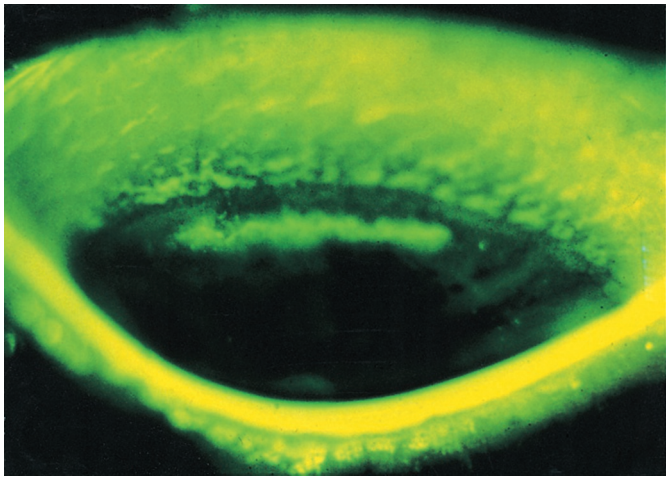


Fig. 18.9 Superior epithelial arcuate lesion (SEAL), otherwise known as 'epithelial splitting'. (Courtesy Arthur Back, Bausch & Lomb Slide Collection.)

low incidence of SEALs is partly because this condition is usually asymptomatic. This condition has also been referred to as 'epithelial splitting'.[41,42]

The aetiology of SEALs is multi-factorial.[43] It is thought that SEALs are produced by mechanical chaffing at the peripheral cornea. This chaffing occurs as a result of inward pressure of the upper lid, in an area where the peripheral corneal topography and lens design, rigidity and surface characteristics combine to create excessive 'frictional' pressure and abrasive shear force on the epithelial surface.[43] Patient characteristics, such as gender, age and specific corneal and lid topographies, also appear to influence the occurrence of SEALs.[40] Earlier-generation silicone hydrogel lenses were made from higher-modulus materials with surfaces that seemed to differ subtly in wettability in some patients; these factors were thought to contribute to the increased prevalence of SEALs with such lenses.[42,44]

Epithelial plug

Perhaps the most devastating form of staining which can be observed is the 'epithelial plug', which refers to a large discrete area (typically round in shape) of full-thickness epithelial loss (Figs. 18.10A,B). This is a rare condition which is observed in some patients who have suffered severe corneal metabolic compromise, presumably because of prolonged low-oxygen-transmissible hydrogel lens-induced hypoxia.

Madigan and Holden[45] investigated the basis for this condition in a feline model. The corneas of both eyes of cats that had worn low-oxygen-transmissible, thick, parallel-design hydrogel contact lenses in one eye only for 8 to 121 days were examined by using both light and transmission electron microscopy. A circular trephined section of the epithelium could be effortlessly lifted away from the stromal bed of all corneas that wore lenses (Fig. 18.11). Contact lens wear induced many changes in the epithelium, including a decrease in the number of cell layers and appearance of cuboidal, rather than columnar, basal cell shapes. In addition, electron microscopy revealed that the number of hemidesmosomes per micrometre of basement membrane was reduced significantly after contact lens wear. Anchoring fibrils in lens-wearing corneas appeared normal, and the reduction in epithelial adhesion occurred without obvious epithelial oedema. The authors concluded that decreased epithelial adhesion after contact lens wear, which is presumably the cause of epithelial plug formation, appears to be directly related to the reduced numbers of hemidesmosomes.

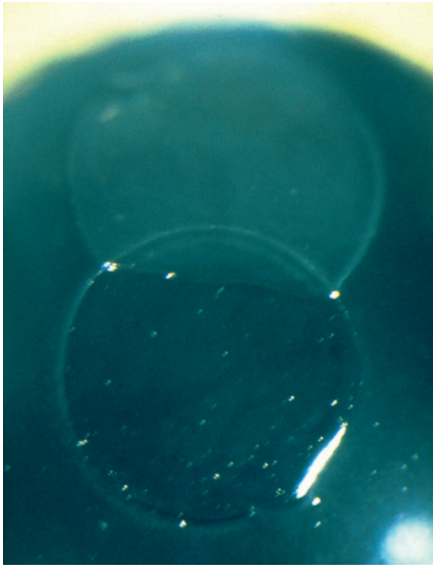


Fig. 18.11 Epithelial layer lifted away from the stromal bed (cat model). (Courtesy Michelle Madigan, Brien Holden Vision Institute.)

Solution-induced corneal staining

Over the past few years, there has been much discussion and debate regarding what has been described as transient 'solution-induced corneal staining' (SICS). This condition is characterised by an increase in asymptomatic, superficial, punctate

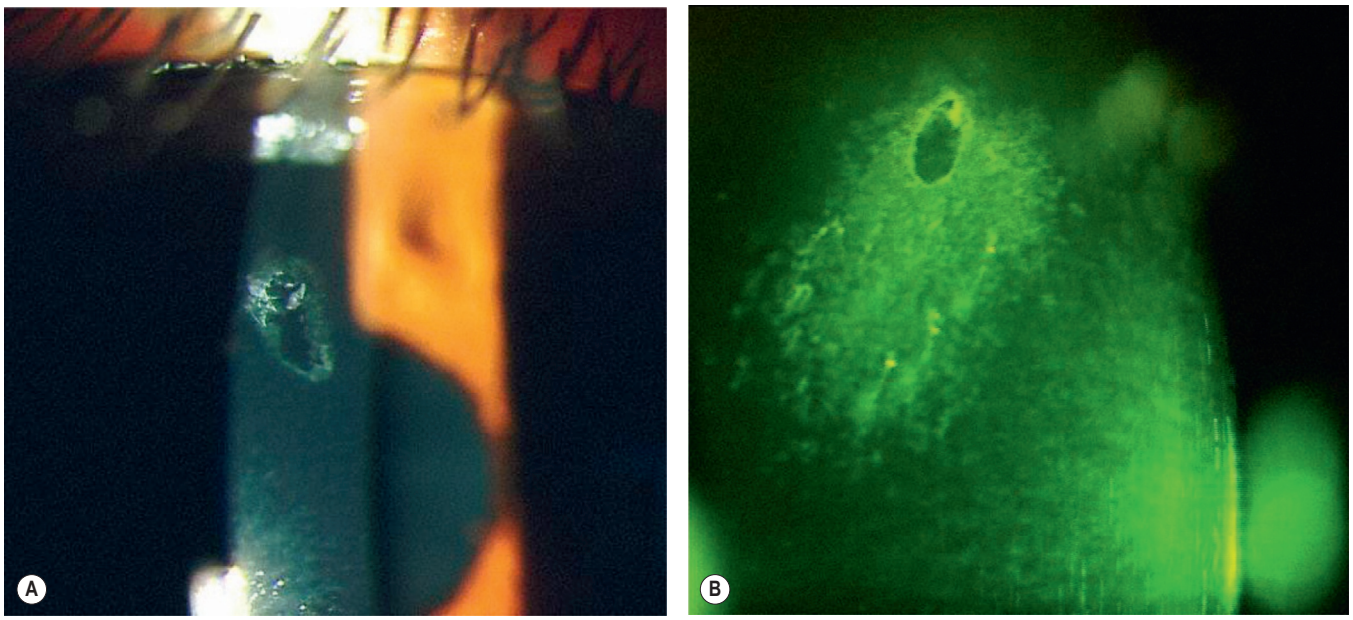


Fig. 18.10 Focal area of full-thickness epithelial loss, known as an 'epithelial plug', observed **(A)** in white light and **(B)** in a different patient, with the assistance of fluorescein. (Courtesy The Centre for Ocular Research & Education.)

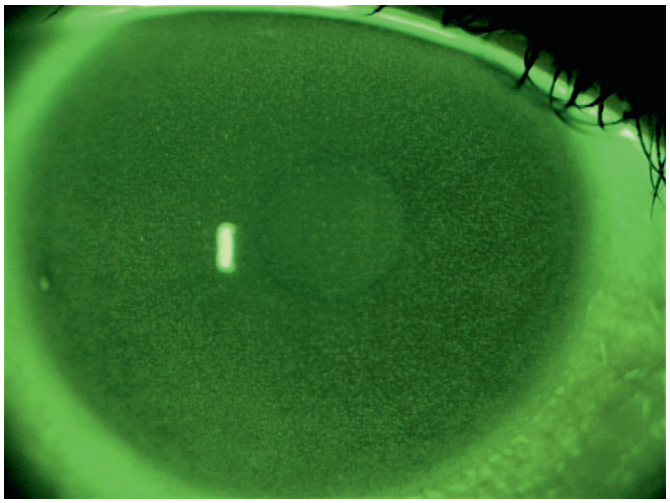


Fig. 18.12 Superficial, punctate corneal hyperfluorescence associated with the use of multi-purpose contact lens solutions. (Courtesy Paul Chamberlain, British Contact Lens Association Slide Collection.)

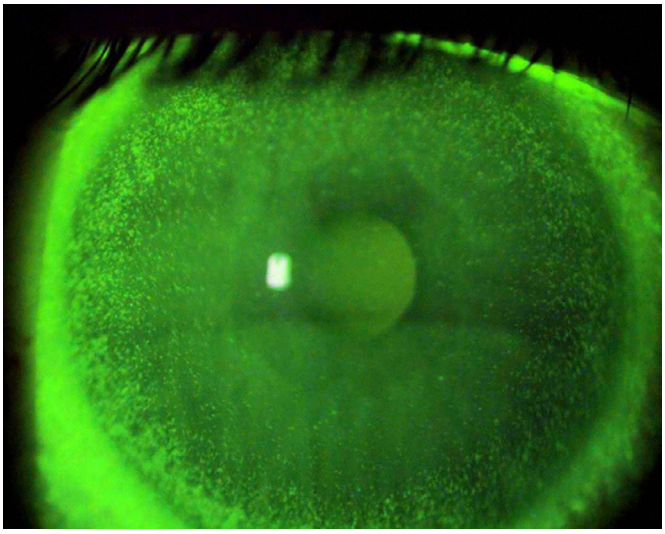


Fig. 18.13 Preservative-associated transient hyperfluorescence (PATH) staining with central sparing. (Courtesy the Centre for Ocular Research & Education.)

corneal hyperfluorescence associated with the use of multi-purpose contact lens solutions (Fig. 18.12).[46-48]

Although the most intense appearance of SICS has been implied by some authors to be a solution toxicity reaction on the cornea,[48,49] it is more likely an artefactual phenomenon relating to hyperfluorescence of fluorescein loosely bound to the corneal epithelium (see 'preservative-associated transient hyperfluorescence' next). True SICS occurs when there has been a toxic reaction causing disruption to epithelial cells, such as occurs when hydrogen peroxide is inadvertently introduced into the eye. Current-generation contact lens preservative solutions typically only induce trace amounts of true pathological corneal staining, if any.

Preservative-associated transient hyperfluorescence

Preservative-associated transient hyperfluorescence (PATH) is observed when fluorescein is instilled into the eye in the first few hours after a lens has been inserted after storage in certain preservative solutions. Although the clinical presentation is dramatic, this condition is benign, asymptomatic[47,48,50] and transient.[47] PATH is generally even but is sometimes more prominent in the mid-peripheral cornea (Fig. 18.13), coinciding with slightly greater bearing of the soft lens against the cornea in those regions.

This phenomenon is seen typically between 30 minutes and 4 hours after soft lens insertion and resolves after 6 to 8 hours, depending on the particular combination of multi-purpose contact lens solutions and contact lens material (Fig. 18.14).[46,47,51]

By contrast, a true toxicity reaction is typically pathological and symptomatic and may require several days to resolve.[52] The dichotomy between PATH and true corneal staining is highlighted by several observational differences. In addition to short duration and absence of symptomatology (e.g. discomfort),[47,48,53] differences include pattern and depth of fluorescence,[46,48,54] lack of concomitant signs (e.g. limbal or bulbar hyperaemia and corneal infiltrates)[47,55] and lack of association with future complications.[54,56] As well, PATH is usually bilateral, so significant unilateral staining may indicate true corneal pathology. It is important, therefore, to understand that the PATH signal is benign and should not form the basis of clinical decision-making.

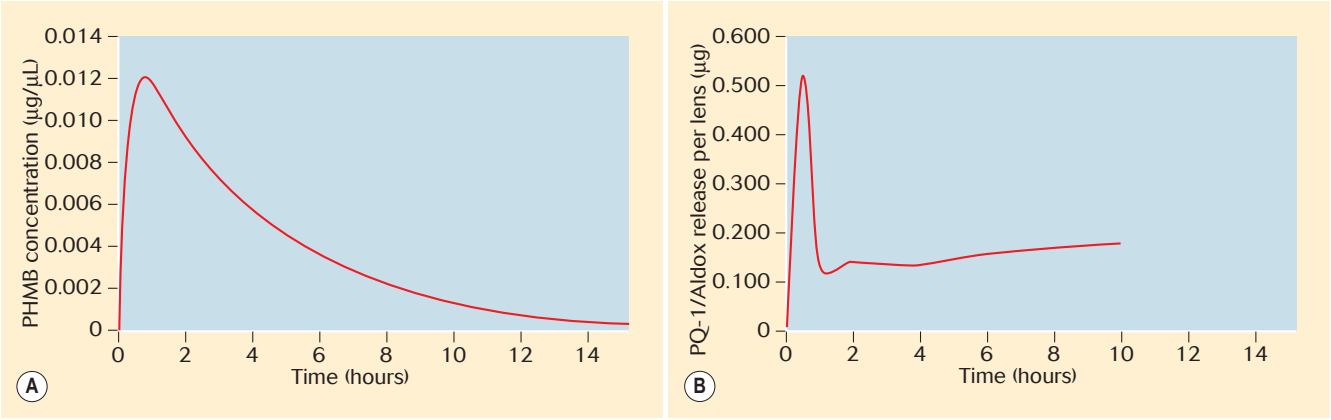


Fig. 18.14 Time course of preservative-associated transient hyperfluorescence. Concentration of **(A)** polyhexamethylene biguanide (PHMB) and **(B)** PQ-1 in the tear film after insertion of lenses that have been stored in multi-purpose solutions containing these preservatives, which essentially defines the time course of fluorescence. (Courtesy BioScience Communications.)

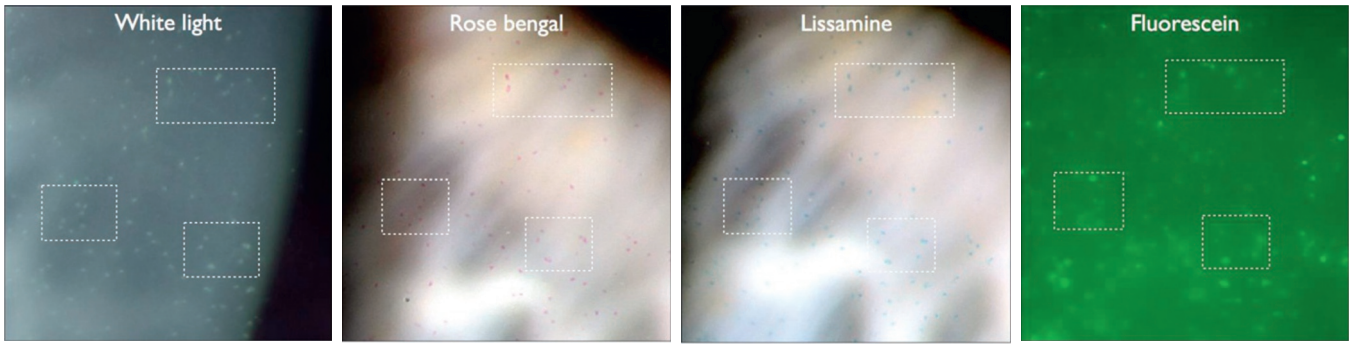


Fig. 18.15 The same region of solution-induced corneal staining (SICS) staining (white boxes) photographed, from left to right, with no stain, rose bengal, lissamine green and fluorescein. (Courtesy Carole Maldonado-Codina and Philip Morgan.)

Maldonado-Codina et al.[57] presented a case report of two subjects who each wore a pair of PureVision contact lenses (Bausch & Lomb, Rochester, New York, USA) which were soaked overnight in ReNu MultiPlus multi-purpose solution (Bausch & Lomb, Rochester, New York, USA) for 2 hours on 3 separate days at least 24 hours apart. Images of the corneas of these subjects were captured before instilling any stains and then after staining with fluorescein, rose bengal and lissamine green (Fig. 18.15). Small punctate 'dots' could be readily seen in the corneal epithelium without the aid of any ophthalmic dyes, indicating that there had been a localised loss of transparency of the corneal epithelium. These dots also stained with the three dyes. Careful inspection of the patterns of dots in the captured images revealed that the same 'dots' observed without dye also 'stained' with the three dyes.

The size of the stained dots (about 22 μm in diameter) is broadly consistent with the known diameter of superficial human corneal epithelial cells, which range in size from 20 to 37 μm. However, the limited magnification provided by slit lamp biomicroscopy precluded the authors from ascertaining the precise cause of this apparent loss of transparency, which could be attributed to changes within individual epithelial cells or to arbitrary regions unrelated to cellular structure but of a similar size (e.g. moieties adherent to the epithelial surface, altering localised refractile properties).

Maldonado-Codina et al.[57] also observed that the 'dots' which stained with either rose bengal or lissamine green disappeared within a few minutes of dye application, whereas fluorescein staining could still be observed at least 10 minutes later.

Gorbet et al.[58] conducted a study in which up to eight participants were unilaterally exposed to a multi-purpose contact lens solution/silicone hydrogel lens combination known to induce corneal staining (Renu and balafilcon A; test eye), with the other eye using a combination of balafilcon A soaked in a hydrogen peroxide care system (Clear Care; control eye). Lenses were worn for 2 to 6 hours. Corneal staining was graded after lens removal, and epithelial cells were collected from the cornea and the contact lens by irrigation. In the test eye, maximum SICS was observed after 2 hours of lens wear. There were significantly more cells collected from the test eye after 4 hours of lens wear when compared with the control eye ($n = 5$; $p < 0.001$). The total cell yield at 4 hours was 813 ± 333 and 455 ± 218 for the test and control eyes, respectively ($N = 5$; $p = 0.003$). A number of cells were observed to have taken up the fluorescein dye from the initial fluorescein instillation. Confocal microscopy of fluorescein-stained cells revealed that fluorescein was present throughout the cell cytoplasm and was retained in the cells for many hours after recovery from the corneal surface.

Other forms of staining

Other terms used to describe staining include 'linear abrasions', 'dimple stains' and 'exposure keratitis'. Severe staining (grades 3 and 4) may be accompanied by bulbar conjunctival redness and chemosis, limbal redness, excessive lacrimation and, in some cases, stromal infiltrates, depending on the cause of the problem.

VISION

Visual acuity is generally unaffected by corneal staining, although a slight loss might be expected in extreme cases (e.g. grade 4 staining as depicted in Fig. 18.5). As will be described later, epithelial recovery is generally rapid, so any vision loss will be also quickly restored.

COMFORT

A paradox of the corneal staining response is that there is no clear relationship between the severity of staining and the degree of ocular discomfort. For example, an exposure keratitis in the form of an extensive inferior arcuate diffuse staining pattern can be virtually asymptomatic, whereas a small tracking stain caused by a foreign body trapped beneath a rigid lens can be excruciatingly painful. Photophobia may be present in the case of an infection.

Pathology

Fluorescence observed in the cornea after instillation of fluorescein is thought to indicate one of three phenomena: (a) fluorescein entering damaged cells, (b) fluorescein entering intercellular spaces or (c) fluorescein filling gaps in the epithelial surface which are created when epithelial cells are displaced. However, Morgan and Maldonado-Codina[52] pointed out that the scientific basis underpinning our clinical understanding and interpretation of corneal surface fluorescence is not strong. Nevertheless, some studies have been conducted to determine the basis for observed fluorescein staining.

Wilson et al.[59] examined rabbit corneas stained with fluorescein with the biomicroscope and later with a higher–magnification epifluorescent microscope after excision. They determined that fluorescein primarily reveals cells that have taken up fluorescein optimally. Typically, this means

degenerated or devitalised cells; however, this is not always the case. The bright fluorescent appearance is concentration dependent, whereby concentrations greater or less than the optimal level will produce a lower level of fluorescence. Thus, cells with a dull fluorescence could actually contain a higher *or* lower concentration of fluorescein compared with a cell displaying bright fluorescence.

In many of their preparations, Wilson et al.[59] observed a dull background fluorescence which indicated that fluorescein had entered inter-cellular spaces, presumably in low concentrations, and on occasions entered the anterior stroma. This background fluorescence can result in a 'salt and pepper' appearance whereby the 'salt' indicates cells that have filled with the optimal concentration of fluorescein, and the 'pepper' indicates cells which are filled with a higher or lower fluorescein concentration that 'blend in' with the background fluorescence.

More controversially, Wilson et al.[59] suggested that bright fluorescence is unlikely to represent pooling of fluorescein as a result of missing cells because repeated irrigation did not change the bright fluorescent appearance (indicating that such fluorescence must come from within the cell). Certainly, in cases of gross epithelial detachment, such as occurs with an epithelial plug (Fig. 18.6), fluorescein clearly fills the void. Using impression cytology and confocal microscopy of excised corneas, Mokhtarzadeh et al.[60] confirmed that punctate epithelial staining indicates fluorescein-filled superficial corneal epithelial cells.

Bakkar et al.[61] utilised Vero and L929 cell culture models to investigate the fundamental biology of fluorescein interactions with cells. The authors observed that all cells take up fluorescein; however, a sub-population internalise much higher levels, giving rise to brightly staining 'hyper-fluorescent' cells within the treated cultures, which contain fluorescein throughout the cell cytoplasm and nucleus. The number of these hyper-fluorescent cells was significantly increased after exposure to multi-purpose solutions associated with SICS. Surprisingly, hyper-fluorescent cells did not show higher levels of staining with propidium iodide, a marker of lysed cells.

Bakkar et al.[61] also observed that treatment with the cytolytic toxin benzalkonium chloride resulted in almost all cells staining with propidium iodide, as well as complete abolition of fluorescein hyperfluorescence. The authors noted that internalization of fluorescein and its loss from treated cells both required cellular activity, as both processes were halted after incubation at 4°C (a temperature at which normal biological processes cease to occur). The authors concluded that clinically observed corneal staining reflects active living cells and is not directly caused by dead cells being produced in response to adverse clinical stimuli.

Figure 18.16 is a schematic representation of current thinking of the way in which the corneal epithelium is stained by fluorescein and rose bengal.

Uptake and release of multi-purpose contact lens solution preservatives (e.g. polyhexamethylene biguanide (PHMB), PQ-1, Aldox or alexidine) by contact lenses has been hypothesised as the root cause of PATH.[62] The quantity that adsorbs/absorbs onto/into the contact lens depends on the preservative, soft lens material and the overall formulation of the multi-purpose solution.[62] The preservatives are known to be released by the contact lens once it is placed on the ocular surface, the rate of which depends on the preservative and lens material type being used.[62,63] If fluorescein is introduced into the eye, it binds strongly to the preservatives and loosely and reversibly to the

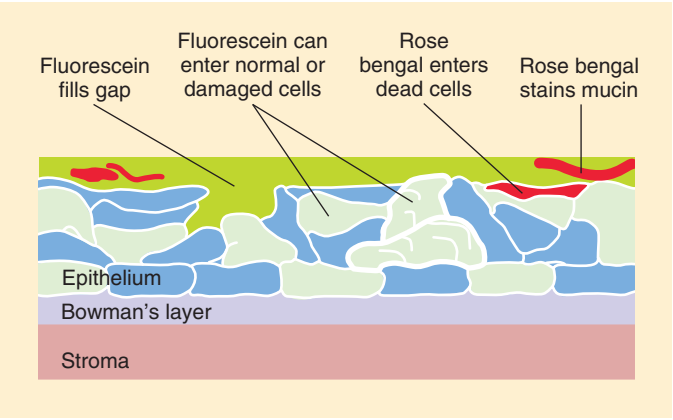


Fig. 18.16 Mechanism of fluorescein and rose bengal staining of the corneal epithelium.

surface of the cornea (Fig. 18.17). The time of maximal release of each preservative (1–3 hours for the biguanides PHMB/alexidine and approximately 30 minutes for PQ-1/Aldox) coincides with peak transient hyperfluorescence observed clinically in subjects wearing lenses that had been soaked in PHMB-based multi-purpose solution (1–4 hours) and in PQ-1/Aldox-based multi-purpose solution (around 30 minutes).[47,63]

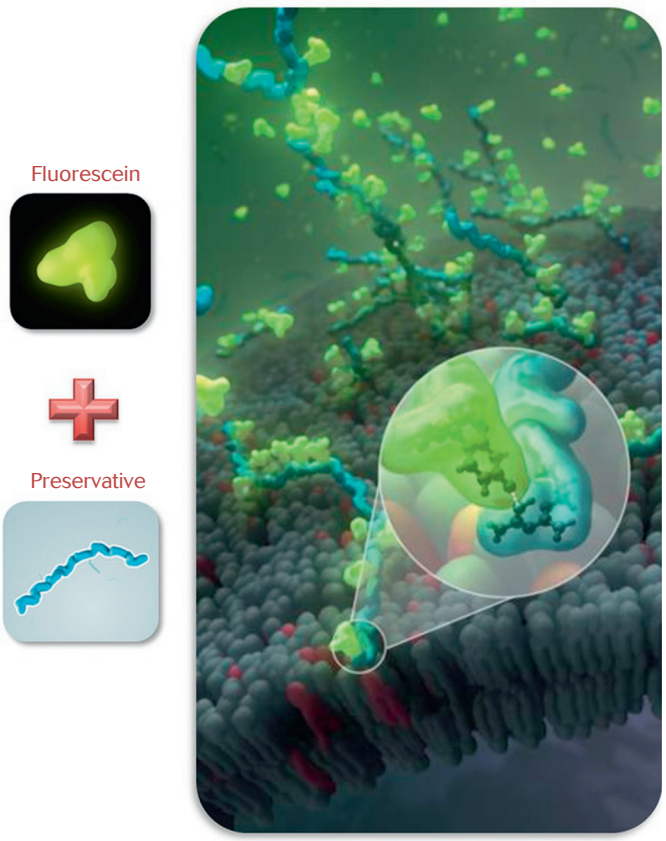


Fig. 18.17 Fluorescein binds with multi-purpose solution preservatives, previously released from the lens, at the surface of the corneal epithelium. (Courtesy BioScience Communications.)

Aetiology

In a cross-sectional/nested case-control study of 413 contact lens wearers, Nichols and Sinnott[64] examined ocular surface and tear film, contact lens, care solution and medical and patient-related factors associated with corneal staining in contact lens wearers. Several factors were shown to be related to increased corneal staining, including increased daily wearing times ($p = 0.0006$), lower income ($p = 0.0008$), lissamine green conjunctival staining ($p = 0.002$), contact lens deposition ($p = 0.007$), increased tear meniscus height ($p = 0.007$) and decreased hydrogel nominal water content ($p = 0.02$). The wearing of silicone hydrogels (as opposed to hydrogels) was protective against corneal staining ($p = 0.0004$). Notably, Nichols and Sinnott[64] reported that neither contact lens care solutions nor disinfectants were associated with corneal staining.

Tran et al.[65] noted that Asian soft lens wearers demonstrated more severe corneal staining overall compared with non-Asians.

There are numerous contact lens–related causes of epithelial staining, which can be broadly classified into six aetiological categories: mechanical, exposure, metabolic, toxic, allergic and infectious. In many cases, the pattern of staining can provide a clue to the cause. Each of these aetiological factors is considered in the following.

MECHANICAL

Sources of mechanical staining include:

- lens defects;
- poor lens finish (e.g. rough edge)[66];
- lens binding (e.g. as can occur with overnight rigid lens extended wear lenses[67]);
- excessive lens bearing (e.g. tight rigid lens fit, bearing of a poorly blended optic zone junction or decentred lens, as depicted in Fig. 18.18);
- foreign bodies beneath the lens;
- deposits on the posterior lens surface; or
- abrasion occurring during lens insertion or removal.

Staining induced by lens defects or posterior lens deposits usually takes the form of discrete areas of fluorescence corresponding to the location of the defect or deposit.[66] The staining may be arcuate as a result of natural lens rotation during wear. Staining caused by lens binding appears as an arc corresponding to the lens edge, whereas excessive lens bearing can result in a more diffuse form of staining.

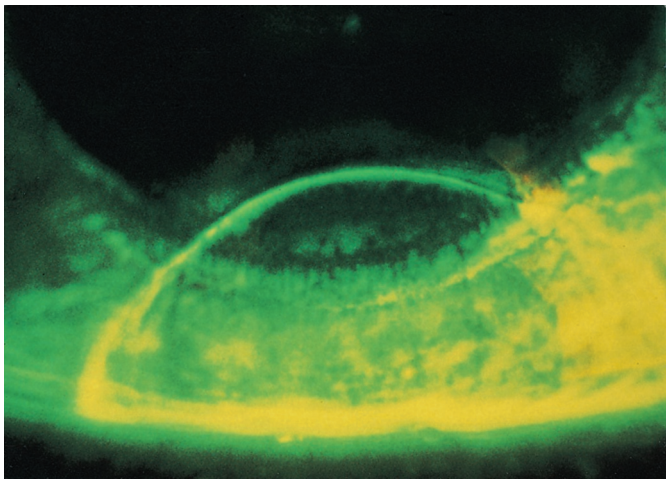


Fig. 18.18 Corneal and conjunctival imprint of edge of decentred rigid lens as revealed by fluorescein. (Courtesy Donna LaHood, Bausch & Lomb Slide Collection.)

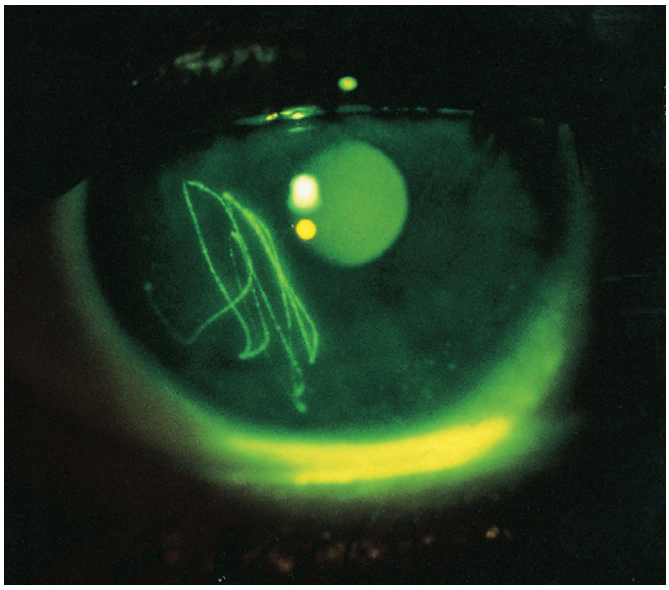


Fig. 18.19 Foreign body track in rigid lens wearer. (Courtesy Deborah Jones, Bausch & Lomb Slide Collection.)

A foreign body often leaves a zigzag track indicating the path it has taken across the corneal surface as a result of blinking (Fig. 18.19). This phenomenon is rarely observed in soft lens wearers.

Staining incurred during lens insertion or removal is often of a linear form. Since such staining is characteristically a 'chance occurrence', it is typically unilateral.

EXPOSURE

In soft lens wearers, exposure keratitis manifests typically as a band of inferior arcuate staining. This is caused by epithelial disruption as a result of drying of the corneal surface.[68] Such staining patterns are observed when soft lenses decentre superiorly, leaving an inferior band of exposed cornea which is not properly wetted because of less frequent blinking.

Desiccation staining with soft lenses can be categorised as a form of exposure keratitis.[69] This condition appears as a central stipple stain. It occurs when high-water-content lenses are made too thin, causing water to be drawn out of the cornea when the lens dehydrates during wear.[70] All forms of exposure keratitis are typically bilateral.

The classic pattern of 3 & 9 o'clock staining in rigid lens wearers is also primarily thought to represent a form of exposure keratitis, whereby the eyelids are bridged away from the corneal surface at the lens edge at the 3 & 9 o'clock corneal locations (Fig. 18.6).[33]

METABOLIC

All contact lenses are known to induce various levels of epithelial hypoxia (oxygen deprivation) and hypercapnia (excessive carbon dioxide),[71] resulting in the production of metabolites

(e.g. lactic acid), which can adversely affect epithelial structure and function and lead to tissue acidosis.

In the case of lenses of low oxygen transmissibility and/or lens overwear, such changes can be exacerbated, and the epithelial decompensation is observed as a generalised, diffuse staining encompassing most of the cornea; it is typically bilateral. The spontaneous focal loss of epithelium depicted in Figure 18.10 was attributed to the effects of severe hypoxia in a soft lens patient wearing −9.00 diopter (D), low-water-content (38%) soft lenses.

Fine punctate staining can be observed when epithelial microcysts break through the anterior epithelial surface (see Chapter 19).

TOXIC

Preservatives used in contact lens disinfection systems are generally formulated in low concentrations so that direct application to the eye is non-toxic. Single-bottle multi-purpose solutions contain surfactant cleaning elements which are below the threshold for ocular toxicity. Some preservatives which were used in the past, such as chlorhexidine, can bind strongly and reversibly to certain hydrogel polymers or to protein deposits on the lens surface, especially in lenses which were disposed of infrequently.[72] This could eventually lead to a toxic reaction, which, in severe cases, presents as diffuse staining across the whole cornea (Fig. 18.20). Hydrogen peroxide, when introduced directly into the eye, can result in a severe and painful toxic reaction.[73]

Although clinical studies demonstrate that current generation multipurpose solutions are non-toxic, *in vitro* studies have revealed subclinical changes to human epithelial cells. For example, Oh et al.[74] have demonstrated that at different concentration levels, several multipurpose solutions show a decrease in viability and an increase in the release of inflammatory cytokines from human corneal epithelial cells *in vitro*. The borate buffer component of multipurpose solutions, as well as polyhexamethylene biguanid, appear to contribute to this pro-inflammatory reaction.

Khan et al.[75] observed that the clinical hyperfluorescence profile observed after exposure to four multipurpose solutions can be reproduced using a simple *in vitro* model of cellular fluorescein uptake, suggesting this is the biological basis for solution-induced corneal staining. They suggest that fluorescein entry does not correlate with necrosis or apoptosis, but instead involves a dynamin-dependent active process. Moreover, they suggested that the non-ionic surfactant Tetronic 1107 is a key multipurpose solution constituent triggering increased fluorescein entry, and may be the major factor responsible for solution-induced corneal staining.

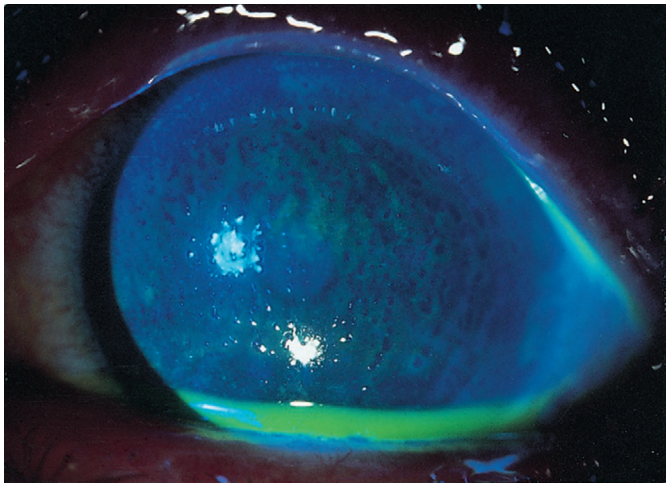


Fig. 18.20 Severe toxicity staining in a patient who inadvertently used a contact lens cleaner as a wetting solution. (Courtesy W Vreugdenhil, Bausch & Lomb Slide Collection.)

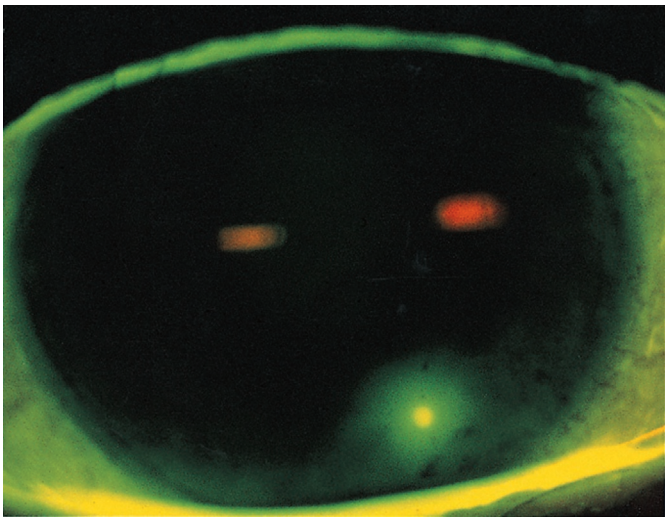


Fig. 18.21 Staining of a sterile peripheral ulcer revealing involvement of epithelium (central intense fluorescence) and stroma (diffuse background glow). (Courtesy Mee Sing Chong, Bausch & Lomb Slide Collection.)

ALLERGIC

An allergic reaction can take the form of a delayed or immediate hypersensitivity response. This is an acquired cell-mediated (antibody) immunological reaction which generally requires previous exposure and sensitisation to the offending antigen. In the immediate form, it may resemble a toxic response. Delayed hypersensitivity can manifest months or years after continued use of an apparently harmless product.

Thimerosal, benzalkonium chloride and chlorhexidine have all been implicated in the aetiology of allergic reactions to contact lens solutions. Fortunately, these substances are now virtually obsolete, and sophisticated preservatives which are essentially non-toxic and non-allergenic now dominate the market.[76] Chlorine-based disinfection systems are also largely non-toxic and non-allergenic, although concerns have been expressed about the disinfection capacity some formulations of these solutions.[77]

Anecdotal reports have suggested that the known increase in contact lens-associated infiltrates in wearers of silicone hydrogel contact lenses is due to an allergic reaction to silicone. Hall et al.[78] conducted a literature review to investigate the antigenic properties of silicone and the causes of contact lens-associated inflammatory reactions. They established that immune cells cannot interact with silicone directly but can interact with antigens on these lenses. These antigens could be due to tear film deposits, microbial contamination, or components of care systems used with these lenses. They concluded that inflammatory reactions associated with silicone hydrogel contact lens wear are *not* caused by an allergic reaction to silicone alone.

INFECTIOUS

Infection by a variety of pathogens can result in corneal staining. Indeed, a corneal ulcer is only defined as such if the affected region of stromal degradation is accompanied by an overlying epithelial defect. In such cases, staining is usually confined to the region of ulceration, which, in the early stages, can be quite small (Fig. 18.21). Fluorescein may also diffuse into the stroma, resulting in a dull background fluorescence.

Observation and grading

In many cases, epithelial defects can be observed using the slit lamp biomicroscope under white light without the aid of fluorescein. As a general rule, observation in white light should always precede observation after instillation of fluorescein. Once the fluorescein is instilled, the cornea should be examined with a broad beam at low magnification (×10, giving a full view of cornea) under cobalt blue light to determine the overall level of staining. This is the preferred technique, for example, for assessing pan-corneal conditions, such as 3 & 9 o'clock staining or desiccation staining. Closer examination with a 1 mm beam at higher magnification (up to ×40) is required to detect more subtle forms of staining (e.g. fine foreign body tracks) and the depth of staining.

Fluorescein has a maximum absorption spectrum at 460 to 490 nm, with a maximum emission spectrum at 520 nm.[20] On the basis of this knowledge, filters can be interposed in the observation and illumination system of a slit lamp biomicroscope to enhance conditions for viewing corneal staining.[79] Specifically, a Wratten #47B excitation filter should be placed in the illumination system; this has a peak transmission between 400 and 500 nm. A Wratten #12 filter (which absorbs all wavelengths below 500 nm and provides maximum transmission at 530 nm and beyond) placed in the observation system further enhances the observed fluorescence.

A grading scale for assessing the severity of corneal staining is provided in Appendix A. Although this scale depicts fluorescein staining, the images can be applied to any stain, as only the colour of the dye would be different.

Management and treatment

Unlike various other forms of ocular compromise with contact lens wear, it is often possible to identify the cause of corneal staining from the patient history, knowledge of the lenses worn and maintenance system used, inspection of the lens and analysis of the form of staining. Clinical intervention is generally not required if the level of staining is less than grade 2.

Minor staining is commonly observed in contact lens wearers; it is typically transient and in a daily lens wearer will have disappeared by the following morning. However, persistent minor staining forming a characteristic pattern and staining greater than grade 2 may require intervention.

It is, of course, not possible to detail all of the possible strategies for alleviating corneal staining which is deemed to be clinically excessive, but the general principles outlined later according to probable aetiology should provide some guidance. Whatever strategy is adopted, lens wear need only be ceased for 1 or 2 days for low-level staining (less than grade 2) and perhaps 4 or 5 days for more intense staining (greater than grade 2).

MECHANICAL

Strategies for resolving staining of a mechanical aetiology are generally self-evident. In the case of disposable lenses with persistent edge defects or poor surface finish, an alternative lens type should be tried. If the mechanical problem relates to posterior lens deposits, the lenses should be replaced more frequently. With rigid lenses, lens replacement is generally the best option.

Numerous and often conflicting strategies have been advocated for alleviating rigid lens binding after overnight wear; Woods and Efron[80] demonstrated that regular rigid lens replacement (say, every 6 months) will significantly reduce the incidence of binding. Excessive rigid lens bearing is alleviated by modifying the lens fit. Foreign bodies are dealt with by rinsing the lens and sometimes also the eye. Abrasion occurring during lens insertion or removal may necessitate re-education of the patient with respect to lens insertion and removal techniques.

EXPOSURE

Exposure keratitis in soft lens wearers is usually caused by a lens decentring superiorly. This is managed by fitting a larger-diameter lens or perhaps a lens of different design that centres better.

In rigid lens wearers, the general principle to be followed in attempting to alleviate 3 & 9 o'clock staining is to ensure that the stained region is wetted properly. Numerous strategies have been advocated to alleviate this condition,[33] including adopting a lens design that allows for greater movement (typically a smaller, looser lens fit), blinking instructions, use of in-eye lubricants[81] or changing to soft lenses.

Desiccation staining, which is generally observed in association with the wearing of thin, high-water-content soft lenses, is prevented by designing lenses with greater average thickness according to the guidelines provided by McNally et al.[82] and/or using a lower-water-content material.

METABOLIC

Corneal staining attributed to epithelial hypoxia and hypercapnia is alleviated by following the general guidelines for alleviating metabolic stress, as described in Chapter 22. In general, treatment options include refitting a lens of higher gas transmissibility (e.g. a silicone hydrogel lens), reducing wearing time or changing from extended wear to daily wear.

TOXIC

The obvious strategy for treating corneal staining caused by solution toxicity is to change to a solution which is non-toxic for that patient. Corneal burns resulting from instillation of hydrogen peroxide may require patient re-education in the use of peroxide systems or the prescription of a different system. Associated strategies include more frequent lens replacement to avoid a build-up of deposits which can absorb and concentrate preservatives, and the use of a lens made from a different polymer which is, again, less likely to absorb and concentrate the offending preservatives.

ALLERGIC

Similar strategies to those described earlier for treating toxicity staining are applied to the treatment of corneal staining because

of solution allergy; that is, change to a solution which is non-allergenic for that patient, replace lenses more frequently and prescribe lenses made from a different polymer. Atopic patients who are prone to suffer a reaction to a variety of preservatives are best fitted with daily disposable lenses so as to avoid contact with solutions all together.

INFECTIOUS

It is essential that the offending organism involved in an infectious episode of corneal pathology is destroyed as quickly as possible to avoid widespread corneal damage. Resolution of the infection will generally result in the re-establishment of a normal epithelium. The issue if contact lens–related corneal infection and ulceration is dealt with in detail in Chapter 27.

Prognosis

Recovery from corneal staining is generally quite rapid after removal of the causative agent. Light staining (less than grade 2) can recover within a few hours, and certainly overnight, assuming that lens wear has ceased. The foreign body track depicted in Figure 18.10 resolved completely in 24 hours. More severe cases of corneal staining (greater than grade 2) may take up to 4 or 5 days to disappear.

Resolution of epithelial staining is slower if lenses are worn during the recovery period because the lenses will inevitably induce a certain measure of anterior corneal hypoxia and mechanical insult, providing a sub-optimal environment for epithelial growth and repair.

Differential diagnosis

There are various issues that relate to the differential diagnosis of corneal staining. The first issue is the clinical interpretation of *different* patterns of staining – a topic that has already been dealt with in some detail in this chapter. The distribution, depth and intensity of staining, whether the staining is unilateral or bilateral, and the associated history can provide strong clues as to the cause of the condition.

Differentiation of the aetiology of corneal staining can be aided by the application of other vital stains – the most common being lissamine green. Dead cells, fibrotic tissue and excess mucus will stain heavily with lissamine green, making this stain especially useful for identifying degenerative conditions and dry eye.

PATH is generally observed with a peak fluorescence occurring 2 hours after insertion of a lens that has been stored in PHMB-based multi-purpose solution or earlier if stored in PQ-1-based solution. One possible way of differentiating between PATH and true corneal staining would be to have the patient stop wearing contact lenses for a few hours and then re-examine the eye. By this time, the PATH signal would have largely subsided, and any residual corneal staining might be indicative of a true pathological disturbance to the ocular surface. PATH is generally even and perhaps more prominent in the mid-peripheral cornea, coinciding with slightly greater bearing of the soft lens against the cornea in those regions. Furthermore, PATH is usually bilateral, so significant unilateral staining may indicate true corneal pathology.

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19 Epithelial Microcysts

The first report of the appearance of corneal epithelial microcysts in association with contact lens wear was published in 1976 by Ruben and co-workers.[1] As will be outlined in this chapter, these authors were correct in surmising that 'corneal microcysts are evidence of chronic changes in the... epithelium...'. This observation was confirmed in 1978 by Zantos and Holden[2] (who used the term 'microvesicles') in a report of a clinical trial and in 1979 by Josephson[3] in a published case report. Numerous scientific papers since then have carefully documented and, in many cases, quantified the appearance of microcysts in patients wearing different types of contact lenses.

Epithelial microcysts can be readily observed with the slit lamp biomicroscope (Fig. 19.1). This sign is considered an important indicator of chronic metabolic stress in the corneal epithelium in response to wearing low-oxygen-transmissibility (Dk) contact lenses.

Prevalence

CASE REPORTS

As many as 10 microcysts[4-6] can be observed in the corneal epithelium of about 50% of non–contact lens wearers.[7] Thus, the appearance of a small number of microcysts in a contact lens wearer should be considered a normal occurrence.

A number of authors have published estimates of the prevalence of a significant microcyst response in association with various types and modalities of lens wear[1,4,8-17]; these estimates are summarised in Table 19.1. Bearing in mind the different methodologies, lens types and study durations employed by the various authors, the concordance of estimates of prevalence is good. In general, a lower prevalence of microcysts is associated with daily wear of contact lenses compared with extended wear of hydrogel lenses. The prevalence of microcysts associated with both hydrogel lens extended-wear and low-Dk rigid lens extended wear approaches 100% and is zero with silicone hydrogel lenses.

Toshida and Murakami[18] reported an atypical case of microcysts associated with silicone hydrogel contact lens wear based on observations with an in vivo confocal laser microscope. They reported that treatment with betamethasone phosphate and levofloxacin eye drops (both five times daily) resulted in alleviation of the condition after 10 days. Since microcysts usually take up to 3 months to resolve (see 'Prognosis'), the formations observed by these authors may have been a different form of pathological entity to the microcyst response described in this chapter.

HOSPITAL SURVEYS

In 1992, Stapleton et al.[19] reported that of 1,104 patients with contact lens–related disorders presenting to an eye clinic, only 11 (1.0%) displayed epithelial microcysts. Of the extensive hospital-based surveys of contact lens complications conducted between 2009 and 2018 – carried out in China,[20] India,[21] Nepal,[22] Singapore,[23] the USA[24] and UK[25] – only one study reported the observation of epithelial microcysts. This was in the UK survey of Radford et al.,[25] where one case of epithelial microcysts was observed among 877 contact lens wearers (0.1%) attending Moorfields Eye Hospital with contact lens–related disorders other than microbial keratitis.



Fig. 19.1 Extensive formation of epithelial microcysts that can be clearly seen against the background of the pupil margin. (Courtesy Craig Woods, British Contact Lens Association Slide Collection.)

TABLE 19.1 Prevalence of contact lens–induced epithelial microcysts

Lens type	Mode of lens wear	Lens Dk	Prevalence of microcysts (%)
No lens wear	–	–	26[4]
PMMA	DW	Zero	29[4]
Rigid	DW	Low	29[8]
Rigid	DW	High	0.7[17]
Rigid	EW	Very low	97[4]
Rigid	EW	Low	23[9], 93[10], 100[4]
Rigid	EW	Low	84[4]
Rigid	EW	Medium	29[4]
Rigid	EW	High	1.6[17]
Hydrogel	DW	Very low	0.9[17], 26[1], 34[4]
Hydrogel	EW	Low	7[17], 43–77[11], 71[10], 86[4], 97[4], 100[8,12,13]
Hydrogel	CW	Low	41[4]
Silicone hydrogel	DW	High	0
Silicone hydrogel	CW	High	0[14–16]

CW, continuous wear; *Dk*, oxygen transmissibility; *DW*, daily wear; *EW*, extended wear; *PMMA*, polymethyl methacrylate.

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Signs and symptoms

SLIT LAMP BIOMICROSCOPE APPEARANCE

Microcysts can be seen in the central and paracentral cornea at low magnification (×15). They appear as minute, scattered, grey, opaque dots with focal illumination and as transparent refractile inclusions with indirect retro-illumination (Fig. 19.2). Microcysts are often said to be irregular in shape, but all of the photomicrographs of microcysts which I have examined suggest that they are generally of a uniform spherical or ovoid shape. Zantos[26] suggested that they can vary in size from 15 to 50 μm^3; however, microcysts as large as the full thickness of the epithelium (50–75 μm) have *not* been reported, so it is likely that microcysts are in the order of 5 to 30 μm in diameter.

Careful observation at high magnification (×40) is required to differentiate epithelial microcysts from other epithelial inclusions, such as vacuoles or bullae, which take on a superficially similar appearance. The preferred observation technique is marginal retro-illumination. The observation and illumination arms should be set at least 45° apart. A 2-mm-wide beam should be directed to one of the lateral margins of the pupil so that, when focused on the cornea, the background is evenly split between the illuminated iris and the black pupil. Microcysts are then readily observed in the region of the epithelium lying in front of the border of the iris and the pupil. It is important to consider the internal illumination characteristics with respect to the background (pupil and iris) and to ignore the directly illuminated corneal section that may be adjacent to the corneal region of interest. By slowly scanning laterally from side to side, an overall estimate of the number of microcysts can be derived.

The greater the number of microcysts, the greater is the probability of detecting slight superficial punctate staining, which represents a breaking open of the anterior epithelial surface as microcysts emerge from the deeper layers and are expunged from the cornea.

Once it has been established under high magnification (×40) that the inclusions being observed are, indeed, microcysts (see 'Differential Diagnosis'), the severity of the overall response can be quantified by once again observing the cornea at a low enough magnification so that it fills the field of view (perhaps ×10 magnification). By scanning back and forth with a 1-mm vertical beam, it is possible to view the microcysts in direct focal illumination. Holden et al.[4] advocated quantifying the severity of a microcyst response by counting the number of microcysts, which, at this low level of magnification, appear as minute, grey dots. An alternative strategy is to grade the response using a grading scale for epithelial microcysts, such as that provided in Appendix A.

OPTICAL EFFECTS

Epithelial microcysts display a characteristic optical phenomenon known as 'reversed illumination' when viewed by using the previously described observation technique; that is, the distribution of light within the microcyst is opposite to the light distribution of the background[26] (Fig. 19.3). It must be emphasised that the illuminated optic section of the cornea adjacent to the area of interest must be ignored; that is, one should concentrate only on the microcyst with respect to the brightness and darkness of background features (the pupil and the iris). Other inclusions, such as vacuoles and bullae, or mechanical epithelial defects, such as dimple veiling (creating fluid-filled epithelial pits), display 'un-reversed illumination' (Fig. 19.3).

Simple optical principles can be used to demonstrate the significance of the optical appearance of microcysts and other epithelial inclusions (Fig. 19.4). The 'reversed illumination' appearance indicates that the inclusion is acting as a converging refractor; therefore, it must consist of material that is of a higher refractive index than the surrounding epithelium.[27] Conversely, the 'un-reversed illumination' appearance indicates that the inclusion is acting as a diverging refractor; therefore, it must consist of material that is of a lower refractive index than that of the surrounding epithelium.

The predominant inclusions which (a) are observed in association with all forms of contact lens wear and (b) display characteristic patterns in terms of the time course of onset and resolution are those which display reversed illumination. These observations and features, together with our current understanding of the pathology and aetiology of the microcyst response, allow inclusions displaying reversed illumination to be defined as 'microcysts'.

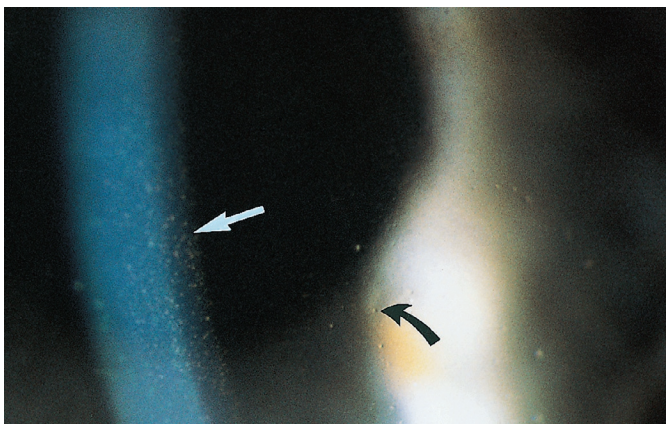


Fig. 19.2 Epithelial microcysts appear as grey dots in focal illumination (white arrow) and refractile inclusions in retro-illumination (black arrow). (Courtesy David Ruston, British Contact Lens Association Slide Collection.)

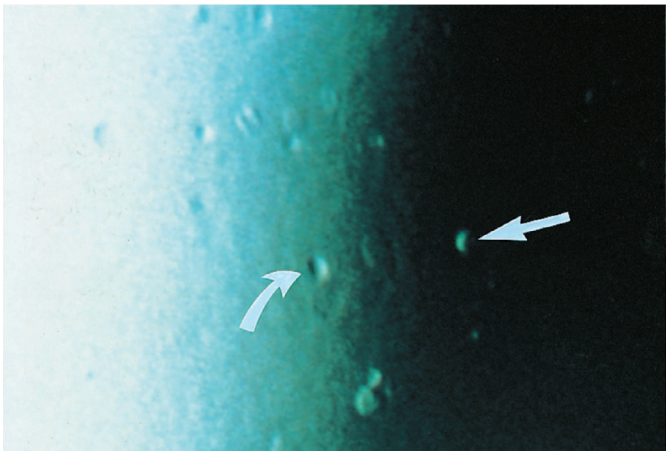


Fig. 19.3 High-magnification slit lamp photomicrograph showing microcysts (displaying reversed illumination; curved arrow) and vacuoles (displaying un-reversed illumination; straight arrow). (Courtesy Steve Zantos, Brien Holden Vision Institute.)

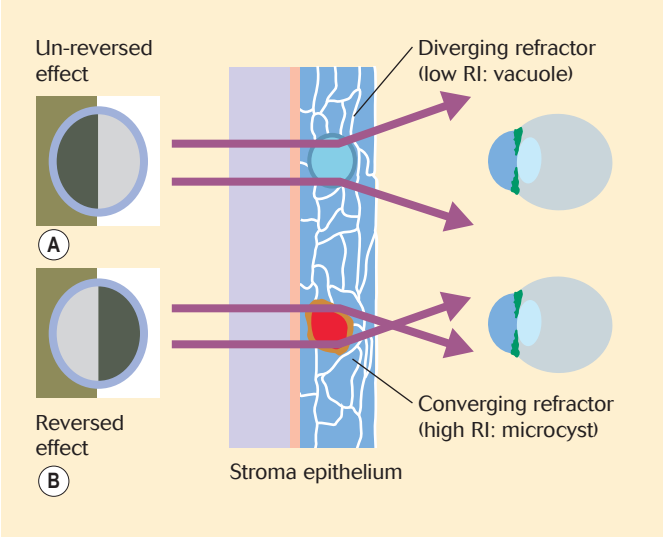


Fig. 19.4 Optical theory illustrating how (**A**) vacuoles act as diverging refractors and display un-reversed illumination and (**B**) microcysts act as converging refractors and display reversed illumination. (Adapted from Zantos SG. Cystic formations in the corneal epithelium during extended wear of contact lenses. Int Contact Lens Clin 1983;10:128–34.)

VISION

Visual acuity is generally unaffected by microcysts, although in extreme cases when the number of microcysts approaches 200, there might be a slight loss of vision. Zantos and Holden[2] reported a case where vision decreased by one line of acuity.

COMFORT

Microcysts are asymptomatic; patients are unaware that they have a microcyst response. Patients displaying an extensive microcystic response may experience some ocular discomfort and lens intolerance; however, this is likely to be the result of concurrent pathology. For example, a patient with a severe microcyst response may also have a mild anterior uveal reaction as part of an overall hypoxia-driven syndrome, which could cause ocular pain.

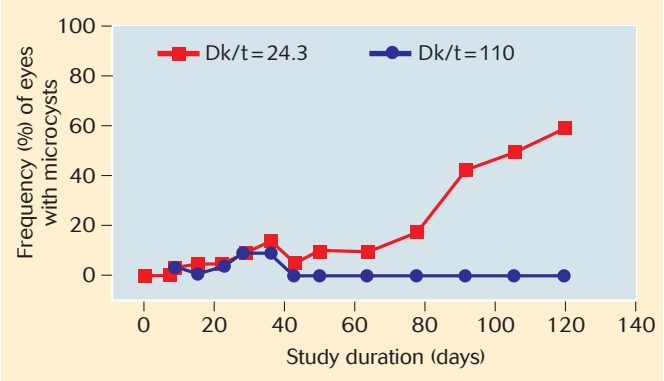


Fig. 19.5 Percentage of eyes developing epithelial microcysts over 140 days while wearing low oxygen transmissibility (Dk/t) (red) and high-Dk/t (blue) lenses. (Adapted from Fonn D, MacDonald KE, Richter D, Pritchard N. The ocular response to extended wear of a high Dk silicone hydrogel contact lens. Clin Exp Optom 2002;85:176–82.)

TIME COURSE OF ONSET

Microcysts can be detected as early as 1 week after commencing extended lens wear[28]; however, the rate of onset is generally slow and microcysts will not begin to appear in significant numbers until lenses have been worn for about 2 months. The number of microcysts will then increase at a more rapid rate over the next 2 to 4 months (Fig. 19.5).[5,16] Fonn and Holden[10] reported that the prevalence of microcysts in new patients fitted with extended-wear hydrogel lenses was 5% after 5 weeks, 33% after 8 weeks and 71% after 13 weeks.

The number of microcysts will eventually reach a steady-state level, although cyclical patterns of microcysts have been reported in some patients.[5]

Pathology

The optical phenomenon of reversed illumination, which microcysts display, suggests that they contain material of a higher refractive index than the surrounding tissue.[27,29] Bergmanson[30] postulated that microcysts represent an extracellular accumulation of broken down cellular material trapped in the basal epithelial layers. In a process similar to that which occurs in Cogan's microcystic dystrophy,[31] the epithelial basement membrane re-duplicates and folds, forming intra-epithelial sheets that eventually detach from the basement membrane and encapsulate the cellular debris.

On the basis of her findings of the effects of 15 months of soft lens extended wear in cats, Madigan[32] suggested that microcysts are not an accumulation of extracellular debris but rather represent apoptotic (dead) cells which either (a) become phagocytosed (ingested) by living neighbouring cells or (b) remain involuted in the inter-cellular spaces (Fig. 19.6).

Figure 19.7 is a schematic representation of the likely pathological process by which microcysts are produced. Microcysts are thought to originate in the deepest layers of the epithelium, where they are difficult to observe because they are only partially formed. They are then carried to the surface of the epithelium, which is constantly growing in the anterior direction. Microcysts approaching the corneal surface are more easily observed because they are now fully formed. They eventually break through the epithelial surface, leaving a minute pit that stains with fluorescein.

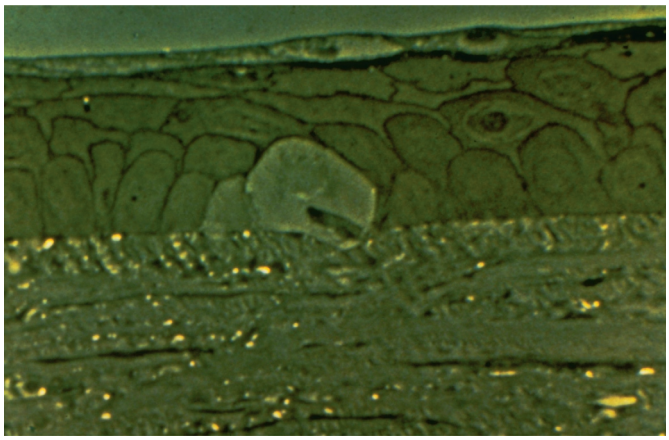


Fig. 19.6 Epithelial microcyst forming in the basal epithelium (rabbit model). (Courtesy Tony Henriquez.)

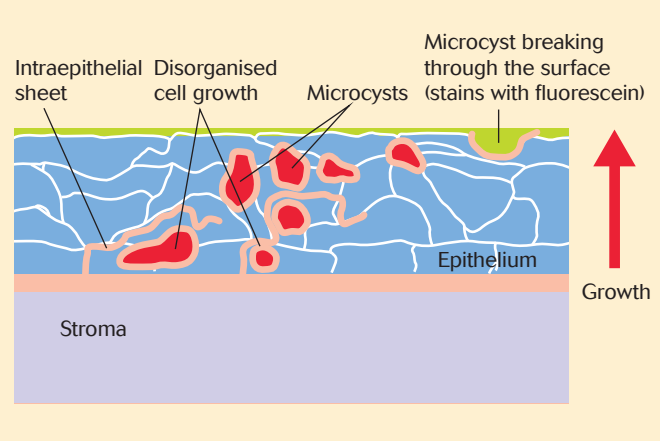


Fig. 19.7 Pathogenesis of epithelial microcysts, which are formed in the basal epithelium and transported anteriorly as the epithelium grows in that direction.

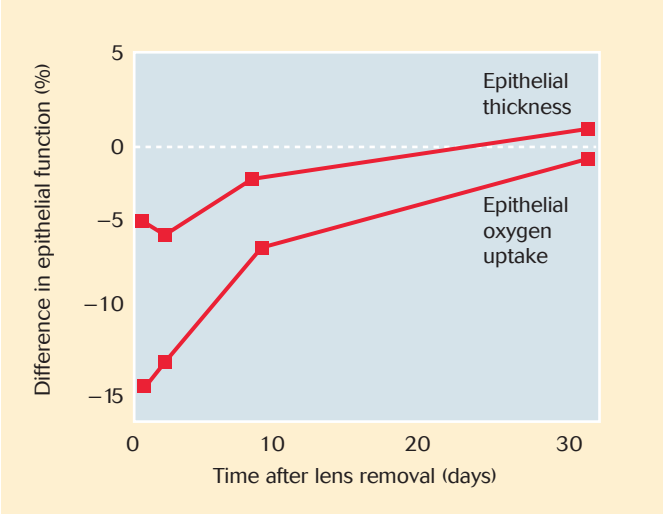


Fig. 19.8 Recovery of epithelial function upon lens removal after 5 years of extended wear of hydrogel lenses. (Adapted from Holden BA, Sweeney DF, Vannas A, et al. Effects of long-term extended contact lens wear on the human cornea. Invest Ophthalmol Vis Sci 1985;26:1489–501.)

Aetiology

There now exists an abundance of evidence to suggest that microcysts primarily represent visible evidence of chronic tissue metabolic stress and altered cellular growth patterns caused by the direct and/or indirect (acidosis) effects of hypoxia and/or hypercapnia.[33] The primary evidence supporting this theory is that the prevalence of microcysts and the number of microcysts present correlates with the modality of lens wear (more microcysts occur with extended versus daily wear),[4] length of lens wear (number of microcysts increases with length of wear)[1,10] and the gas transmissibility (Dk/t) of the lens (lenses of lower Dk/t induce more microcysts).[4,34]

Sweeney[35] reviewed the literature up to 2013 to determine if use of silicone hydrogel lenses has eliminated corneal hypoxia. In particular, the author considered the results from clinical studies, including short-term laboratory studies and retrospective and prospective clinical trials, which assessed the response of the cornea to silicone hydrogels. Sweeney[35] concluded that silicone hydrogels have eliminated the physiological signs associated with lens-induced hypoxia, including epithelial microcysts, noting that the extent of microcysts reported in these studies was similar to those observed with non–lens wearers. Given that silicone hydrogel lenses represent three-quarters of all reusable soft lenses prescribed worldwide at the present time,[36] this sign of hypoxic distress should now be seldom seen in contact lens practice.

Holden et al.[12] demonstrated that after 5 years of soft lens extended wear, the epithelium suffers a 15% reduction in oxygen uptake and a 6% reduction in thickness (Fig. 19.8). These findings concur with the observation of Hamano and Hori[37] that hydrogel lenses cause a 94% suppression of mitosis after only 48 hours in rabbit cornea. Therefore, microcysts indicate that the corneal epithelium is not respiring or growing normally.

Other factors have been suggested as playing a role in the aetiology of microcysts. Efron and Veys[28] provided evidence that lens-induced mechanical trauma can induce microcysts. Furthermore, Rah et al.[38] reported a significant microcyst response after 3 months of reverse geometry rigid lens wear in an orthokeratology study. Reverse geometry lenses exert forces on the cornea to change corneal shape via a combination of direct mechanical effects and indirect fluid forces. Dart[39] suggested that microcysts are a toxic response to preservatives or other foreign substances in contact lens care solutions; however, this is unlikely because microcysts have been observed in patients using disposable lenses, in which no preservatives are used.

Management and treatment

The presence of a small number of microcysts is not thought to be dangerous; however, a large number of microcysts is worrying as this is representative of epithelial metabolic distress. On the basis of the working hypothesis that the severity of the microcyst response is related to the level of hypoxia/hypercapnia-induced by lens wear, a variety of strategies can be employed in an attempt to minimise the number of microcysts; these are outlined here.

- Increase Dk/t – the number of microcysts will diminish if lenses of higher Dk/t are fitted.[4, 34]
- Decrease frequency of overnight wear – the number of microcysts will diminish if lenses are worn only one or two nights per week, instead of every night.[40]
- Increase frequency of lens replacement – this strategy is controversial. Pritchard et al.[41] fitted 119 non–contact lens wearers with 0.04-mm-thick hydroxyethyl methacrylate (water content: 38%) lenses and randomly assigned them to groups with 1- or 3-month replacement schedules or a non-replacement (control) group. The lenses were worn on a daily-wear basis only, and a single multi-purpose solution was prescribed for cleaning and disinfection. Over a 2-year period, significantly fewer subjects in the more-regular-replacement groups exhibited microcysts. In contrast to this finding, Grant et al.[40] reported that the frequency of lens disposal had no effect on the cumulative hypoxic microcyst response of the cornea.
- Change from extended wear to daily wear – the number of microcysts will diminish if lenses are not worn overnight.[4]

- Change from hydrogel lenses to rigid lenses – rigid lenses induce fewer microcysts than hydrogel lenses of the same Dk/t because (a) corneal oxygenation beneath rigid lenses is enhanced by the blink-activated tear pump that does not function with soft lenses and (b) rigid lenses leave a significant area of the cornea exposed directly to the atmosphere.[4,10]
- Change to silicone hydrogel lenses – these lenses have such a high Dk/t that hypoxia is obviated and there will be no microcyst response.[14-16,42]
- Change to hyper-permeable rigid lenses – these lenses also have a very high Dk/t and negligible microcyst response.[17]
- Avoid defective lenses – since lens defects are known to induce epithelial microcysts, the fitting of lenses that can induce mechanical trauma to the cornea should be avoided.[28]
- Avoid reverse geometry lens fits – reverse geometry rigid lenses induce a microcyst response after 3 months[38]; this adverse response, if significant, can be avoided by fitting conventional lenses instead.

It is perhaps also worth noting strategies that are unlikely to be successful at alleviating the microcyst response. Kenyon et al.[8] demonstrated that the number of microcysts was unaffected by the wearing schedule (lens removal every 4, 7, 14 or 28 days); thus, altering the extended-wear, overnight removal schedule will be of no benefit. The number of microcysts is unaffected by the solutions used in conjunction with lens wear, so changing the lens maintenance system will similarly fail to alleviate the microcyst response.

Prognosis

CEASING HYDROGEL EXTENDED LENS WEAR

The prognosis for eliminating microcysts is good, although the immediate post-lens-wear response may alarm the unwary clinician. Holden et al.[12] observed an average of 17 microcysts in the corneal epithelium of 27 patients who had worn high-water-content hydrogel lenses on an extended-wear basis for 5 years. Upon lens removal, the number of microcysts at first *increased* to a peak of 34 after 7 days; the number of microcysts then decreased gradually towards total recovery within 3 months[3] (Fig. 19.9). This phenomenon – of an initial increase followed by a decrease in the microcyst response – was noted earlier by Zantos.[26]

The initial increase and subsequent decrease in the number of microcysts after cessation of lens wear is thought to result from the following mechanism: When the lens is removed, epithelial metabolism begins to return to normal, as evidenced by the recovery of epithelial oxygen consumption and thickness (refer again to Fig. 19.6). Regular cell mitosis resumes. This resurgence in epithelial metabolism and growth results in an accelerated removal of cellular debris (formation of microcysts) and a rapid movement of existing microcysts towards the surface. Because microcysts are more visible in the superficial epithelium (as a consequence of being fully formed), more microcysts are observed a few days after lens removal.

As the epithelium continues to function normally, the remaining microcysts are brought to the surface. In the absence of further microcystic development, the number of microcysts gradually decreases until they are eliminated from the cornea.

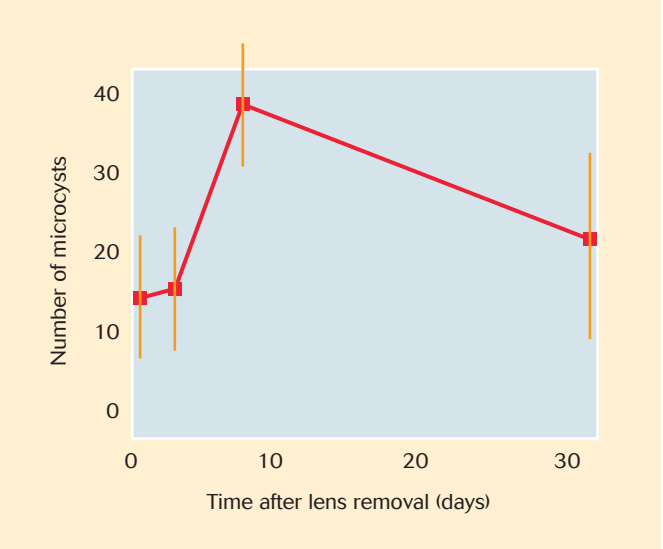


Fig. 19.9 Pattern of recovery of epithelial microcysts upon lens removal after 5 years of extended wear of hydrogel lenses. (Adapted from Holden BA, Sweeney DF, Vannas A, et al. Effects of long-term extended contact lens wear on the human cornea. Invest Ophthalmol Vis Sci 1985;26:1489–501.)

MICROCYST 'REBOUND'

A phenomenon known as 'microcyst rebound' has been observed in about 33% of patients refitted from low-Dk/t lenses to silicone hydrogel lenses or hyper-permeable rigid lenses. The patients develop large numbers of microcysts within the first few weeks of being refitted; the number of microcysts then decreases over the following month to normal levels.[6]

The mechanism for these reactions is presumed to be the same as that which underpins the normal process of recovery after ceasing wear of low-Dk/t lenses, as described previously. That is, silicone hydrogel lenses or hyper-permeable rigid lenses have such high Dk/t values that it is as if lenses are not being worn. In the absence of ongoing hypoxic stress while wearing silicone hydrogel lenses or hyper-permeable rigid lenses, the number of microcysts at first increases and then decreases, in a similar time course to that shown in Figure 19.9. Therefore, patients who transfer from low- to high-Dk/t lenses need not discontinue lens wear because the increase in microcysts is transitory.[6]

Differential diagnosis

Upon casual observation, it is easy to overlook epithelial microcysts, which can take on the appearance of tear film debris. A differential diagnosis can be made after the patient performs a blink; debris will be washed across the corneal surface, whereas microcysts will remain in a fixed position.

Once it is established that fixed entities in the epithelium are being observed, differential diagnosis is more problematic. Microcysts need to be differentiated from vacuoles, bullae, dimple veiling, mucin balls and fluid filled pits (left behind when mucin balls dislodge). Differential diagnosis can be effected by considering the size, shape, colour, distribution and optical configuration of the entities being observed, whether or not they stain with fluorescein and the type of lenses that induced the response. A scheme for applying these considerations in

differentiating the previous features is outlined in Chapter 10 and summarised in Table 10.1.

Deposits on the endothelium, such as endothelial bedewing, also take on the 'reversed illumination' appearance when viewed by using retro-illumination; however, these *endothelial* deposits can be differentiated from *epithelial* microcysts by determining, with use of an optic section, whether they are at the posterior (endothelial) or anterior (epithelial) surface of the cornea.

Microcysts can also be observed in certain dystrophies. For example, Lisch et al.[43] described five family members and three unrelated patients (four women, four men, ages 23 to 71 years) who had a dystrophy of the corneal epithelium. Direct slit lamp examination showed bilateral or unilateral, grey, band-shaped and feathery opacities, which sometimes appeared in whorled patterns. Retro-illumination showed intra-epithelial, densely crowded, clear microcysts. Light microscopy and electron microscopy disclosed diffuse vacuolisation of the cytoplasm of the epithelial cells in the affected area. Visual acuity was so reduced in three patients that abrasion of the corneal epithelium had to be performed. The corneal abnormalities recurred within months, with the same reduction in visual acuity as before. The authors found no other ophthalmic irregularities or associated systemic abnormalities and no indication of drug-induced keratopathy.

It is interesting to note that Lisch et al.[43] found that the microcyst response diminished noticeably in one patient after he began wearing rigid lenses. Bourne[44] reported a similar phenomenon whereby soft contact lens wear decreased the number of epithelial microcysts in a patient with Meesmann's corneal dystrophy. The reason for this apparent therapeutic effect of contact lenses on microcysts in patients with corneal epithelial dystrophies is unclear.

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20 Epithelial Oedema

A small number of vacuoles and/or bullae (singular: 'bulla') can sometimes be observed in the corneas of contact lens wearers. Although they appear to be clinically innocuous, vacuoles and bullae can be confused with other small epithelial inclusions that have potentially more serious clinical ramifications, and it is for this reason that their clinical presentation is given due consideration in this book.

One of the earliest recorded visual disturbances of contact lens wear was the appearance of haloes. Research conducted periodically throughout the past 60 years has concluded that the source of these haloes is a pathological disturbance to the corneal epithelium, in the form of oedema.[1-7] Epithelial vacuoles and/or bullae may represent exaggerated clinical manifestations of the tissue abnormalities that cause epithelial oedema.

Signs and symptoms

EPITHELIAL THICKNESS IN UNCOMPLICATED CONTACT LENS WEAR

Ersan et al.[8] evaluated corneal epithelial thicknesses of 30 soft lens wearers, 30 refraction-matched controls and 30 patients with emmetropia by using anterior segment optical coherence tomography. The mean corneal epithelial thicknesses in the soft contact lens–wearing, spectacle-wearing and emmetropic groups were 48.97 ± 5.45, 52.18 ± 4.84 and 53.18 ± 5.05 μm, respectively. The corneal epithelium of soft lens wearers was significantly thinner than in both the spectacles and emmetropic groups ($p = 0.044$ and 0.006, respectively).

Lei et al.[9] measured epithelial thickness in 56 subjects immediately after cessation of contact lens wear and 2 weeks later, as well as in 94 non-lens-wearing control subjects, by using the RTVue-100 Fourier-domain anterior segment optical coherence tomography system. Immediately after cessation of lens wear, the corneal epithelium was significantly thinner than that of control subjects. After 2 weeks, the corneal epithelium had increased in thickness but was still less than that of the controls. This finding suggests that normal, uncomplicated contact lens wear induces corneal epithelial thinning (Fig. 20.1).

Corneal epithelial thinning is attributed to a number of factors, including physical compression of the epithelium by the contact lens, metabolic disturbances to the epithelium beneath the lens and hyperosmolarity of the tear film, leading to epithelial deturgescence.

Observations of contact lens–induced epithelial thinning suggest that in clinical trials investigating contact lens–induced corneal epithelial oedema, the thickness of the corneal epithelial of uncomplicated soft lens wearers should serve as the experimental control.

EPITHELIAL OEDEMA IN RESPONSE TO CONTACT LENS WEAR

Gleason et al.[10] monitored the level of epithelial oedema in patients wearing various lens types over a 12-month period (Fig. 20.2). Epithelial oedema was found to occur at an incidence (expressed as the percentage of eyes per year) of 0.3% for daily wear of super-permeable rigid lenses, 1.1% for extended wear of super-permeable rigid lenses, 1% for daily-wear low-Dk (58%

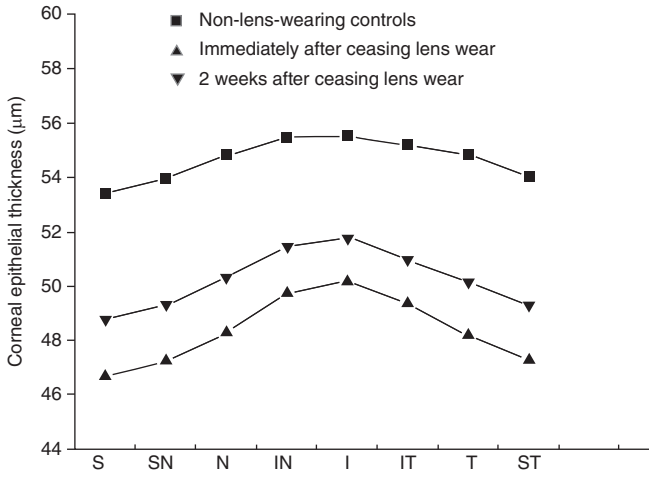


Fig. 20.1 Corneal epithelial thickness distribution in regions with a radius of 1.0 to 2.5 mm from the corneal centre. T, temporal; N, nasal; S, superior; I, inferior. (Adapted from Lei Y, Zheng X, Hou J, Xu B, Mu G. Effects of long-term soft contact lens wear on the corneal thickness and corneal epithelial thickness of myopic subjects. Mol Med Rep 2015;11:2020–6.)



Fig. 20.2 Haziness of the epithelium may indicate epithelial oedema. (Courtesy Suzanne Efron.)

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water content) hydrogel lenses and 3.6% for extended-wear low-Dk (58% water content) hydrogel lenses.

In 1992, Stapleton et al.[11] reported that of the 1,104 patients with contact lens–related disorders presenting to an eye clinic, two (0.2%) displayed 'epithelial thickening'. Of the extensive hospital-based surveys of contact lens complications conducted between 2009 and 2018 – carried out in China,[12] India,[13] Nepal,[14] Singapore,[15] the USA[16] and the UK[17] – only one study reported the observation of epithelial oedema. This was in the survey conducted in Singapore by Teo et al.,[15] where 12 cases of epithelial oedema were observed among 953 contact lens wearers (1.3%).

Corneal epithelial oedema can be observed in association with other pathological changes in contact lens wear. For example, Tabatabaei et al.[18] observed corneal epithelial oedema, amongst other pathologies, in a case of atypical sterile ring infiltrates occurring as a result of poor lens care during soft silicone hydrogel contact lens wear. Smear, culture and confocal microscopy confirmed this to be a sterile inflammatory reaction.

It is possible to quantify the level of epithelial oedema by determining the pixel intensity of confocal microscopic images of the basal cell layer of the corneal epithelium.[19] This technique has been used to assess epithelial oedema occurring after cataract surgery and in patients with bullous keratopathy, but this has yet to be validated for the assessment of contact lens-induced epithelial oedema.

VACUOLES

According to Hickson and Papas,[20] epithelial vacuoles can be observed in 10% of the normal non-lens-wearing population. Zantos[21] reported that the prevalence of vacuoles in patients wearing low-Dk/t extended-wear hydrogel lenses is about 32%. He also suggested that this value may be higher in patients with aphakia.

When viewed under high magnification with the slit lamp biomicroscope, vacuoles appear to be spherical bodies located within the corneal epithelium, about the same size as epithelial microcysts (5–30 μm in diameter). They are almost perfectly round in shape and have distinct edges.[21] When viewed under indirect illumination against the background of a dark pupil and an illuminated iris, vacuoles display 'un-reversed illumination'; that is, the distribution of light within the vacuole is the same as that of the background (Fig. 20.3).

Zantos[21] noted that fewer than 10 vacuoles were observed in a given eye of a patient wearing hydrogel lenses on an extended-wear basis. He noted that they may occur concurrently – but apparently unrelated to – microcysts in the same eye.

Vacuoles are usually observed towards the mid-periphery of the cornea. They occur as discrete units in most cases but occasionally are observed in clusters of two or four vacuoles. Apart from this, there is no particular pattern or distribution. Single epithelial vacuoles are sometimes observed in non–lens wearers, but, almost invariably, these are located at the corneal periphery.[21] A curious feature of vacuoles is that they tend to occur in areas directly overlying corneal opacities in patients with aphakia.[21]

BULLAE

Zantos[21] described a form of epithelial inclusion that is similar to vacuoles, known as epithelial 'bullae'. The prevalence of

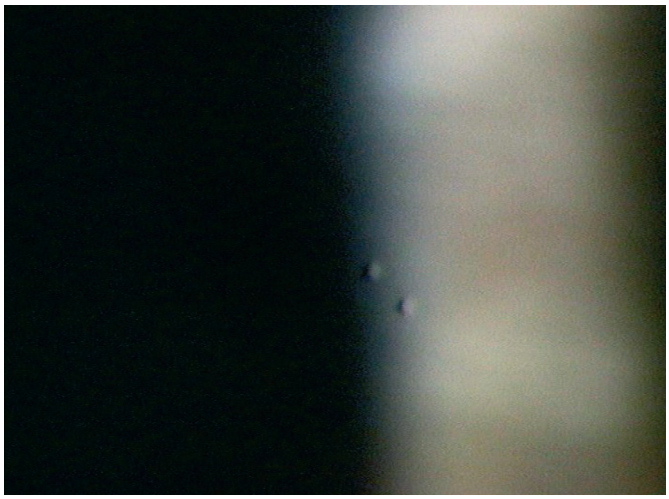


Fig. 20.3 Two vacuoles viewed under high magnification (×40) with the slit lamp biomicroscope. The dark background to the left is the pupil, and the brighter background to the right is the illuminated iris. The vacuoles display un-reversed illumination. (Courtesy Brian Tompkins.)



Fig. 20.4 A single bulla in a non–lens wearer (arrow). (Courtesy Suzanne Efron.)

bullae in contact lens wearers is very low.[21] Upon close inspection, these are differentiated from vacuoles by their irregular shape (roughly oval) and less distinct edges. They appear as flattened, pebble-like formations in the epithelium. Bullae can present as single entities (Fig. 20.4) or they can coalesce into clusters containing many distinct elements. They can be widespread or be confined to a small area, typically near the centre of the cornea.

The severity of vacuole or bullae formation can be graded by using the grading scale for microcysts in Appendix A. Although individual vacuoles and bullae appear different from microcysts, the progressive increase in the number of microcysts as depicted in the grading scale can be considered to have universal application for all forms of epithelial inclusions.

VISION

Vacuoles and bullae, as such, do not cause vision loss. However, epithelial oedema – which may represent a sub-clinical

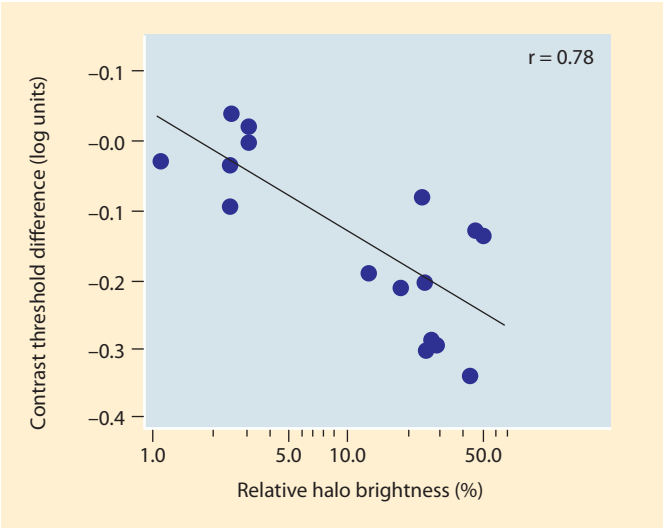


Fig. 20.5 Relationship between contrast sensitivity and relative halo brightness. (Adapted from Cox IG, Holden BA. Can vision loss be used as a quantitative assessment of corneal edema? Int Contact Lens Clin 1990;17:176–9.)

manifestation of vacuoles and bullae – have been demonstrated to reduce contrast sensitivity. Specifically, Cox and Holden[6] demonstrated that osmotically induced epithelial oedema led to halo formation, and this was associated with a loss of contrast sensitivity (Fig. 20.5). Furthermore, they demonstrated that the source of the visual disturbance was likely to be oedema of the basal cells of the corneal epithelium, which act as a diffraction grating.

Pathology

INFERENCES FROM CLINICAL OBSERVATIONS

As is the case with microcysts, the pathology of vacuoles and bullae can only be inferred from their optical configuration and clinical appearance. Because they display un-reversed illumination, their contents must be of a refractive index lower than that of the surrounding epithelium. Thus, vacuoles must be gaseous or liquid in nature. Zantos,[21] however, believed that vacuoles are more likely to be gaseous because the distinct edges of the vacuoles indicate that the difference in the refractive indices of the vacuoles and the surrounding tissue is greater than would be expected if the vacuoles had a fluid composition.

Zantos[21] applied the same logic to infer the likely composition of bullae. Because bullae also display un-reversed illumination, they also must be of a refractive index lower than that of the surrounding epithelium. However, unlike vacuoles, bullae have indistinct edges, indicating that the difference in the refractive indices is not great. Therefore, bullae are more likely to be composed of fluid than gas.

ELECTRON MICROSCOPIC STUDIES

Bergmanson[22] demonstrated the co-existence of epithelial oedema and thinning after periods of rigid lens wear (Fig. 20.6). Extracellular oedema is evident around the apex of the basal cells. This appearance can be compared with that of the normal non-lens-wearing cornea (Fig. 20.7). This evidence is consistent with the notion that vision loss and haloes induced by rigid lens wear are caused by lens-induced oedema of the basal cells of the corneal epithelium.[7]



Fig. 20.6 Transmission electron micrograph of the epithelium after 24 hours of wear of a polymethyl methacrylate (PMMA) contact lens in a rhesus monkey. This transverse section illustrates epithelial thinning and oedema. Epithelial thinning is largely caused by partial collapse of cellular shape. The tall columnar basal cells (B) have become almost cuboidal in shape. The epithelial oedema (asterisk) is inter-cellular with little or no fluid within the cells. Magnification ×5,000. (Bergmanson JPG. Light and electron microscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford: Butterworth-Heinemann; 2001. p. 136–77.)

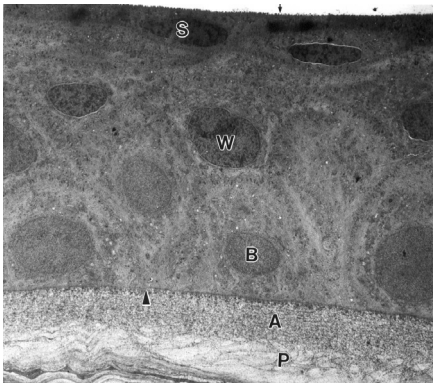


Fig. 20.7 Transverse section through normal epithelium (no lens wear). The epithelial surface is anteriorly lined by microvilli (arrow) and posteriorly by a basement membrane (triangle). The cells forming the epithelium are classified according to their shape and location as basal (B), wing (W), and squamous (S) cells; here, the letters 'B', 'W' and 'S' are overlaid on the cell nuclei. Internally, the basement membrane faces the anterior limiting lamina (A), which itself internally merges into the stroma (P). Primate. Electron micrograph, magnification ×5,100. (Bergmanson JPG. Light and electron microscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford: Butterworth-Heinemann; 2001. p. 136–77.)

Aetiology

The aetiology of vacuoles and bullae is not known. Zantos[21] suggested that vacuoles may be associated depressions in the epithelium, as occurs with dimple veiling (Fig. 20.8); he based this assumption on his observation that vacuoles have been seen

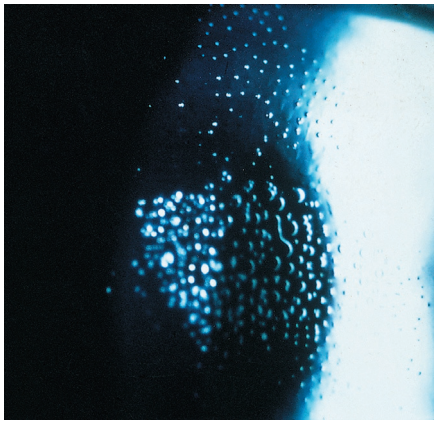


Fig. 20.8 Dimple veiling resulting from bubbles previously trapped beneath a rigid lens. (Courtesy Sylvie Sulaiman, Bausch & Lomb Slide Collection.)

to precede the occurrence of bullae. Bullae seem to occur in cases where there is excessive or persistent oedema during contact lens wear and, as such, may serve as an indicator of contact lens–induced oedematous stress.[21]

The aetiology of epithelial oedema is two-fold. Firstly, epithelial oedema follows traumatic loss of surface epithelial cells. The fluid barrier (zonula occludens) is found between the surface epithelial cells, and thus, when the barrier is removed, fluid may enter the deeper corneal layers. Since the cells are tightly fitted and attach snuggly together, the oedema may not occur instantly or be widespread. Secondly, epithelial oedema follows hypotonic ocular exposure, which has an inhibiting effect on the fluid barrier. Reflex tears, which are of low tonicity, may disrupt the fluid barrier and provoke epithelial oedema, for instance, during adaptation to rigid lenses.[22] It should be noted that epithelial oedema does not occur in response to lens-induced hypoxia.[23]

Management

Epithelial vacuoles appear to be innocuous and are not apparently associated with any adverse symptoms.[21] It is always prudent, however, to note their appearance and to carefully monitor the patient to confirm that they eventually disappear.

Although far less common, bullae are potentially more problematic because they may indicate the presence of chronic epithelial oedema. This being the case, other tests of epithelial oedema should be conducted. This could involve the measurement of corneal sensitivity, which would be expected to be reduced.[6] Furthermore, the patient can simply be directed to look at a bright point source of light (e.g. a penlight held at distance of 3 m) in a darkened room and to report what he or she sees. If the patient reports seeing haloes, the tentative diagnosis of epithelial oedema is confirmed. The brighter the haloes, the more extensive is the oedema.

Gonzalez-Meijome et al.[24] demonstrated that high-resolution spectral-domain optical coherence tomography can be used to measure changes in corneal epithelial thickness occurring in response to contact lens wear.

Hypotonic stress, rather than hypoxia, is more likely to be the cause of epithelial oedema,[6] and the most likely cause of tear hypotonicity is excess lacrimation. Although there are many causes of excess lacrimation (being in a windy environment, emotional tearing, noxious smells etc.), the most likely cause in a contact lens wearer is lens discomfort. Increased lacrimation during adaptation to rigid contact lenses is an obvious candidate. Should adaptation be especially difficult or prolonged for a patient, then reverting to soft lenses may alleviate the problem.

Prognosis

The corneal epithelium has a rapid turnover rate, and cells are constantly moving in the anterior direction, differentiating and eventually sloughing off the corneal surface. By virtue of this process, any inclusion within the epithelium will be removed within a few days. Thus, the prognosis for the recovery of vacuoles is good, that is, if they occurred as the result of an ad-hoc disturbance to the epithelium.

The prognosis for the recovery from epithelial bullae is also good, that is, if the cause can be identified and removed. Failing that, the presence of chronic oedema will result in a continual turnover of bullae, which may persist but appear to change location as they are reformed in various regions of affected epithelium.

In severe cases, vacuoles and bullae may break through the epithelial surface *en masse*. Figure 20.9 is the cornea of a 42-year-old Caucasian male, highlighting the eruption of vacuoles through the anterior layers of the epithelium. The patient had been wearing low-Dk hydrogel lenses on an extended-wear basis for 3 years. He awoke with a stinging sensation and blurred vision. The epithelial disturbance was characterised by localised oedema, staining and poor wetting.

Differential diagnosis

Vacuoles and bullae need to be differentiated from other inclusions, such as microcysts, dimple veiling, mucin balls and fluid-filled pits (left behind when mucin balls dislodge), which can be observed in the epithelium of contact lens wearers. Differential diagnosis can be achieved by considering the size, shape, colour, distribution and optical configuration of the entity being observed, whether or not it stains with fluorescein, and the types of lenses that induced the response. A scheme for applying these considerations in differentiating the previous features is outlined in Chapter 10 and summarised in Table 10.1.

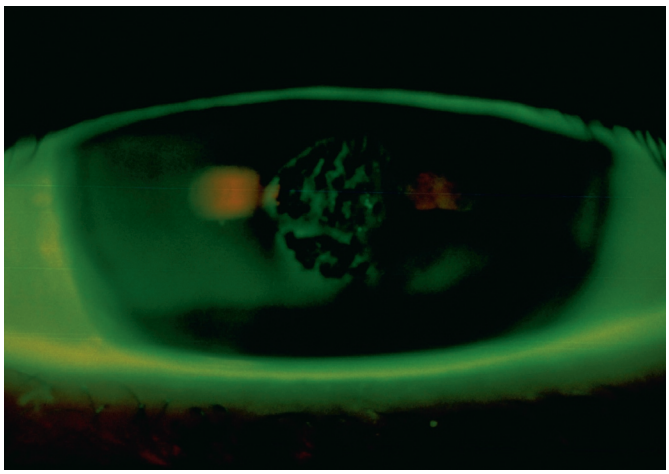


Fig. 20.9 Heavy central corneal staining as a result of vacuoles and bullae breaking through the epithelial surface. (Courtesy Ruth Cornish.)

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21 Epithelial Wrinkling

Epithelial wrinkling is a severe ocular complication of contact lens wear and is characterised by the appearance of a series of deep parallel grooves in the corneal surface, giving the impression of a 'wrinkled' effect (Fig. 21.1). This condition was originally described as 'epithelial folds' by Quinn[1] and was later described more fully by Lowe and Brennan,[2] who coined the term 'corneal wrinkling'. Epstein[3] referred to this condition as 'epithelial wrinkling'.

As will be discussed in the 'Pathology' section later, there is a difference of opinion in the literature as to the depth of the wrinkles in the cornea. Specifically, it is unclear whether the phenomenon occurs purely at the level of the epithelium or whether there is also some stromal involvement. Since two of the previously mentioned authors[1,3] adopted a name for this condition that implies primarily epithelial involvement and two adopted the word 'wrinkling',[2,3] the term 'epithelial wrinkling' is used in this book. It follows, therefore, that this condition is discussed in this section on 'Corneal epithelium'.

Prevalence

Epstein[3] deemed epithelial wrinkling to be 'a very rare complication of soft lens wear'. However, in a prospective clinical trial of 330 subjects wearing disposable hydrogel lenses on a six-night extended-wear and replacement schedule, Sankaridurg et al.[4] found a prevalence of 1.7 events of 'corneal wrinkling' per year of lens wear and that the condition eventually resolved without sequelae. It is unclear whether Sankaridurg et al.[4] were observing true epithelial wrinkling, as characterised in this chapter, or an unrelated form of pathology, such as oedematous folds in the deeper corneal layers.

There have apparently been no reports of contact lens–associated epithelial wrinkling since the early 2000s; however, it is possible to induce wrinkling if inappropriate parameters are chosen for the design of custom-made hydrogel lens, as explained later. It is, therefore, still pertinent to present an account of this condition to avoid such occurrences in the future and to assist practitioners in identifying this condition in the unlikely event that they come across corneal wrinkling in the future.

Signs

The case described by Lowe and Brennan[2] took the form of two linear wave patterns of fluorescein pooling across the central cornea and intersecting at an angle of 70° (Fig. 21.2). Several discrete spots were observed at the points of intersection of the two wave patterns. The intensity of fluorescein within the troughs of the wrinkles was observed to increase with time after a blink. The patient was wearing a very thin (0.036 mm centre thickness) mid-water-content (52.5% water) custom-designed hydrogel lens in one eye. The lens was said to be made of a highly elastic material ('Snoflex 50; Smith & Nephew, Australia), with a power of −0.50 diopter (D) and a back optic zone radius of 8.20 mm. The patient had a keratometer reading of 8.00/7.92 mm; thus, the lens was fitted very steep in relation to the cornea.

Lowe and Brennan[2] assessed the extent of corneal distortion by observing the reflected mires of an optical keratoscope. The formation of ridges and troughs can clearly be seen to mimic the observed fluorescein pattern (Fig. 21.3).

Burnett-Hodd[5] reported the case of a patient wearing a very thin, custom-designed hydrogel toric lens. The lenses had a back

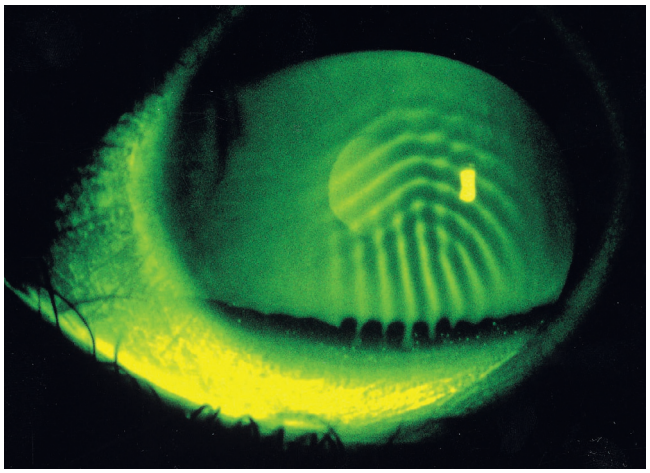


Fig. 21.1 Epithelial wrinkling with two sets of furrows arranged orthogonally. (Courtesy Gary Orsborn, Bausch & Lomb Slide Collection.)

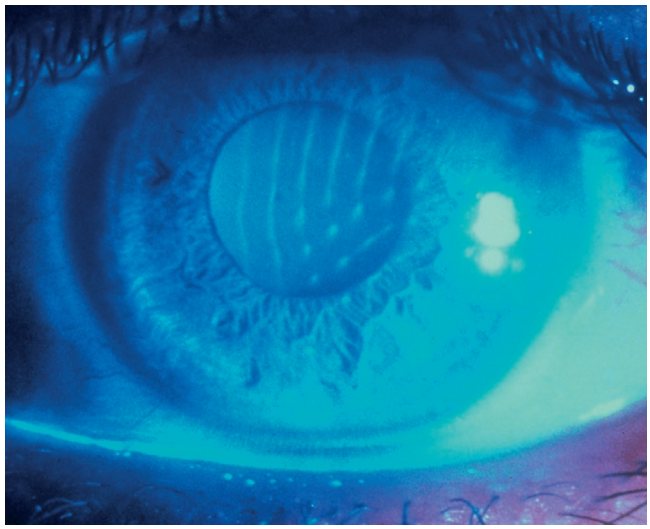


Fig. 21.2 Epithelial wrinkling displaying a remarkably similar pattern to that shown in Figure 21.1. (Courtesy Russell Lowe, Bausch & Lomb Slide Collection.)

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Fig. 21.3 Photokeratogram of a cornea displaying epithelial wrinkling. (Courtesy Russell Lowe, Bausch & Lomb Slide Collection.)

optic zone radius of 7.40 mm, and the patient had a mean keratometer reading of 7.80 mm. The reason for fitting this lens very steep in relation to the cornea was to stop the rotation of the lens which had occurred with flatter designs. These lenses displayed profound wrinkling during wear; this effect can be seen for one eye in Figure 21.4. When this lens was removed and fluorescein instilled, a series of linear wrinkles could be observed both in white light (Fig. 21.5) and in cobalt blue light (Fig. 21.6), corresponding to the previously observed wrinkling of the lens.

Wrinkles can occur in any orientation or, indeed, in multiple orientations in the one eye. In the case reported by Burnett-Hodd[5] (Fig. 21.6), the wrinkles were at an angle of about 160° (ophthalmic lens axis notation). In another case, shown in Figure 21.7, the wrinkles were at an angle of about 80°. The wrinkles ran in different directions in the same eye in the case depicted in Figures 21.1 and 21.2.

Giese[6] described a 17-year-old patient who had Marfan's syndrome and developed central epithelial wrinkling in his right eye while he was wearing low-water-content hydrogel lenses. No visual discomfort or distortions were noted. The patient was

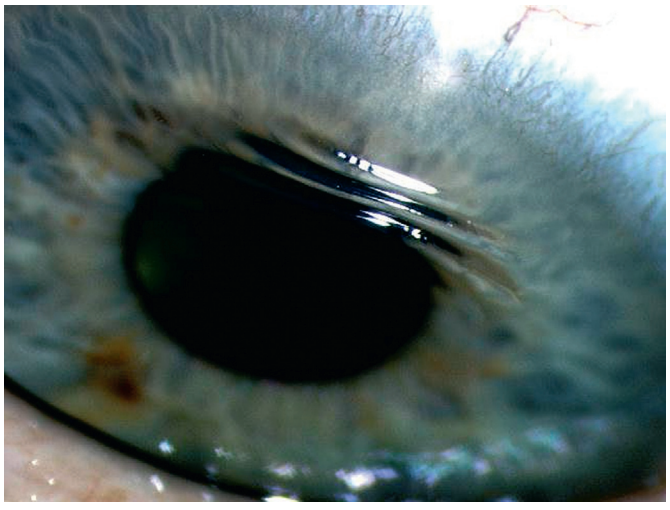


Fig. 21.4 Wrinkling of a contact lens. (Courtesy Nigel Burnett-Hodd.)



Fig. 21.5 Epithelial wrinkling highlighted with fluorescein and observed in white light (same case as in Fig. 21.4). (Courtesy Nigel Burnett-Hodd.)

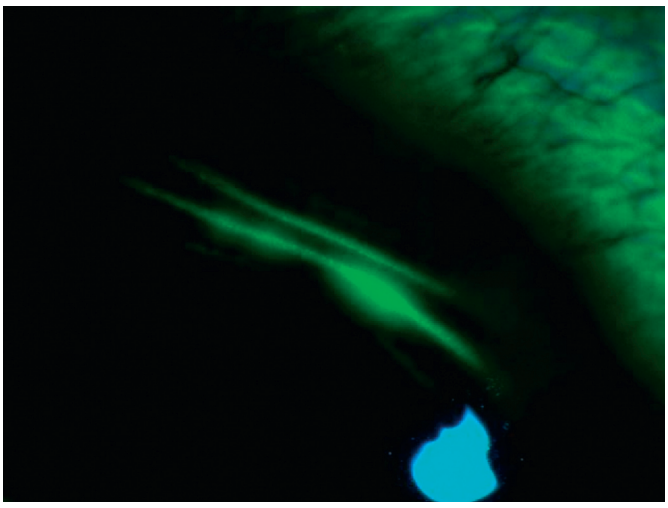


Fig. 21.6 Epithelial wrinkling highlighted with fluorescein and observed in cobalt blue light (same case as in Fig. 21.4). (Courtesy Nigel Burnett-Hodd.)

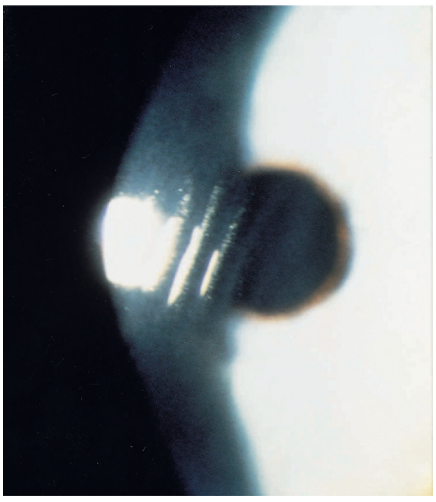


Fig. 21.7 Epithelial wrinkling of the central cornea after removal of a lens of 42.5% water content and of 0.035 mm centre thickness. (Courtesy C Euwijk, Bausch & Lomb Slide Collection.)

refitted with a non–hydroxyethyl methacrylate hydrogel contact lens, with no further episodes of wrinkling observed during subsequent care of the patient. Although Giese[6] expressed the view that the wrinkling was unrelated to Marfan's syndrome, there may be a link because Marfan's syndrome is primarily a heritable connective tissue disorder. Bowman's layer, which is composed almost entirely of collagen (a connective tissue), is implicated in the appearance of wave-like patterns that mimic contact lens–induced epithelial wrinkling[7] (see 'Differential diagnosis'). Therefore the corneas of patients with Marfan's syndrome may well be prone to developing wrinkle-like patterns when the cornea is subjected to physical stresses of contact lens wear.

Symptoms

As one would expect with such a dramatic distortion of the cornea, vision loss in patients exhibiting epithelial wrinkling can be dramatic. It appears that the extent of vision loss is proportional to the degree of epithelial distortion. Lowe and Brennan[2] reported that vision dropped to less than 6/60 within 5 minutes of lens insertion. Burnett-Hodd[5] noted that vision was poor 10 minutes after lens insertion. In the case reported by Quinn,[1] the 15-year-old male patient reported a gradual reduction in vision over a number of months.

Epithelial wrinkling is also extremely painful, with the degree of discomfort commensurate with the time course of vision loss.

Pathology

Lowe and Brennan[2] argued that wrinkling involves the epithelium and the anterior stroma. This view is based on their observations of the extreme variance in intensity of fluorescence across the ridges of a wrinkled cornea (Fig. 21.2), implying deep troughs, and the extreme distortion of photokeratometric mires reflected off a wrinkled cornea (Fig. 21.3). The intensity of the wrinkling pattern increases with time after a blink, indicating fluorescein pooling within the deep troughs.

With the lens removed from the eye, vision improves momentarily after each blink and declines rapidly to a steady-state level thereafter.[2] This phenomenon is consistent with the apparent smoothing of the anterior refracting surface immediately after a blink, whereby fresh tears are swiped across the cornea and fill the troughs of the wrinkled epithelium. As the eye is held open, the tears drain from the troughs, leaving an uneven corneal surface that degrades vision.

Epstein[3] drew a distinction between epithelial wrinkling and full-thickness corneal folds. However, Epstein[3] may have been describing different severities of the same condition. A case of severe epithelial wrinkling (and what Epstein[3] referred to as 'full-thickness epithelial folds') is shown in Figure 21.8. When viewed in white light, the vertical furrows are so deep as to give the impression that the whole cornea is involved. The depth of the furrows is confirmed with the aid of fluorescein (Fig. 21.9). The extreme distortion of the surface of the contact lens is evident from the photokeratogram shown in Figure 21.10. Considerable distortion of the corneal surface can be observed in the keratoscope mires after removal of the lens (Fig. 21.11).

Aetiology

It is interesting to observe that in all reported cases of epithelial wrinkling, in which the details of the lenses worn were

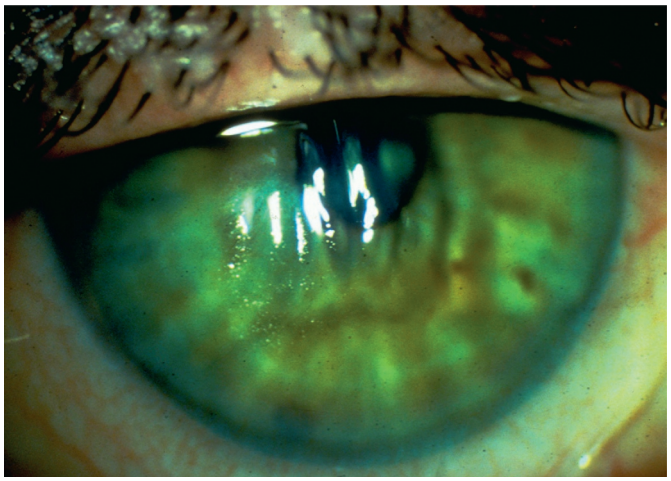


Fig. 21.8 Severe epithelial wrinkling observed in white light. (Courtesy Brien Holden, Brien Holden Vision Institute.)

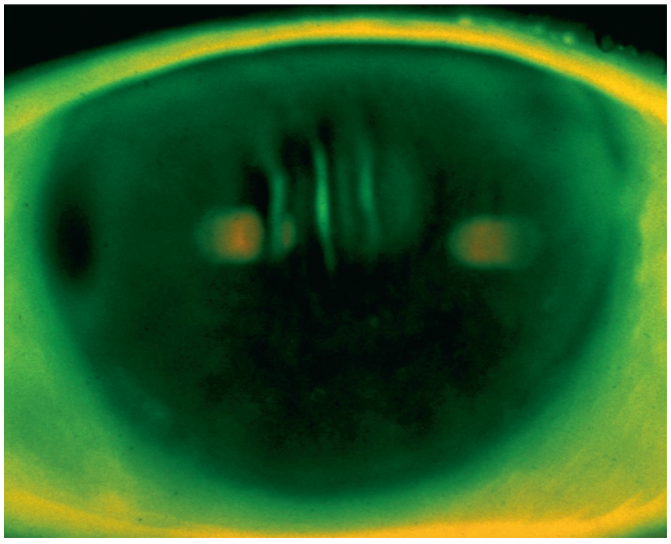


Fig. 21.9 Severe epithelial wrinkling highlighted with fluorescein and observed in cobalt blue light (same case as in Fig. 21.8). (Courtesy Brien Holden, Brien Holden Vision Institute.)

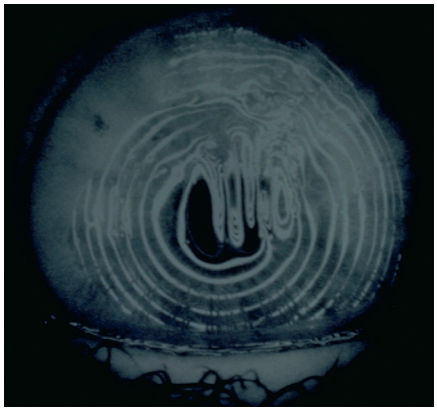


Fig. 21.10 Photokeratogram of lens surface displaying a heavily wrinkled pattern. (Same case as in Fig. 21.8.) (Courtesy Brien Holden, Brien Holden Vision Institute.)

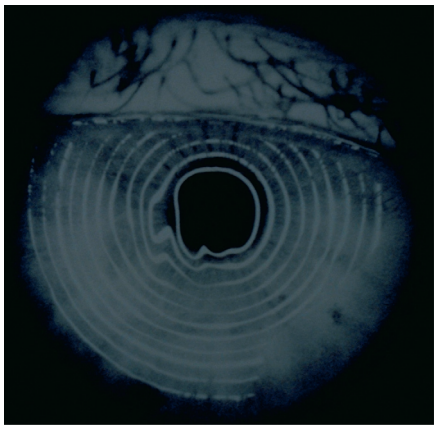


Fig. 21.11 Photokeratogram of cornea displaying severe epithelial wrinkling after lens removal (same case as in Fig. 21.8). (Courtesy Brien Holden, Brien Holden Vision Institute.)

known,[1,2,5] the features of the type of lens that caused the problem were remarkably similar. Specifically, the offending lenses typically exhibited the following properties:

- highly elastic hydrogel material;
- custom-design;
- extremely thin;
- mid-water content (50–55% water); and/or
- steep fitting.

Lowe and Brennan[2] proposed that excessive elastic forces draw corneal tissue inwards from the limbus, causing the superficial corneal tissue to collapse in a concertina-like action, creating a wrinkled appearance (Fig. 21.12). They suggested that this intrinsic elastic force is created when a relatively steep lens is compressed against the eye; when the eye attempts to return to its original shape, an inward force is created.

If the lens also displays a high propensity for dehydration, lens dehydration (and associated base curve steepening) and lens diameter reduction will provide an additional inward force. However, in the case reported by Lowe and Brennan,[2] the lens was made of a vinyl pyrrolidone–methyl methacrylate co-polymer and thus would be categorised by using the US Food and Drug Administration system as Group II (high water content; non-ionic). Such lenses are characteristically dehydration resistant.[8]

Epithelial wrinkling is observed in patients wearing highly elastic, ultra-thin mid-water-content lenses. In the three reported cases discussed in this chapter,[1,2,5] the lenses which induced epithelial wrinkling were either specifically designed by the practitioner or were experimental; that is, they were apparently not standard commercially available products.

Bruce and Brennan[9] suggested that epithelial wrinkling may also have an osmotic aetiology in view of the observation of Dixon[10] that complete evaporation of the tear film in normal individuals can cause an almost identical epithelial wrinkling and vision loss to that observed in cases of lens-induced epithelial wrinkling.

Lowe and Brennan[2] noted that no wrinkling was observed in subjects who wore the offending lenses overnight; the effect was only observed in subjects wearing lenses during the day. This observation led Lowe and Brennan[2] to propose that lid movement, and the specific lens–cornea bearing relationship are integral to the causation of this effect.

Epstein[3] proposed an alternative theory to explain the appearance of epithelial wrinkling. He suggested that epithelial oedema is the cause whereby epithelial swelling pushes the cornea up against the lens, causing it to fold back on itself. According to Epstein,[3] full-thickness corneal folds are likely to be a combination of mechanical and osmotic pressures which combine to produce both suction and moulding forces.

Treatment

The treatment protocol for a patient experiencing epithelial wrinkling is to immediately cease lens wear. Patients suffering from this condition may be alarmed at the extreme discomfort and loss of vision; it is, therefore, important to reassure patients that this is only a transient problem and that vision and comfort will be restored within 24 hours.

Although the appearance of wrinkling will indeed have disappeared within 24 hours, the patient should not wear lenses for 1 week as a precaution to allow any possible sub-clinical compromise to resolve. The patient should then be refitted with a soft lens which is devoid of inherently high elastic forces. Specifically, lenses should never be designed and fitted with the combination of parameters listed in 'Aetiology' earlier. True epithelial wrinkling does not occur with rigid

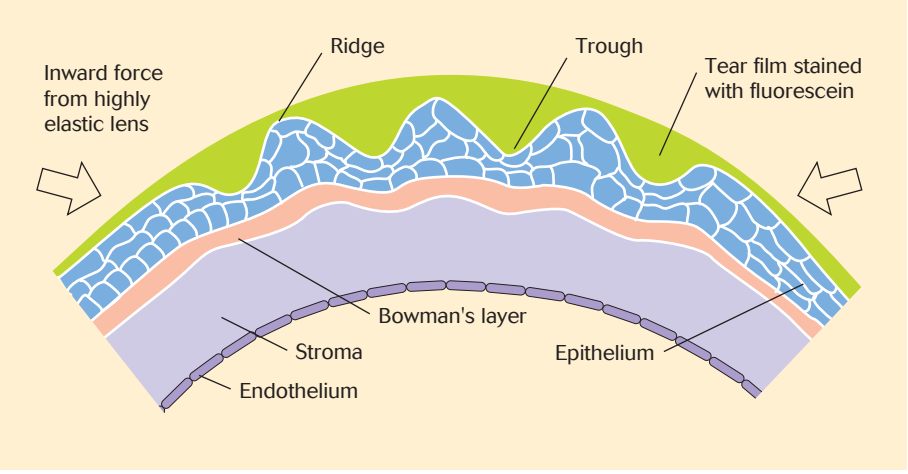


Fig. 21.12 Schematic representation of the forces acting to cause the corneal tissue to collapse in a concertina-like action. The epithelium and Bowman's layer, and to a lesser extent the anterior stroma, become wrinkled. The posterior stroma is largely unaffected. (Not to scale.)

lenses, although the pressure induced by rigid lenses can cause a transient pattern of linear formations (see 'Differential diagnosis' later).

Prognosis

The prognosis for recovery of the cornea after an episode of epithelial wrinkling is good. The time course of recovery from epithelial wrinkling has been demonstrated to be directly related to the period of wear of the lens that induced the changes. Lowe and Brennan[2] noted that epithelial wrinkling took 3, 90 and 240 minutes to recover after 5, 90 and 300 minutes of lens wear, respectively. In the two cases of full-thickness epithelial folds reported by Epstein,[3] the cornea recovered to normal within about 60 minutes. Epithelial folds took about a week to resolve in the case reported by Quinn.[1]

Differential diagnosis

A clinical phenomenon that appears remarkably similar to epithelial wrinkling is the Fischer-Schweitzer polygonal mosaic, which can sometimes be observed after rigid lens extended wear, thick hydrogel lens wear or aggressive rubbing of the eyes through closed eyelids (Fig. 21.13).[11] This pattern, which may be localised or may cover the whole corneal surface, appears as minute branching lines or furrows in the epithelial surface that are revealed with fluorescein. The Fischer-Schweitzer mosaic disappears within 10 minutes of removing the initiating corneal stress.

This phenomenon is thought to result from epithelial groove formation caused by wrinkling of Bowman's membrane during physical deformation of the cornea. The appearance of this mosaic in rigid lens wearers may indicate that the lens is exerting undue pressure on the cornea, and an alternative fit might need to be sought. The Fischer-Schweitzer polygonal mosaic is asymptomatic and thus can be differentiated from epithelial wrinkling, which is extremely painful.

Tripathi and Bron[7] described the clinicopathological features and pathogenesis of a chronic secondary mosaic degeneration of the cornea known as *anterior crocodile shagreen of Vogt*. According to these authors,[7] there is a structural basis for a normal anterior corneal mosaic pattern, which is attributed to the particular arrangement of many prominent collagen lamellae of the anterior stroma. These lamellae take an oblique course to gain insertion into Bowman's layer. Since Bowman's layer is under tension at normal intra-ocular pressure, the cornea appears smooth when viewed from the anterior surface. By releasing the tension, however, a reproducible polygonal ridge pattern becomes manifest. It is suggested that a prolonged phthisic state of the eye is one condition where the mosaic pattern may become permanent. This is followed by irregular calcification of Bowman's layer as a secondary event, which particularly involves the ridges projecting into the epithelium.

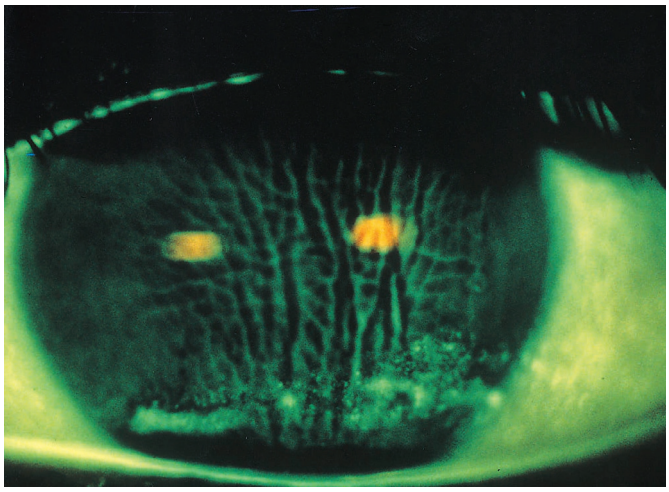


Fig. 21.13 Fischer-Schweitzer polygonal mosaic following removal of a thick hydrogel lens. (Courtesy Meredith Reyes, Bausch & Lomb Slide Collection.)

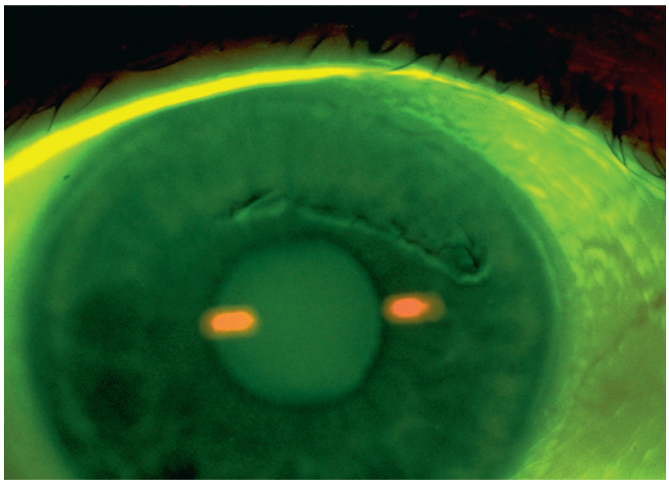


Fig. 21.14 A single large horizontal wrinkle in a patient wearing a rigid lens. (Courtesy Sylvie Sulaiman, Bausch & Lomb Slide Collection.)

Biomicroscopically, these ridges corresponded to the branching reticular arrangement of the mosaic opacities.[7] This phenomenon is therefore only seen in severely and chronically diseased eyes and is unlikely to be seen in contact lens wearers.

A single large wrinkle, presumed to be in Bowman's membrane, is shown in Figure 21.14. This event occurred in a 47-year-old Caucasian female patient and was seen after 1 month of daily rigid lens wear. The patient suffered no discomfort but experienced a slight reduction in low-contrast visual acuity. It took 2 weeks for the condition to resolve.

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22 Stromal Oedema

Contact lens–induced corneal oedema was recognised in the first two written accounts of the clinical application of contact lenses published over a century ago. In his original treatise on contact lenses, published in 1888, Adolf Fick noted that the cornea became cloudy within hours of insertion of a glass haptic shell.[1] Although Fick would not have been aware of the exact cause of this disturbing pathological change, it is clear that he was observing contact lens–induced corneal oedema. Even more remarkably, Fick observed that the onset of corneal clouding could be delayed by trapping an air bubble between the lens and cornea.[1]

In his inaugural dissertation to the University of Kiel in Germany, August Müller provided a graphic subjective description of what was undoubtedly a marked contact lens–induced corneal oedema.[2] Müller correctly identified inadequate tear exchange beneath the lens as the cause of this problem but was unable to find a solution at the time.

These pioneering works signalled the beginning of the battle against corneal oedema – yet, despite numerous significant advances in lens materials, designs, fitting techniques and possible modalities of wear, we are still unable to claim an absolute victory over lens-induced oedema.

Definition

Oedema refers to an increase in the fluid content of tissue. Since the cornea is only able to swell in the anteroposterior direction as a result of the collagen fibre network in the stroma, the physical dimensions of the cornea can only increase in that dimension – that is, in thickness. Corneal oedema is usually expressed as the percentage increase in corneal thickness. Thus, for example, a cornea that swells from a thickness of 550 µm before lens wear to become 605 µm thick after lens wear has swollen 55 µm, or has experienced 10% oedema. As will be discussed in this chapter, it is typically the corneal stroma that swells. The corneal epithelium can also become oedematous, but it usually swells in response to osmotic stress (see Chapter 20), whereas the stroma swells in response to hypoxic stress. As a result of this analysis, it can be seen that in a cornea suffering from only stromal oedema, the percentage increase in total corneal thickness will slightly underestimate the percentage increase in stromal thickness.

Laboratory scientists have developed techniques for the precise measurement of corneal thickness and have noted that oedema is a reliable and repeatable index of the physiological integrity of the cornea.

Central corneal clouding

Early textbook accounts describing the detection of corneal oedema associated with the wearing of contact lenses made from polymethyl methacrylate (PMMA) cited 'central corneal clouding' as the key diagnostic criterion indicating corneal compromise.[3] This condition occurred in patients wearing tightly fitted PMMA lenses, which restricted tear exchange beneath the lens and hence created hypoxic oedema. A discrete, round area of clouding could be clearly observed in the central cornea (Fig. 22.1).

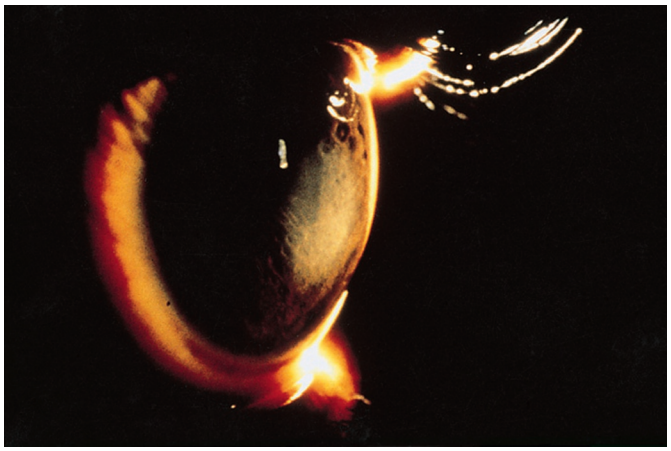


Fig. 22.1 Profile view of cornea, illuminated using sclerotic scatter technique, displaying marked central corneal clouding. (Courtesy Patrick Caroline, Bausch & Lomb Slide Collection.)

Central corneal clouding indicates a gross level of oedema that is rarely observed in modern contact lens practice. Fernandez-Velazquez[4] reported three cases of severe bilateral central corneal clouding in association with ClearKone SynergEyes hybrid contact lenses for vision rehabilitation in patients with keratoconus. Despite attempts to modify the parameters of the lenses to reduce the oedema, two patients had to discontinue lens wear, and one patient was able to wear lenses only on a limited basis.

Central corneal clouding is an obvious sign of gross oedema; however, careful observation of the cornea using a slit lamp biomicroscope reveals the existence of more subtle signs that can be used to predict the level of oedema in response to lens wear. In this chapter, the oedema response to contact lens wear will be reviewed, techniques available to the clinician for evaluating the extent of oedema will be described and treatment alternatives for minimising the oedema response will be provided.

Prevalence

Every human experiences corneal oedema during sleep. Upon awakening in the morning, the cornea immediately begins to reduce in thickness ('de-swell'). A new steady-state thickness – representing a thinning of about 3% – is reached after about 4 hours, indicating that the cornea had swollen about 3% overnight.[5]

The prevalence of contact lens–induced oedema is essentially 100%, since *all* contact lenses induce some level of oedema, including extremely high oxygen permeable silicone elastomer

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TABLE 22.1 Prevalence of stromal oedema among hospital-presenting contact lens wearers

Author	Country	Year	Population size studied	Retrospective or prospective	Prevalence
Li et al.[8]	China	2018	141	Retrospective	0.7%
Sapkota et al.[10]	Nepal	2013	4064	Retrospective	0.0%
Lee et al.[12]	USA	2012	1369	Prospective	8.3%
Teo et al.[11]	Singapore	2011	953	Prospective	1.1%
Nagachandrika et al.[9]	India	2011	1255	Retrospective	0.1%
Radford et al.[13]	UK	2009	877	Prospective	2.1%

lenses.[6] The amount of oedema is related primarily to the extent of corneal hypoxia that is induced by the lens (see later).

In 1992, Stapleton et al.[7] reported that of 1104 patients with contact lens–related disorders presenting to an eye clinic, 32 (2.9%) displayed stromal oedema. Table 22.1 displays the results of hospital surveys of contact lens complications, conducted between 2009 and 2018 – carried out in China,[8] India,[9] Nepal,[10] Singapore,[11] the USA[12] and the UK.[13] Besides the relatively high figure of 8.3% reported by Lee et al.[12] (8.3%), all other surveys noted a prevalence of stromal oedema of 2.1% or less.

Signs and symptoms

OBSERVATION AND MEASUREMENT OF STROMAL OEDEMA

Although central corneal swelling data are usually quoted in the literature, it should be noted that the oedema response across the cornea is not uniform.[14] This results from (a) the variation in thickness across powered contact lenses whereby blink-induced tear mixing does *not* act to equalise the distribution of oxygenated tears beneath the lens[15] and (b) the resistance of the peripheral cornea to swell as a result of 'limbal clamping'.[16] Topographical corneal swelling plots for a silicone hydrogel lens and a conventional mid-water-content hydrogel lens are shown in Figures 22.2 and 22.3, respectively. The apparently greater swelling of the temporal and nasal mid-peripheral cornea compared with the central cornea may be an artefact of the experimental methodology; nevertheless, the difference in overall swelling induced by these lenses is substantial.

A variety of sophisticated clinical and laboratory techniques can be employed to measure precisely the extent of lens-induced corneal oedema, the most popular being optical pachometry and ultrasonic recording.[17] Orbscan topographical thickness mapping,[18] specular microscopy, confocal microscopy, optical coherence tomography,[14] femtosecond laser ranging and interferometry can also be used to measure corneal thickness. It is often necessary to use these more sophisticated techniques in clinical trials and laboratory research on contact lenses or for the provision of baseline information before corneal surgery. The clinical utilisation of these techniques has increased substantially in recent years as these instruments have become more affordable.

Clinicians can estimate the magnitude of corneal oedema via careful observation with the slit lamp biomicroscope, as a number of structural changes can be identified that correlate with various levels of oedema. These structural changes – striae, folds and haze – act as useful reference points or 'yardsticks' to form the basis of clinical decision-making.

Striae

When viewed under direct focal illumination, striae appear as fine, wispy, white, vertically oriented lines (Fig. 22.4) and are always located in the posterior stroma.[19] They can also appear as dark lines against the orange fundus pupillary reflex when observed by using retro-illumination. Striae are only observed when the level of oedema reaches about 5%. As the level of oedema increases, striae become greyer and thicker, and they increase in number.[20] Striae do not cause vision loss.

Folds

Folds can be observed in the endothelial mosaic as a combination of depressed grooves or raised ridges or as a general area of apparent buckling, when the level of oedema reaches about 8% (Fig. 22.4). They also increase in number as the level of oedema increases.[20] Folds are best observed by using specular reflection. Vision is thought to be unaffected by folds.

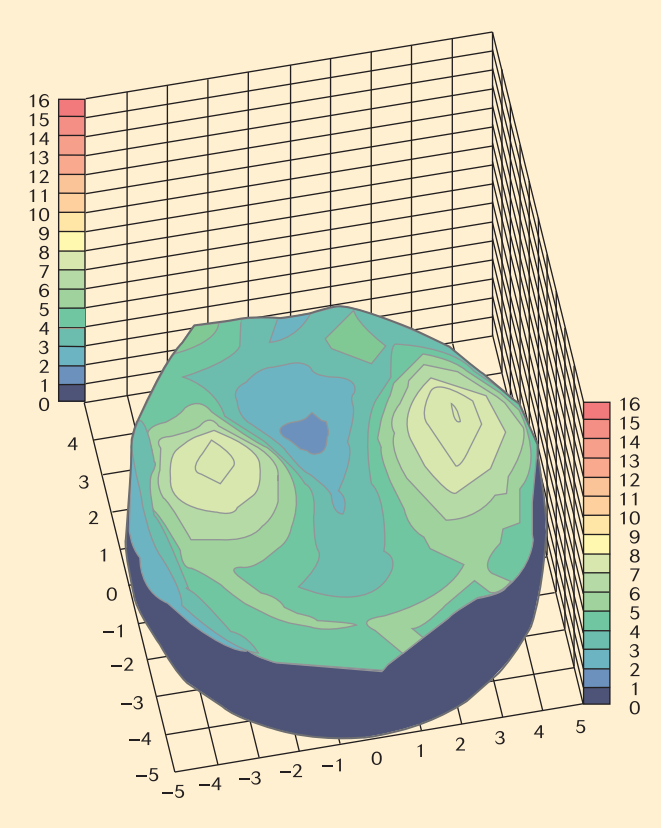


Fig. 22.2 Three-dimensional representation of topographical corneal oedema response to wearing of silicone hydrogel lenses under closed-eye conditions. To the right is the nasal direction, and the closer region is the inferior cornea. The vertical scale is the percentage increase in corneal thickness over baseline.

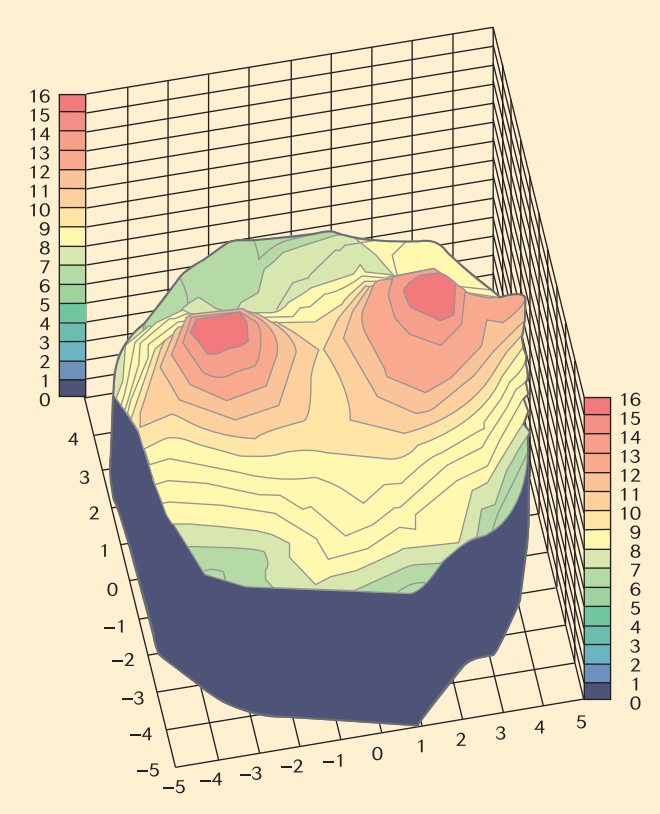


Fig. 22.3 Three-dimensional representation of topographical corneal oedema response to wear of conventional mid-water-content hydrogel lenses under closed-eye conditions. To the right is the nasal direction, and the closer region is the inferior cornea. The vertical scale is the percentage increase in corneal thickness over baseline.

Haze

The stroma takes on a hazy, milky or granular appearance when the level of oedema reaches about 15% (Fig. 22.4). In essence, the stroma has suffered a loss of transparency. This can be viewed using a variety of observation techniques. The milky appearance is evident when the cornea is viewed against the pupil under indirect illumination. Instead of the normal dark appearance, a fine grey haze is detected and fine iris detail is partially obscured. Sclerotic scatter technique will enhance this clinical picture. Contact lens–induced stromal haze can cause a slight degradation of vision when the level of oedema exceeds 20%.

In a clinical setting, stromal haze indicates gross oedema and will often be associated with other signs and symptoms of ocular distress. It would perhaps be more appropriate to consider oedema of this level as a frank bullous keratopathy. Contact lens wear is more likely to be an exacerbating factor rather than the primary cause of the development of stromal haze, so other possible causes of this complication ought to be investigated.

MAGNITUDE AND TIME COURSE OF LENS-INDUCED STROMAL OEDEMA

A large number of papers were published towards the end of the 20th century documenting the magnitude and time course of stromal oedema during lens wear. It is impractical to review all of these reports; however, one classic paper 'pushed the boundaries' and perhaps defined the maximum extent of stromal oedema during lens wear. This was the report of Holden et al.,[21] who demonstrated the large changes in stromal oedema that can occur during extended contact lens wear.

Figure 22.5 shows changes in stromal thickness recorded by Holden et al.,[21] who used optical pachometry in subjects wearing low-water-content (38% hydroxyethyl methacrylate) hydrogel contact lenses continuously over 8 days. Lenses of three different powers were worn: −1.25 diopters (D), −6.00 D and −9.00 D. Over the 8-day period, stromal thickness was measured immediately upon awaking, during the day and immediately before going to sleep. As can be seen from Figure 22.5, levels of oedema exceeding 15% were observed on some mornings, with the level of oedema dropping to about 1% to 3% during the day.

The findings from the study of Holden et al. can be contrasted with the corneal swelling response to 21st century lenses. Del Aguila-Carrasco et al.[22] assessed the effect of seven representative daily disposable contact lenses on corneal thickness by using optical coherence tomography. Responses to seven different hydrogel and silicone hydrogel daily disposable soft contact lenses – Delefilcon A, Nelfilcon A, Omafilcon A, Filcon II3, Narafilcon A, Etafilcon A and Hilafilcon B – were assessed, each for a period of 12 hours of open-eye wear. Central corneal thickness was measured while patients were wearing these lenses at baseline and after 4, 8 and 12 hours. Measurements were also recorded without any contact lenses being worn during the day.

The results of this experiment are shown in Figure 22.6. In the no-lens scenario, a small but significant ($p < 0.05$) thinning in the cornea was observed after the 12-hour period. Highly oxygen transmissible silicone hydrogel lenses caused a similar stromal de-swelling response to the no-lens condition. Unsurprisingly, a small amount of stromal oedema (about 1% oedema averaged across all lens types) was evident in response to daily hydrogel lens wear.[22]

The lesson learned from these two studies is clear. In the latter part of the 20th century, low-oxygen-transmissibility lenses worn for extended periods caused high levels of stromal oedema. In stark contrast, in the 21st century, highly oxygen transmissible silicone hydrogel lenses worn on a daily-wear basis have a clinically insignificant effect on stromal thickness. When used on an extended-wear basis, silicone hydrogel lenses of a range of lens powers (−3.00 D, −10.00 D and +6.00 D) induce 6% to 9% overnight oedema.[23]

Pathology

The cornea is a sophisticated five-layered tissue and is 78% water. The stroma, which constitutes 90% of the thickness of the cornea, has a constant tendency to imbibe water and swell. This tendency is counteracted by a fluid control mechanism (described as the 'pump leak' model[24]), which is located in the endothelium and acts to move water out of the stroma and back into the aqueous via a bicarbonate ion pump. If this mechanism is disrupted, or other physiological challenge is posed to the cornea, the demand on the endothelial pump to maintain deturgescence may become too great. Water will then enter the stroma, and the cornea will increase in thickness.[25]

STRIAE

Striae are thought to represent fluid separation of the predominantly vertically arranged collagen fibrils in the posterior stroma (Fig. 22.7). This creates a local refractile optical effect whereby

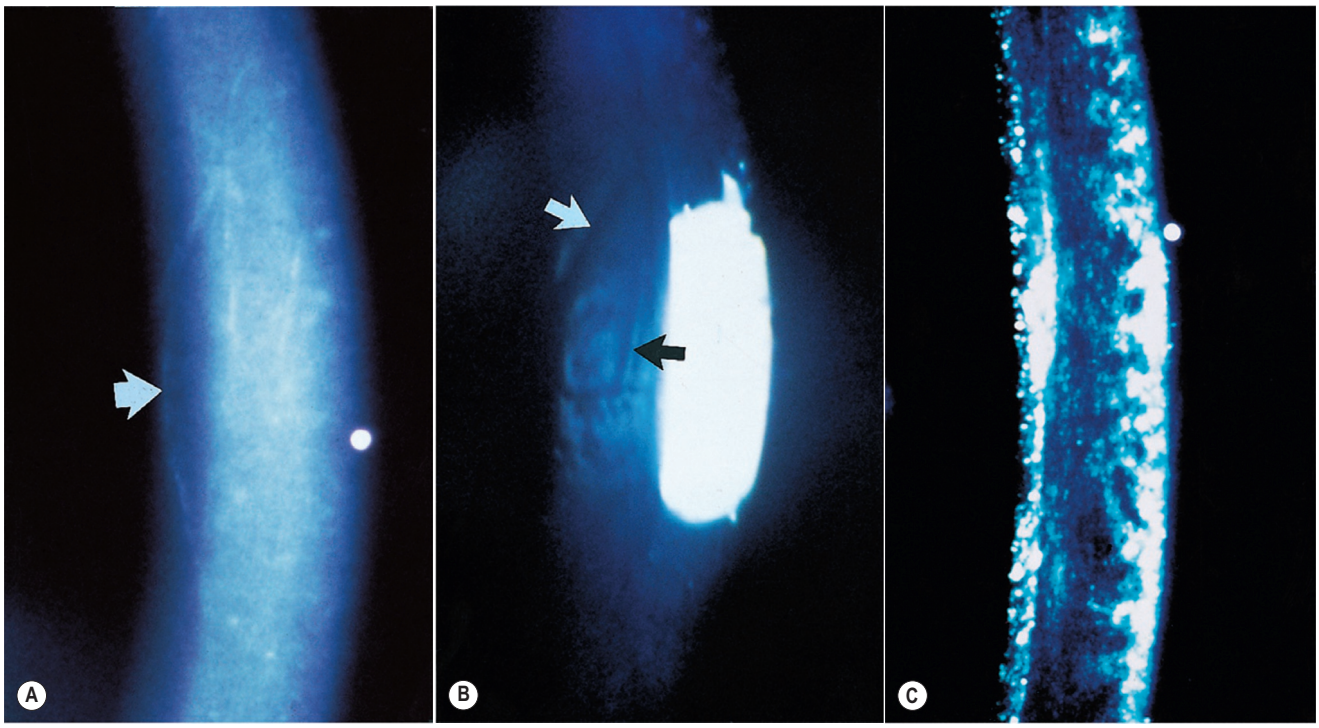


Fig. 22.4 Slit lamp photographs depicting corneal signs of increasing oedema from left to right. **(A)** Striae – a vertical striate line (arrow) can be observed in the posterior stroma in direct focal illumination. **(B)** Folds – a depressed groove (white arrow) and raised ridge (black arrow) observed in specular reflection. **(C)** Haze – the stroma takes on a granular appearance at high levels of oedema as viewed in direct focal illumination. (A, Courtesy Desmond Fonn. **B, C,** Courtesy Brien Holden, Brien Holden Vision Institute.)

stromal transparency is reduced in the immediate vicinity of the separated fibrils. It was originally postulated that the vertical orientation of striae is an artefact of the vertical orientation of the slit beam of the biomicroscope and/or the horizontal binocular displacement of the eyepieces of the objective; however, rotating the beam to a horizontal orientation does not alter this appearance (i.e. horizontally oriented striae do not appear suddenly).

FOLDS

It is thought that folds indicate a physical buckling of the posterior stromal layers in response to high levels of oedema (Fig. 22.7). Because of the inherent transparency of the stroma, it is not possible to directly observe folding of stromal tissue. Instead, folding can be seen as an alteration to the topography of the endothelial layer observed in specular reflection (Fig. 22.8). Efron et al.[26] confirmed the appearance of oedematous folds by using the confocal microscope (Fig. 22.9). These folds appeared as long, straight, dark, orthogonal lines in the posterior stroma of the eyes of patients who had worn hydrogel lenses overnight. The fact that both vertical and horizontal folds were observed supports the notion that the appearance of only vertically oriented striae and folds with the slit lamp biomicroscope is an artefact of the configuration of the slit lamp biomicroscope earlier.

HAZE

Haze is essentially a more advanced form of striae whereby there is a gross separation of collagen fibres throughout the full thickness of the stroma, disrupting the regular geometry and orderly arrangement of the stromal lamellae. This causes a failure of the optical coherence of the stromal collagen layers, and transparency is reduced.[24] The greater the oedema, the greater is this disruption, and the greater is the extent of haze.

Aetiology

A number of possible mechanisms have been suggested as playing a role in lens-induced corneal oedema. These include hypoxia,[25,27,28] retardation of carbon dioxide efflux (leading to tissue acidosis),[27] mechanical effects,[29] temperature changes,[30] hypotonicity,[31] inflammation[32] and increased humidity. The extent to which these factors contribute to overnight corneal oedema[33] is indicated in Figure 22.10. Although the factors contributing to *contact lens–induced* corneal oedema have not been investigated in this manner, it would seem reasonable to explain lens-induced oedema primarily in terms of the effects of anterior surface hypoxia.

Contact lenses restrict corneal oxygen availability, creating a hypoxic environment at the anterior corneal surface. To conserve energy, the corneal epithelium begins to respire anaerobically. Lactate, a by-product of anaerobic metabolism, increases in concentration and moves posteriorly into the corneal stroma. This creates an osmotic load that is balanced by an increased movement of water into the stroma. The sudden influx of water cannot be matched by the removal of water from the stroma by the endothelial pump, resulting in corneal oedema[34,35] (Fig. 22.11).

Nguyen et al.[36] showed that the variability in contact lens-induced corneal swelling is associated with both corneal metabolic activity and endothelial function (percentage of recovery

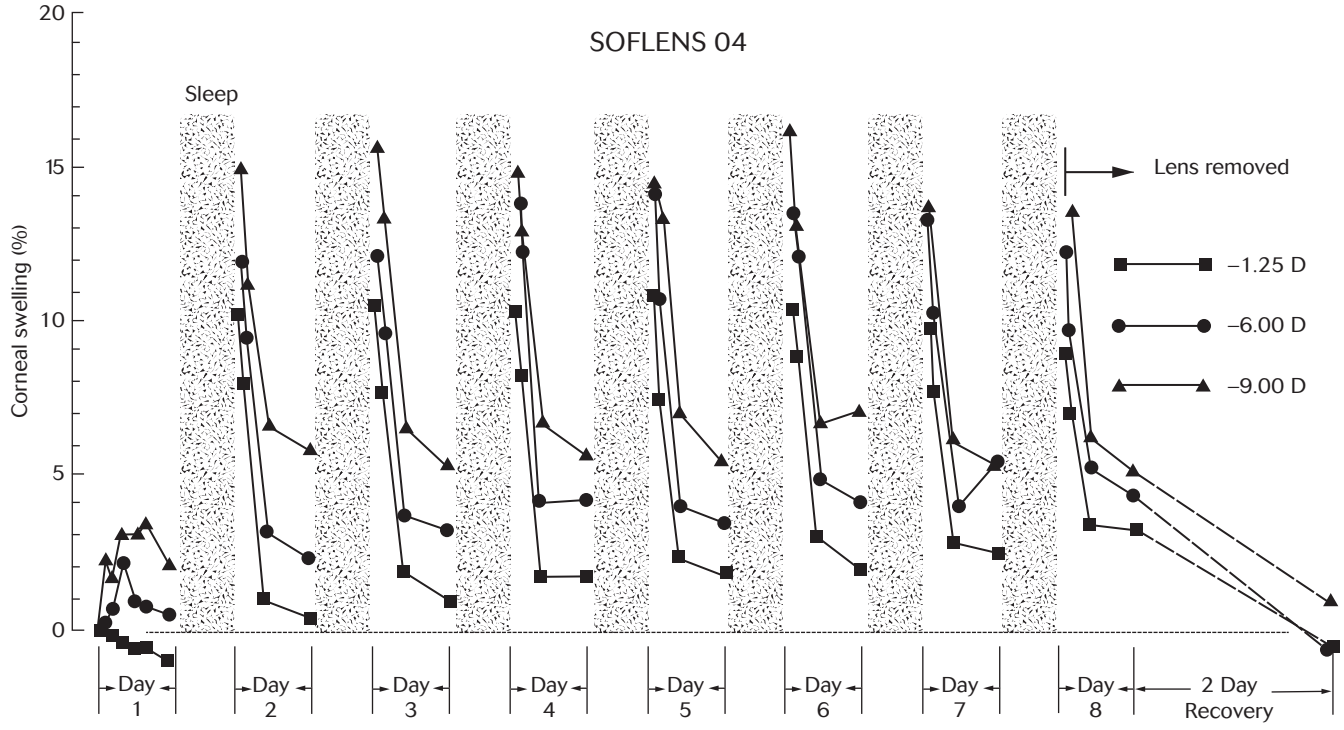


Fig. 22.5 Corneal swelling vs. time for 10 un-adapted subjects wearing Bausch & Lomb Soflens 04 series hydrogel contact lenses continuously for a period of 1 week. All subjects wore −1.25 D lenses on one eye; half wore −6.00 D lenses, and half wore −9.00 D lenses on the other eye. (From Holden BA, Mertz GW, McNally JJ. Corneal swelling response to contact lenses worn under extended wear conditions. Invest Ophthalmol Vis Sci 1983;24:218–26.)

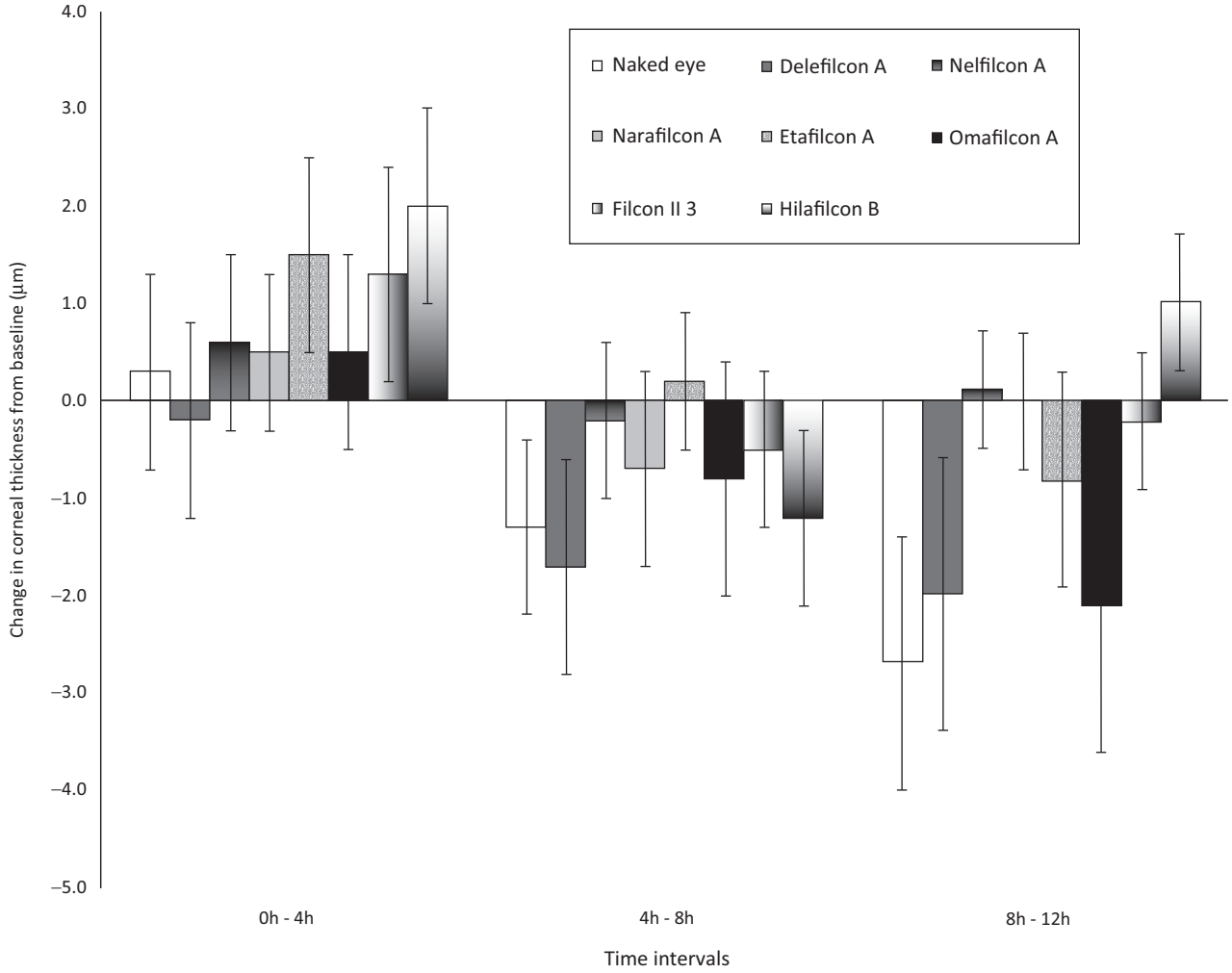


Fig. 22.6 Changes in central corneal thickness from baseline measurements for each of the seven contact lenses studied, in addition to the no-contact-lens condition, recorded at three time intervals. (From Del Aguila-Carrasco AJ, Ferrer-Blasco T, Garcia-Lazaro S, et al. Assessment of corneal thickness and tear meniscus during contact-lens wear. Cont Lens Anterior Eye 2015;38:185–93.)

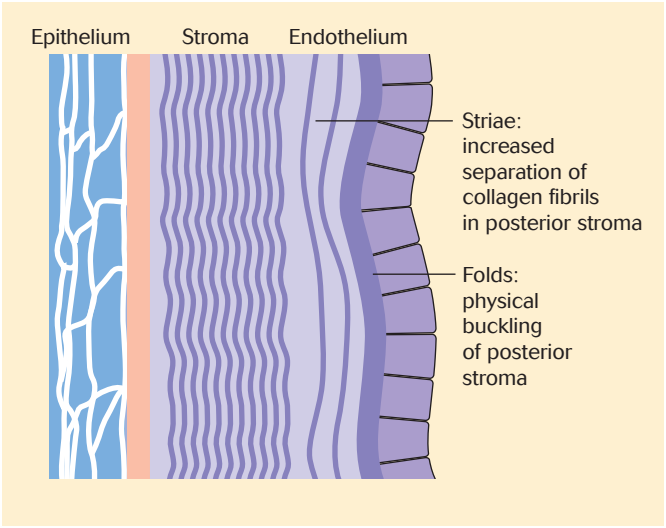


Fig. 22.7 Location of striae and folds.

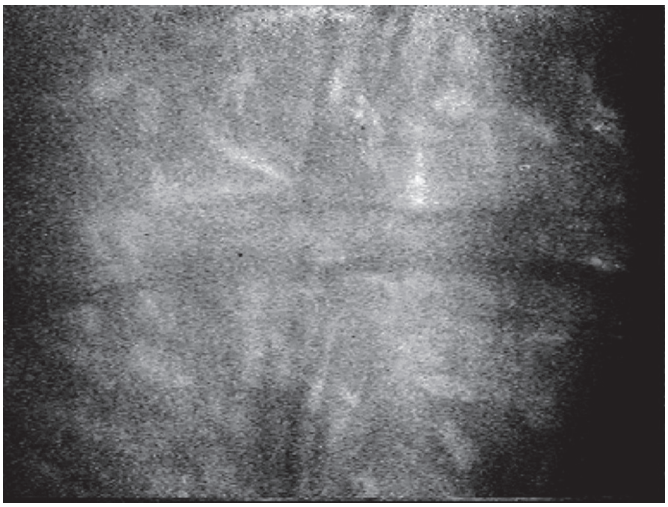


Fig. 22.9 Confocal micrograph of vertical and horizontal folds in an eye that had worn a hydrogel contact lens overnight (the image was captured within 30 minutes of awakening). (Courtesy Haliza Mutalib.)

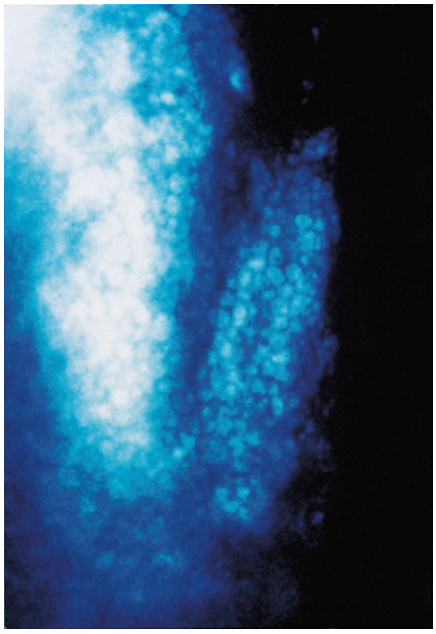


Fig. 22.8 High-magnification slit lamp photomicrograph of deep folds in the endothelial mosaic, indicating buckling of the posterior stroma caused by excessive oedema. (Courtesy Steve Zantos, Brien Holden Vision Institute.)

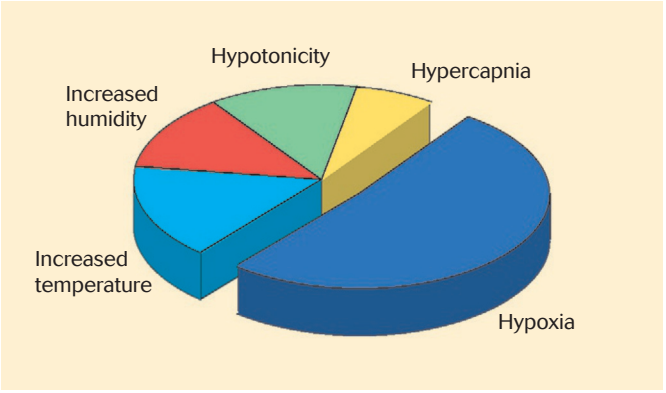


Fig. 22.10 Factors contributing to corneal oedema after sleep, revealing hypoxia to be the major cause.

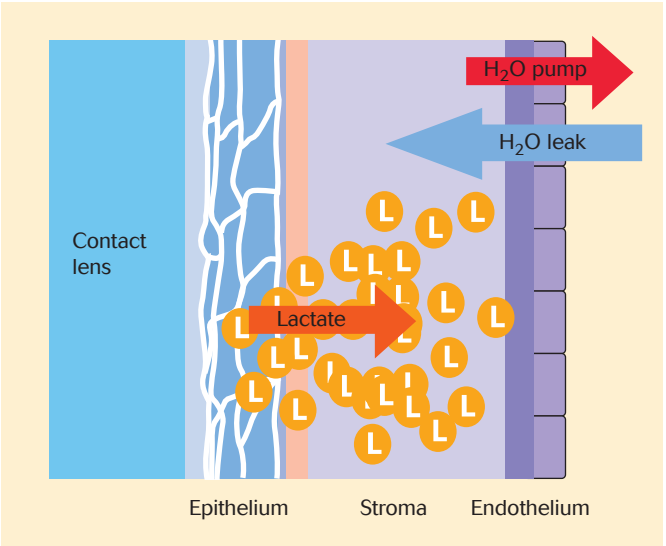


Fig. 22.11 Aetiology of contact lens–induced oedema. Excess lactate in the stroma resulting from anaerobic respiration of the epithelium draws water osmotically into the stroma.

per hour). This suggests that individuals with larger levels of corneal metabolic activity produce more lactic acid (i.e. more swelling), whereas stronger endothelial function resists swelling.

O'Donnell and Efron[37] assessed the acute swelling response to contact lens–induced corneal hypoxia in patients with diabetes who wore contact lenses. A thick, low-water-content soft contact lens was fitted under a light patch to one eye of 23 patients with diabetes and one eye of 23 control subjects without diabetes in a single-masked, controlled clinical study. After 2.5 hours, an ultrasonic pachometer was used to measure the induced corneal oedema. The induced corneal oedema was significantly less in the patients with diabetes compared with the control subjects

without diabetes ($p = 0.004$), suggesting that metabolic alterations to the cornea in diseases, such as diabetes mellitus, can alter the corneal swelling response to contact lens wear.

Observation and grading

The level of corneal oedema in a contact lens wearer can be assessed using the grading scale for corneal oedema shown in Appendix A. An analysis of the clinical changes depicted in each level of grading is given in the following.

GRADE 0

This is the normal non-lens-wearing situation of 0% oedema during the day.

GRADE 1

This grade denotes slight changes, up to 4% oedema, which could include the normal 3% oedema experienced by all humans overnight. Pachometric techniques must generally be employed to detect grade 1 oedema; however, trace levels of striae formation may be present.

GRADE 2

Observation of between one and three striae in the posterior stroma is designated as representing grade 2 oedema. This represents 5% to 7% swelling. In the clinic, grade 2 oedema will only be observed in patients who (a) are wearing contact lenses of extremely low oxygen transmissibility and/or (b) have slept wearing low-oxygen-permeability (Dk) lenses. Examples of the former case would include the wearing of low-Dk lenses used to correct high hyperopic (over +8.00 D) or high myopic (over −12.00 D) corrections. In the case of patients wearing hydrogel lenses for an extended period, striae will typically be observed only within 4 hours of awakening because the cornea de-swells back to steady-state thickness within this timeframe.[38] It is advisable to schedule patients who sleep in lenses to present for early-morning appointments so that the full effect of overnight lens wear on the cornea can be assessed.

GRADE 3

If one to 10 folds are detected, the oedema should be classified as grade 3. A significant number of striae (5–14) should also be observed. This suggests oedema levels of 8% or greater. Because the cornea de-swells at such a rapid rate upon eye opening, folds will only be observed within 1 hour of awakening in patients who have slept wearing low-Dk lenses. Day-time-only lenses, even those used for the correction of high myopia, are unlikely to induce oedema levels as high as 8%.

GRADE 4

Corneal swelling of 15% or greater is typically associated with the presence of at least 15 striae and 11 folds (Fig. 22.12). The stroma takes on a hazy appearance, the degree of which increases with increasing oedema. The epithelium may appear cloudy with possible bullous formations. The severe central corneal clouding viewed by using the sclerotic scatter technique, as depicted in Figure 22.13, would be classified as grade 4.

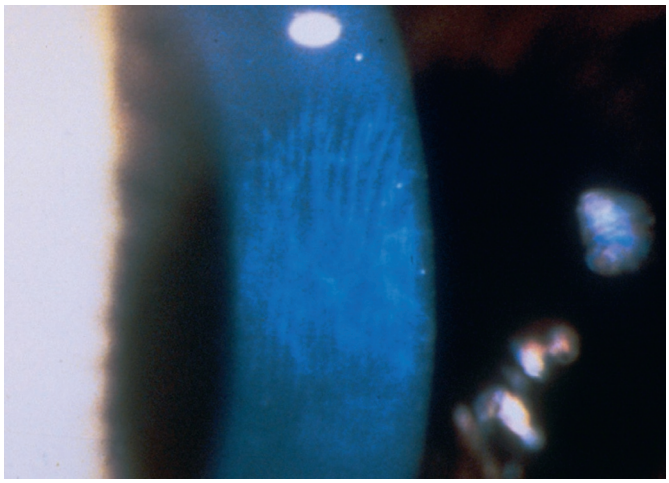


Fig. 22.12 Grade 4 oedema, showing extensive formation of striae and folds. (Courtesy A Miller, Brien Holden Vision Institute.)



Fig. 22.13 Frontal view of severe central corneal clouding viewed by sclerotic scatter technique. (Courtesy Patrick Caroline, Bausch & Lomb Slide Collection.)

Management and treatment

Since oxygen starvation is the primary cause of contact lens–induced oedema, strategies for reducing the oedema response are generally directed towards mechanisms for increasing corneal oxygen availability during lens wear. There are some important differences between rigid and soft lenses in the way oxygen reaches the cornea; thus, it is necessary to consider alternative oedema-reducing strategies for rigid and soft lenses separately, along with general strategies that apply equally to both types of lenses.

ALLEVIATING RIGID LENS–INDUCED OEDEMA

Material Dk

Materials of higher Dk will allow greater levels of oxygen to reach the cornea. However, increasing the Dk of rigid lenses can have disadvantages, such as increased lens flexibility (which

reduces lens stability), increased susceptibility to scratching,[39] reduced wettability and lower deposit resistance.

Lens thickness

A thinner lens will have a higher oxygen transmissibility (Dk/t) compared with a thicker lens made of the same material.[40] Again, there are some disadvantages to reducing lens thickness; a thinner lens will be more flexible (tending to reduce lens stability), mask less astigmatism and offer less resistance to breakage.

Base curve

A flatter base curve will allow the lens to move more freely, resulting in a greater tear exchange and increased corneal oxygenation.[41]

Edge lift

Increasing the edge lift may enhance tear exchange by affording a larger reservoir of oxygenated tears at the lens periphery.[42] However, increasing edge lift may also increase lens awareness.

Lens diameter

A smaller lens, as well as covering a smaller area of the cornea, will allow greater lens movement and will therefore enhance tear exchange and oxygenation.[43]

Fenestrations

It was originally thought that fenestrations in rigid lenses reduce oedema by providing additional avenues for oxygen passage to the cornea.[44] However, this does not seem to be the case. Fenestrations are now thought to act by altering the fluid forces between the lens and the cornea; this serves to enhance lens movement, which, in turn, leads to an increased tear exchange and greater corneal oxygenation.

ALLEVIATING SOFT LENS–INDUCED OEDEMA

Material Dk

With hydrogels, increasing material Dk essentially means increasing lens water content.[40] The potential drawbacks of higher-water-content hydrogels is that they are more fragile and lenses will therefore need to be thicker, and this can reduce comfort slightly. Silicone hydrogel lenses have such high Dk levels[45] that corneal oxygen availability is almost unimpeded.

Lens thickness

Reducing lens thickness will increase Dk/t.[40] However, thinner lenses are more fragile and can lead to unacceptable corneal staining, particularly with higher-water-content materials.

Base curve

There has been some debate as to whether flattening the base curve of hydrogel lenses results in an increased tear exchange despite the observation that flatter lenses move more freely over the cornea.[46] Florkey et al.[47] showed that blink-induced tear exchange enhances corneal oxygenation beneath silicone hydrogel lenses, which generally have a higher modulus compared with hydrogel lenses. Flatter lenses allow tear film debris and desquamated epithelial cells to be flushed out more readily from beneath the lens, thus minimising metabolic disturbance to the cornea and reducing the potential for inducing oedema.

Lens diameter

A smaller lens will move more freely over the cornea, and this may allow more oxygen to reach the cornea via an increased tear pump.

Microfenestrations

Conventional fenestrations (0.2–1.0 mm in diameter) in hydrogel lenses can increase corneal oxygenation[48] and reduce oedema,[49,50] but fenestrated lenses are very uncomfortable.[51] A strategically positioned array of microfenestrations can reduce lens-induced corneal oedema significantly.[51] In particular, microfenestrations positioned towards the lens edge may be useful in reducing peripheral corneal oedema during the wearing of medium to high minus hydrogel lenses (say, over −3.00 D). Microfenestration arrays have also been shown to improve tear mixing in silicone hydrogel lenses,[52] although the benefit being sought in these studies related more to revealing strategies for removal of debris and waste products from beneath the lens, rather than to enhance corneal oxygenation[53] (Fig. 22.14). The clinical viability of microfenestrations is yet to be established.

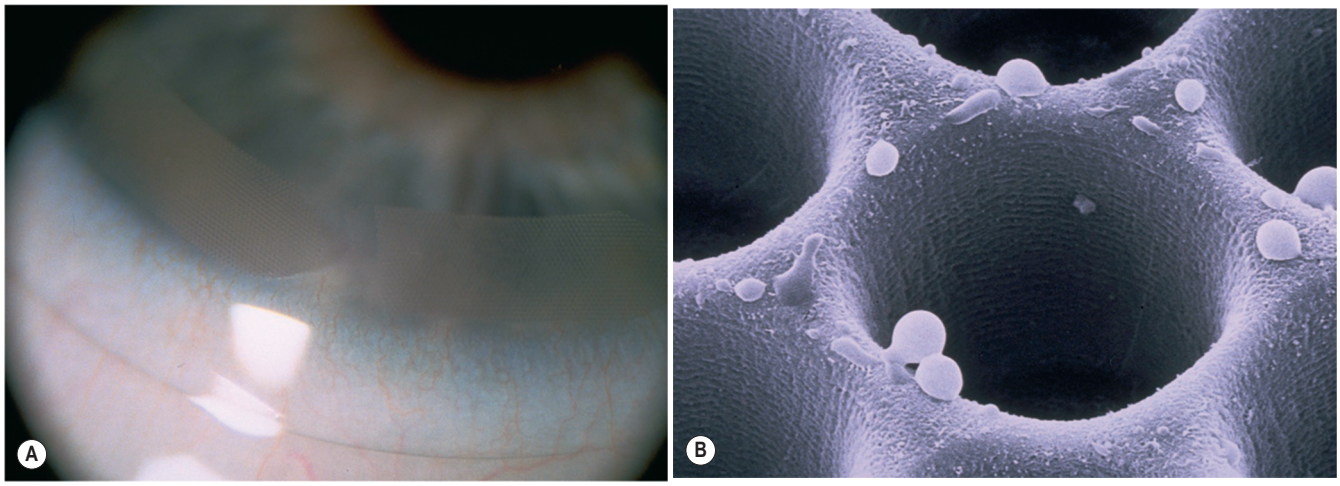


Fig. 22.14 **(A)** An array of thousands of microfenestrations in the mid-periphery of a soft lens. **(B)** Microfenestrations (40 μm diameter) viewed under the electron microscope, revealing smooth, rounded edges.

GENERAL STRATEGIES FOR REDUCING OEDEMA

Changing from extended wear to daily wear

Overnight wear of hydrogel lenses is generally associated with increased levels of oedema because corneal oxygen availability is significantly reduced when the eyelid is closed. Thus, switching from extended wear to daily wear will reduce the overall oedema response.

Changing from soft lenses to rigid lenses

With regard to soft and rigid lenses of the same Dk/t, rigid lenses will generally deliver more oxygen to the cornea during open-eye wear because of the lid-activated tear pump.[54] In patients with extended-wear lenses, converting from a soft lens to a rigid lens of the same Dk/t will alleviate the physiological effect of lens wear by allowing a more rapid oedema reduction after awakening.

Reducing wearing time

After lens insertion, oedema initially increases rapidly and then increases more gradually over the first 6 to 8 hours of lens wear. Limiting the time that lenses may be worn each day will therefore reduce both the magnitude and the duration of corneal oedema.

Anti-inflammatory drugs

A possible strategy for reducing lens-induced oedema is the use of non-steroidal anti-inflammatory drugs. Although it would not be feasible to use such drugs on a routine basis, they could prove useful for the treatment of acute episodes of severe (grade 4) oedema. There is no conclusive evidence that contact lens–induced oedema can be modified by drug therapy.[32]

Postponing lens wear

It may be prudent to temporarily cease lens wear after an acute oedema episode, especially if associated with other pathological changes, such as limbal redness, infiltrates or corneal staining. Lens wear should be ceased until all pathological signs and associated symptoms have resolved.

Abandonment of lens wear

Clearly a last resort, abandonment of lens wear must be considered if chronic oedema persists after all other possible treatment alternatives have failed.

GENERAL CONSIDERATIONS

The various strategies described previously for reducing lens-induced oedema should be employed in a systematic manner, with respect to (a) the severity of oedema as gauged biomicroscopically (based on the appearance of striae, folds and haze) and (b) the modality of lens wear (rigid vs. soft; daily wear vs. extended wear). Consideration should also be given to the time of day – morning or afternoon – that the observations of oedema are made.

LENS PERFORMANCE CRITERIA FOR MAINTAINING CORNEAL HEALTH

Contact lens oxygen transmissibility

For daily, open-eye wear of contact lenses, Holden and Mertz[55] provided a criterion of 24×10^{-9} (cm × mLO_2)/(sec × mL × mmHg) for the minimum contact lens Dk/t required to avoid excessive levels of central corneal oedema. Harvitt and Bonanno[56] found that to prevent anoxia throughout the entire corneal thickness during open-eye lens wear, the Dk/t needs to be at least 35×10^{-9} (cm × mLO_2)/(sec × mL × mmHg).

Morgan et al.[57] reported open-eye lens wear criteria of 19.8 and 32.6×10^{-9} (cm × mLO_2)/(sec × mL × mmHg) for the central and peripheral cornea, respectively (Fig. 22.15). These authors went on to demonstrate that although some conventional hydrogel soft lenses are able to achieve this criterion for either central or peripheral lens areas (depending on lens power), in general, no conventional hydrogel soft lenses meet both the central and peripheral thresholds. They showed that silicone hydrogel contact lenses typically meet both the central and peripheral thresholds; that is, the use of these lenses helps prevent swelling in all regions of the cornea (Fig. 22.16).[57]

Given that three-quarters of all reusable soft lenses prescribed today are silicone hydrogel lenses,[58] very few cases of elevated stromal oedema should be observed in modern contact lens practice.

For closed-eye extended wear of contact lenses, Holden and Mertz[55] provided a Dk/t criterion for the minimum contact lens Dk/t required to prevent excessive levels of central corneal oedema of 87×10^{-9} (cm × mLO_2)/(sec × mL × mmHg) (the exponential and the units will not be repeated in subsequent text) (Fig. 22.17). Only silicone hydrogel soft lenses and

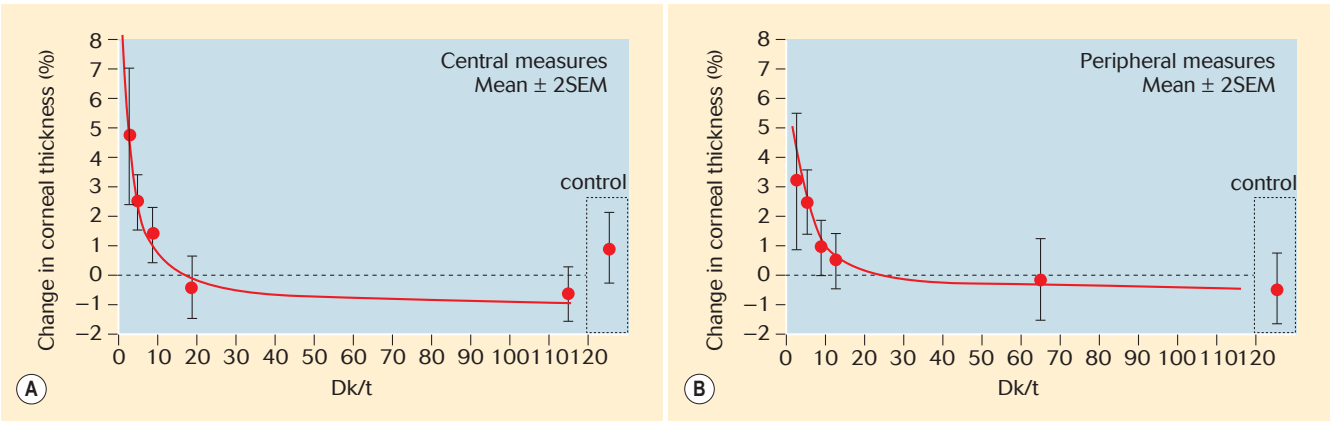


Fig. 22.15 Corneal swelling versus Dk/t for **(A)** central and **(B)** peripheral measures. (Adapted from Morgan PB, Brennan NA, Maldonado-Codina C, Quhill W, Rashid K, Efron N. Central and peripheral oxygen transmissibility thresholds to avoid corneal swelling during open eye soft contact lens wear. J Biomed Mat Res Part B, Appl Biomater 2010;92:361–5.)

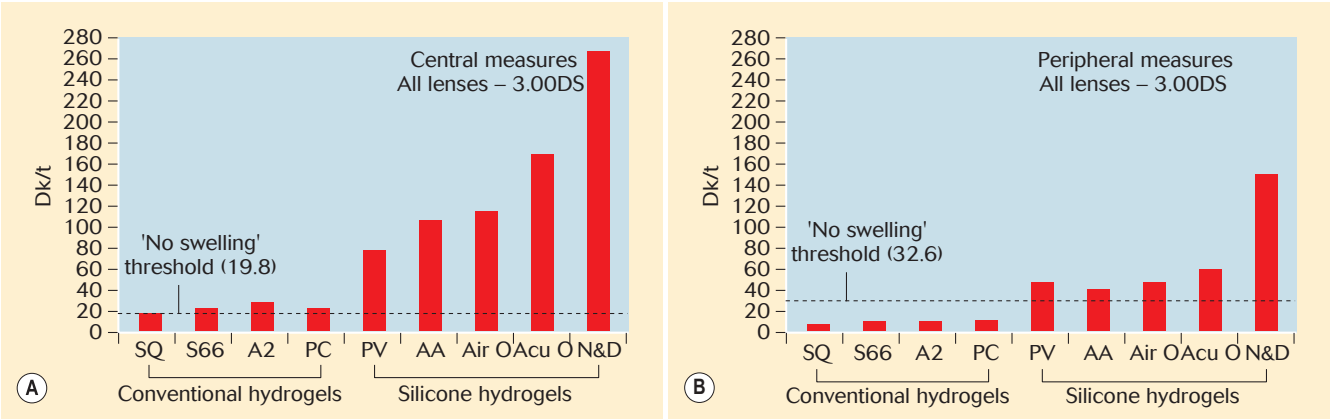


Fig. 22.16 **(A)** Central and **(B)** peripheral Dk/t values for a range of representative hydrogel and silicone lenses. SQ – SeeQuence; S66 – SofLens 66; A2 – Acuvue 2; PC – Proclear; PV – PureVision; AA – Acuvue Advance; Air O – Air Optix; Acu O – Acuvue Oasys; N&D – Night & Day. (Adapted from Morgan PB, Brennan NA, Maldonado-Codina C, Quhill W, Rashid K, Efron N. Central and peripheral oxygen transmissibility thresholds to avoid corneal swelling during open eye soft contact lens wear. J Biomed Mat Res Part B, Appl Biomater 2010;92:361–5.)

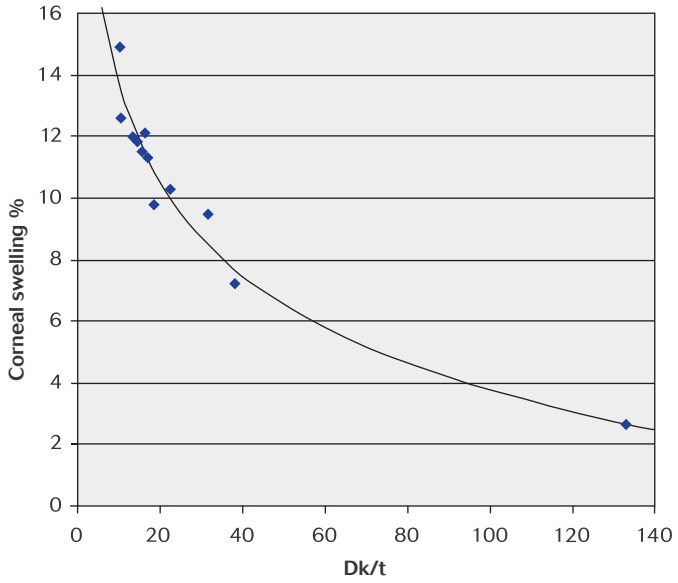


Fig. 22.17 Relationship between contact lens Dk/t and oedema for extended wear. (Adapted from Holden BA, Mertz GW. Critical oxygen levels to avoid corneal oedema for daily and extended wear contact lenses. Invest Ophthalmol Vis Sci 1984;25:1161–7.)

hyper-permeable rigid lenses meet the Holden–Mertz criterion for extended wear.

Attempts at revising the Holden–Mertz criteria

A number of authors[56,59,60] suggested that the critical contact lens Dk/t required to maintain normal anterior eye physiology should be revised upwards to 125. Sweeney et al.[59] fitted a new curve to the original Holden–Mertz graph. Harvitt and Bonanno[56] attempted to correct for corneal acidosis effects and determine the Dk/t required to prevent anoxia throughout the entire corneal thickness during closed-eye lens wear. Papas[60] assessed the Dk/t required to prevent limbal redness. Remarkably, all three authors arrived at exactly the same 'revised' value of 125.

Brennan et al.[61] reviewed this proposed revision of the Dk/t threshold by critically reviewing the studies of Sweeney et al,[59] Harvitt and Bonanno[56] and Papas.[60] They also considered work from laboratory, theoretical and clinical studies to assess general corneal oxygen requirements. Brennan et al.[61] observed that the study of Sweeney et al.[59] failed to account for Dk 'edge effect' correction, combined select data from two different studies when the sample populations may have different characteristics and altered the original Holden–Mertz[55] equation to one of poorer statistical fit. The study of Harvitt and Bonanno[56] used layer thickness values that were not representative of human population values, as reported in more recent studies. Papas[60] generated data for the peripheral cornea under open-eye conditions, whereas the other two studies generated data for the central cornea under closed-eye conditions; most importantly, this study, as well as others, necessarily lacks an appropriate scientific control since one cannot make a lens with infinite Dk/t. Brennan et al.[61] pointed out that clinical signs of hypoxic changes suggest a lower threshold than laboratory-based or theoretical predictions and concluded that a threshold Dk/t value of 125 is scientifically indefensible.

In view of these, the Dk/t criteria for preventing oedema of the central cornea should be taken to 20 and 87 for open-eye wear[57] and closed-eye wear,[55] respectively.

Corneal oxygen flux

Although oxygen transmissibility has been a favoured index to describe the physiological performance of contact lenses, some authors have maintained that the flux through a contact lens would be a more useful guide. *Oxygen flux* refers to the rate at which oxygen enters the cornea from the atmosphere. Being a physiological measurement which relates directly to the eye, flux is a preferred measure over Dk/t (a laboratory measurement).

Brennan[62] described a model that allows contact lens oxygen flux to be estimated under open-eye and closed-eye wearing conditions. The equivalent oxygen potential (EOP) was used to approximate the oxygen concentration beneath a contact lens. A logarithmic relation between corneal oxygen consumption and this oxygen level was substituted into Fick's Law to provide a mathematical model. Paired data of EOP and Dk/t, from a previous empiric derivation, were entered into a non-linear regression analysis of this model. The modelling procedure

produces a good fit to the selected data. The estimated maximum flux during open-eye wear is 7.5 μl/cm^2 × h, consistent with previous determinations. Error estimates increased from 0 to 0.55 μl/cm^2/h at Dk/t values of 0 and 200, respectively, for the open eye.

Brennan's analysis[62] provided a workable model for estimating the oxygen flux through contact lenses. Varying the underlying relation between the oxygen tension beneath a lens and the oxygen flux produces minimal variation to the result. The model has a number of clinical applications, such as demonstrating the advantages of highly transmissible contact lenses and the limits to which increasing oxygen transmissibility can alter the corneal physiological environment. This is illustrated in Figure 22.18 and has been termed the 'law of diminishing returns'. It can be seen that for low-Dk/t lenses, such as those made from conventional hydrogel materials, increasing Dk/t also increases oxygen flux. However, for high-Dk/t lenses, such as those made from silicone hydrogel materials, there is little to be gained by increasing Dk/t beyond a value of about 50.

Total corneal oxygen consumption

Brennan[63] went on to compute total corneal oxygen consumption during contact lens wear and to consider the concept as an index for describing corneal oxygenation during contact lens wear as opposed to flux, partial pressure or Dk/t. Estimates of total corneal oxygen consumption were generated by using an eight-layer model based on oxygen diffusion equations and by using contemporary estimates of tear and corneal layer thicknesses. Relative consumption, expressed as %Q (percentage of normal consumption without contact lens wear), was also calculated for daily-wear and continuous-wear modes, thereby providing an index of the chronic hypoxic effect of contact lens wear.

Brennan[63] calculated that corneal oxygen consumption converged to the same value of 44.8 nL/cm/sec above a Dk/t of approximately 20 and 300 for the open-eye and closed-eye scenarios, respectively. Lenses with Dk/t values of 15 and 50 allow about 96% of normal long-term total oxygen consumption without a contact lens in place for daily wear and continuous wear, respectively. Thus, both the corneal oxygen flux[62] and total corneal oxygen consumption[63] models derived by Brennan support the notion of the law of diminishing returns.

Brennan[63] considered the total corneal oxygen consumption model to be an attractive means of describing corneal oxygenation, for the following reasons:

- It is based on physical parameters.
- It represents a direct index of corneal oxygen metabolism and thus cellular energy (adenosine triphosphate) production.
- It allows for direct comparison of two lenses or lens-wearing and non-lens-wearing states.
- It eliminates the ambiguity of other measures.

IMPLICATIONS WHEN MEASURING INTRA-OCULAR PRESSURE

Corneal hysteresis is a measure of viscous damping in the corneal tissue. It is considered the 'energy absorption capability' of the cornea. According to Lu et al.,[64] corneal hysteresis, as measured by using a Reichert Ocular Response Analyser, is not associated with corneal swelling induced by soft contact lens wear.

Oh et al.[65] reported that mean intra-ocular pressure measurements determined by using Goldmann applanation tonometry and dynamic contour tonometry were decreased by 0.43 ± 1.95 mmHg and 0.75 ± 1.74 mmHg, respectively, in the presence of significant levels of contact lens–induced corneal oedema. Hamilton et al.[66] reported an increase in intra-ocular pressure of 2.8 ± 2.2 mmHg in the presence of corneal oedema of 41.9 ± 14.4 μm and concluded that a small increase in corneal hydration and thickness may cause a clinically significant overestimation of intra-ocular pressure when measured by using Goldmann applanation tonometry.

Prognosis

In general, the prognosis for recovery of the cornea from lens-induced oedema is excellent. In laboratory experiments, it can be demonstrated that the oedema induced when a patient wears a contact lens for the first time will resolve within 4 hours when the lens is removed.[38,67]

Chronic oedema takes a lot longer to resolve. Holden et al.[68] reported that oedema took 7 days to resolve after lens removal in patients who had worn extended-wear lenses for 5 years. Nourouzi et al.[69] examined 100 eyes of patients who had been

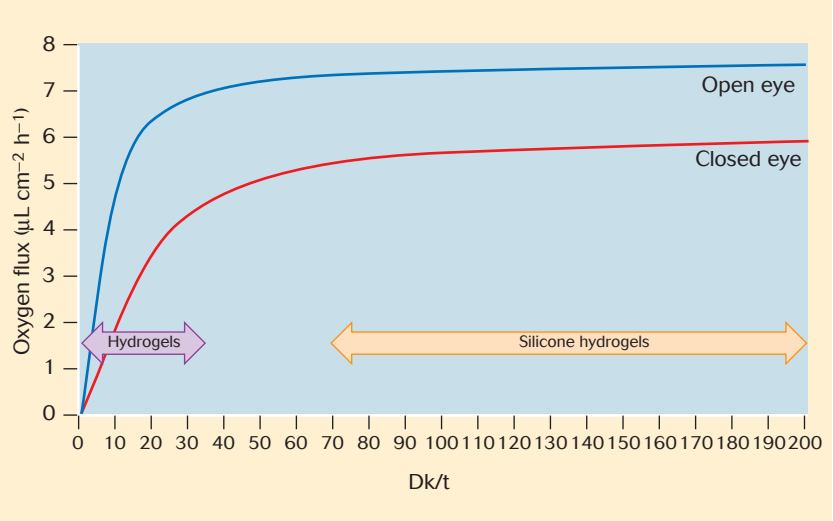


Fig. 22.18 Relationship between contact lens Dk/t and corneal oxygen flux for open-eye and closed-eye contact lens wear, highlighting the 'law of diminishing returns'. It can be seen that to maintain adequate levels of corneal oxygen flux, there is little benefit in increasing Dk/t beyond about 30 and 50 for open-eye and closed-eye wear, respectively. (Adapted from Brennan NA. A model of oxygen flux through contact lenses. Cornea 2001;20:104–8.)

using daily-wear soft lenses for at least 6 months. They found that corneal oedema required 2 to 15 days after discontinuation of soft lens wear to resolve. Corneal thickness stabilised in 74% of patients within the first week and in 26% of patients during the second week. Older patients needed a longer time to recover.

These cases are likely to represent the two extremes (4 hours vs. 7 days) of rate of recovery from lens-induced oedema. It may be that, within this range, the rate of recovery of oedema after lens wear is related to the total accumulated lens wear experience.[70,71] There do not appear to have been any reports of the failure of contact lens–induced oedema to resolve.

The rate at which the cornea recovers from lens-induced oedema has been suggested as a test of the health of the cornea. For example, corneas of patients suffering from Fuch's endothelial dystrophy[72] have an impaired capacity to eliminate excess oedema. It has been suggested that patients with diabetes also have an impaired capacity to eliminate excess oedema[73,74]; however, O'Donnell and Efron[37] found that the corneas of the patients with diabetes recovered from induced oedema at a similar rate seen in the corneas of control subjects without diabetes. The corneal de-swelling rate is thought to reflect the integrity of the endothelium, which is responsible for corneal hydration control (see Part 8).

Differential diagnosis

Striae can take on an appearance similar to that of ghost vessels and nerve fibres. The characteristics that allow these entities to be differentiated are discussed in Chapter 25. Fonn and Gauthier[75] described the presence of fibrillary lines in both lens wearers and non–lens wearers; these seem to be very similar to oedema-related striae but are thought to be neural in origin and are apparently permanent.

Folds can occur naturally in a small proportion of normal patients and are often observed in patients with diabetes.[76] Folds observed in daily lens wearers with diabetes do not alter their appearance over a number of months.[77] Again, the capacity of lens-induced folds to resolve rapidly after lens removal is a key diagnostic criterion.

Various corneal dystrophies and diseases of the cornea and associated ocular structures, as well as iatrogenic interventions, such as ophthalmic surgery or drug therapy, can result in stromal oedema. It is beyond the scope of this chapter to review all of these possible causes of oedema; however, in most instances, there will be associated signs and symptoms that cannot be reconciled with contact lens–induced oedema. For example, in addition to stromal oedema, Fuch's endothelial dystrophy is characterised by permanent and pronounced endothelial guttata, bullous keratopathy (large fluid vacuoles in the stroma), loss of vision and pain.

A condition known as acute hydrops can occur in severe keratoconus, where there is an acute influx of aqueous into the cornea as a result of a rupture in Descemet's membrane. This causes a sudden drop in visual acuity and is associated with discomfort and watering. This condition is treated initially with hypertonic saline and either patching or a bandage contact lens. Acute hydrops usually clears within 6 weeks, although a variable amount of stromal scarring may remain.[78]

The key feature that distinguishes the signs of contact lens–induced corneal oedema – striae, folds and haze – from other clinical entities that take on a similar appearance is that lens-induced oedema will resolve soon after lens removal.

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23 Stromal Thinning

As discussed in Chapter 22, stromal oedema is a reliable indicator of the level of hypoxic stress induced by contact lens wear. It is an acute response in that the oedema will increase to steady state within a few hours when the cornea is subjected to hypoxic stress and will return to baseline within a few hours of the hypoxic stress being removed. Of course, oedema can be considered to be chronic if a patient wears oedema-inducing lenses over long periods, but even in these circumstances, the oedema still resolves when the cornea is no longer subjected to hypoxia.

Stromal thinning is an insidious chronic change, which is often masked by acute lens-induced oedema. In fact, the only way that stromal thinning can be properly assessed is to measure stromal thickness after a long period of cessation of lens wear (at least 1 week). This chapter shall examine the phenomenon of contact lens–induced stromal thinning and consider its clinical implications.

Signs and symptoms

LONGITUDINAL TRIALS ON LENS WEARING

Stromal thinning was identified and defined for the first time in 1985 by Holden et al.,[1] although this phenomenon had been observed anecdotally by earlier workers. For example, Millodot[2] noted that the corneas of patients who had worn polymethyl methacrylate (PMMA) contact lenses on a daily wear basis for 10 to 21 years became thinner, after ceasing lens wear, compared with the corneas of a matched control group of non–lens wearers. Lebow and Plishka[3] reported apparent corneal thinning in an 11-month longitudinal extended-wear study of 22 patients with myopia wearing low-Dk hydrogel contact lenses (Hydrocurve II, CIBA Vision) (Fig. 23.1). These authors were unsure of the cause of the progressive decrease in corneal thickness over the course of their study. It was thought at the time that these changes may have represented either some form of physiological adaptation or a methodological artefact relating to the progressive drop-out of subjects exhibiting adverse responses that were partially or wholly characterised by excessive corneal oedema.

Schoessler and Barr[4] monitored corneal thickness changes in eight patients with myopia wearing low-permeability (low-Dk) hydrogel contact lenses (Permalens, CooperVision) continuously for 18 months. The averaged results showed maximal corneal swelling after 1 week of wear, with the cornea gradually returning to near pre-fitting thickness levels. These authors noted that 'some patients [showed] chronic corneal thickening and some [showed] corneal thinning after the 18-month wearing period'.

Holden et al.[1] detected stromal thinning by measuring the presenting stromal thickness of patients who had been wearing a lens in one eye only on an extended-wear basis for an average of 5.2 ± 2.4 years. A lens was worn in one eye only in these patients because they were suffering from either unilateral myopia or amblyopia in the contralateral eye. Upon ceasing lens wear after 5.2 years, it was noted that the stroma in the lens-wearing eye decreased in thickness to a steady-state level that was thinner than the fellow non-lens-wearing eye (Fig. 23.2).

THEORETICAL ANALYSIS

Assuming that the stromal thickness of both eyes was the same before lens wear (this was validated in a non-lens-wearing control group of individuals with unilateral myopia and amblyopia), the

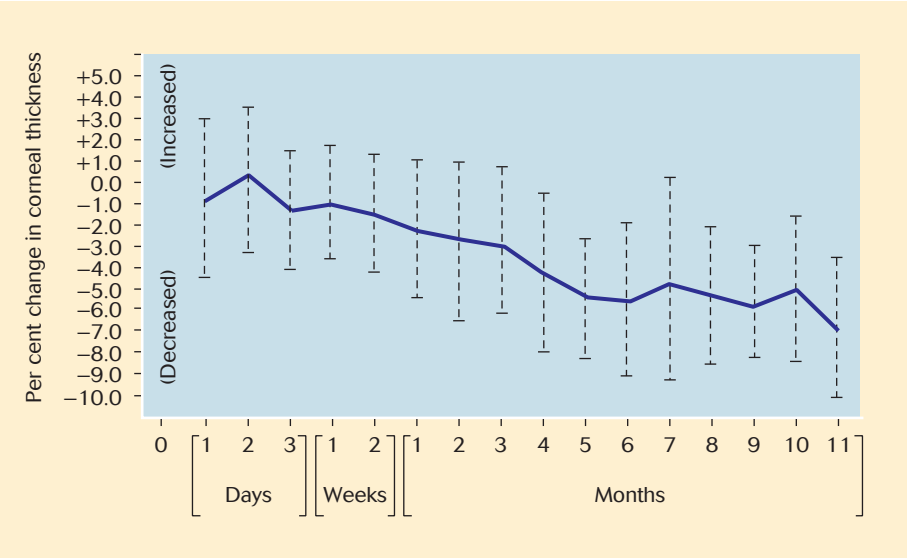


Fig. 23.1 Change in corneal thickness over time in patients wearing low-Dk hydrogel extended-wear lenses. (Adapted from Lebow KA, Plishka K. Ocular changes associated with extended wear contact lenses. Int Contact Lens Clin 1980;7:49–55.)

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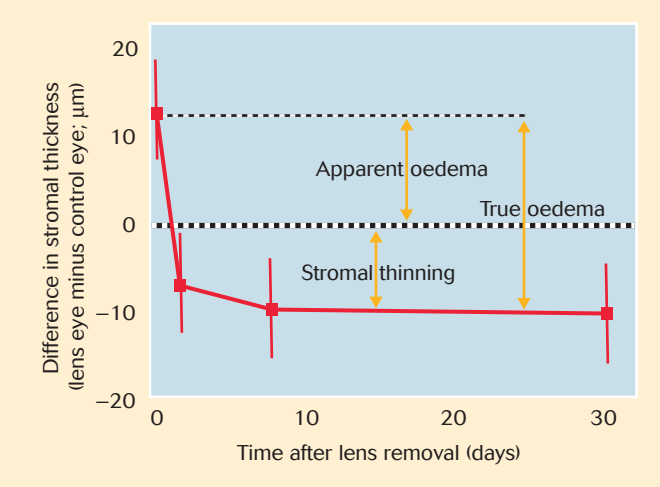


Fig. 23.2 Recovery of corneal oedema after cessation of lens wear for 1 month after 5 years of soft lens extended wear, illustrating the relationship between true oedema, apparent oedema and stromal thinning. (Adapted from Holden BA, Sweeney DF, Vannas A, et al. Effects of long-term extended contact lens wear on the human cornea. Invest Ophthalmol Vis Sci 1985;26:1489–501.)

only assumption that can be drawn is that contact lenses induce stromal thinning. It can be seen from Figure 23.2 that the stroma had thinned an average of 11 µm in 5.2 years of lens wear; representing an average of 2.1-µm thinning per year of lens wear. The revelation of stromal thinning by Holden et al.[1] has facilitated interpretation of data from earlier longitudinal studies on lens wearing which had failed to take this phenomenon into account. The following equation, derived from Figure 23.2, can be used to determine the extent of stromal thinning:

$$\text{Stromal thinning} = \text{True oedema} - \text{Apparent oedema}$$

It is important for clinicians to recognise that the phenomenon of contact lens–induced stromal thinning does not confound or invalidate interpretation of the clinical signs of acute oedema discussed in Chapter 22. The signs of striae, folds and haze represent a given level of acute oedema irrespective of whether or not the stroma has thinned; that is, these signs still indicate the level of true oedema.

CROSS-SECTIONAL STUDIES

Liu and Pflugfelder[5] evaluated the effect of long-term contact lens wear on corneal thickness in 35 subjects who had been wearing contact lenses for 13.5 ± 6 years; these data were compared with data from 40 control eyes. Those authors observed that the mean corneal thickness in the centre and in eight peripheral areas measured in contact lens–wearing subjects was significantly reduced by about 30 to 50 µm compared with normal subjects and that these changes were unrelated to the degree of myopia.

Chang et al.[6] compared corneal thickness in 34 subjects and 42 subjects who had been wearing daily-wear soft lenses for less than 5 years and more than 5 years, respectively. They noted a significant tendency towards corneal thinning with a longer history of contact lens wear ($r = -0.31$; $p = 0.002$). The results of Liu and Pflugfelder[5] and Chang et al.[6] support the original observation of Holden et al.[1] – that long-term contact lens wear causes a decrease in corneal thickness.

Myrowitz et al.[7] measured corneal thickness in 124 consecutive patients (248 eyes) who underwent comprehensive evaluations in consideration of refractive surgery. These authors observed that 39 patients (78 eyes) who had previously worn soft contact lenses for an average of 16 years had a mean corneal thickness of 543.2 ± 3.8 µm (standard error); 23 patients (46 eyes) who had worn rigid contact lenses for an average of 19 years had a mean corneal thickness of 509.4 ± 6.9 µm; and 62 patients (124 eyes) who had not previously worn contact lenses had a mean corneal thickness of 546.4 ± 3.5 µm. These authors[7] concluded that long-term rigid contact lens wear is associated with a decrease in the average central corneal thickness of 37 µm compared with no contact lens wear. They were unable to confirm the earlier findings by Holden et al.[1] and Liu and Pflugfelder[5] that such an effect existed among soft-lens wearers.

Lei et al.[8] measured corneal thickness in 56 subjects immediately after cessation of contact lens wear and 2 weeks later, as well as in 94 non-lens-wearing control subjects by using the RTVue-100 Fourier-domain anterior segment optical coherence tomography system. Corneal thickness in the control group was 534 ± 27 µm. Immediately after ceasing lens wear, corneal thickness was 529 ± 28 µm. Two weeks after ceasing lens wear, corneal thickness was 521 ± 26 µm; this value was significantly less than the corneal thickness immediately after ceasing lens wear and that of control corneal thickness. This finding suggests that normal, uncomplicated contact lens wear induces corneal thinning.

METHODOLOGICAL CONSIDERATIONS

An important methodological issue needs to be taken into account when considering reported data of lens-induced corneal thinning. Holden et al.[1] specifically measured stromal thickness, whereas all of the other researchers referred to earlier measured total corneal thickness; that is, the combined thickness of the stroma (typically 550 µm thick) and the epithelium (typically 50 µm thick). Long-term contact lens wear is also known to induce epithelial thinning; this is estimated to be 5.6% by Holden et al.[1] and between 8.7% and 18.4% by Perez et al.[9] Therefore, published estimates of stromal thinning may be confounded by effects of lens wear on the epithelial thickness.

Consider the results of Liu and Pflugfelder,[5] who observed 40 µm of corneal thinning (taking the mid-point of their reported range of 30–50 µm thinning). Their subjects may also have suffered about 10% of epithelial thinning, or about 5 µm, assuming a 50-µm-thick epithelium. This would leave about 35 µm of stromal thinning, which represent about 2.6 µm/year of stromal thinning over the 13.5 years of lens wear of the subjects in the cohort of Liu and Pflugfelder.[5] For the data of Myrowitz et al.,[7] 37 µm of corneal thinning in rigid lens wearers may equate to 32 µm of stromal thinning. The calculated rate of stromal thinning over the 19 years of lens wear is therefore 1.7 µm per year. In the case of Lei et al.,[8] subtracting the 2-week data from the control data gives 13 µm of corneal thinning and may equate to 8 µm of stromal thinning; however, a rate of stromal thinning cannot be determined in this case because Lei et al.[8] did not report the length of time lenses had been worn.

The calculated stromal thinning rates of 2.1, 2.6 and 1.7 µm per year based on the data of Holden et al.,[1] Liu and Pflugfelder[5] and Myrowitz et al.,[7] respectively, are remarkably similar.

SYMPTOMS

None of the studies reporting stromal thinning has noted any symptomatic associations. However, should the stroma become so thin that corneal warpage takes place, some loss of visual function might be expected (see Chapter 28).

Pathology

Of course, recognition that the stroma has become thinner is in itself a statement of pathological change, but further to this, subtle ultrastructural changes have been observed in the cornea as a result of contact lens wear. These changes may offer valuable insights into the process of stromal thinning.

A good starting point for considering lens-induced structural changes that may be of relevance to stromal thinning is to note the critical role of stromal keratocytes in the synthesis and maintenance of the collagen and extracellular matrix that comprise the bulk of the stroma.[10] Any disruption to the capacity of keratocytes to function normally might be expected to compromise the structural integrity of the cornea. Specifically, if keratocytes are not laying down and maintaining the collagen and extracellular matrix, then there will be a gradual reduction in tissue mass, which may manifest as stromal thinning.

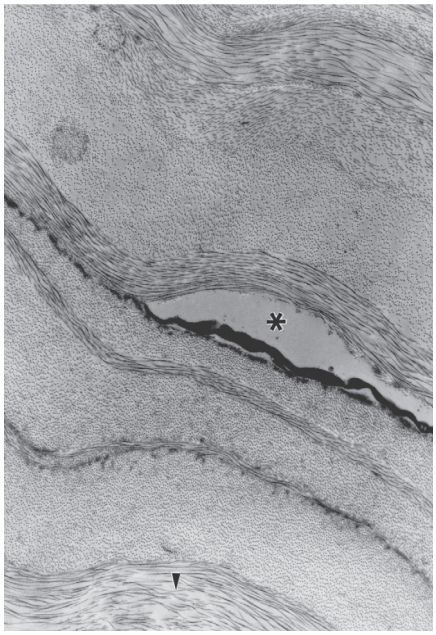


Fig. 23.3 After polymethyl methacrylate (PMMA) lens wear, stromal oedema is most conspicuous around keratocytes and between lamellae, where pooling of extracellular fluid (asterisk) may be present. Intralamellar swelling (triangle) is also evident in places. Primate. Electron micrograph. Magnification × 8,500. (Bergmanson JPG. Light and electron microscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford: Butterworth-Heinemann; 2001. p. 136–77.)

ELECTRON MICROSCOPY

In a primate model, Bergmanson and Chu[11] found that PMMA lens wear induces changes in stromal keratocytes, including the formation of clear zones around the keratocytes along with spaces filled with granular tissue (Fig. 23.3). The theoretical background outlined earlier, coupled with the experimental observations of Bergmanson and Chu,[11] highlighted the need to focus attention on the effect of contact lens wear on stromal keratocytes in human subjects; however, keratocytes are beyond the resolution of the slit lamp biomicroscope, precluding clinical studies using this instrument. It is only through the development of the corneal confocal microscope in the 1990s that the monitoring of keratocytes in the corneas of human subjects has been possible.

CONFOCAL MICROSCOPY

Initial observations of keratocyte populations

Studies of keratocyte populations in humans using the confocal microscope have revealed a loss of keratocytes resulting from contact lens wear (Fig. 23.4). Bansal et al.[12] reported that anterior stromal keratocyte density (KD) (757 ± 243 cells/mm^2) in patients wearing contact lenses on a daily-wear basis was significantly less than that in non–lens wearers (925 ± 276 cells/mm^2). Jalbert and Stapleton[13] used the confocal microscope to measure stromal KD in nine subjects wearing extended-wear hydrogel lenses and nine age- and gender-matched non-lens-wearing control subjects. They reported that stromal KD was lower in the lens-wearing group in both the anterior stroma (544 ± 206 cells/mm^2 vs. 804 ± 145 cells/mm^2 in the non-lens-wearing group) and posterior stroma (514 ± 111 cells/mm^2 vs. 628 ± 101 cells/mm^2 in the non-lens-wearing group). They also described haziness around some keratocytes in the lens-wearing group, which may denote areas of oedema. Jalbert and Stapleton[13] concluded that extended wear of hydrogel lenses reduces stromal KD.

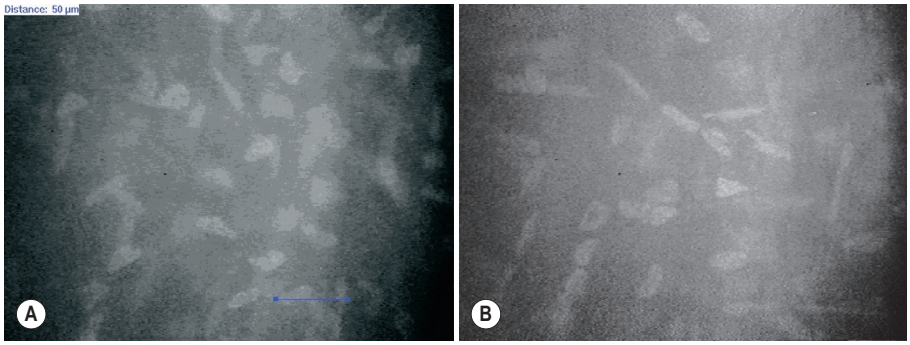


Fig. 23.4 Confocal microscope images of the posterior corneal stroma. The white shapes are keratocytes. **(A)** Control eye (no lens wear). **(B)** Lens-wearing eye. (Courtesy Haliza Mutalib.)

Solving the oedema artefact

A potential error in the studies of Bansal et al.[12] and Jalbert and Stapleton[13] is the failure to account for a methodological problem when using the confocal microscope relating to the confounding influence of oedema on estimates of KD.[14] Simply put, the confocal microscope samples the keratocyte population by capturing an image within a fixed depth of field (10 µm). If the stroma swells and the keratocytes redistribute evenly with the swelling, then fewer keratocytes will be counted within the fixed depth of field, assuming that the total number of keratocytes has remained constant. Thus, the presence of oedema will lead to an underestimation of KD unless measures are taken to account for this effect (Fig. 23.5). A binomial expansion model applied to this problem suggests that the magnitude of the apparent loss of keratocytes should be roughly equivalent to the level of oedema[14]; thus, for example, 10% corneal swelling would lead to an apparent loss of 10% of keratocytes.

Efron et al.[15] followed 23 neophyte myopic subjects who wore a high-Dk/t lens (PureVision) in one eye and a low-Dk/t lens (Acuvue 2) in the other eye on an extended-wear basis for 6 months. Confocal microscopy and ultrasonic pachometry were performed on both eyes at baseline (before lens wear), after 3 and 6 months of lens wear and 1 week after cessation of lens wear (the 'post-cessation' visit). No differences were established between the two lenses or among the three study visits for anterior stromal KD. Posterior stromal KD was similar for the two lenses throughout the study. However, there was an overall drop in posterior KD of 14% in both eyes at the 6-month visit, compared with the initial visit (Fig. 23.6). Posterior KD at the 6-month visit was no different from that at the post-cessation visit. Corneal thickness was similar for the two lenses at the initial and post-cessation visits but was 3% greater for the eye wearing the Acuvue 2 lens at the 6-month visit.

Subsequent observations of keratocytes

Patel et al.[16] examined the corneas of 20 daily contact lens wearers (who had worn lenses for greater than 10 years) and 20 corneas of 20 age-matched control subjects who had never worn contact lenses. Full-thickness central and temporal KDs

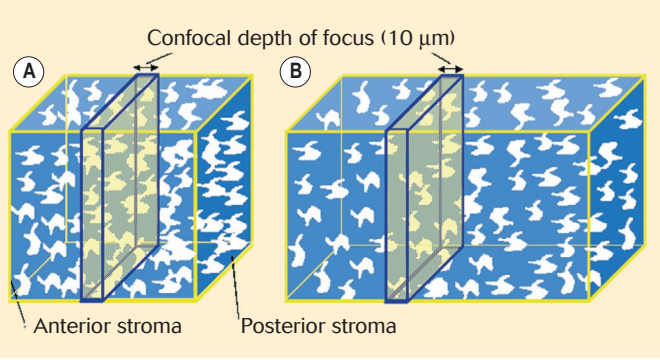


Fig. 23.5 **(A)** Stromal keratocytes (white) can be seen in the 10-µm- thick section (yellow) of stromal tissue (blue) with the confocal microscope. **(B)** The stromal tissue has become swollen and expanded in one dimension (along the anteroposterior axis). Assuming that the number of keratocytes has remained constant, fewer keratocytes will be seen in the 10-µm-thick swollen section with the confocal microscope, giving rise to the illusion of a reduction in the number of keratocytes. (Adapted from Efron N, Mutalib HA, Perez-Gomez I, Koh HH. Confocal microscopic observations of the human cornea following overnight contact lens wear. Clin Exp Optom 2002;85:149–55.)

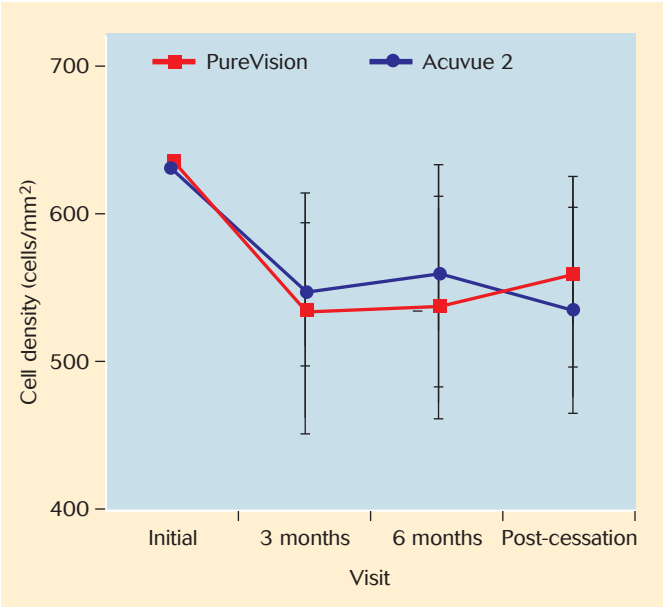


Fig. 23.6 Posterior stromal keratocyte density (mean ± standard deviation) at the initial, 3-month, 6-month and 1-week post-cessation visits. (Adapted from Efron N, Perez-Gomez I, Morgan PB. Confocal microscopic observations of stromal keratocytes during extended contact lens wear. Clin Exp Optom 2002;85:156–60.)

in contact lens wearers were 22,122 ± 2,676 cells/mm^3 and 20,731 ± 2,627 cells/mm^3, respectively, and were not significantly different from central and temporal KDs in control subjects. These authors[16] concluded that long-term daily contact lens wear has no demonstrable effect on KD. This 'negative' result may relate to the fact that lenses were worn on a daily-wear basis, whereas the subjects in the studies of Jalbert and Stapleton[13] and Efron et al.[15] were wearing lenses on an extended-wear basis. However, the negative results of Patel et al.[16] disagree with the findings of keratocyte loss reported by Bansal et al.[12] in that the subjects in both studies were using daily-wear lenses.

It is unclear why baseline estimates of anterior keratocyte density differ between the studies of Efron et al.[15] (1,112 ± 96 cells/mm^2), Bansal et al.[12] (925 ± 276 cells/mm^2) and Jalbert and Stapleton[13] (804 ± 145 cells/mm^2). These differences may be related to the different methods used for cell counting. Interpretation of the data of Bansal et al.[12] and Jalbert and Stapleton[13] has been confounded by the fact that the loss of keratocytes could be attributable, at least in part, to an artefact relating to the presence of residual oedema in the cornea at the time of undertaking confocal microscopy,[14] as outlined earlier. Although Bansal et al.[12] and Jalbert and Stapleton[13] did have patients remove the contact lenses a few hours before performing confocal microscopy, the presence of residual oedema cannot be discounted in view of the demonstration by Holden et al.[1] and Nourouzi et al.[17] that chronic lens-induced oedema can take up to 2 weeks to dissipate.

The study of Efron et al.[15] into the effects of extended contact lens wear on stromal keratocyte populations was designed to account for the potential confounding effects of hypoxic oedema on the determination of KD.[14] This was achieved by comparing the performance of a hydrogel lens of relatively low oxygen performance (Acuvue 2) fitted to one eye (this lens would be expected to induce corneal hypoxia and oedema) with that of a silicone hydrogel lens of relatively high oxygen

performance (PureVision) fitted to the other eye (this lens would not be expected to induce significant hypoxia or oedema). Indeed, the corneal thickness changes observed at the 6-month visit were entirely consistent with the relative oxygen performances of the two lens types; that is, corneal thickness with the Acuvue 2 lens was overall about 3% greater at the 6-month visit than at the initial visit, whereas there was no change in corneal thickness with the PureVision lens.

The 14% reduction in posterior stromal KD with the extended wear of both the Acuvue 2 and PureVision lens reported in the study of Efron et al.[15] is in close agreement with the earlier observations of Jalbert and Stapleton,[13] who reported an 18% drop. The results of the study of Efron et al.[15] indicate that this decrease is not dependent on the oxygen performance of the lens or the effects of oedema; that is, that hypoxia and/or oedema are not of aetiological significance in lens-induced reduction in posterior stromal KD. Furthermore, the reduction in posterior stromal KD cannot be explained by an artefact relating to presence of residual oedema[14] because the decrease noted at 6 months in the oedematous cornea of the eye wearing the Acuvue 2 lens was still evident 1 week after ceasing lens wear, at which time the residual oedema had resolved. It is unclear why Bansal et al.[12] and Jalbert and Stapleton[13] reported a reduction in anterior stromal KD of 18% and 32%, respectively, whereas no change in anterior stromal KD was found in the study of Efron et al.[15]

To further determine the extent of keratocyte loss at various depths throughout the stroma in response to soft and rigid lenses, Kallinikos et al.[18] recruited 33 subjects aged 32 ± 11 years to participate in a 12-month cross-sectional study. Eleven subjects had worn silicone hydrogel (Si-H) lenses on a 30-day continuous-wear basis, 11 had worn rigid gas-permeable lenses on the same basis for 12 months, and 11 age-matched control subjects were observed. Ultrasound pachometry, confocal microscopy and tear fluid sample collection were performed on all subjects. Tear samples were assayed for epidermal growth factor (EGF), hepatocyte growth factor (HGF) and interleukin (IL)-8. Corneal thickness was similar for all subject groups. Total KD was not different among the three groups; however, KD was lower for rigid lens wearers in the anterior to mid-stroma and lower for Si-H lens wearers in the posterior stroma compared with control subjects. Rigid lens wearers exhibited an irregular keratocyte distribution across the corneal stroma (Fig. 23.7).

The tear fluid analysis revealed that EGF concentration and rate of release were greater in the tears collected from the rigid lens wearers and Si-H lens wearers, and IL-8 concentration was higher in the samples collected from the rigid lens wearers compared with the samples collected from the control subjects.

Ohta et al.[19] fitted seven neophyte subjects with rigid lenses (Dk/L 35) and nine with soft lenses (Dk/L 34). After 6 months of lens wear, KD in the anterior and posterior stroma of both groups had decreased by 10% to 20%.

Aetiology

It was originally presumed that stromal thinning is a result of the effects of chronic oedema, and Holden et al.[1] proposed two possible mechanisms. Firstly, stromal keratocytes may lose their ability to synthesise new stromal tissue as a result of (a) the direct effects of lens-induced tissue hypoxia and/or (b) the indirect effects of chronic lens-induced tissue acidosis because of accumulation of lactic acid and carbonic acid. Secondly, constantly elevated levels of lactic acid associated with chronic lens-induced oedema may lead to some dissolution of the mucopolysaccharide ground substance of the stroma.

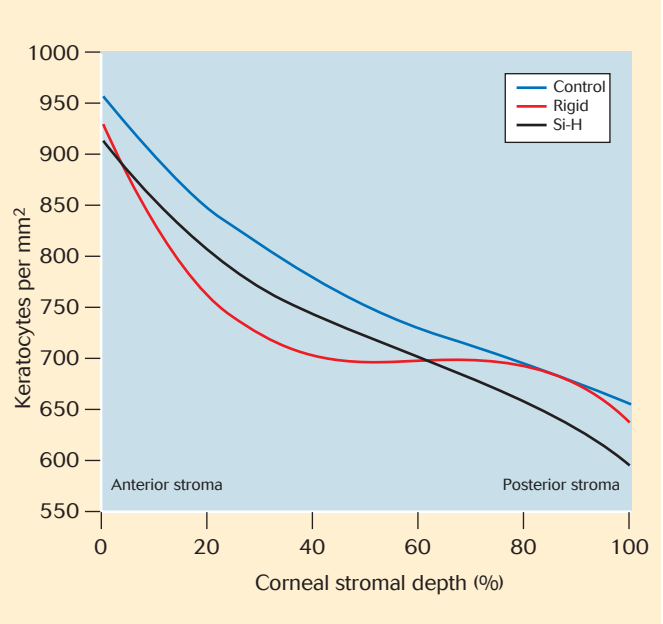


Fig. 23.7 Total keratocyte density for each subject group throughout the stroma. (Adapted from Kallinikos P, Morgan P, Efron N. Assessment of stromal keratocytes and tear film inflammatory mediators during extended wear of contact lenses. Cornea 2006;25:1–10.)

MECHANICAL EFFECTS OF LENS WEAR

The first mechanism referred to previously implies that a full appreciation of contact lens–induced keratocyte dysfunction is fundamental to developing an understanding of lens-induced stromal thinning. As described earlier, the confocal microscope has allowed attention to be focused on the fate of keratocytes during lens wear. Jalbert and Stapleton[13] attributed contact lens–induced keratocyte loss to three possible aetiologies – hypoxia, cytokine-mediated effects and mechanically induced effects. In view of the results of Efron et al.,[15] hypoxia and oedema can be discounted. An obvious common influence of the Acuvue 2 and PureVision lenses on the cornea that could explain the loss of keratocytes in the posterior stroma is the physical presence of the lenses creating a direct (mechanical) or indirect (cytokine-mediated) effect. Certainly, it has been reported that other mechanical effects on the cornea, such as epithelial debridement, are associated with keratocyte loss.[20]

Kallinikos and Efron[21] investigated the aetiology of keratocyte loss after short-term contact lens wear by monitoring quantitative changes in KD. Twenty neophyte subjects aged 26 ± 3 years participated in the study, which was conducted over the course of three experimental sessions. In the first session, one eye of each subject was fitted with a silicone hydrogel contact lens, and the other eye served as the control. Both corneas were exposed to an anoxic environment for 2 hours. Ultrasound pachometry and confocal microscopy were performed on both eyes at baseline, immediately after the experiment and 2 hours after the experiment. This procedure was repeated after 72 hours, but in this case, one eye of each subject was fitted with

a hyper-Dk rigid contact lens, and the fellow eye served again as the control. In the third experimental session, each subject was asked to periodically rub one eye only. Tear samples collected from the rubbed and control eyes were assayed for EGF, HGF and IL-8.

A similar increase in corneal thickness was observed in the experimental and control eyes. Both anterior and posterior KDs decreased in the experimental eyes compared with the control eyes, in all sessions. EGF and IL-8 concentrations were increased in the rubbed eyes compared with the control eyes. On the basis of these findings, Kallinikos and Efron[21] proposed that the mechanical stimulation of the corneal surface resulting from the physical presence of a contact lens induces the release of inflammatory mediators that cause keratocyte dysgenesis or apoptosis. Increased levels of nitric oxide and anti-oxidant enzymes in tears of contact lens wearers may also be implicated in contact lens–associated keratocyte apoptosis.[22]

REFRACTIVE SURGERY

Erie et al.[23] noted a reduction in anterior stromal KD of 25% to 45% during a 36-month period after photorefractive keratectomy. Mitooka et al.[24] and Perez-Gomez and Efron[25] observed a 22% and 34% drop in anterior stromal keratocyte density 6 and 12 months after myopic laser-assisted in situ keratomileusis (LASIK), respectively. Differences in the severity and duration of these two different forms of mechanical and thermal interventions – epithelial debridement and photoablation versus lens-induced epithelial microtrauma – could account for the differences in the extent of keratocyte loss between contact lens[12,13,15] and refractive surgery studies.[20,23,25] Nevertheless, these findings serve to confirm that a combination of mechanical and photorefractive interventions alters keratocyte populations, perhaps in some ways that are analogous to contact lens–induced effects.

MECHANICAL SCRAPE WOUNDS

Wilson et al.[26] detected cell shrinkage, blebbing with formation of membrane bound bodies, condensation and fragmentation of the chromatin and DNA fragmentation in anterior stromal keratocytes after the epithelium was damaged by creating scrape wounds. These authors concluded that the disappearance of keratocytes from the underlying anterior stroma after epithelial debridement is mediated by apoptosis. Clearly, any mechanical effect induced by contact lens wear will be less severe than the overt epithelial damage induced by the experiment of Wilson et al.[26]; nevertheless, this work establishes the principal of keratocyte apoptosis being governed by changes in the epithelium. In any case, the earlier analogy may not apply because the contact lens–induced reduction in stromal KD reported in the study of Efron et al.[15] only occurred in the posterior stroma, and the results of Wilson et al.[26] relate primarily to the anterior stroma.

The loss of posterior keratocytes reported in the 6-month study of Efron et al.[15] was not associated with stromal thinning; perhaps the reason is that stromal thinning is a long-term change that may not become apparent until lenses have been worn for many years. Long-term studies of stromal thickness changes in patients wearing silicone hydrogel contact lenses (which do not induce corneal hypoxia) may provide valuable insights into the aetiology of stromal thinning; the absence of stromal thinning in such circumstances will point strongly to hypoxia as the cause, whereas the presence of stromal thinning associated with silicone hydrogel lenses will suggest an aetiology relating to the physical presence of the lens.

Management

The standard strategy for alleviating any contact lens–related condition is to remove the cause. However, the application of this general strategy in the case of stromal thinning is problematic because the cause is presently unknown. Certainly, Holden et al.[27] failed to develop a predictive model for stromal thinning based on their experimental data.[1]

If it is determined in the future that hypoxia is of aetiological significance in stromal thinning, then the solution to this problem will be to fit lenses that optimise corneal oxygen availability. If the physical presence of a contact lens is deemed to be a key determinant of stromal thinning, then the designing and fitting of lenses that minimise physical contact with the eye will provide the solution. Of course, it is difficult to see how a perfect solution to the avoidance of physical contact could be found; the device is, after all, called a *contact lens*!

ESTIMATING STROMAL THINNING

There are important clinical ramifications of contact lens–induced stromal thinning, in addition to this being of interest from the standpoint of understanding fundamental mechanisms of corneal physiology. Stromal thinning may be associated with a structural weakening of the cornea, leading to a greater susceptibility to contact lens–induced corneal warpage and refractive changes (see Chapter 28). Thus, measurement of corneal thickness may at least assist practitioners in reconciling clinical phenomena thought to be related to structural weakening of the cornea.

Assuming that (a) the cornea of a contact lens wearer was 550 μm before commencing lens wear, (b) the epithelium will thin by a total of about 5 μm, and (c) the stroma thins by about 2.5 μm per year of lens wear, then one might expect the presenting corneal thickness of a lens wearer to be as follows:

$$\text{Presenting corneal thickness} = 545 - [2.5 \times (\text{Years of lens wear})]\mu\text{m}$$

For example, a patient who has been wearing lenses for 16 years might be expected to have a corneal thickness of 505 μm (i.e. $545 - [2.5 \times 16]$).

ADVICE REGARDING REFRACTIVE SURGERY

A significant percentage of patients who contemplate corneal refractive surgery wear contact lenses. Lens-induced stromal thinning may preclude a patient with myopia from undergoing refractive surgery because there may be insufficient corneal tissue available for ablation to safely create the desired refractive change. Indeed, pachometry is an important pre-screening test for all potential refractive surgery patients, and Seiler et al.[28] suggested that the minimum residual corneal thickness after ablation should be 250 μm to prevent ectasia. Thus, contact lens wearers should be warned at an early stage that long-term lens wear may preclude them from having refractive surgery at a later date because of lens-induced stromal thinning.

Prognosis

In the study of Holden et al.,[1] the subjects discontinued lens wear for 1 month so that recovery of any lens-induced changes over this period could be monitored. As can be seen from Figure 23.2, the stromal thinning that was evident after 7 days (once the acute lens-induced oedema had subsided) displayed no signs of recovery over the following 23 days. Five subjects were convinced by Holden et al.[29] to refrain from wearing lenses for a further 5 months, and it was observed that stromal thickness appeared to be gradually returning to normal. These authors[29] concluded, therefore, that lens-induced stromal thinning is 'very long lasting'.

Ohta et al.[19] observed that the 10% to 20% reduction in KD in the anterior and posterior stroma of soft lens wearers was reversed within 5 weeks of discontinuing soft lens wear; that is, KD had returned to baseline levels.

MICRODOTS

In what may be a corollary of stromal thinning, Bohnke and Masters[30] described a condition which they termed 'stromal microdot degeneration' (Fig. 23.8). They suggested that numerous small white dots seen with the confocal microscope in long-term contact lens wearers may be a sign of stromal degeneration, and that this '… may be the early stage of a significant corneal disease, which eventually may affect large numbers of patients after decades of contact lens wear'. This rather bleak prognosis must be tempered by the fact that Bohnke and Masters[30] apparently failed to notice that microdots can also be observed in normal non–lens wearers, albeit in lower numbers.[31,32]

Trittibach et al.[33] used a confocal microscope to examine 36 patients with myopia and a 15- to 43-year history of PMMA, rigid gas-permeable lens wear or soft hydrogel contact lens wear and 12 age-matched non-lens-wearing control subjects. Microdots were encountered throughout the entire depth of the corneal stroma in all contact lens wearers. None of the control subjects showed microdot deposits. They suggested that microdots may represent granules of lipofuscin-like material within the corneal stroma of long-term contact lens wearers, formed as a result of chronic oxygen deprivation and chronic microtrauma to the cornea. Among the independent variables examined, soft contact lens wear time had the most profound influence on numerical microdot density and size.

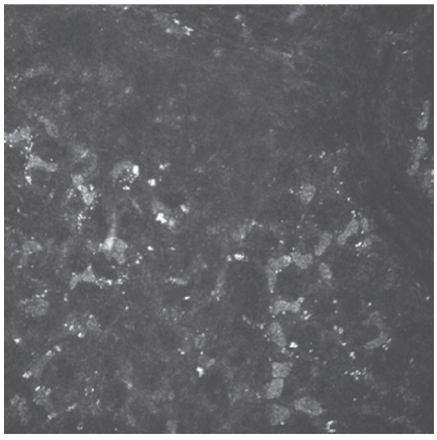


Fig. 23.8 Extensive formation of stromal microdot deposits in a 43-year-old male who has been wearing rigid lenses for many years. (Courtesy Nicola Pritchard.)

Hollingsworth and Efron[34] reported an increased number of microdot opacities in the corneas of patients wearing rigid lenses compared with a matched control group of non-lens-wearing subjects.

Thus, stromal microdots may represent visible evidence of accelerated keratocyte apoptosis. If keratocyte apoptosis is associated with stromal thinning, then stromal microdots may be an associated feature in advanced cases. Further research would be required to validate such an association.

Differential diagnosis

Contact lens–induced stromal thinning needs to be differentiated from stromal thinning associated with corneal diseases and dystrophies.

RECURRENT MICROBIAL KERATITIS

Cardona and Saona-Santos[35] reported the case of a 38-year-old Caucasian female who developed corneal thinning resulting from recurrent episodes of microbial keratitis. The thinning was so extensive that the patient had to undergo bilateral corneal grafting.

KERATOCONUS

An obvious candidate for differential diagnosis is keratoconus, a condition characterised by apical corneal thinning (Fig. 23.9), distortion and steepening; irregular astigmatism; and poor spectacle visual acuity. Pflugfelder et al.[36] demonstrated that two indices generated from measurements obtained from the Orbscan Corneal Topography System (CTS; Orbscan, Inc., Salt Lake City, Utah, USA) can be used to distinguish contact lens–induced corneal thinning from keratoconus. These are the 'corneal thickness index' and a mathematically derived 'discriminant function'.

PELLUCID MARGINAL DEGENERATION

Pellucid marginal degeneration is an uncommon variant of keratoconus. A corneal protrusion occurs inferiorly, usually above a narrow band of clear, neovascularised, thinned corneal stroma, and is concentric with the limbus. The corneal protrusion is steepest directly above the band of corneal thinning, resulting in a 'beer belly' appearance. The thinning can also occur superiorly. In Figure 23.10, the classic inferior 'beer belly' appearance is evident, as well superior thinning. The key aspect of differential diagnosis is that contact lens–induced stromal thinning occurs across the whole cornea, whereas thinning occurs at the corneal margin in pellucid marginal degeneration.

TERRIEN'S MARGINAL CORNEAL DEGENERATION

Peripheral corneal thinning is also a characteristic of Terrien's marginal corneal degeneration. This is a symmetrical, ectatic, marginal corneal dystrophy, seen more often in middle-aged men.[10] The degeneration usually occurs in the superior cornea but may occur anywhere around the limbus. It begins as a fine, punctate stromal opacity similar to corneal arcus. The affected region becomes vascularised and an indentation develops

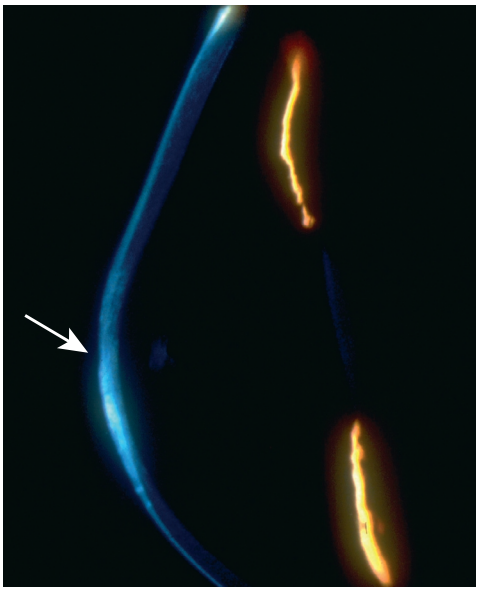


Fig. 23.9 Keratoconus displaying stromal thinning (arrow). (Courtesy Albert Aandekerk, Bausch & Lomb Slide Collection.)

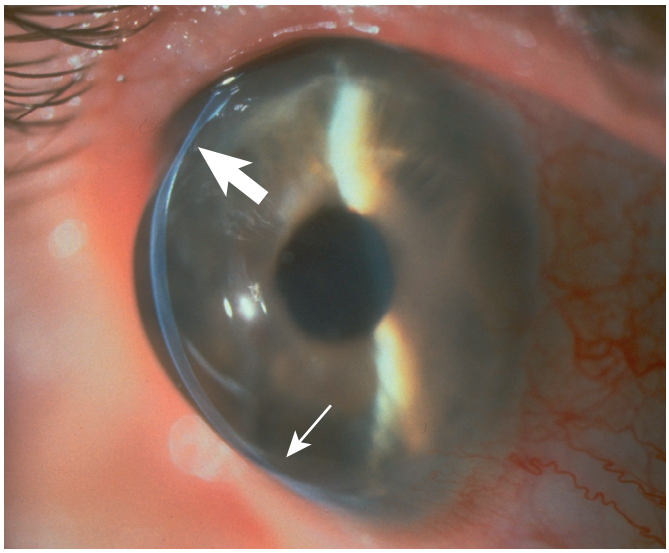


Fig. 23.10 Pellucid marginal degeneration, showing thinning of the superior cornea (thick arrow) and inferior cornea (thin arrow). (Courtesy Albert Aandekerk, Bausch & Lomb Slide Collection.)

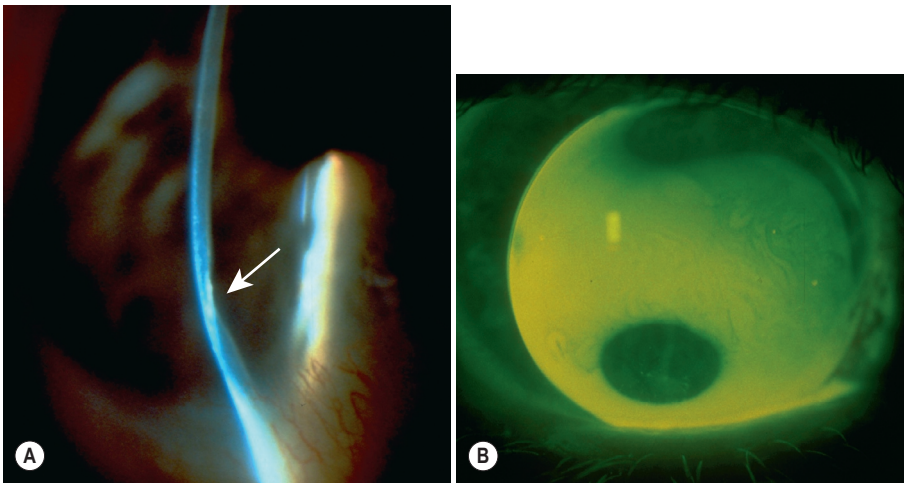


Fig. 23.11 Terrien's marginal corneal degeneration. **(A)** Stromal thinning (arrow). **(B)** Fluorescein pattern of rigid lens fit on the cornea in **(A)** showing heavy bearing inferiorly at the region of protrusion. (Courtesy Jan Kok, Bausch & Lomb Slide Collection.)

parallel to the limbus, followed by progressive thinning (Fig. 23.11A). The thinned region may eventually bulge ectatically (Fig. 23.11B). As in the case of pellucid marginal degeneration, differential diagnosis relates to the identification of pan-corneal versus marginal stromal thinning.

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24 Deep Stromal Opacities

A limited number of reports have been published in the literature detailing the appearance of deep stromal opacities in the eyes of contact lens wearers. As will be discussed in this chapter, the evidence in some of these reports supporting the notion that deep stromal opacities are caused by contact lens wear is not entirely convincing. However, the possibility of a causative relationship in some of the reported cases cannot be discounted. In view of the uncertainty surrounding causation, this condition shall be referred to as contact lens–*associated* deep stromal opacification.

Signs

Reports of deep stromal opacities can be traced as far back as 1982.[1] There have been relatively few publications describing this condition and accounts of the clinical presentation vary considerably. It is therefore not possible to provide a definitive description of contact lens–associated deep stromal opacities. In view of this, each of the reports of this condition shall be reviewed in chronological sequence of their date of publication.

Pinckers et al.[2] observed whitish dots in the stroma of the cornea, resembling a cloudy dystrophy, in four patients wearing hydroxyethyl methacrylate (HEMA) contact lenses. They referred to this condition as 'contact lens–induced pseudodystrophy of the cornea'. A lattice-like corneal pattern was seen in another patient wearing HEMA contact lenses. Corneal sensitivity was normal or reduced.

In 32 long-term contact lens wearers (up to 19 years), deep whitish opacities directly adjacent to Descemet's membrane were observed by Remeijer et al.[3] in the central part of the cornea. These opacities were seen in HEMA contact lens wearers and polymethyl methacrylate (PMMA) contact lens wearers. Endothelial cell density was normal, but there was marked polymegethism of the endothelium commensurate with the duration of lens wear.

A case of deep stromal opacities is shown in Figure 24.1. This 24-year-old female patient had been wearing HEMA lenses for only 4 years. There were no visual complaints or reports of discomfort. Viewed using a thin optic section (Fig. 24.2), it can be seen that the opacities are confined to the posterior stroma.

In their review of deep stromal opacification, Loveridge and Larke[4] reported the case of a 42-year-old white Caucasian female displaying deep stromal opacification centrally and slightly inferior to the pupil, and just anterior to Descemet's membrane (Fig. 24.3). Stellate folds were visible in Descemet's membrane. The patient had a history of 19 years of PMMA lens wear, followed by 6 years of soft HEMA lens wear. There was a degree of polymegethism and pleomorphism of the endothelium consistent with the duration of lens wear. Her contact lenses had a prescription of R −3.75 D, L −5.00 D, and she had worn lenses 13 hours per day without any apparent problems. The patient had been using a care system containing the preservatives chlorhexidine and thimerosal.

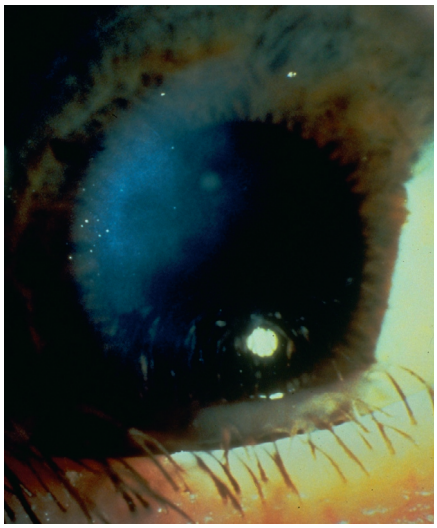


Fig. 24.1 Deep stromal opacities observed in a contact lens wearer. (Courtesy F.E. Ros, Bausch & Lomb Slide Collection.)

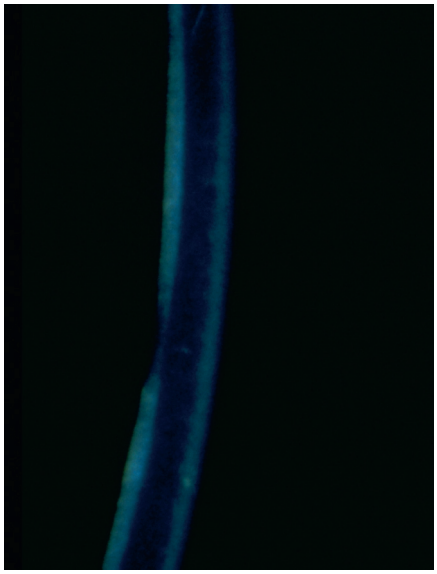


Fig. 24.2 Optic section of cornea shown in Figure 24.1, demonstrating the posterior location of the opacification. (Courtesy FE Ros, Bausch & Lomb Slide Collection.)

Brooks et al.[5] described two cases in which deep corneal stromal opacities occurred after prolonged contact lens wear. The opacities were associated with folds or striae in Descemet's membrane. Although the corneal endothelial cell counts were within the normal range, the count was reduced in the affected eye in the patient with the unilateral deep stromal opacity, and there was mild polymegethism of the endothelial cells.

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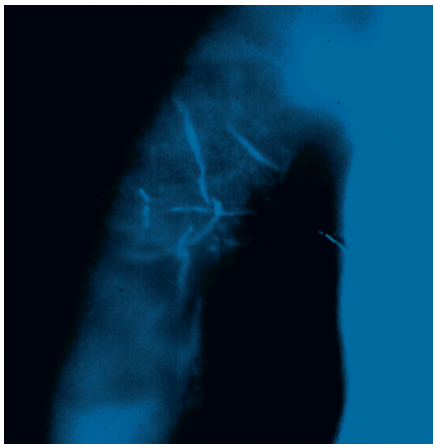


Fig. 24.3 Deep stromal opacities observed in a contact lens wearer. (Loveridge R, Larke JR. Deep stromal opacification: A Review. J Br Contact Lens Assoc 1992;15:109–14.)

Hoang-Xuan et al.[6] reported two cases of patients who had worn soft contact lens for 5 and 8 years on a daily-wear basis. These patients presented with bilateral central avascular haze immediately anterior to Descemet's membrane, and the haze was associated with mild stromal oedema and Descemet's folds. Endothelial polymegethism was observed with the specular microscope.

Holland et al.[7] reported six cases where the patients presented with a mottled cyan opacification at the level of Descemet's membrane. These opacities were located in the peripheral and mid-peripheral cornea. All patients had bilateral findings, and all patients had worn soft contact lenses bilaterally for periods ranging from 7 to 14 years.

Pimenides et al.[8] reported the cases of one male and three female long-term HEMA contact lens wearers (mean age 30.3 years; range 26–33 years) who demonstrated deep stromal opacities which were predominantly just anterior to Descemet's membrane. None had any history of corneal dystrophy. These opacities were more common centrally but were also identified in the corneal periphery. Lenses had been worn for a mean of 14.3 years (range 10–17 years), and lenses had been worn for a mean of 14.3 hours per day (range 12–16 hours). Specular microscopy disclosed cell densities within normal limits (mean 3,041.5 cells/mm^2), and the coefficient of variation of mean cell area was 0.31. Refractive errors ranged from −12.25 diopter (D) to +6.25 D best vision sphere.

Confocal microscopy was used by Hsu et al.[9] to examine a 45-year-old white male who presented with 3 weeks of photophobia and foreign body sensation after extended contact lens wear. Initial slit lamp examination showed central stromal opacities, thinning and hyperopic shifts, more in the right eye than in the left eye. Confocal microscopy revealed the presence of collagen fibril oedema and rearrangement with cellular infiltration and sparse refractile elements.

Symptoms

COMFORT

Although Brooks et al.[5] and Hsu et al.[9] noted that the development of the opacities was associated with ocular discomfort and photophobia, other authors suggested that deep stromal opacities are asymptomatic.[2,7]

VISION

The degree of vision loss is variable. Pinckers et al.[2] reported that visual acuity was normal in the four patients they examined. All four patients in the case series reported by Pimenides et al.[8] attained at least 6/9 visual acuity. The six patients examined by Holland et al.[7] had visual acuities of 6/6 or better.

Some authors have reported reduced vision in cases of deep stromal opacification. Vision loss was severe in the two cases reported by Hoang-Xuan et al.,[6] and in the case report of Loveridge and Larke,[4] the patient had corrected visual acuity of R 6/18$^+$ L 6/12. Remeijer et al.[3] noted that deep stromal opacities could reduce visual acuity, and the patients examined by Brooks et al.[5] suffered from reduced vision.

Hsu et al.[9] reported that resolution of the opacity was accompanied by a 2.00 D hyperopic shift in refraction.

Pathology

COMPARISON WITH PRE-DESCEMET'S DYSTROPHIES

There do not appear to have been any published ultrastructural studies of corneal tissue from patients suffering from contact lens–associated deep stromal opacification. However, an important defining characteristic of this condition is that the region of affected tissue is just anterior to Descemet's membrane and the endothelium (Fig. 24.4) – a characteristic which also defines a spectrum of sporadically appearing degenerative changes collectively referred to as pre-Descemet's dystrophies.[10]

The opacities in pre-Descemet's dystrophies usually appear between the fourth and seventh decades of life and may show a variety of morphologies. Familial occurrences have been described, but not in all cases. Histopathological studies obtained in one case of pre-Descemet's dystrophy showed the pathological involvement to be limited to the posterior stromal keratocytes, with vacuolization and enlargement of the affected cells and histochemical staining of lipid-like material.[11] Transmission electron microscopy showed cytoplasmic membrane-bound vacuoles containing a fibrillogranular material and electron-dense lamellar inclusions,[11] suggesting an accumulation of lipofuscin-like material. No extracellular deposition of a similar material was noted.

ENDOTHELIAL INVOLVEMENT

Brooks et al.[5] advanced the interesting hypothesis that that the long-term effects of subtle endothelial cell changes induced by lens wear cause a keratopathy with later scarring and opacification; that is, lens-induced endothelial dysfunction is the *cause* of deep stromal opacities (see Part VIII: 'Corneal endothelium'). An alternative explanation is that long-term contact lens wear induces the formation of deep stromal opacification, which, in turn, adversely affects the endothelium.

Although it is unclear which of the previous hypotheses is true, deep stromal opacities are in such close proximity to the endothelium that the function of this tissue layer may be adversely affected. This possibility was examined by Gobbels et al.,[12] who used a computerised automated fluorophotometer to measure corneal endothelial permeability in 21 patients who had worn HEMA contact lenses on a daily-wear basis for more than 10 years and who displayed deep stromal and pre-endothelial corneal opacities. They made the same measurements on an

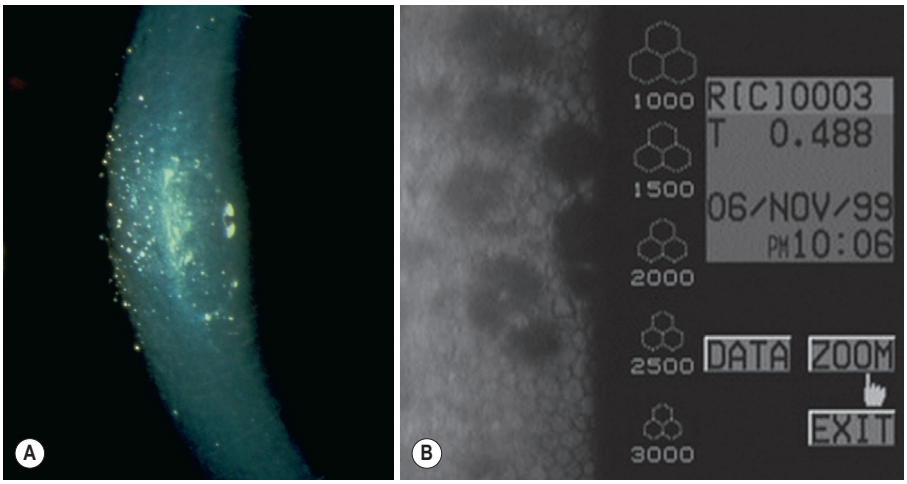


Fig. 24.4 **(A)** Pre-Descemet's dystrophy, appearing on slit lamp biomicroscopic examination as a localised region of deep stromal opacities just anterior to the endothelium. **(B)** Pre-Descemet's dystrophy, appearing on specular microscopic examination as a series of dark shadows just anterior to and obscuring the endothelium. (A, Courtesy Jan Kok, Bausch & Lomb Slide Collection. B, Courtesy Sydney Bush.)

age-matched group of eight healthy individuals without ocular disease. These authors[12] found that the corneal endothelial permeability of contact lens wearers with deep corneal opacities was significantly greater compared with that of contact lens wearers without this condition. Furthermore, contact lens wearers without corneal opacities showed no significant increase in endothelial permeability compared with the control group.[12]

MICRODOT DEPOSITS

Using corneal confocal microscopy, Böhnke and Masters[13] found highly reflective 'microdot deposits' throughout the corneal stroma of contact lens wearers (see Figure 23.8). These microdots, which could be the magnified appearance of deep stromal opacities, are seen with confocal microscopy as small, discrete, brightly reflective spots or dots scattered throughout the stroma; they are generally round or oval in shape and vary in diameter from about 1 to 4 μm.

Böhnke and Masters[13] characterised this finding as being indicative of disease and established a grading scale to quantify the severity of the microdot response in various groups of lens wearers and non–lens wearers (from 0 (none) to 4 (severe)). All 13 patients who had worn soft contact lens for an average of 26 years displayed pan-stromal microdot deposits with a mean score of 3.1. In the hard contact lens group (average 25 years wear), all 11 subjects displayed corneal microdot deposits, with a mean score of 1.9. In the control group, none of 29 patients had stromal microdot deposits (mean score 0.0). The authors concluded that stromal microdot degeneration as observed with confocal microscopy may be the early stage of significant corneal disease, which eventually may affect large numbers of patients after decades of contact lens wear.

Trittibach et al.[14] used confocal microscopy to examine 36 myopic patients with a 15- to 43-year history of PMMA, rigid gas-permeable or soft hydrogel contact lens wear and 12 age-matched emmetropic or spectacle-corrected myopic volunteers. They observed microdot deposits throughout the entire depth of the corneal stroma in all contact lens wearers and noted that none of the control subjects showed microdot deposits. The density (65,100 ± 26,900 dots/mm^2) and size (3.04 ± 0.92 μm) of microdots were similar in each of the stromal layers (anterior, middle and posterior). An association was also noted between soft contact lens wear time and the size and density of microdot deposits. These authors suggested that microdot deposits may represent granules of lipofuscin-like material within the corneal stroma of long-term contact lens wearers and that this material is formed as a result of chronic oxygen deprivation and chronic microtrauma to the cornea.

The corneas of one eye of 13 patients (age 32 ± 7 years) who had worn contact lenses for an average of 8.2 years were examined by Efron and Mutalib[15] using the confocal microscope, as was the cornea of one eye of each of 13 age- and gender-matched control subjects who had never worn contact lenses. Considerable variation in the intensity of microdots was observed throughout the stroma of a given eye; therefore, three frames from the confocal video sequence that displayed the greatest number of microdots were selected for analysis. To facilitate quantification of the severity of microdots, Efron and Mutalib[15] constructed a microdot grading scale, along the lines of that devised by Böhnke and Masters,[13] from a series of five images depicting the span from 'no microdots observed' (grade 0) to a severe case of microdots (grade 4).

Microdot deposits were observed in the stroma of all 13 lens wearers, with a mean severity of grade 2.0 ± 1.1. However, contrary to the findings of Böhnke and Masters[13] and Trittibach et al.,[14] microdots were observed in 10 of the 13 non-lens-wearing subjects, with a mean severity in the 10 eyes displaying microdots of 1.5 ± 0.7. The difference in the severity of microdots was statistically significant ($t = -2.47$; $p < 0.02$). The microdots had an identical appearance in lens-wearing and control subjects, apart from the difference in grading relating to the number of microdots. They were all fairly similar in size (1–2 μm diameter).

In response to a challenge as to the accuracy of their findings,[16] Trittibach[17] speculated that their failure to record microdot deposits in non–lens wearers related to their criterion for considering a 'white dot' observed in a confocal microscopy image as a stromal microdot. Specifically, Trittibach et al.[14] counted only 'clearly visible, hyper-reflective, round or near-round structures as 'true' stromal microdot deposits.' Trittibach[17] also noted that 'dust-like, low reflective structures in the

sub-micron range' were not regarded as distinct microdots and were, therefore, not counted.

Bastion and Mohamad[18] reported the presence of microdot deposits in regular soft contact lens users. Amongst 56 soft lens wearers examined, 10 displayed microdot deposits. Those who displayed microdot deposits had been wearing lenses for 13.6 ± 4.4 years, whereas those soft lens wearers who did not display microdot deposits had been wearing lenses for 8.2 ± 5.1 years. This observation supports the finding of Trittibach et al.[14] of an association between soft contact lens wear time and the size and density of microdot deposits.

In a study of 22 subjects wearing rigid lenses on a daily-wear basis, Hollingsworth and Efron[19] observed that the maximum number of microdots seen with scanning slit confocal microscopy in the right eye was 1.68 ± 1.55 per 315 μm × 235 μm image frame (mean ± SD; range 0–6), compared with 0.91 ± 1.07 (range 0–3) in an age- and gender-matched non-lens-wearing control group. The difference between the two groups was shown to be statistically significant ($t = 2.05$; $p = 0.05$).

Linke et al.[20] reported the case of a 46-year-old woman who was referred with the suspected diagnosis of posterior polymorphous dystrophy. Slit lamp biomicroscopy revealed bilateral small-sized deposits in the posterior part of the cornea. Examination of the cornea using confocal microscopy identified hyper-reflective 'dot-like' structures in the deep stromal layer and anterior to the endothelial cell layer. The morphology and number of keratocytes of the posterior stroma and of endothelial cells appeared normal. This patient was not a contact lens wearer, indicating that microdot deposits may also be associated with corneal diseases or dystrophies.

Yagmur et al.[21] performed confocal microscopy on 142 eyes of 71 myopic contact lens wearers and 142 eyes of 71 matched non–contact lens wearers. The mean duration of contact lens wear was 43.9 ± 15.3 months (range 6–240 months). Stromal microdots were observed in 39% of lens wearers; no microdots were observed among non–lens wearers. Fifteen per cent of lens wearers who had been wearing lenses 30 months or longer displayed microdots versus 62% who had been wearing lenses for longer than 30 months.

Böhnke and Masters[13] stated that the condition of stromal microdot degeneration as observed with confocal microscopy may be the early stage of significant corneal disease. The fact that microdot deposits are observed in all subjects, whether or not contact lenses have been worn, suggests that this phenomenon *per se* cannot be properly characterised as a disease. However, the higher grade assigned to microdots in contact lens wearers indicates that lens wear exacerbates otherwise normal corneal morphological features or processes. It is possible that stromal microdot degeneration is a precursor to some forms of contact lens–associated deep stromal opacification, especially in view of the demonstration by Curran et al.[11] that pathological involvement in this condition is limited to the posterior stromal keratocytes, as discussed earlier.

Aetiology

There does not appear to be any consensus among the authors of case reports of deep stromal opacities as to the cause of this condition. Indeed, a wide variety of aetiological factors has been advanced, including the following:

- long-term contact lens wear[3,5,7];
- exposure to heavy metals[7];
- allergic reaction to thimerosal[3];
- exposure to chlorhexidine[3];
- chronic hypoxia[3,5,6];
- chronic hypercapnia[3,5];
- endothelial dysfunction[3-6];
- suction effects by the lens.[5]

Hsu et al.[9] suggested that the clinical findings in their patient resembled central toxic keratopathy which is sometimes seen after refractive surgery, suggesting a similar mechanism. These authors suggested that the absence of necrotic debris supports a cytokine-triggered apoptosis mechanism, rather than inflammatory cell-mediated necrosis, as the cause of stromal tissue loss.

Treatment

Recommendations offered by the authors of case histories of deep stromal opacification regarding treatment of this condition generally relate to the perceived aetiology. Brooks et al.[5] emphasised the importance of early recognition and treatment, particularly with a better-fitting lens of high oxygen transmissibility. Avoidance of the use of solution preservatives, such as chlorhexidine and thimerosal, is no longer an issue because these chemicals are not used in modern contact lens care systems.

In cases where the cornea appears to be severely compromised, lens wear should be ceased for up to 12 months,[4,6] or discontinued permanently. Loveridge and Larke[4] obtained apparent success in a patient who had suffered from deep stromal opacities by refitting the patient with rigid lenses after cessation of lens wear for 12 months. Pinckers et al.[2] and Remeijer et al.[3] also achieved success after replacement of HEMA lenses with rigid lenses.

Hsu et al.[9] treated their patient with topical corticosteroids, and the patient was advised to discontinue lens wear.

Prognosis

The prognosis for recovery from deep stromal opacities is, at best, protracted. Pimenides et al.[8] reported that the density of the stromal opacities diminished over a period of months after cessation of contact lens wear in two cases. Hoang-Xuan[6] observed that more than 1 year after removal of contact lenses, only one patient fully recovered her initial visual acuity. Remeijer et al.[3] noted that the lesions gradually diminished and resolved completely in most patients. According to Brooks et al.,[5] once the opacities develop, they regress only slowly and may result in permanent visual impairment. Pinckers et al.[2] reported that the pseudo-dystrophies vanished after changing the lens type.

Loveridge and Larke[4] monitored their patient for 12 months after cessation of lens wear because of deep stromal opacities. Although the appearance of folds and corneal distortion slowly resolved and vision improved – factors which would normally discount the possibility of the condition being diagnosed as a dystrophy – this resolution may have been related more to the subsidence of lens-induced oedema than to the regression of stromal opacities.

In the case reported by Hsu et al.,[9] only trace corneal haze was evident after 7 months of treatment.

Differential diagnosis

STROMAL DYSTROPHIES

It is highly likely that some of the cases reported as deep stromal opacification in contact lens wearers are, in fact, stromal

dystrophies that present coincidentally with, but are unrelated to, contact lens wear. Perhaps it is this uncertainty that led Pinckers et al.[2] and Hoang-Xuan et al.[6] to refer to this condition as a 'pseudo-dystrophy' of the cornea. Consider, for example, the report of Loveridge and Larke[4] of an apparent case of contact lens–associated deep stromal opacities. The photograph of that condition (Fig. 24.3) is almost identical to Figure 18.34 in Kaufman et al.,[22] depicting lattice dystrophy of the stroma.

The three major stromal dystrophies are described as granular dystrophy (Fig. 24.5), macular dystrophy and lattice dystrophy. The characteristics of these dystrophies are presented in Table 24.1. Comparison of the features observed in a suspected case of contact lens–associated deep stromal opacification with the characteristics of stromal dystrophies described in Table 24.1 will facilitate differentiation of these conditions.

Stromal dystrophies characterised by additional distinct features that have been described in the literature[22] include

- central crystalline dystrophy of Schnyder;
- fleck dystrophy;
- central cloudy corneal dystrophy of Francois;
- posterior amorphous corneal dystrophy;
- congenital hereditary stromal dystrophy; and
- pre-Descemet's dystrophy.

Because of the wide variety of appearances of both contact lens–associated deep stromal opacities and stromal dystrophies, it is not possible to define differentiating features of these conditions in terms of appearance, except to state that contact lens–associated deep stromal opacities, by definition, are located deep in the stroma. This consideration would at least facilitate differentiation of contact lens–associated deep stromal opacities from some dystrophies that are characteristically located at more anterior locations in the stroma.

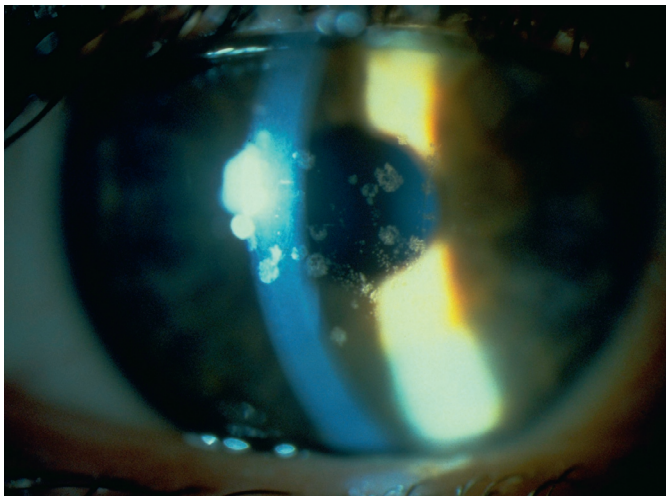


Fig. 24.5 Granular dystrophy. (Courtesy Charline Gauthier, Bausch & Lomb Slide Collection.)

TABLE 24.1 Characteristics of the three major stromal dystrophies

Feature	Granular dystrophy	Macular dystrophy	Lattice dystrophy
Age at onset of deposits	First decade	First decade	First decade
Age at onset of symptoms	Third decade	First decade	Second decade
Age at onset of vision loss	Fourth decade	First decade	Second decade
Heredity	Autosomal dominant	Autosomal recessive	Autosomal dominant
Erosions	Uncommon	Common	Frequent
Opacities	Discrete with sharp borders Intervening stroma clear early, but becoming progressively cloudy Not to limbus	Indistinct margins Hazy intervening stroma early Extends to limbus Endothelium affected Central lesions more anterior Peripheral lesions more posterior	*Early:* Tiny refractile lines and dots Sub-epithelial spots Diffuse central haze *Late:* Lattice lines with knobs Amorphous various-sized deposits Stromal haze Limbal zone clear, except in extreme cases
Corneal thickness	Normal	Thinned	Normal
Characteristic histochemical stains	Masson's trichrome Luxol fast blue Anti-bodies to microfibrillar protein	Periodic acid–Schiff Colloidal iron Alcian blue Metachromatic dyes	Periodic acid–Schiff Congo red Thioflavine-T Crystal violet Positive birefringence and dichroism
Material accumulated	Phospholipids Microfibrillar protein	Glycosaminoglycans	Amyloid
Ultrastructure	Electron-dense, rod-shaped structures surrounded by 8 to 10 nm microfibrils	Intra-cytoplasmic membrane-limited vacuoles filled with fibrillogranular material or lamellar bodies Similar vacuoles in endothelium	Characteristic 8 to 10 nm electron-dense, non-branching amyloid fibrils
Distinguishing clinical characteristics	Clear limbal zone	Opacities reach limbus Cornea thinned unless decompensated	Lattice lines

After Kaufman HE, Barron BA, McDonald MB. The Cornea. 2nd ed. Boston, MA: Butterworth-Heinemann; 1998.

Perhaps the key feature that differentiates contact lens–associated deep stromal opacities from corneal dystrophies is that dystrophies are invariably irreversible and progressive, whereas contact lens–associated deep stromal opacities appear to have the capacity to resolve once lens wear has ceased.

STROMAL INFILTRATES

Corneal infiltrates can appear as a discrete, white, region of haze in the stroma. The aetiology of this condition is multi-factorial; infiltrates may represent a sub-clinical inflammatory reaction to bacterial endotoxins, or could be caused by such factors as toxicity, immunological reaction, metabolic disturbance and trauma (see Chapter 26). Infiltrates can be differentiated from deep stromal opacities in that the former are usually present in the anterior stroma, often overlapping into the epithelium.

STROMAL SCARS

Dense scars often remain in the cornea after a severe infection (Fig. 24.6). These can penetrate deep into the cornea. A complete ocular history ascertained from the patient should reveal the occurrence of a previous infection and thus assist in differential diagnosis from deep stromal opacification.

Stromal scarring is often evident in advanced cases of keratoconus (Fig. 24.7), and it is likely that the extent of opacification is exacerbated by rigid lens wear. Confirmation of other signs of keratoconus facilitates differentiation of this cause of stromal opacification from contact lens–associated deep stromal opacities.

OTHER CAUSES

A variety of other influences can cause stromal opacification, which, in turn, can manifest in various forms. A number of these are likely to be observed in contact lens practice.

Figure 24.8 shows the cornea of a female patient with aphakia referred for soft contact lenses to treat band calcification of the cornea. The calcification is suspected to have been caused by incomplete lid closure caused by partial upper lid paresis. The patient history and characteristic band appearance of the opacity allow this condition to be differentiated from contact lens–associated deep stromal opacities.

A bizarre case of a defined, bilateral and symmetrical ring of stromal opacification in the mid-peripheral stroma is shown in Figure 24.9. The rings had been present for 8 years and the cause remains unknown.

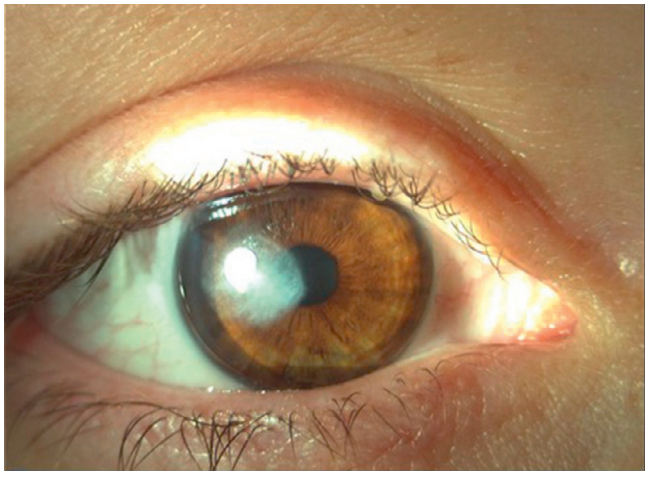


Fig. 24.6 Dense stromal scar after severe infection.

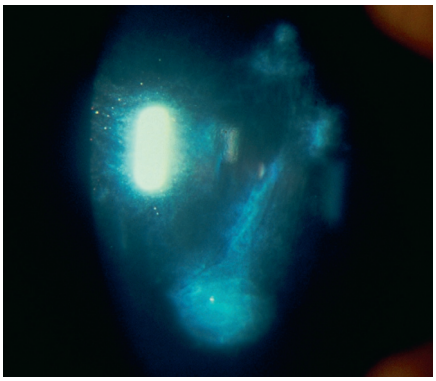


Fig. 24.7 Stromal scarring in keratoconus. (Courtesy Patricia Hyrnchak, Bausch & Lomb Slide Collection.)

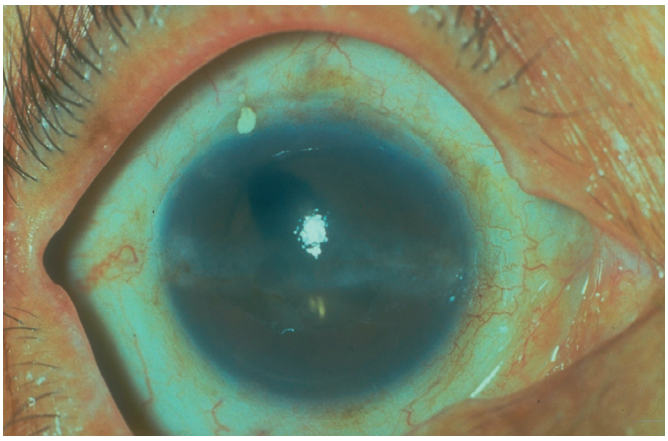


Fig. 24.8 Band keratopathy. (Courtesy Meredith Reyes, Bausch & Lomb Slide Collection.)

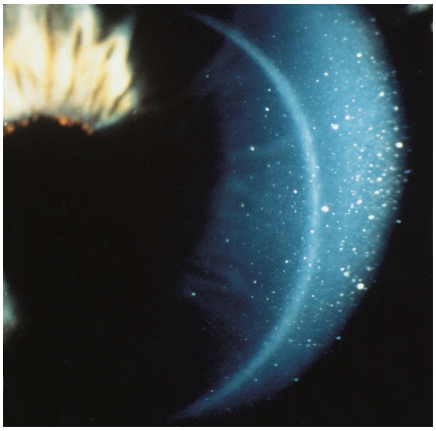


Fig. 24.9 Idiopathic ring of opacification in the mid-peripheral stroma. (Courtesy Patrick Caroline, Bausch & Lomb Slide Collection.)

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25 Corneal Neovascularization

Although reports of contact lens–induced corneal neovascularization can be traced back as far as 1929[1] it is only in the past five decades that this problem has attracted the attention of contact lens practitioners at large. A variety of terms can be used to describe the vascular response of the cornea to lens wear. This has unfortunately resulted in some ambiguity in the literature, with various authors using different terms to describe the same phenomenon or using the same term to describe different phenomena. Some of the more commonly used terms that are used to define the presence of blood vessels in the cornea are as follows:

Vascularization: The normal existence of vascular capillaries within the cornea (encroaching no more than 0.2 mm into the cornea from the limbus).

Neovascularization: The formation and extension of vascular capillaries within and into previously non-vascularised regions of the cornea.

Limbal hyperaemia: Increased blood flow, resulting in distension of the limbal blood vessels. Hyperaemia may be active, when caused by dilation of blood vessels, or passive, when the drainage is hindered. It is also termed *limbal redness*, *limbal injection* or *limbal engorgement*.

Vessel penetration: Apparent ingrowth of vessels, typically toward the corneal apex, measured from an arbitrary reference at the corneo-scleral junction.

Vasoproliferation: Increase in the number of vessels.

Vascular pannus: Vascularization and connective tissue deposition beneath the epithelium; usually in the superior limbal region. Pannus is Latin for 'cloth'; an advancing vessel plexus has the appearance of a cloth draping over the cornea.

Vascular response: A general term encompassing any alteration to the normal vasculature, including those entities described earlier.

Prevalence

The original haptic lenses were capable of inducing corneal neovascularization, although there is little data on the magnitude of the problem apart from isolated case reports.[1-4] Certainly, the prevalence of corneal neovascularization amongst wearers of polymethyl methacrylate (PMMA) lenses has been reported to be very low.[5]

Reports of the prevalence of corneal neovascularization amongst patients wearing hydrogel lenses on an extended-wear basis for cosmetic reasons are inconsistent, with retrospective studies indicating substantially fewer cases of abnormal vascularization than do prospective studies. The prevalence of neovascularization during rigid (gas-permeable) lens wear appears to be extremely small.

The earlier literature reported a greater prevalence of corneal neovascularization in patients using extended-wear hydrogel lenses for correction of aphakia[6] than in cosmetic lens wearers. Such a finding was not unexpected in view of the surgical trauma that the cornea has endured, the compromised physiological status of the cornea as a result of surgery[7] and the necessarily thick lenses needed to be worn to provide the optical correction for an aphakic eye.

The reported prevalence of corneal neovascularization in patients wearing soft lenses for therapeutic reasons varies markedly. The extent of neovascularization in such patients may be related to the underlying corneal pathology being treated, the type of lens fitted and the mode and duration of lens wear.

Published estimates of the prevalence of lens-induced neovascularization reported in clinical trials and surveys are presented in Table 25.1.[5,8-22] When considering the data presented in this table, it is important to bear in mind that there are significant differences among studies with respect to sample sizes, experimental protocols, patient characteristics and criteria chosen for considering a vascular response as being normal versus abnormal.

In 1992, Stapleton et al.[23] reported that, of 1,104 patients with contact lens–related disorders presenting to an acute referral hospital eye clinic, none presented with corneal neovascularization. Of the extensive hospital-based surveys of contact lens complications conducted between 2009 and 2018 – carried out in China,[24] India,[25] Nepal,[26] Singapore,[27] the USA[28] and the UK[29] – the prevalence of corneal neovascularization ranged from 0.1% in the UK to 37% in the USA (Table 25.2). These differences may relate more to the types of clinics (acute referral clinics or general contact lens clinics) and mode of data collection than reflect true differences in prevalence.

Signs

'NORMAL' VASCULAR RESPONSE

By using the limit of visible iris as a reference point, McMonnies and co-workers[30] found the mean linear extent of limbal vessel filling, measured inferiorly, to be 0.13 mm in non–lens wearers, 0.22 mm in rigid lens wearers and 0.47 mm in hydrogel lens wearers (daily wear). Stark and Martin[17] and Holden et al.[31] reported an increased vascular response of 0.52 mm and 0.50 mm, respectively, associated with extended hydrogel lens wear.

Whether reports of vascular responses represent filling of capillaries that were empty, dilation of fine vessels that were barely visible, true penetration of vessels into the stroma or a combination of these is often unclear. Nevertheless, the fact that a number of authors[17,30,31] have independently established that various modes of lens wear can alter the appearance of the limbal vasculature provides support for the concept of a normal (although in many cases undesirable) lens-induced vascular response.

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TABLE 25.1 Prevalence of contact lens–induced corneal neovascularization reported in clinical trials and surveys

Lens type	Mode of lens wear	Lenses replaced regularly?	Patient type	Prevalence of vascularization (%)
PMMA	Daily wear	No	Cosmetic	0.03[5]
Low-Dk rigid	Daily wear	No	Cosmetic	0.0[8]
Low-Dk rigid	Extended wear	No	Cosmetic	0.0[8, 9]
High-Dk rigid	Daily wear	No	Cosmetic	7.3[10]
High-Dk rigid	Extended wear	No	Cosmetic	7.4[10]
Hydrogel	Daily wear	No	Cosmetic	0.64[11], 1.25[12], 14.2[10]
Hydrogel	Extended wear	Yes	Cosmetic	0.86[11], 14.5[10], 65[13]
Hydrogel	Extended wear	No	Cosmetic	0.0[14], 0.2[15], 1.75[11], 7.0[16], 8.7[17]
Hydrogel	Extended wear	No	Aphakic	14.2[18]
Hydrogel	Extended wear	No	Therapeutic	2.88[19], 35.0[20]
Silicone hydrogel	Daily wear	Yes	Cosmetic	0[21]
Silicone hydrogel	Extended wear	Yes	Cosmetic	0[13, 22]

TABLE 25.2 Prevalence of corneal neovascularization among hospital-presenting contact lens wearers

Author	Country	Year	Population size studied	Retrospective or prospective	Prevalence
Li et al.[24]	China	2018	141	Retrospective	5%
Sapkota et al.[26]	Nepal	2013	4,064	Retrospective	3%
Lee et al.[28]	USA	2012	1,369	Prospective	37%
Teo et al.[27]	Singapore	2011	953	Prospective	S – 7% D – 0.6%
Nagachandrika et al.[25]	India	2011	1,255	Retrospective	4%
Radford et al.[29]	UK	2009	877	Prospective	0.1%

D, deep corneal neovascularization; *S*, superficial corneal neovascularization.

'ABNORMAL' VASCULAR RESPONSE

Adjacent to the limbus, there exists a vascular plexus at all levels from which ingrowing vessels typically emerge. A variety of neovascularization patterns can occur, which are best considered under the following three headings.

Superficial neovascularization

This is the most common form of contact lens–induced vascular response.[32] In the undisturbed eye, episcleral branches of the anterior ciliary artery form a plexus around the limbus known as the 'superficial marginal arcade'. Minute branches form at right angles to this plexus, encroaching the cornea and looping inward toward the corneal apex (Fig. 25.1). The resultant vascular loops or arcades are typically semi-circular; they tend to anastomose with each successive arc becoming smaller, ultimately forming a rich vascular plexus around the limbus.[32]

New vessels often leak a creamy, lipid-like fluid, which can be seen around vessels on high magnification (see Figure 15.9). The combination of extensive vessel formation surrounded by this extravascular fluid can lead to vision loss; however, reduced vision in the case of superficial neovascularization is rare and will only occur if vessels encroach the pupillary axis.

Deep stromal neovascularization

Contact lenses can induce neovascularization at all levels of the stroma, from just beneath the anterior limiting lamina down to the posterior limiting lamina.[32-34] It develops insidiously and may progress in the absence of acute symptoms.[35] The typical appearance is that of a large feeding vessel emerging sharply from the limbus, usually in the mid-stroma, rapidly developing into finer, wildly tortuous branches and ending in buds with numerous small vessel anastomoses (Fig. 25.2). This irregular pattern is thought to result from a breakdown of structure of the stroma.[35,36]

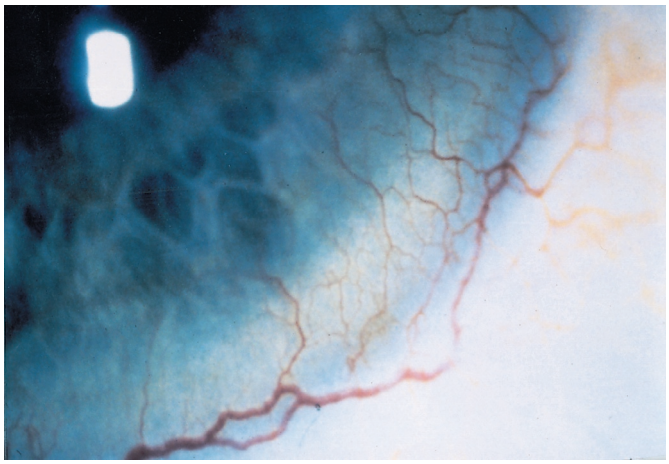


Fig. 25.1 Extensive superficial neovascularization extending approximately 2.5 mm into the cornea.

Rozenman et al.[37] observed deep stromal neovascularization in five eyes and scarring in five patients wearing soft contact lenses during a 6-month period. There was no evidence suggestive of other causes of interstitial keratitis. Two patients had aphakia and required a penetrating keratoplasty. Weinberg[6] reported the case of a 61-year-old man who developed deep corneal neovascularization, decreased visual acuity and associated corneal opacity at the level of Descemet's membrane after prolonged wear of a soft contact lens for aphakia. The vascularization

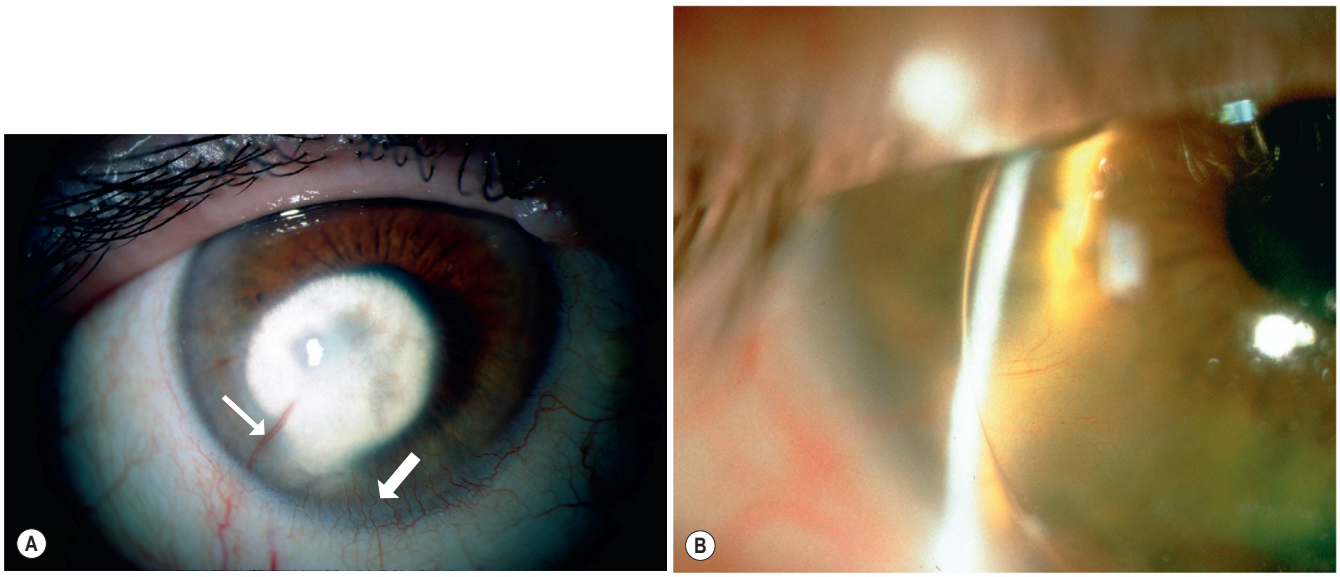


Fig. 25.2 Deep stromal neovascularization. **(A)** A large feeding vessel (arteriole with accompanying venule) extending from the limbus towards a dense central corneal scar in a contact lens wearer (thin arrow). Superficial neovascularization is also evident in the inferior cornea (thick arrow). **(B)** Branching vessels in the deep stroma of a patient who has been refitted with rigid lenses. (A, Wong AL, Weissman BA, Mondino BJ. Bilateral corneal neovascularization and opacification associated with unmonitored contact lens wear. Am J Ophthalmol 2003; 136:957–8. B, Courtesy Barry Weissman.)

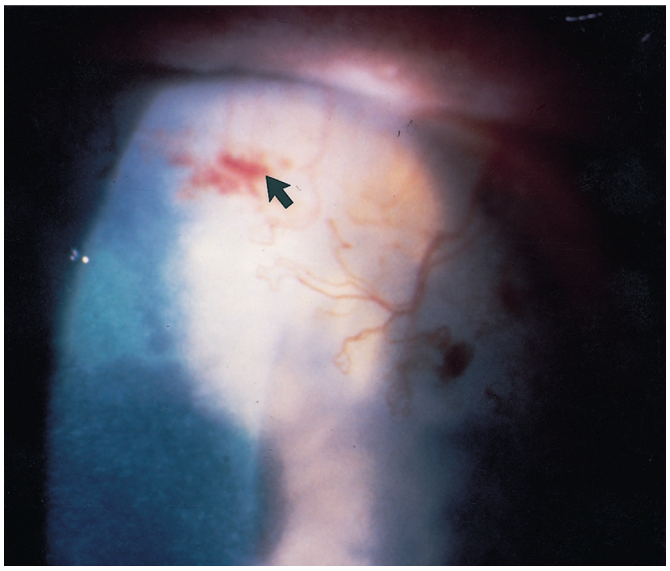


Fig. 25.3 Haemorrhaging of a deep stromal vessel. (Courtesy Desmond Fonn, British Contact Lens Association Slide Collection.)

markedly diminished and vision improved after cessation of soft lens use; however, the associated opacity remained.

Loss of vision can occur when there has been leakage of lipid into the stroma.[38] Donnenfeld et al.[38] documented five cases of haemorrhaging of deep corneal vessels that were induced by contact lens wear (Fig. 25.3); in one of these cases, a penetrating keratoplasty was required for visual rehabilitation.

Wong et al.[39] reported a case of severe bilateral deep stromal neovascularization and opacification associated with unmonitored contact lens wear. A 46-year-old woman who had been using hydrogel contact lenses, bought without a prescription on the internet, for 5 years was found to have dense, bilateral corneal opacities with deep stromal neovascularization. The contact lenses of the patient were found to be tight-fitting. Medical history and serological studies were negative for infectious or rheumatological causes of interstitial keratitis. The authors concluded that this condition was most likely related to the unmonitored contact lens use and the lack of routine eye examinations.

Ang et al.[40] described a technique of adapting a swept-source optical coherence tomography angiography instrument to image stromal vascularization, which enabled them to differentiate between superficial and deep vascular progression.

Vascular pannus

A pannus is an extensive ingrowth of tissue from the limbus onto the peripheral cornea. The penetration occurs between the epithelium and the anterior limiting lamina, resulting in a separation of these layers and often leading to a destruction of the anterior limiting lamina.[41] The term 'micropannus' is used when the extent of invasion is less than 2.0 mm from the limbus[42] (Fig. 25.4)

There are two forms of pannus – active (inflammatory) and fibro-vascular (degenerative); both types may be observed in contact lens wearers.[43] An active pannus is avascular and is composed of sub-epithelial inflammatory cells. In the later stages, it may be associated with secondary scarring of the stroma.

A fibro-vascular pannus consists of an ingrowth of collagen and vessels and often contains fatty plaques.[41] The clinical appearance of a fibro-vascular pannus is a congested band of vessels penetrating in an orderly fashion in the cornea, with the limit of penetration remaining even across its width. The invading end of the pannus often contains a considerable amount of fibrotic tissue, which stains brightly with rose bengal (Fig. 25.5). This condition is observed in contact lens–wearing patients in association with superior-limbic keratoconjunctivitis.[44] As this name suggests, the pannus is observed at the superior limbus.

Symptoms

Corneal neovascularization is generally considered asymptomatic, which is why the condition is so insidious. However,

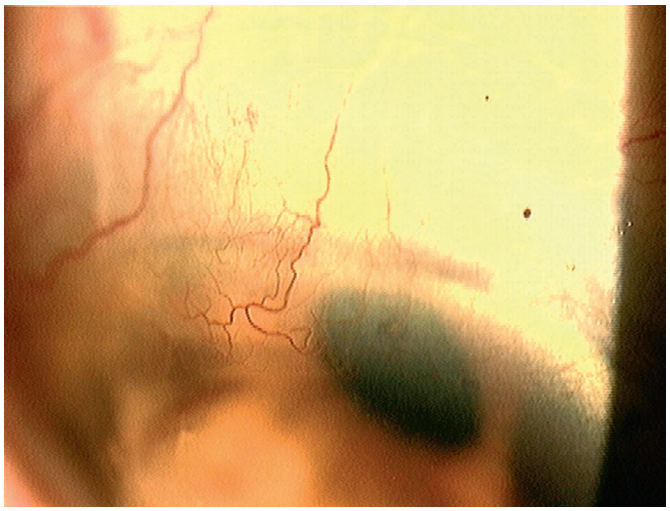


Fig. 25.4 Vascular micropannus. Slight loss of tissue transparency between the vessels indicates early fibro-vascular degeneration. (Courtesy Michael Hare.)

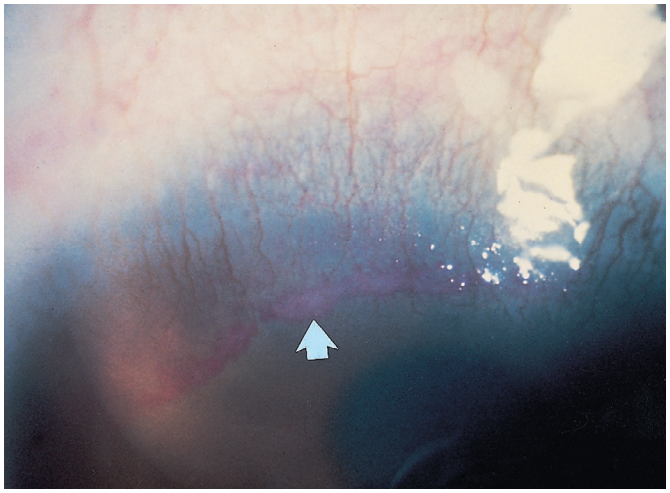


Fig. 25.5 Fibro-vascular pannus, with an even leading edge of fibrous tissue stained with rose bengal. (Courtesy Brien Holden, Brien Holden Vision Institute.)

Nomura et al.[45] examined 181 Japanese adults visiting an eye clinic for contact lens fitting and graded the degree of corneal neovascularization. These authors found a significant association between the extent of neovascularization and the subjective symptom of dryness.

Pathology

The ultrastructural tissue changes observed in contact lens-induced corneal neovascularization were described by Madigan et al.[46] in a primate model. Vessel lumina were approximately 15 to 80 μm in diameter and contained erythrocytes and sometimes leucocytes. Numerous extravascular leucocytes were observed around blood vessels, and the surrounding stromal lamellae were disorganised and separated with lines of keratocytes lying between them (Fig. 25.6). The overlying corneal epithelium was often affected, with general oedema, cell loss, and the presence of large fluid-filled vesicles. The underlying Descemet's layer and endothelium were apparently unaffected.

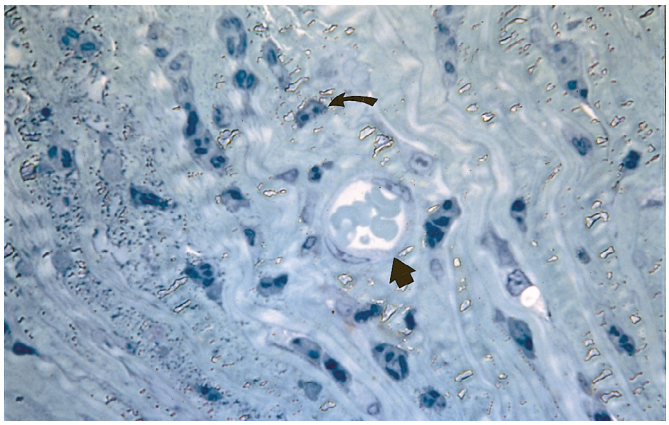


Fig. 25.6 Light micrograph of single blood vessel (thick arrow) induced by contact lens wear in primate stroma. Note the erythrocytes within the vessel lumen, the single endothelial cell wall, distorted stromal lamellae and lines of keratocytes (curved arrow).

The likely sequelae of events in the development of a vascular response can be predicted based on general vascular response studies in lower animals. In particular, detailed investigations of corneal neovascularization in the rat[47] occurring after focal injury caused by chemical cautery have allowed three distinct phases of vessel formation to be defined – the pre-vascular latent period, neovascularization and vascular regression.

Aetiology

Numerous theories have been advanced to explain why corneal neovascularization occurs, all of which are potentially relevant to the contact lens–induced vascular response. These theories are summarised in the following.

METABOLIC THEORY

Hypoxia

Lack of oxygen is known to induce neovascularization in other body tissues; it stands to reason that similar mechanisms could also occur in the cornea.[48] Certainly, hydrogel contact lenses are known to cause corneal hypoxia,[49] and hypoxia has been shown to upregulate the expression of vascular endothelial growth factor in the eye and to promote neovascularization.[50]

There is, however, evidence that factors other than hypoxia must be involved in corneal neovascularization. Imre[51] pointed out that some hypoxic tissues do not vascularise. Michaelson and co-workers[52] found that the development of neovascularization occurring after chemical burns in rabbits was unaffected by the ambient oxygen tension. Josephson and Caffery[53] provided evidence of progressive corneal neovascularization associated with extended wear of silicone elastomer contact lenses, which allow full oxygenation of the cornea because of their extremely high oxygen transmissibility.

Lactic acid

Lactic acid could be implicated in lens-induced corneal neovascularization in two ways. First, contact lenses can create hypoxia in the cornea leading to lactic acid production.[54] Second, tight-fitting soft lenses may indent the conjunctiva and restrict venous drainage, causing lactic acid to accumulate in the peripheral cornea.[55]

Oedema

The presence of excess fluid in the cornea (oedema) was thought by Cogan[56] to be sufficient to induce neovascularization. This is supported by the finding of Thoft and co-workers[57] that oedema facilitates anterior stromal neovascularization in rabbits. Clinically, corneal oedema is frequently present before neovascularization,[58] and some authors are of the opinion that corneal neovascularization does not occur in the absence of swelling[59] Certainly, contact lenses can induce significant levels of oedema, particularly during hydrogel lens extended wear.[60] The aetiological role of oedema can be challenged on the basis of the absence of neovascularization in conditions where there is permanent oedema (i.e. congenital endothelial dystrophy and long-term extended lens wear). Baum and Martola[61] suggested that stromal oedema alone is insufficient stimulus for corneal neovascularization.

Stromal softening

Chronic oedema as a result of contact lens wear may cause a breakdown of stromal ground substance or individual collagen fibrils, resulting in stromal thinning (see Chapter 23). Oedema could also cause the stroma to soften, or lose compactness, thus reducing the physical barrier to vessel penetration. Sholley and co-workers[62] suggested that infiltrating neutrophils could release collagenases, proteases and elastases, which degrade the stroma and facilitate the ingrowth of vascular endothelial cells. Although this theory could have some relevance to the normal vascular response to contact lens wear described earlier, experimental verification of a physical degradation or softening of stromal tissue in response to contact lens wear has not been produced.

The growth of vessels from the limbus along radial keratotomy scars (Fig. 25.7) lends support to the 'stromal softening' theory in that loose and disorganised scar tissue can be considered an avenue of weakness through the normally compact stroma, thus having the same effect as a softened stroma.

VASOGENIC HOMEOSTASIS MODEL

It is now recognised that the normally avascular corneal state represents an exquisite balance between many endogenous positive and negative mediators of neovascularization. This may be referred to as the 'vasogenic homeostasis' model.

Vasogenic stimulation

According to this aspect of the model, corneal neovascularization is produced by locally generated or introduced vasostimulatory factors,[47] and vessels grow in the direction of a concentration gradient of these substances. Neovascularization is usually preceded by inflammation, so it is likely that infiltrating leukocytes provide these vascular stimulating factors.[63] An extensive scientific literature describes numerous candidates as vasostimulatory agents; the most important factors are listed in Table 25.3.

Vasogenic suppression

This aspect of the model proposes that the normal cornea contains substances which inhibit neovascularization.[64, 65] Some of the key anti-angiogenic factors are identified in Table 25.3. These substances need to be inactivated if neovascularization is to occur. However, this part of the model lacks solid experimental support, and Fromer and Klintworth[63] argued that positive chemotaxis towards a vasostimulating factor is a more suitable explanation of observed patterns of corneal neovascularization.

NEURAL CONTROL THEORY

Cassel and Groden[66] suggested that there may be a neural influence on corneal vascularization. They have provided experimental support for this theory by examining the limbal vascular response to a cautery burn within a central trephined areas of cornea in rabbits. Limbal vessel growth was more advanced in the trephined corneas compared with matched controlled corneas that were not trephined. Since trephination produces denervation within the trephined zone,[67] the impaired limbal vascular response in the trephinated cornea could be attributed to an absence of neural influence. The effects of contact lenses on corneal neurology and sensitivity have been well documented.[68] If one accepts the neural control theory

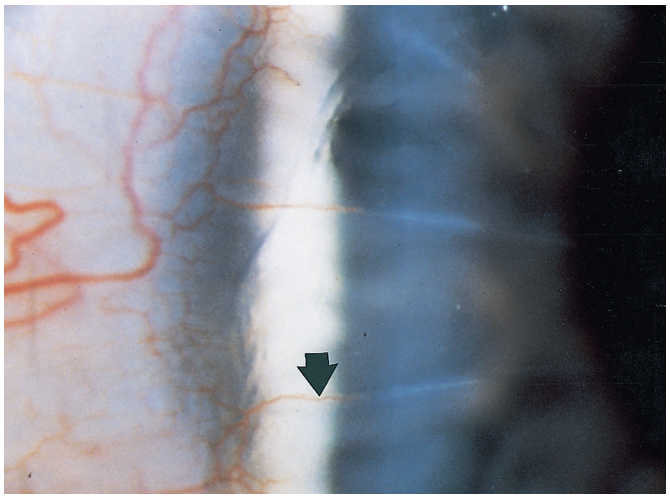


Fig. 25.7 Ingrowth of vessels (arrow) from the limbus along radial keratotomy scars. (Courtesy Patrick Caroline, Bausch & Lomb Slide Collection.)

TABLE 25.3 Factors that promote and inhibit corneal neovascularization

Angiogenic factors	Anti-angiogenic factors
Vascular endothelial growth factor	Angiostatin
Basic fibro-vascular growth factor	Endostatin
Acidic fibro-vascular growth factor	Thrombospondin
Transforming growth factor alpha	Platelet factor 4
Transforming growth factor beta	Fibronectin
Tumour necrosis factor alpha	Prolactin
Platelet-derived endothelial cell growth factor	Interleukin-12
Angiogenin	Steroids
Interleukin-8	Heparin
Interleukin-8	
Prostaglandin E1	
Biogenic amines	
Bradykinin	
Histamine	
Serotonin	

After Weissman BA. Corneal vascularization: The superficial and the deep. Contact Lens Anterior Eye 2001;24:3–8.

of Cassel and Groden,[66] it could be argued that the vascular response to lens wear is mediated by lens-induced changes to corneal neurology.

OVERALL MODEL

No single theory can account for corneal neovascularization in response to contact lens wear. Indeed, virtually all of the mechanisms discussed earlier can be triggered by some aspect of contact lens use. Many of these theories can be incorporated into a model of lens-induced neovascularization. Such a model is presented in Figure 25.8; two main aetiological factors are presented. First, the contact lens creates tissue hypoxia, leading to corneal oedema and stromal softening. Second, the contact lens has somehow contributed to a mechanical injury to the epithelium, resulting in a release of enzymes. Inflammatory cells migrate to this site and release vasostimulating agents that cause vessels to grow in that direction. As is obvious from the preceding discussion, this is only one of a number of possible models that could be proposed to explain stromal neovascularization in response to contact lens wear.

Observation and grading

The distinguishing characteristic of superficial vessels is that they can be observed to be continuous with the superficial marginal arcade. They can be observed by using direct focal illumination but are best observed by using either direct or indirect retro-illumination (Fig. 25.9). High magnification (×40) is often required to trace the path of the returning venules deeper in the cornea. Individual blood corpuscles can usually be observed at this magnification. Fine vessels can be observed more easily under red-free illumination (i.e. green filter) because the red vessels appear very dark and are therefore seen in higher contrast[35] (Fig. 25.10).

The extent of corneal neovascularization can be designated by using the grading scales provided in Appendix A. Because of the 'normal' or expected vascular encroachment observed in response to different types and modalities of lens wear discussed earlier, the grading in an uncomplicated lens wearer will be low, but not necessarily zero. A guide to the expected level of vascular encroachment can be derived from published data.[69] Calculation of the mean plus one standard deviation gives the range within which approximately 85% of the population will fall, which would be an acceptable criterion to adopt for 'normality'. Thus, the limits of 'normal' vascular ingrowth, measured from the limit of visible iris, should be (rounded upward) 0.2 mm for no lens wear or silicone hydrogel lens wear, 0.4 mm for daily wear of rigid lenses, 0.6 mm for daily wear of hydrogel lenses and 1.4 mm for extended wear of hydrogel lenses, respectively.

The maximum level of contact lens–induced neovascularization in a cosmetic lens wearer should not exceed grade 1.5 (see Appendix A). This would equate to about 0.5 mm of superficial vessel encroachment. That being the case, the 'normal' level of encroachment observed with hydrogel lenses worn on an extended-wear basis is considered to be unacceptable.

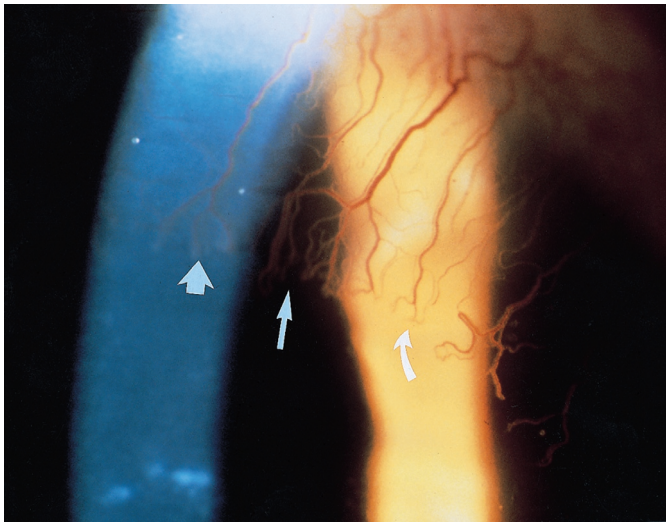


Fig. 25.9 Extensive superficial neovascularization at the level of the anterior stroma, viewed by direct focal illumination (thick arrow), direct retro-illumination (curved arrow) and indirect retro-illumination (thin arrow). (Courtesy Patrick Caroline, Bausch & Lomb Slide Collection.)

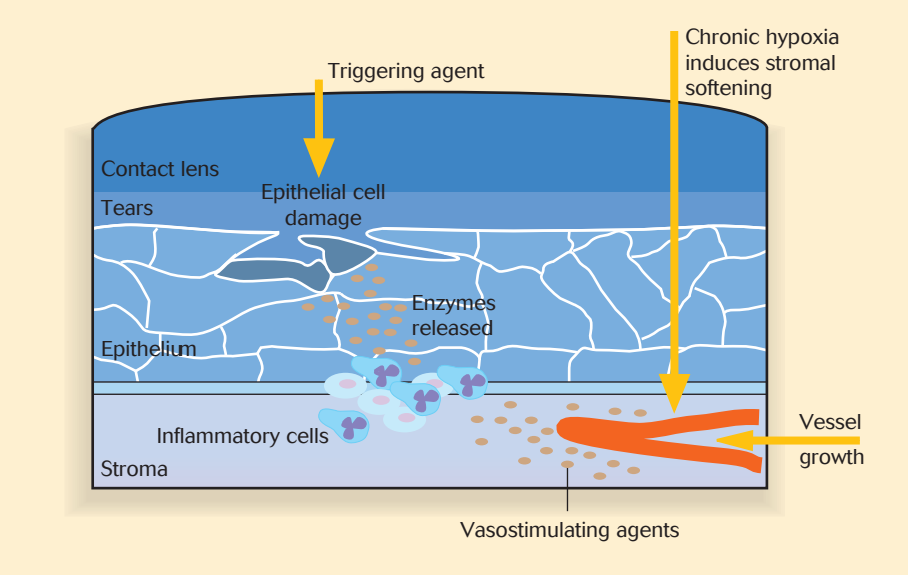


Fig. 25.8 Dual aetiology model of contact lens–induced neovascularization, depicting chronic hypoxia leading to stromal softening as a precursor, and epithelial irritation acting as a stimulus to vessel growth.

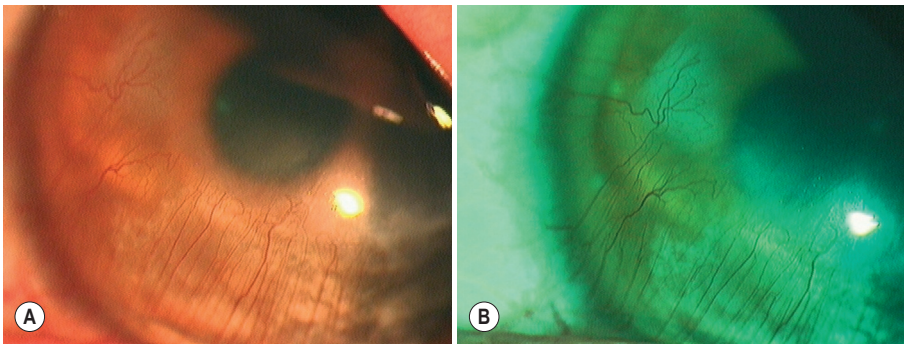


Fig. 25.10 Extensive contact lens–induced superficial neovascularization. **(A)** Observed in white light. **(B)** Observed in red-free (green) light. (Courtesy Michael Hare.)

Fig. 25.11 Schematic representation of the various patterns of contact lens–induced corneal neovascularization. DW, daily wear; EW, extended wear; Si-H, silicone hydrogel.

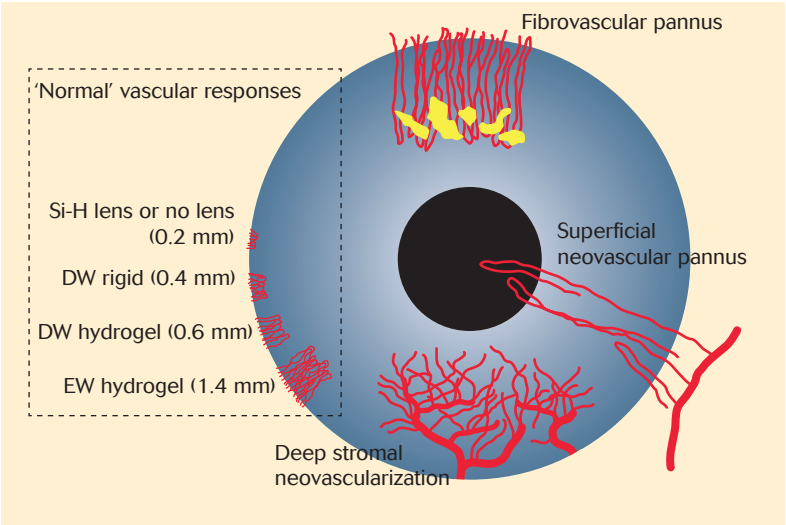


Figure 25.11 is a schematic representation of the various patterns of contact lens–induced corneal neovascularization. The various levels of 'normal' superficial neovascularization are depicted.

Management and treatment

Needless to say, the best form of treatment of corneal neovascularization is prevention. Adherence to this maxim could be achieved by fitting a lens that does not touch the cornea, provides zero resistance to the passage of oxygen or carbon dioxide (therefore creating no oedema or tissue acidosis) and does not involve the use of any form of chemical. As such a lens does not exist, practitioners are faced with a compromise situation.

GENERAL PRINCIPLES

If corneal neovascularization is a primary concern, lens design features known to provide minimal interference with corneal physiology are required, namely, high oxygen transmissibility (to minimise hypoxic oedema and hypercapnic acidosis), minimal mechanical effect (as judged by patient comfort[70]) and good movement (to prevent venous stasis resulting from limbal compression in soft lenses[55]). Care systems likely to induce toxic or allergic responses should be avoided, and regular after-care visits are essential.

If neovascularization of grade 1.5 or greater develops, action should be taken to arrest and possibly reverse the vascular ingrowth. Since it is rarely possible to identify the specific cause of the vascular response, a systematic trial-and-error approach must be adopted. If an epithelial injury with or without localised keratitis is present, lens wear should be ceased until the condition resolves. In the absence of obvious concurrent pathology, the most prudent action would be to replace the lens with one likely to provide an optimal physiological response. For example, a silicone hydrogel lens might be fitted to a patient who had previously been wearing hydrogel lenses to optimise corneal oxygen availability.[71] If chemical toxicity or allergy is thought to be the cause of a neovascular response, it may be advisable to change to a lens type (e.g. daily disposable lenses) or a care system (e.g. hydrogen peroxide system) that will virtually eliminate exposure of the eye to chemicals.

Other options to be considered include changing from extended wear to daily wear, using frequent replacement or disposable lenses, reducing wearing time or even ceasing lens wear. In view of the extremely low prevalence of corneal neovascularization in patients wearing rigid contact lenses, a change to rigid lenses should be considered if the problem persists with soft lenses. Certainly, Chan and Weissman[43] demonstrated that conversion from hydrogel contact lenses to daily-wear rigid lenses successfully reversed vascular pannus formation (Fig. 25.12).

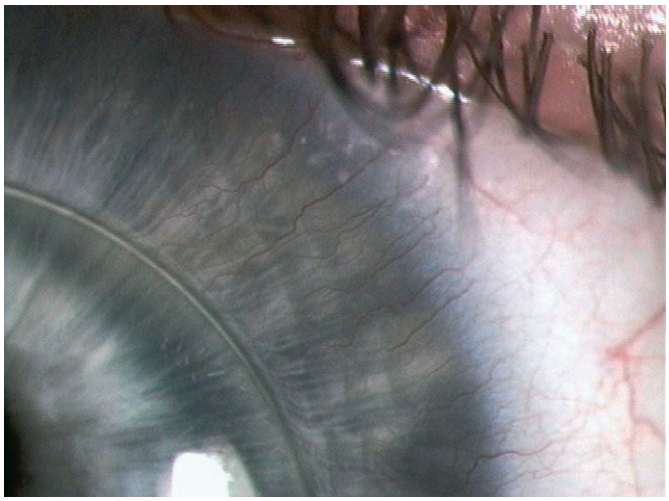


Fig. 25.12 Extensive hydrogel lens–induced superficial neovascularization treated by refitting the patient with rigid lenses. (Courtesy Brian Tompkins.)

High myopia, high astigmatism and steep corneas were found by Lee et al.[72] to be risk factors in the development of corneal neovascularization in soft-lens wearers.

SILICONE HYDROGEL LENSES

In view of the role of hypoxia in the aetiology of contact lens–induced stromal neovascularization, a key preventative or therapeutic measure when dealing with this condition is to prescribe contact lenses that provide sufficient corneal oxygenation to prevent stromal neovascularization from occurring or progressing. Yeung et al.[73] determined that maintaining a peripheral Dk/t above 30 to 40 Fatt units with daily-wear soft lenses should protect most normal corneas from stromal neovascularization. Given that all silicone hydrogel lenses exceed these values, this lens type is clearly indicated, especially if a lens wearer is thought to have an increased risk for stromal neovascularization.

TORIC LENSES

Toric soft lenses are typically designed with asymmetrical thickness profiles because of the cylindrical power requirement and the need to provide thick and thin zones for stabilization purposes. Even with the best lens designs, sections of the lens will be relatively thick. In some toric lens designs which employ inferior prism ballast, the thick zone is located inferiorly, and this can result in lower oxygen transmissibility in these regions, especially if the lens material has a low Dk.[74] Westin et al.[75] noted the formation of inferior corneal neovascularization associated with extended wear of prism ballasted toric hydrogel contact lenses. Changing to a different toric lens design, using silicone hydrogel lens materials or fitting a rigid lens, should solve such a problem.

THERAPEUTIC AGENTS

It is clear that certain drugs can control or reduce corneal neovascularization. For example, Duffin and co-workers[76] demonstrated that topical administration of a non-corticosteroid anti-inflammatory agent (flurbiprofen; a prostaglandin inhibitor) significantly suppressed contact lens–induced corneal neovascularization in rabbits wearing rigid lenses. Topical corticosteroids can also prevent vascular ingrowth of the cornea.[77] However, Ruben[32] warned that the use of such drugs is not without danger; for example, the use of steroids in patients with dry eye syndrome can result in viral and fungal infections.

The effect of sub-conjunctival bevacizumab injection in patients with corneal neovascularization was investigated by Zaki and Farid.[78] Ten eyes were examined; all had both major and minor vessel neovascularization caused by such factors as healed corneal ulcers, long-standing chronic inflammatory diseases and corneal ischemia caused by contact lenses. All eyes received a single sub-conjunctival injection of 2.5 mg (0.1 mL) bevacizumab. At 2 weeks after injection, a conspicuous recession of both minor and major vessels was observed in all eyes. The level of neovascularization continued to decrease noticeably for 3 months and then stabilised for the remainder of the 6-month follow-up period. During the 6-month follow-up, none of the 10 eyes showed any complication that could be related to sub-conjunctival bevacizumab injection. The authors concluded that bevacizumab can be used safely and effectively to treat contact lens–associated corneal neovascularization.

HYPERBARIC TREATMENT

Other radical approaches have been applied to the treatment of contact lens–induced neovascularization. Nishida et al.[79] reported the case of a 39-year-old man who suffered from corneal neovascularization, which was thought to have resulted from hypoxia caused by improper use of PMMA lenses. The condition was successfully treated by using hyperbaric oxygenation of the corneas delivered under swimming goggles.

FLUORESCEIN ANGIOGRAPHY

The pattern of vascular progression in contact lens wearers can be enhanced with the use of fluorescein angiography.[3] Mackman et al.[80] used this technique to study the corneas of two patients who had aphakia; these patients had undergone penetrating keratoplasty and were subsequently wearing extended-wear hydrogel lenses. The vascularization was demonstrated to be more extensive than was apparent by observing the cornea by using conventional methods of illumination and observation techniques with a slit lamp biomicroscope. Further, the ingrowing vessels were shown to be leaky, and this leakage was thought to have contributed to graft oedema and graft rejection.

SURGICAL INTERVENTIONS

In extreme cases, surgical intervention may be required, such as diathermy, bipolar galvanic electrolysis or laser or microcautery occlusion of the vessels.[32,81,82] Where vision loss occurred as a result of secondary fibrosis, keratoplasty may be necessary to restore useful vision.[38]

SUSPENDING OR ABANDONING LENS WEAR

Grade 2 or greater neovascularization indicates that there may be a serious threat to vision, and immediate action is required. Lens wear should be ceased for an extended period – at least

until the vessels no longer lie in the pupillary area. Patients should be monitored carefully if lens wear is recommenced because ghost vessels may refill rapidly, and the neovascularization process may recur (see further in the chapter). If vessels remain in the pupillary area, the patient should be counselled about the possibility of abandoning lens wear permanently.

Prognosis

The 'normal' form of peripheral vascular ingrowth may undergo regression when contact lens wear is ceased. Holden and co-workers[83] observed that 1 month after removal of extended-wear hydrogel lenses that had been worn for an average of 5 years, the extent of limbal vessel penetration appeared to decrease. However, Holden et al.[83] were unable to provide statistical verification of this observation (Fig. 25.13).

Klintworth and Burger[47] noted that large vessels which invaded the rat cornea after chemical cautery injury persisted as long as 2 months. Ausprunk and co-workers[84] observed complete regression of vessels in rabbit corneas 10 weeks after the vascularizing stimulus was removed. Madigan et al.[46] reported a gradual decrease in visibility of vessels after cessation of lens wear in vascularised monkey corneas; larger vessels emptied leaving 'ghost vessels' of reduced diameter (10–25 μm), whereas the smaller, superficial vessels apparently regressed (Fig. 25.14). Only a few ghost vessels were observed 14 months after lens removal. McMonnies[35] noted that fully established corneal vessels do not seem to regress in human eyes and can persist indefinitely, remaining as ghost vessels (Fig. 25.15)

Woo et al.[85] reported the long-term clinical courses of eight aphakic eyes of two sets of siblings who used hydrogel contact lenses for both refractive correction and amblyopia treatment after neonatal cataract extraction. The most common contact lens–related complication was corneal neovascularization, which developed in two patients initially wearing soft hydrogel lenses. Refitting to the silicone elastomer and custom silicone hydrogel lenses led to regression of the neovascularization, and no other contact lens–related problems were observed thereafter.

Although the rate of vascular regression in humans is still open to debate, practitioners should note that cessation of lens wear will at least halt the progression of vessel infiltration into the cornea. Madigan et al.[46] re-inserted lenses into monkey eyes which had suffered contact lens–induced neovascularization 9 months previously. Within 36 hours, the existing 'ghost vessels' had refilled, and the overall appearance, including associated epithelial oedema, was similar to that observed during the original phase of neovascularization.

Resumption of lens wear must be treated with extreme caution and be accompanied by a rigorous and frequent after-care protocol since it is evident from the primate model of Madigan et al.[46] that ghost vessels will refill rapidly if a stimulus to neovascularization – which may simply be lens wear – is re-introduced.

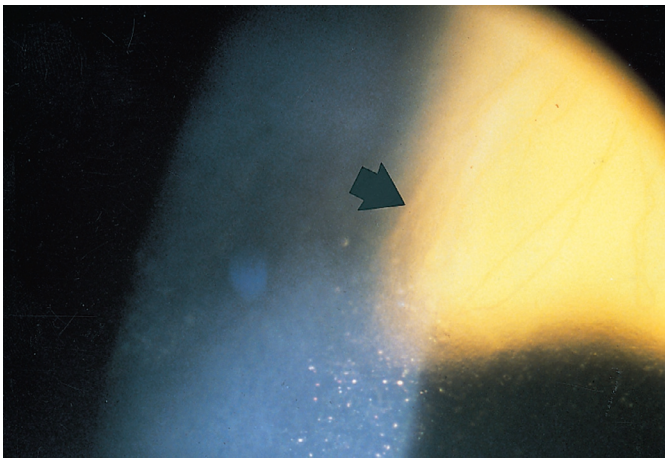


Fig. 25.14 Ghost vessels (arrow) in primate cornea 3 months after cessation of lens wear.

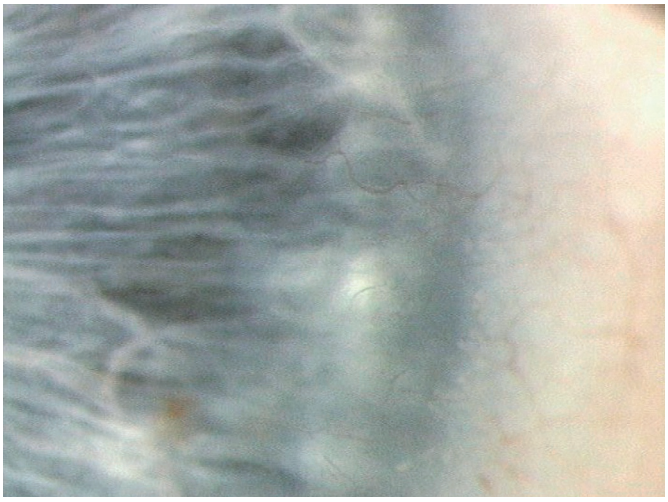


Fig. 25.15 Extensive plexus of ghost vessels. (Courtesy Brian Tompkins.)

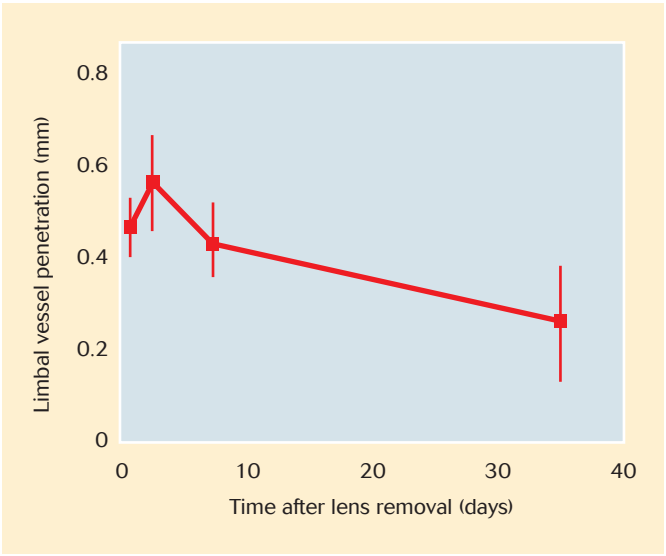


Fig. 25.13 Regression of neovascularization after cessation of lens wear for 1 month after 5 years of soft lens extended wear. (Adapted from Holden BA, Sweeney DF, Vannas A, et al. Effects of long-term extended contact lens wear on the human cornea. Invest Ophthalmol Vis Sci 1985;26:1489–501.)

Differential diagnosis

Stromal neovascularization has a distinct appearance, so it is unlikely that this condition will be confused with other complications of contact lens wear. It is perhaps more important to distinguish between the various forms of vascular response with a view to determining the aetiology of the condition. This is not always straightforward; for example, the only difference between vascularization induced by contact lens wear and that which may be occurring coincidentally as part of an unrelated pathological process may be the extent of the reaction.

Ghost vessels have a similar appearance to nerve fibres but appear less like striae. The distinguishing features of these three structures are compared in Table 25.4.

TABLE 25.4 Differential diagnosis of ghost vessels

	Ghost vessels	Nerve fibres	Striae
Connected to limbus	Yes	Yes	No
Colour	Grey/white	Grey/white	Grey/white
Bifurcations	Yes	Yes	No
Stromal depth	Any	Any	Deep
Orientation	Radial	Radial	Vertical
Form	Discrete; abrupt end	Discrete; can be long	'Feathery'; faded ends
Diameter	10–25 μm	0.1–0.25 μm	5 μm
Permanence	Resolution in months	Permanent	Resolution in minutes

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26 Corneal Infiltrative Events

One of the most challenging aspects of contact lens practice is the diagnosis and management of potentially sight-threatening microbial keratitis (MK). When involved in any such form of clinical decision-making, practitioners rely on their own clinical experience and draw upon guidance that can be found in the relevant literature. This latter aspect has become problematic. Notwithstanding the evolution of a solid body of basic and clinical research into this topic over the past four decades, attempts at defining contact lens–associated keratitis have resulted in the adoption of various terms, definitions and classification systems which are ambiguous and difficult to apply in a clinical setting.

Two terms emerging from the contemporary literature which are used to describe inflammatory reactions of the cornea are 'keratitis' and 'corneal infiltrative event' (CIE).[1] The latter entity has also been referred to as a 'corneal inflammatory event'.[2] *Dorland's Medical Dictionary*[3] defines 'keratitis' as 'inflammation of the cornea' and defines 'inflammation' as being characterised by ' … leukocytic migration into the inflammatory focus' (Fig. 26.1). The terms 'keratitis', 'corneal infiltrative event' and 'corneal inflammatory event', therefore, can be considered as being synonymous because all these terms imply an infiltration or migration of cellular elements into the cornea.

Considerable confusion has emerged because some authors have used these terms to denote severity. The term 'CIE' has been taken to mean low-grade, innocuous corneal infiltration/inflammation (Fig. 26.2), whereas 'keratitis' has been taken to imply a severe event (e.g. 'severe microbial keratitis') (Fig. 26.3).

Keratitis may be infectious, suggesting that replicating microorganisms are responsible. This is referred to as 'microbial keratitis'. As will be discussed in detail in this chapter, it is not possible to distinguish whether or not a low-grade, early-stage CIE is MK. The relationship between these conditions is demonstrated as a Venn diagram in Figure 26.4. Simply put, all cases of MK are also CIEs, but not all cases of CIEs are MK. As well as being caused by microorganisms, a CIE might be caused by such factors as toxicity, immunological reaction, metabolic disturbance or trauma.

These considerations created some difficulty in terms of how the discussion of such conditions could be organised in this book. Given that these two conditions are generally treated as separate entities in the literature, separate chapters are presented on CIEs (this chapter) and MK (Chapter 27). This chapter will cover the full spectrum of keratitis more from the standpoint of definitions and epidemiology and will outline general principles of management. Chapter 27 will consider MK from a clinical standpoint. In considering the information in these chapters, readers must remain mindful of the overlap of these conditions as defined in Figure 26.4.

This chapter will consider the various approaches that have been advocated in respect of the clinical diagnosis of keratitis and will highlight the difficulties that each of these pose. It will be demonstrated that problems often relate to the adoption of arbitrary terminology that is self-contradictory and/or inconsistent with classic, universally accepted definitions enshrined in the medical literature. These semantic problems have been compounded by a failure to challenge or depart from traditional concepts. This chapter will challenge the 'conventional wisdom' and present a rational, logical and coherent basis for underpinning

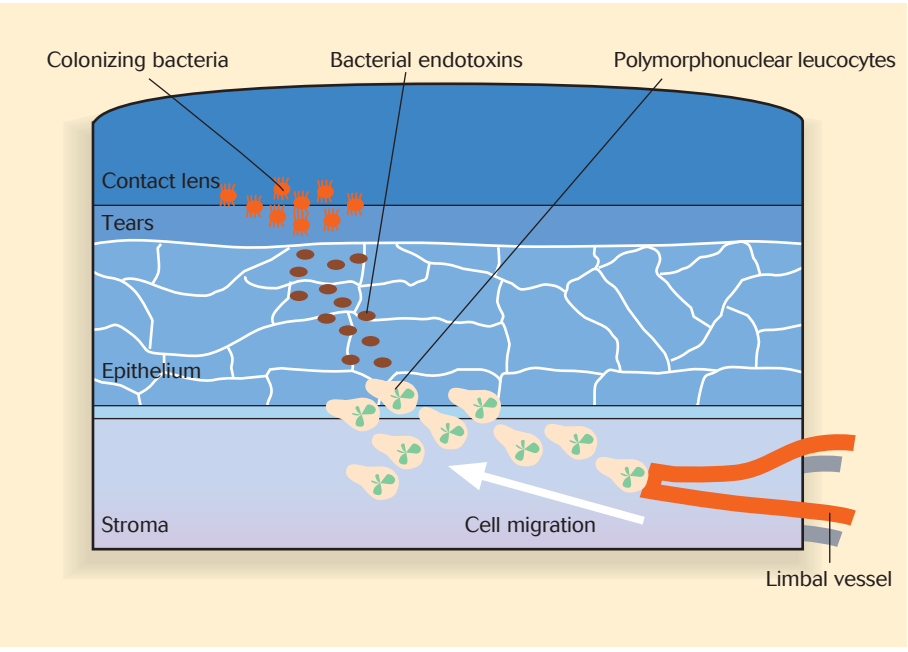


Fig. 26.1 Aetiology of infiltrates caused by endotoxins released from bacteria colonizing on the posterior surface of a contact lens.

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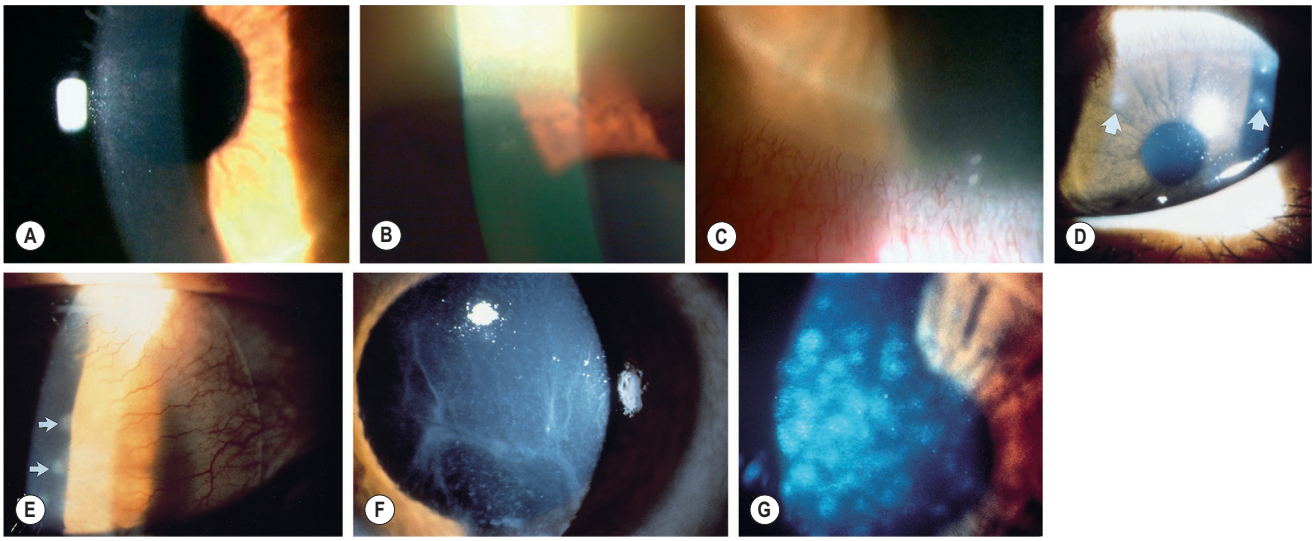


Fig. 26.2 Various forms of presentations of corneal infiltrative events (CIEs). **(A)** Infiltrate in the central cornea, which is diffuse and restricted to the anterior cornea. **(B)** A group of small, faint focal infiltrates can be seen near the superior limbus, in the centre of the slit beam. **(C)** Two small focal infiltrates can be seen near the inferior limbus, and the surrounding cornea is slightly hazy. **(D)** Infiltrates (arrows) near a region of limbal redness in the case of a patient suffering from superior limbic keratoconjunctivitis. **(E)** Infiltrates in the corneal mid-periphery (arrows) in association with soft lens–induced stromal neovascularization. **(F)** A severe CIE caused by solution toxicity. In this case, the patient was wearing soft lenses in association with solutions containing thimerosal and chlorhexidine. **(G)** Focal infiltrates with characteristic 'fluffy' edges in a patient suffering from epidemic keratoconjunctivitis. (A, Courtesy Sarah Morgan. B, Courtesy Brian Tompkins. C, Courtesy Suzanne Efron. F, Courtesy Gisele Sachs, Bausch & Lomb Slide Collection. G, Courtesy Brian Tompkins.)

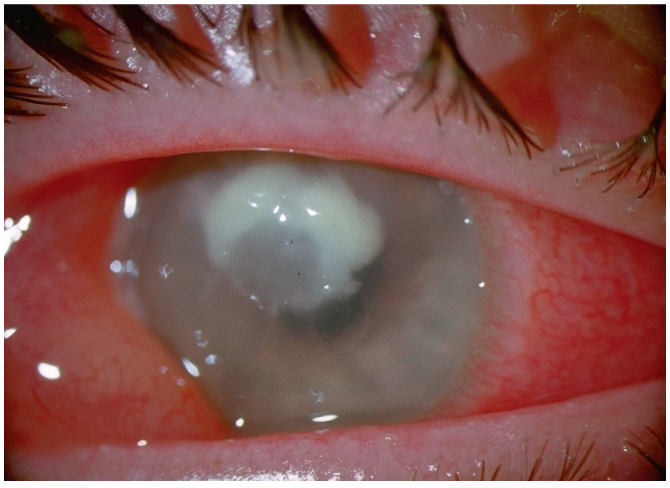


Fig. 26.3 Creamy, pussy ulcer in the advanced stage of a contact lens-induced microbial keratitis. (Courtesy Barry Weissman.)

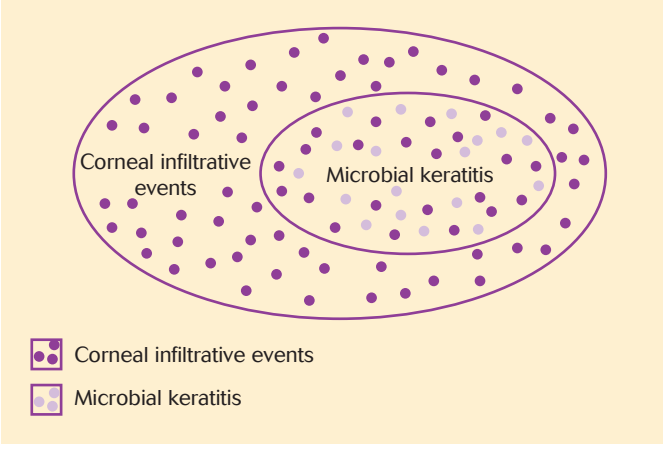


Fig. 26.4 Venn diagram showing the relationship between microbial keratitis and corneal infiltrative events. The key message here is as follows: All that is 'microbial keratitis' is also 'corneal infiltrative events'.

clinical decision-making in this area. Unless otherwise stated, it should be assumed that throughout this chapter, reference is being made to contact lens–associated keratitis (so the descriptor 'contact lens–associated' will not always be used).

The Manchester Keratitis Study

To test and challenge the various approaches that have been used to define and classify keratitis, a substantial body of data was generated to document the clinical characteristics of all forms of this disease, from mild, self-limiting and clinically innocuous manifestations to the most severe and painful forms of MK. This was achieved by conducting a prospective survey between January 25, 2003, and January 24, 2004, of all patients who were wearing contact lenses (irrespective of the primary reason for presentation) and attending the acute service of the Royal Eye Hospital, Manchester, United Kingdom.

The details of this work – collectively referred to as 'The Manchester Keratitis Study' – have been published previously[4-10] and will be referred to extensively throughout this chapter. The design of this experiment is represented schematically in Figure 26.5. In essence, all presenting patients who habitually wore contact lenses completed a patient survey questionnaire which gathered information about whether or not they slept wearing lenses (i.e. wearing modality), the type of lenses they wore (rigid, hydrogel daily disposable, all other hydrogel or silicone hydrogel) and other personal, health and lifestyle factors.

If a CIE was noted upon ocular examination, the attending clinician completed a survey form that detailed clinical information

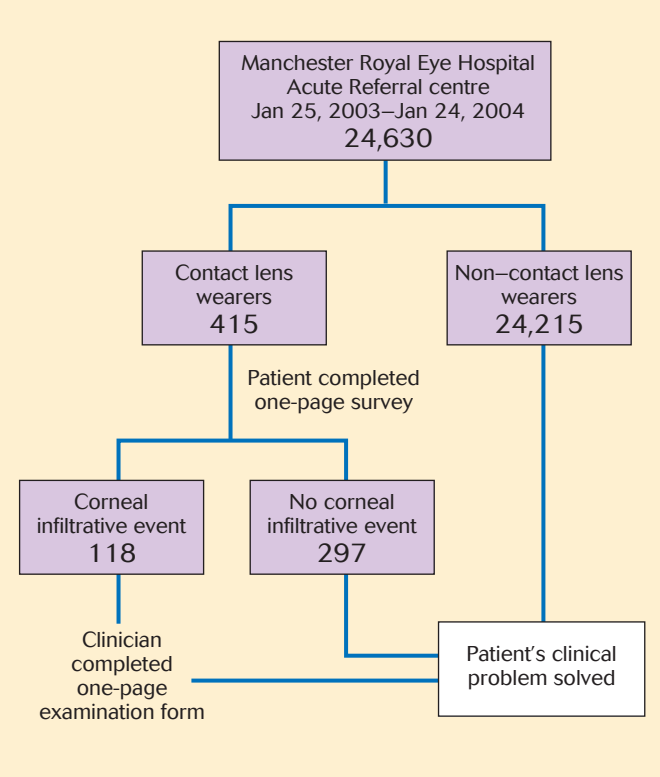


Fig. 26.5 Design of the Manchester Keratitis Study. (Adapted from Efron N, Morgan PB. Rethinking contact lens associated keratitis. Clin Exp Optom 2006;89:280–98.)

relevant to this study. An important feature of this form was a 'clinical severity matrix' – a schema described by Aasuri et al.[11] and advocated by other authors.[12] This involved the clinician scoring the severity of each of 10 signs and symptoms on a 0-to-3 scale, as shown in Table 26.1. The cumulative score for each event – the 'clinical severity score' – was between 2 (the minimum score relating to the criterion for this study of only including patients exhibiting an infiltrative response) and 22, and thus, the higher the score, the more clinically severe was the event. A total of 118 CIEs were observed during the survey period; the severity distribution of these events is shown in Figure 26.6.

An important feature of the Manchester Keratitis Study[4-10] is that no attempt was made to distinguish between MK and sterile (non-infectious) keratitis, in view of the difficulties in making this clinical distinction, as will be described later in this chapter. However, to relate the results of the Manchester Keratitis Study[4-10] to the existing literature and to form a basis for testing different characteristics of the various binomial and polynomial classification schemes that have been advocated previously, the criterion of Aasuri et al.[11] was adopted. According to this scheme, CIEs with clinical severity scores greater than 8 could be considered 'severe keratitis', which would be analogous to the traditional definition of 'presumed microbial keratitis', and CIEs with clinical severity scores of 8 or less could be considered 'non-severe keratitis', which would be analogous to the traditional definition 'sterile keratitis'.

The size and position of the infiltrate or ulcer on the cornea in 111 of these patients were also carefully documented.[7] For analytical purposes, this information is presented in the form of a cartogram whereby each CIE is depicted by a circle, the diameter of which is equivalent to the largest dimension of the infiltrate as observed on the cornea of the patient (Fig. 26.7). The cartogram is generated as a 'right eye only' representation whereby the location of any event occurring in the left eye is horizontally mirror-transposed; this form of analysis facilitates consideration of possible nasal/temporal effects.

Previous classification systems

A number of binomial classification systems (defining two categories of CIE) and polynomial classification systems (defining three or more categories of CIE) have been advocated. It appears that a primary aim of these systems has been to separate out those cases that do or do not require therapeutic intervention. Conceptually, this makes sense because the fundamental clinical decision that must be made with respect to any presenting case of keratitis is whether or not to prescribe anti-microbial drugs (if the practitioner is therapeutically endorsed) or refer the patient for medical attention.

BINOMIAL CLASSIFICATION SYSTEMS

The binomial classification 'microbial versus sterile' keratitis attempts to address directly the question of whether or not to prescribe anti-microbial drugs. Other binomial systems, such

TABLE 26.1 Clinical severity matrix used in the Manchester Keratitis Study

	SEVERITY SCORE			
Parameter	**0**	**1**	**2**	**3**
Symptoms	None	Mild	Moderate	Severe
Lid swelling	Absent		Present	
Conjunctival redness	Absent	Localised	Generalised	
Infiltrate shape		Round		Irregular
Infiltrate size		<1 mm	1–2 mm	>2 mm
Fluorescein staining	Absent	Present		
Surrounding cornea	Clear	Slight haze	Severe haze	
Endothelial debris	Absent	Present		
Hypopyon	Absent		Present	
Effect of lens discontinuation	Resolving	No change	Slight worsening	Significant worsening

Based on Aasuri et al.[11] Reprinted from Efron and Morgan[4] with permission of Lippincott Williams & Wilkins.

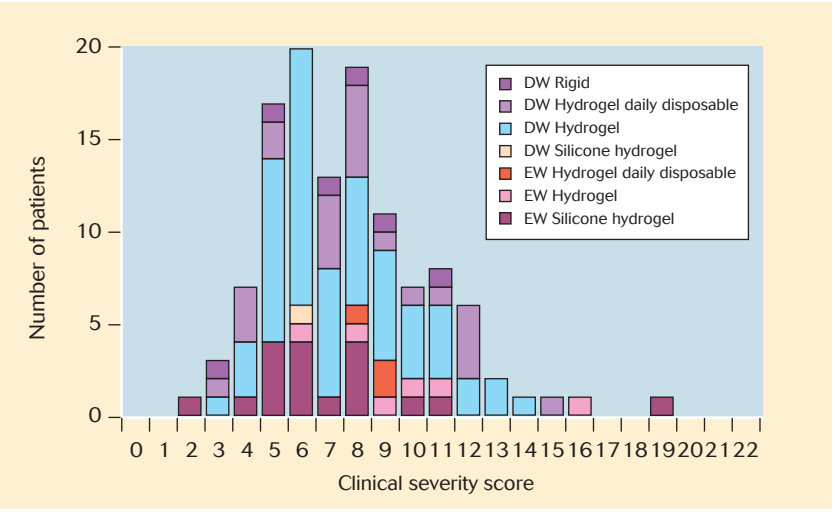


Fig. 26.6 Distribution of clinical severity scores for corneal infiltrative events (CIEs) with respect to wearing modality and lens type. DW, daily wear; EW, extended wear. (Adapted from Efron N, Morgan PB, Hill EA, Raynor MK, Tullo AB. The size, location, and clinical severity of corneal infiltrative events associated with contact lens wear. Optom Vis Sci 2005;82:519–27.)

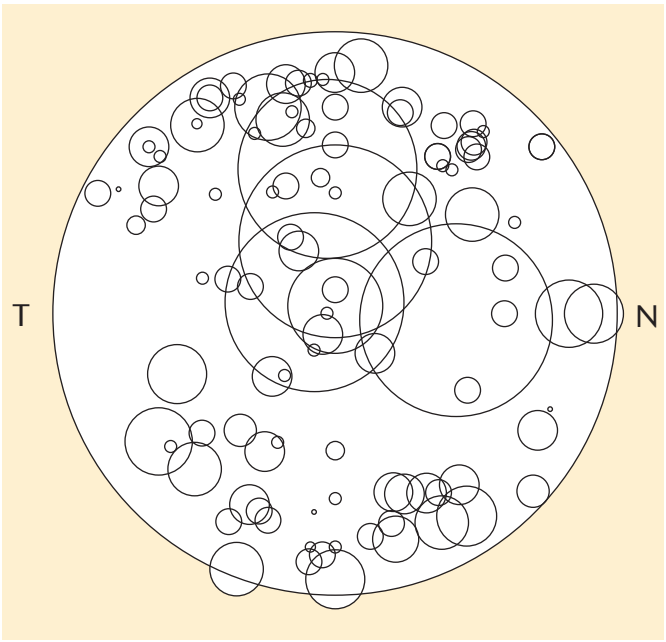


Fig. 26.7 Cartogram showing the size and location of infiltrates for all wearing modalities and lens types. The large outer circle represents a 12-mm-diameter cornea. Data from left eyes have been horizontally mirror transposed so that all infiltrates are represented as if for the right eye only. N, nasal; T, temporal. (Adapted from Efron N, Morgan PB, Hill EA, Raynor MK, Tullo AB. The size, location, and clinical severity of corneal infiltrative events associated with contact lens wear. Optom Vis Sci 2005;82:519–27.)

as 'ulcerative versus non-ulcerative', 'suppurative versus non-suppurative' and 'central versus peripheral', can be considered as surrogate measures, in that specific ocular signs and symptoms are assessed so as to infer whether the condition is microbial or sterile as the basis for deciding whether or not to prescribe. As will be demonstrated, all of these binomial classification systems suffer, to a greater or lesser degree, from definition overlap and ambiguity.

MK versus sterile keratitis

The adoption of criteria that classify a condition as being MK versus sterile keratitis is problematic from a microbiological perspective, because of the difficulties in identifying definitively whether or not a given CIE is infective in aetiology, especially those of mild to moderate severity. True confirmation of MK is dependent upon proof of microbial infection, which is sought by scraping the cornea and culturing for evidence of pathogenic microorganisms. However, in the Manchester Keratitis Study,[10] 57% of cases of severe keratitis (i.e. presumed MK) were found to be culture negative. This finding is consistent with previous studies,[13-15] which have found that on approximately 50% of occasions, when a corneal scrape is taken from a patient with presumed MK (based on clinical signs and symptoms), the result turns out to be culture-negative. It is difficult to interpret a culture-negative result because it is not possible to determine whether this indicates that microorganisms were truly absent (a true-negative result) or whether microorganisms were present but simply not picked up in the course of the scraping procedure (a false-negative result). A culture-negative result can also occur as a result of the patient having used antimicrobial medication prior to corneal scraping.

A positive culture is generally presumed to be a true finding (a true-positive result); however, it may indicate the presence of potentially pathogenic microorganisms that were part of the normal ocular flora, which were cultured coincidentally and therefore were unrelated to the CIE under investigation. Such a false-positive result, which was observed in 10.3% of cases scraped for bacterial keratitis by Sharma et al.,[15] can occur as a result of the vast array of potentially pathogenic bacteria that constitute the normal flora of asymptomatic contact lens wearers (and non–lens wearers).[16] However, microbiology laboratories employ protocols involving the use of multiple cultures that guard against false-positive reporting.

Notwithstanding the difficulties outlined earlier, it must be recognised that although corneal scraping and culturing may be of limited assistance in discerning the difference between MK and sterile keratitis, performing such procedures may be of benefit for a different reason. The results of scraping might help identify the causative bacteria in a case of severe keratitis and, in conjunction with antibiotic sensitivity testing, can form the basis for choosing an appropriate antibiotic therapy.

Because it is only possible to *presume* a difference between microbial and sterile keratitis, many clinicians have chosen to use clinical definitions instead of microbiological definitions as the basis for deciding whether or not to prescribe anti-microbial

medication. However, there is little agreement with respect to the various criteria adopted, which are all problematic in various respects. Poggio et al.[14] defined MK as '…a corneal stromal infiltrate with an overlying epithelial abnormality (ulceration) clinically diagnosed as microbial keratitis … [and the patient] … received antibiotic treatment for presumed microbial keratitis…'. To diagnose a condition as MK because it was 'clinically diagnosed as MK' is tautological and of little value to others attempting to use this definition. The problems in defining MK in terms of the presence or absence of ulceration will be discussed later.

The definition of Lam et al.[17] that MK is characterised as '…a corneal stromal infiltrate more than 1 mm^2 but not necessarily with an overlying epithelial defect' is over-simplistic because, as Weissman and Mondino[18] noted, MK begins as a minor epithelial anomaly, which progressively increases in size. To discount any CIE less than 1 mm^2 is to ignore the natural history of the condition; that is, the size of an infiltrate in a case of MK will self-evidently be less than 1 mm^2 during the very early phase of the natural history of the disease. Indeed, it must start with an area of 0 mm^2. The question of diagnosing CIEs without regard to the natural history of the disease process is highly problematic, as discussed later in this chapter.

Stapleton et al.[19] adopted a complex definition for 'moderate to severe MK', which is a based on a combination of microbiological and clinical criteria. This condition is said to occur if the following criteria are met:

a) the CIE is culture proven, or
b) the CIE is culture negative with at least one of the following:
   - the lesion is within the central 4 mm of the cornea;
   - there is an anterior chamber reaction and the infiltrate is 2 mm or greater in diameter;
   - the patient is suffering from significant pain and the infiltrate is 2 mm or greater in diameter.

This definition is problematic because it appears to rely largely upon the unfounded assumption (for reasons outlined later) that a CIE occurring in the central cornea is MK and a CIE occurring in the peripheral cornea is a sterile, non-infectious entity referred to as 'contact lens–induced peripheral ulcer' (CLPU) (also discussed later).

The Manchester Keratitis Study[7] revealed that the vast majority of CIEs are less than 2 mm in diameter; therefore, in effect, according to the definition of Stapleton et al.,[19] such CIEs cannot be classified as MK if they occur outside the central 4 mm of the cornea. Of the *severe* CIEs in the corneal periphery in the Manchester Keratitis Study (i.e. those that would generally be considered to be 'presumed microbial keratitis'), only 18% were culture positive[10] and 3% were greater than 2 mm in diameter.[7] Thus, only a minority of cases of severe keratitis seen in the Manchester Keratitis Study would have been classified as moderate to severe MK if the criteria of Stapleton et al.[19] had been applied. This indicates that the criteria of Stapleton et al.[19] are likely to misrepresent what others[10,11,13,14,17] would call 'severe' or 'microbial' keratitis, and to substantially underestimate the incidence of such events.

A 'high probability of MK' was defined in the study of Schein et al.[20] as one or more corneal stromal infiltrates greater than 1 mm in size with more than mild pain and one or more of the following: anterior chamber reaction more than minimal, mucopurulent discharge or positive corneal culture. This definition suffers from the same difficulties as that of Lam et al.[17] in that it ignores the natural history of severe CIE. The criteria that Schein et al.[20] set for the classification of MK also appear to be far more stringent than those adopted by others and are likely to substantially under-estimate the incidence of such events.

To illustrate the effect of adopting different criteria for the diagnosis of MK, the criteria of Poggio et al.,[14] Lam et al.,[17] Stapleton et al.[19] and Schein et al.[20] were each applied separately to the data set of 111 CIEs observed in the Manchester Keratitis Study.[7] Those CIEs that would have been classified as MK according to each definition are shown in the cartograms in Figure 26.8. Also included in this figure is a cartogram showing the CIEs that were classified as severe keratitis as a result of a clinical severity score of greater than 8 in the Manchester Keratitis Study.[7] As can be seen from this figure, the use of different criteria results in vastly different sets of CIEs being identified as severe or MK, thus highlighting the problems in deriving a meaningful clinical definition for this condition. The criteria of Lam et al.[17] and Schein et al.[20] can be seen to select out larger CIEs; the criteria of Stapleton et al.[19] tend to identify central CIEs; and the criteria of Stapleton et al.[19] and especially Schein et al.[20] select out fewer CIEs. The results of this analysis are entirely consistent with predictions adduced from the descriptions of these various criteria, as outlined earlier.

The confounding influence of the use of different criteria for MK can be illustrated by comparing the criteria adopted in separate studies published in 1989[14] and 2005[20] by the same author (Oliver Schein, who was third author of the 1989 study of Poggio et al.[14] and first author of the 2005 study[20]). It can be inferred from Figure 26.8 that the criteria adopted in Schein's 2005

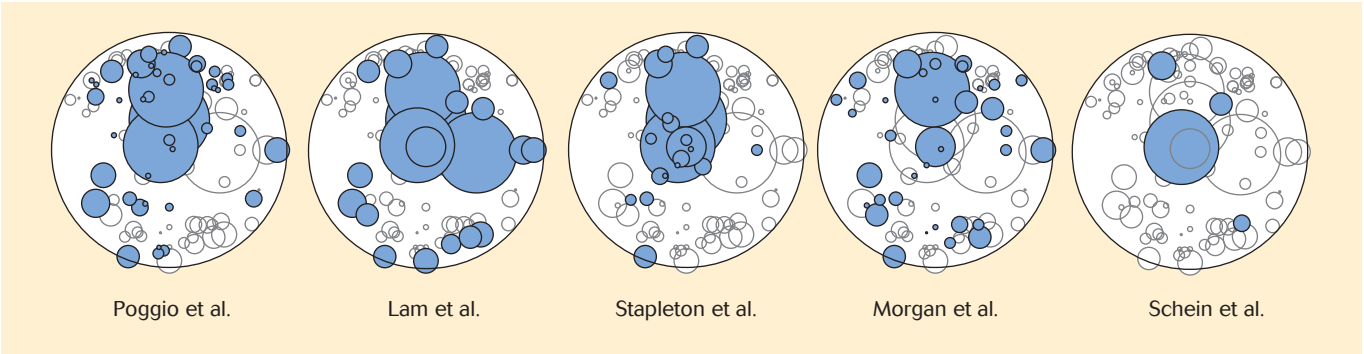


Fig. 26.8 Cartogram showing the size and location of infiltrates for all wearing modalities and lens types, with the corneal infiltrative events (CIEs) that would have been classified as microbial keratitis according to each definition highlighted in blue. (Adapted from Efron N, Morgan PB. Rethinking contact lens associated keratitis. Clin Exp Optom 2006;89:280–98.)

study[20] generate a lower incidence figure compared with the criteria adopted in his 1989 study[14]; indeed, this difference is 9.8-fold. Thus, had Schein adopted the criteria used in his 1989 study[14] when determining the incidence of MK in patients wearing Focus Night & Day silicone hydrogel lenses (CIBA Vision Corp, Duluth, Georgia, USA) in his 2005 study,[20] he might have reported an incidence of MK of 176, rather than 18, cases per 10,000 wearers per year. This analysis does not imply a criticism of Schein's work; indeed, both the 1989[14] and 2005[20] studies are internally consistent. However, this analysis does highlight that caution that must be exercised when comparing incidence figures from different studies – even by the same author – that have adopted different criteria for distinguishing between microbial versus sterile keratitis. Further consideration of the incidence figures derived from such studies can be found later in this chapter (see 'Incidence of Keratitis').

Ulcerative keratitis versus non-ulcerative keratitis

The use of the clinical case definition 'ulcerative' keratitis versus 'non-ulcerative' keratitis is similarly problematic as this distinction depends upon the criterion for corneal ulceration. *Dorland's Medical Dictionary*[3] defines 'ulcer' as 'a local defect, or excavation, of the surface of an organ or tissue, which is produced by the sloughing of inflammatory necrotic tissue'. Therefore, strict confirmation of the presence of an ulcer would require evidence of inflammation and a local tissue defect, which, in the case of the cornea, would mean the presence of infiltrates with overlying corneal staining.

Stein et al.[21] defined a corneal ulcer in terms of its size and shape and the presence or absence of corneal staining overlying stromal infiltrates. They distinguished between 'epithelial defects' and 'superficial punctate keratitis'; however, they did not define either of these conditions, which would generally be considered as being synonymous. Although Stein et al.[21] attempted to provide broad guidelines for the classification of ulcerative keratitis versus non-ulcerative keratitis, they documented considerable overlap in the features of these two conditions. Furthermore, diagnoses were made in relation to whether or not the condition was culture positive, which introduces further uncertainties as discussed previously.

In essence, the definition of Stein et al.[21] implies that a CIE with overlying corneal staining is 'ulcerative keratitis' (a surrogate for 'MK'), whereas a CIE without overlying corneal staining is 'non-ulcerative keratitis' (a surrogate for 'sterile keratitis'). In the Manchester Keratitis Study,[4-10] 68% and 89% of cases of non-severe and severe keratitis, respectively, displayed fluorescein staining in the region of the infiltrates. This suggests that the presence of corneal staining overlying a CIE (and, therefore, a corneal ulcer according to Stein et al.[21]) is not a reliable method of classifying keratitis with a view to determining which patients require anti-microbial treatment.

Suppurative versus non-suppurative keratitis

Classification of contact lens–associated keratitis on the basis of the presence of suppuration[22] (indicating 'MK') or absence of suppuration (indicating 'sterile keratitis') is problematic because this sign may be observed in cases of sterile keratitis and may be absent in cases of MK. For example, Stein et al.[21] reported four cases of severe keratitis (three bacterial and one *Acanthamoeba*) in which there was no discharge, whereas Sweeney et al.[1] reported that a purulent or mucopurulent discharge was evident in 18% of non-infectious CIEs.

Central versus peripheral keratitis

There is a sound physiological basis for assuming that CIEs occurring in the peripheral cornea are less clinically severe than those occurring in the central cornea. If the site of insult (e.g. a localised infection) is close to the limbus, a relatively rapid host immune response might be expected to limit the extent of tissue compromise as a result of the relatively short distance that polymorphonuclear leucocytes and other defensive cellular elements need to migrate from the limbal vessels to the site of tissue insult. It follows that disturbances in the central cornea will be less well protected and any progressive form of pathology in this region is likely to advance further before the host immune response can dampen the reaction.

Many clinicians have anecdotally observed that CIEs, which occur more towards the corneal periphery, are less likely to be clinically severe than those sited further from the limbus.[23-25] Indeed, this is implicit in the polynomial classification schema

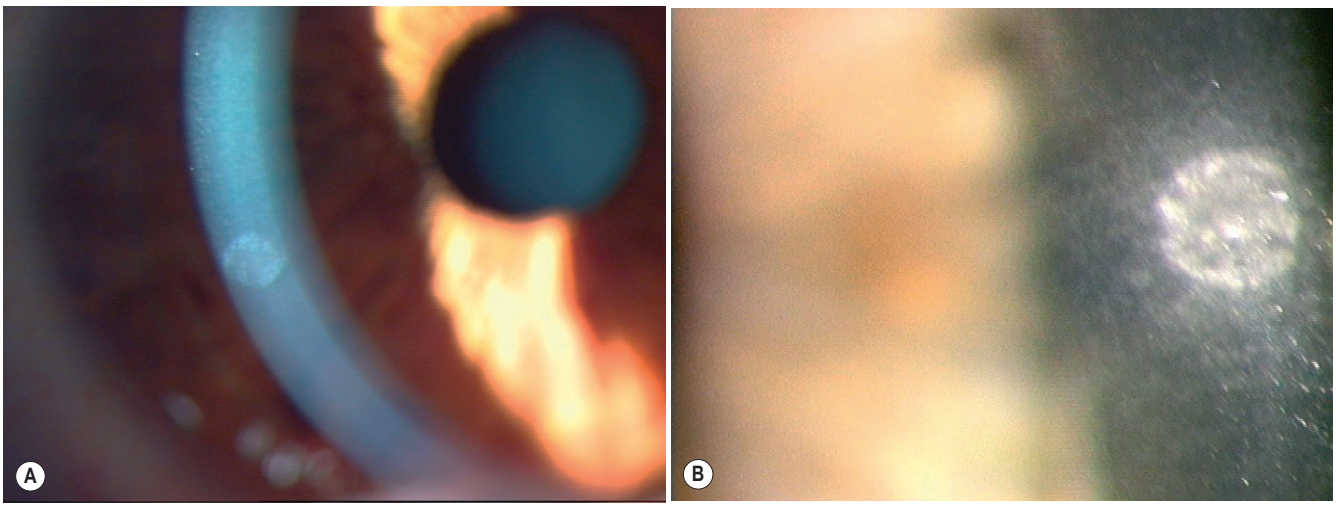


Fig. 26.9 Appearance of the so-called contact lens peripheral ulcer (CLPU). **(A)** Residual scar from a CLPU. **(B)** 'Bull's eye' appearance of a CLPU scar viewed at high magnification. (A, Courtesy Suzanne Efron. B, Courtesy Brian Tompkins.)

of Sweeney et al.[1] in which 'contact lens-induced *peripheral* ulcer' is considered to be a non-serious event (Fig. 26.9). This concept has been extended further, and it has been suggested that because a CLPU is non-serious, it must be non-infectious. Sweeney et al.[1] defined a CLPU as being an event in the mid-peripheral or peripheral cornea, characterised by focal excavation of the epithelium, infiltration and necrosis of the anterior chamber. Symptoms include limbal and bulbar redness and tearing, and patients with this condition are said to experience any level of discomfort ranging from asymptomatic to severe. Besides 'location' (itself a flawed criterion), there is nothing in this description to differentiate a case of so-called CLPU from MK.

Holden et al.[26] attempted to draw a distinction between CLPU and MK by suggesting that Bowman's membrane remains intact in CLPU but is destroyed in MK. However, of three of the patients who were suffering from what was diagnosed as a CLPU and had a biopsy specimen taken from their cornea, one actually displayed a ruptured Bowman's membrane.[26] Wu et al.[27] attempted to induce CLPU-like lesions in rabbit eyes. These authors reported that such lesions could only be induced by a combination of three factors: (a) the presence of *Staphylococcus aureus*, (b) a scratch in the cornea and (c) contact lens wear. However, scratches were only induced in the peripheral cornea, so the obvious question as to whether CLPU-like lesions can also be observed in the central cornea was not tested.

On the basis of observations of histological samples taken from rabbit CLPUs, Wu et al.[27] suggested that their failure to observe replicating bacteria within CLPU-like lesions indicated that these lesions were probably caused by toxins released from bacteria present remotely from the lesion. Their failure to identify bacteria in a selected number of histological sections could be a function of the sampling methodology employed; however, assuming that some CIEs can be caused by bacterial endotoxins, it is not possible to clinically differentiate such events from those caused by replicating bacteria.

The Manchester Keratitis Study[7] has provided evidence, for the first time, of a significant correlation between the distance of the infiltrate from the limbus and the clinical severity score ($F = 9.9$; $p = 0.002$; $r^2 = 0.08$) (Fig. 26.10). This correlation also holds for the grouped data relating to daily wear ($F = 4.3$; $p = 0.04$; $r^2 = 0.05$) and extended wear ($F = 5.7$; $p = 0.03$; $r^2 = 0.19$); that is, this relationship applies irrespective of lens wearing modality. Notwithstanding these statistical associations, the data are of limited predictive value with respect to an individual patient; that is, a significant proportion of clinically severe CIEs also occur at the corneal periphery and a significant proportion of clinically non-severe CIEs are often observed in the central cornea.

Anecdotal observations purporting to support the concept of non-infectious CLPUs, with respect to the diagnostic indicator that the condition occurs in the peripheral cornea, have been further confounded by the fact that there is much more 'peripheral cornea' than 'central cornea' by way of area. The cornea can be considered as having central, mid-peripheral (sometimes referred to as 'paracentral') and peripheral zones, as shown in Figure 26.11, and CLPUs are said to occur 'in the periphery to mid-periphery'.[1] A distinction is not generally drawn between the mid-peripheral and peripheral zones, and the term 'peripheral' usually implies both.

According to the model in Figure 26.11, the 'peripheral' cornea (i.e. mid-peripheral and peripheral cornea combined) represents 89% of the total area of the cornea, when treating the cornea as a flat surface viewed from the front, which is the way the cornea is viewed clinically and the context in which CIEs are noted on a record card. Thus, if infiltrative events were to occur at random locations across the cornea, 89% of such events would be characterised as occurring in the 'peripheral' cornea. Clearly, therefore, the criterion that an event occurs in the 'peripheral' cornea is of limited diagnostic value (i.e. most of the cornea can be described as 'peripheral'). Accordingly, the

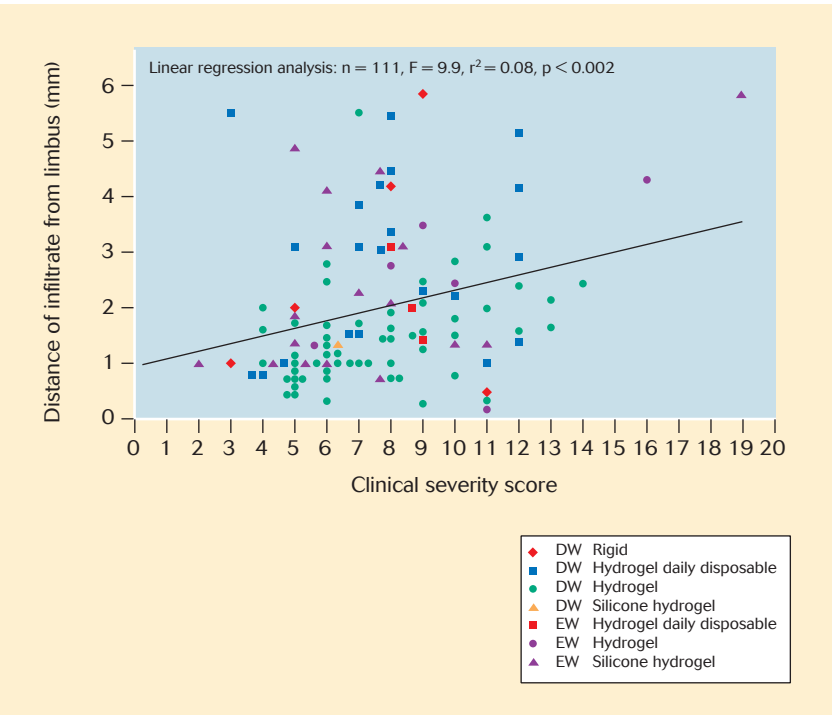


Fig. 26.10 Relation between the distance of the infiltrate from the limbus and the clinical severity score. (Some data points have been offset for clarity of presentation.) DW, daily wear; EW, extended wear. (Adapted from Efron N, Morgan PB, Hill EA, Raynor MK, Tullo AB. The size, location, and clinical severity of corneal infiltrative events associated with contact lens wear. Optom Vis Sci 2005;82:519–27.)

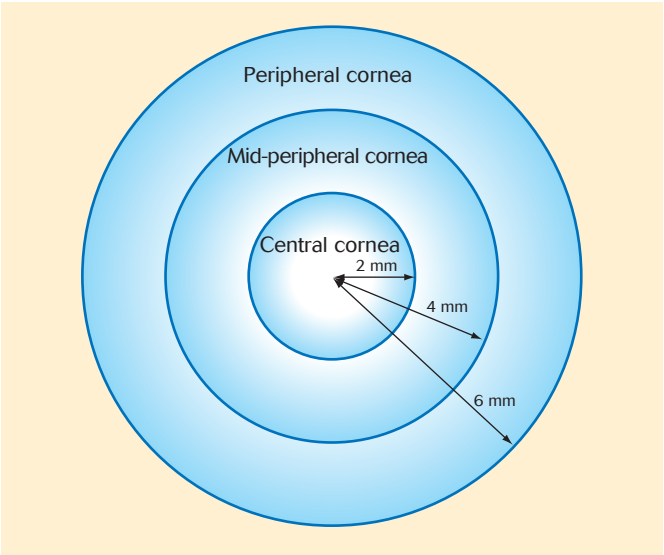


Fig. 26.11 Schematic representation of the central, mid-peripheral and peripheral zones of the cornea. The mid-peripheral and peripheral zones represent 89% of the corneal surface. (Adapted from Efron N, Morgan PB. Rethinking contact lens associated keratitis. Clin Exp Optom 2006;89:280–98.)

term 'CLPU' should discontinued, and such events should simply be referred to as CIEs.

A classification scheme that differentiates between central versus peripheral CIEs would be useful for the purposes of clinically differentiating between microbial versus sterile keratitis if it were true that all CIEs occurring in the peripheral cornea were non-infectious. However, this is not the case. A small CIE in the 'peripheral' cornea could be an early-stage MK, or a late-stage MK caused by an infective agent of low virulence. Of course, such an event could also be a true sterile keratitis that has occurred as a result of a mechanical, toxic or allergic insult. Such an event could also be caused by bacterial endotoxins (rather than replicating microorganisms at the site of inflammation). Although the Manchester Keratitis Study[7] documented a variance in the clinical severity of CIEs with respect to corneal location – whereby those occurring in the peripheral cornea were less severe than those occurring in the central cornea – there is no evidence to support the notion that a CIE located in the corneal periphery is most likely to be sterile or that a CIE located in the central cornea is most likely to be infectious.

POLYNOMIAL CLASSIFICATION SYSTEMS

Attempts have been made to classify CIEs into a number of categories or sub-types. Josephson and Caffery[28] used aetiology as the basis of their classification scheme, whereas Sweeney et al.[1] classified CIEs in terms of clinical severity. Both these works represented significant contributions, but for different reasons. The study of Josephson and Caffery,[28] published over 30 years ago, was a pioneering effort that first drew attention to the complexity and diversity of clinical presentation of CIEs. The work of Sweeney et al.[1] is a substantial analysis of over 900 cases of CIEs observed over a 10-year period in two leading research clinics. However, there are considerable difficulties in applying the classification schemes devised by these authors – again, for different reasons.

Classification according to aetiology

Josephson and Caffery[28] were probably the first to undertake a detailed analysis of contact lens–associated CIEs, which they categorised into the following eight types according to aetiology: (a) traumatic, (b) viral, (c) allergic, (d) preserved solutions, (e) lens fit, (f) coated lenses, (g)toxic vapours and (h) idiopathic. The various signs and symptoms associated with the each category were also documented.

The system proposed by Josephson and Caffery[28] was published in 1979 and is of reduced relevance to contact lens practice today for the following reasons: Modern-generation contact lens solutions do not contain potentially toxic preservatives, such as chlorhexidine and thimerosal, which Josephson and Caffery[28] attributed as being the cause of CIEs associated with preserved solutions. 'Coated lenses' ceased being a significant clinical problem after the introduction of disposable lenses in the late 1980s.

Lens fit was an important issue in the 1970s, when virtually all lenses on the market were made from relatively thick, low-water-content hydroxyethyl methacrylate. Furthermore, such lenses were provided in a wide range of base curves, and soft lenses were fitted along the lines of rigid lens fitting – relating base curves to central corneal curvature. With modern, thin, hydrogel and silicone hydrogel materials, lenses are more 'forgiving', and lens fit is a less critical consideration. It would appear that Josephson and Caffery[28] did not include MK as one of their categories because they probably considered 'CIE' to mean 'non-severe' or sterile keratitis.

Classification according to appearance

Sweeney et al.[1] devised a system for classifying CIEs, which proposes that such events can manifest as a variety of distinct clinical entities.[29] On the basis of a largely retrospective meta-analysis of 916 contact lens wearers suffering from CIEs, these authors proposed a model that classifies CIEs into three broad categories with six sub-types, as follows: (a) serious and symptomatic, of which MK is the only sub-type; (b) clinically significant and symptomatic, which comprises CLPU, contact lens–induced acute red eye (CLARE) and infiltrative keratitis (IK); and (c) clinically non-significant and asymptomatic, which comprises asymptomatic infiltrative keratitis (AIK) and asymptomatic infiltrates (AI). This schema is illustrated in Figure 26.12.

The classification system devised by Sweeney et al.[1] has been challenged by Baum and Donshik[30] as being confusing and ambiguous because of the considerable overlap between the signs and symptoms that describe the six sub-types of CIE. Baum and Donshik[30] stated: 'Although … [Sweeney at al[1]] … have defined six sub-sets of infiltrates, we believe that they have failed to distinguish any'. Other authors have expressed similar concerns. Barr[31] questioned the use of the various terms proposed by Sweeney et al.[1] and Nilsson[32] questioned whether CLPU can be said to exist as a discrete condition.

Data from the Manchester Keratitis Study[4-10] were used to evaluate the clinical utility of the system for classifying CIEs as proposed by Sweeney et al.[1] This evaluation[33] was undertaken by determining the percentage of cases documented in the Manchester Keratitis Study,[4-10] which can be unambiguously categorised into one or more of the four symptomatic sub-types of CIE proposed by Sweeney et al.[1] That is, the Manchester Keratitis Study[4-10] adopted an 'open-choice' decision-making

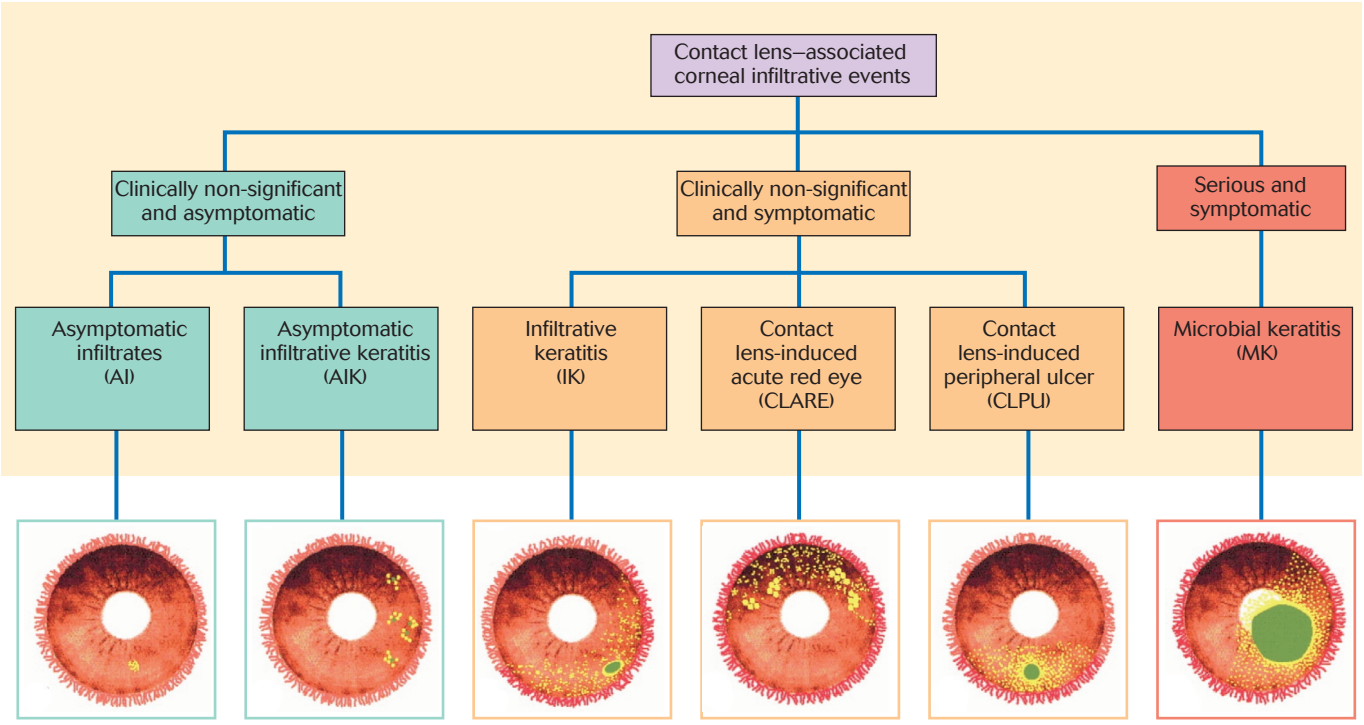


Fig. 26.12 Classification schema of Sweeney et al. (Adapted from Sweeney DF, Jalbert I, Covey M, et al. Clinical characterization of corneal infiltrative events observed with soft contact lens wear. Cornea 2003;22:435–42.)

paradigm, which contrasts with the 'forced-choice' decision-making paradigm used by Sweeney et al.[1] whereby the panel of clinicians assessing the CIEs in that study were obliged to classify each CIE as a single condition.

The criteria for MK, CLPU, CLARE and IK as defined by Sweeney et al.[1] were applied retrospectively to the data set of 111 CIEs observed in the Manchester Keratitis Study[4-10] and a Venn diagram analysis was used to determine the extent to which these conditions can be clinically differentiated (Fig. 26.13). This analysis indicated that only 20% of CIEs could be classified unambiguously as MK, CLPU, CLARE or IK, and 56% and 13% of CIEs could be classified as one of two and three conditions, respectively. Eleven per cent of CIEs could not be classified as any of the four conditions.

Although the aetiology of CIEs is multi-factorial, the considerable overlap between the presentations of MK, CLPU, CLARE and IK in terms of signs and symptoms is such that it is not possible to clinically differentiate between them with any degree of certainty. Perhaps the only exception to this conclusion is that the diagnosis of a very severe case of MK is unmistakable (Fig. 26.14). When a contact lens wearer presents with a large soupy ulcer, circumlimbal redness, intense corneal staining, anterior chamber flare, hypopyon, mucopurulent discharge, photophobia and extreme pain, there is little doubt as to the diagnosis (although differential diagnosis between bacterial, *Acanthamoeba* and fungal keratitis can still present a challenge). These issues are discussed in more detail in Chapter 27. There is, however, little to distinguish less severe cases of MK from so-called CLPU, CLARE and IK.

The difficulties in diagnosing 'CLPU' were discussed earlier in this chapter. The reason for Sweeney et al.[1] designating one of the CIE sub-types as 'contact lens–induced acute red eye' is unclear because eye redness is self-evidently not a corneal problem. Baum and Donshik[30] raised similar concerns. Putting this question of terminology aside, 92% and 44% of cases of severe and non-severe keratitis, respectively, were associated with generalised conjunctival redness in the Manchester

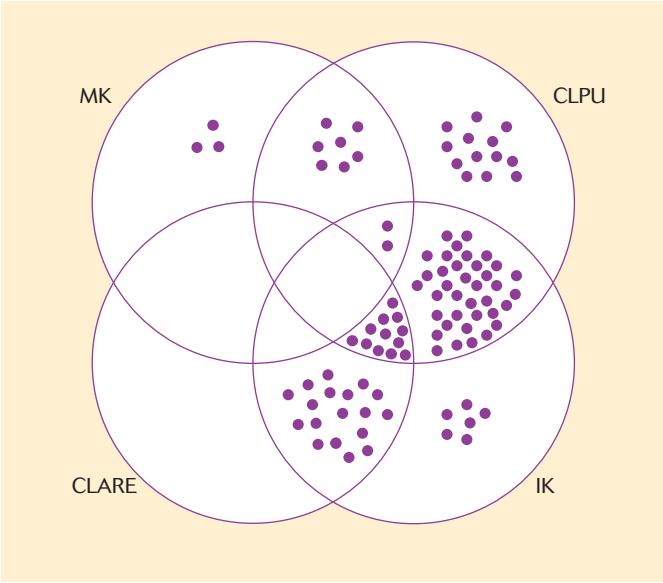


Fig. 26.13 Venn diagram showing how the 111 corneal infiltrative events (CIEs) observed in the Manchester Keratitis Study were classified according to the criteria of Sweeney et al.[18] Each dot represents a single CIE. Thirteen CIEs are not shown because they did not fit into any category. CLARE, contact lens–induced acute red eye; CLPU, contact lens–induced peripheral ulcer; IK, infiltrative keratitis; MK, microbial keratitis. (Adapted from Efron N, Morgan PB. Can subtypes of contact lens-associated corneal infiltrative events be clinically differentiated? Cornea 2006;25:540–4.)

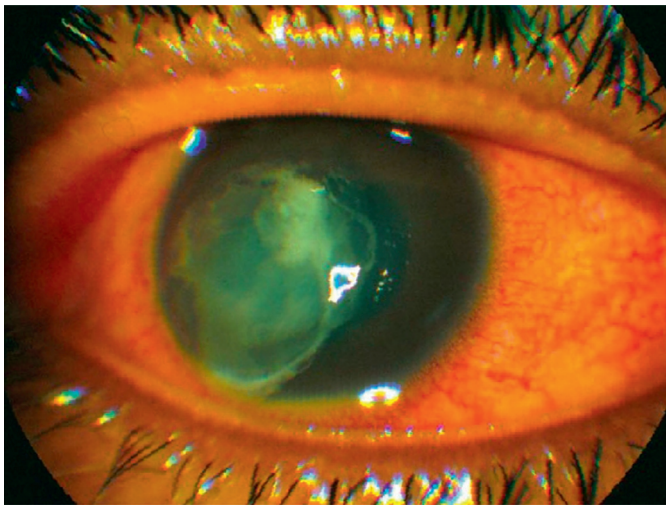


Fig. 26.14 Severe microbial keratitis in a patient who was wearing silicone hydrogel lenses on an extended-wear basis. (Courtesy Andrew Tullo.)

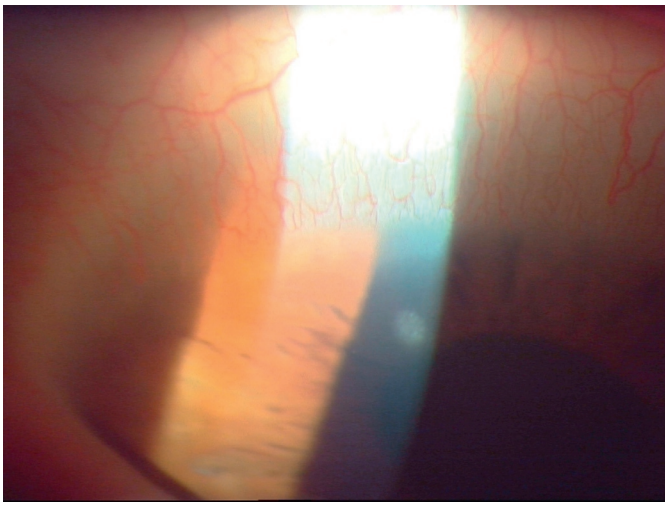


Fig. 26.15 Active corneal infiltrative event (CIE) in a patient who was wearing silicone hydrogel lenses on an extended-wear basis. (Courtesy Carole Maldonado-Codina.)

Keratitis Study.[4-10] Thus, the association of CIEs and generalised eye redness cannot be considered a reliable indicator of a discrete condition such as 'CLARE'. Since the term 'infiltrative keratitis' implies the presence of infiltrates in the cornea, all CIEs can be considered a form of IK. Baum and Donshik[30] observed that IK overlaps with MK except for the location of the infiltrate, with CLPU except for the intensity of the infiltrate and with CLARE except for the link with sleep.

To illustrate the clinical overlap of the four symptomatic subtypes of CIE proposed by Sweeney al,[1] consider Figure 26.15, which is the image of the eye of a contact lens–wearing patient who presented with mild ocular discomfort, mild lacrimation and photophobia. A small active infiltrate can be observed in the superior cornea, associated with moderate limbal injection. Slight punctate staining (not shown in Fig. 26.15) was observed over the infiltrate after instillation with fluorescein. This appearance is entirely consistent with early-stage MK, but it could also be called CLPU because of its peripheral location. Much of the limbus and bulbar conjunctiva is hyperaemic (the entire limbus is not visible in the figure), so this could be described as CLARE, which, according to Sweeney et al.,[1] can be associated with numerous infiltrates in the cornea, with or without staining. In addition, the appearance of the CIE in Figure 26.15 is in accordance with the description given by Sweeney et al.[1] for IK, which is as follows: (a) there is anterior stromal infiltration, with or without epithelial involvement; (b) the infiltrate resides near the limbus and is less than 1 mm in diameter; (c) diffuse infiltration may or may not be present; (d) symptoms are mild to moderate; (e) localised or generalised conjunctival redness is present; and (f) there is occasional discharge. Thus, the condition illustrated in Figure 26.15 could be classified as MK, CLPU, CLARE or IK.

Another difficulty with the polynomial schema of Sweeney et al.[1] is that a considerable amount of attention is given to the severity of the six sub-types of CIE, with little regard to the natural history of the disease process. Figure 26.16 is a theoretical model of the natural history of a CIE experience by two patients – 'patient A', who has keratitis caused by a high-virulence, rapidly replicating bacterial species; and 'patient B', who has a low-virulence, self-limiting bacterial keratitis. The

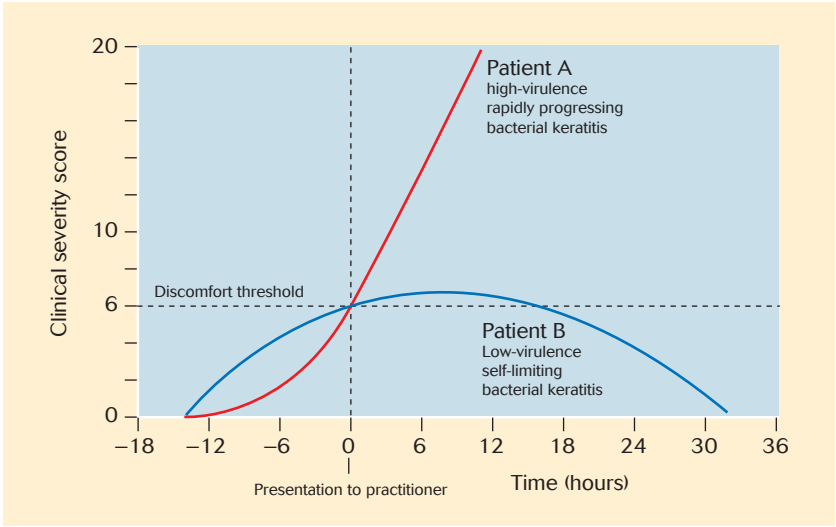


Fig. 26.16 Theoretical model of the natural history of a corneal infiltrative event (CIE) experience by two patients. 'Patient A' has keratitis caused by high-virulence, rapidly replicating bacteria. 'Patient B' has a low-virulence, self-limiting bacterial keratitis. (Adapted from Efron N, Morgan PB. Rethinking contact lens associated keratitis. Clin Exp Optom 2006;89:280–98.)

overall severity rate of the conditions in these patients at presentation is identical, with the severity score being less than 8 (non-severe). In the schema of Sweeney et al.,[1] both these patients could be diagnosed as having one of the five non-serious forms of CIE despite the fact that patient A is in the early stages of a severe keratitis. Indeed, in the paper describing their classification scheme, Sweeney et al.[1] discussed the case of a patient who was initially diagnosed as having a so-called CLPU when, in fact, the patient went on to develop a serious MK.

Baum and Donshik[30] concluded: 'The classification system proposed by … [Sweeney et al.[1]], … splitting the non-infectious inflammatory responses into five subsets, does not, in our opinion, help the clinician either in the diagnosis or in the management of these adverse effects of contact lens wear.'[30] The previous theoretical considerations of this particular polynomial system and the objective analysis of this system using data from the Manchester Keratitis Study[4-10] serve to validate the conclusion of Baum and Donshik.[30]

Distribution of CIEs across the cornea

The distribution of the 111 CIEs recorded in the Manchester Keratitis Study,[7] as shown in Figure 26.7, is a collective representation that pertains to different lens types and wearing modalities. To see if specific influences of lens type and wearing modality can be discerned, the CIEs displayed in Figure 26.7 were disaggregated into eight separate cartograms showing the size and distribution of CIEs for each of the four lens types and two wearing modalities investigated (Fig. 26.17). As explained previously with respect to Figure 26.7, all cartograms displayed in Figure 26.17 are 'right eye' representations. The important feature to consider in these cartograms is the *distribution* of CIEs. The *number* of CIEs in each cartogram is related to the proportion of the population that wears each lens type and gives no indication of the incidence of CIEs.

Analysis of superior versus inferior distribution of infiltrates[7] reveals a significantly higher proportion of infiltrates in the superior cornea of patients using extended-wear silicone hydrogel lenses than would be expected of a random distribution of infiltrates ($\chi^2 = 9.9$; $p = 0.002$). This is not the case for daily-wear hydrogel daily disposable lenses ($\chi^2 = 0.0$; $p = 0.83$) or daily-wear hydrogel lenses ($\chi^2 = 0.1$; $p = 0.79$).

A combination of physiological and physical effects may explain the preponderance of CIEs in the superior cornea of patients wearing silicone hydrogel lenses on an extended-wear basis. The superior cornea is constantly covered by the upper lid, so the persistent hypoxic status of this region[34] might be a contributing factor. Silicone hydrogel lenses have a significantly greater modulus of elasticity (i.e. stiffness) relative to hydrogel lenses.[35] Material stiffness is thought to be a contributing factor to the development of superior epithelial arcuate lesions in the corneas of patients wearing silicone hydrogel lenses,[36,37] and a diffuse infiltrative response is one of the signs of advanced forms of this condition.[36,37] Such damage to the superior corneal epithelium, coupled with constant eyelid pressure on the superior lens and cornea during sleep[35] (which might also act to reduce local tear exchange) and the sub-clinical inflammatory status of the ocular surface and post-lens tear-film overnight,[38] may combine to nurture the development of an infiltrative event in the superior cornea during the extended wear of silicone hydrogel lenses.

None of the CIEs ocurring during extended wear of silicone hydrogel lenses was associated with the characteristic arcuate staining observed in superior epithelial arcuate lesions; however, most infiltrates were located in the superior cornea. It is likely that some of these events were of mechanical, rather than

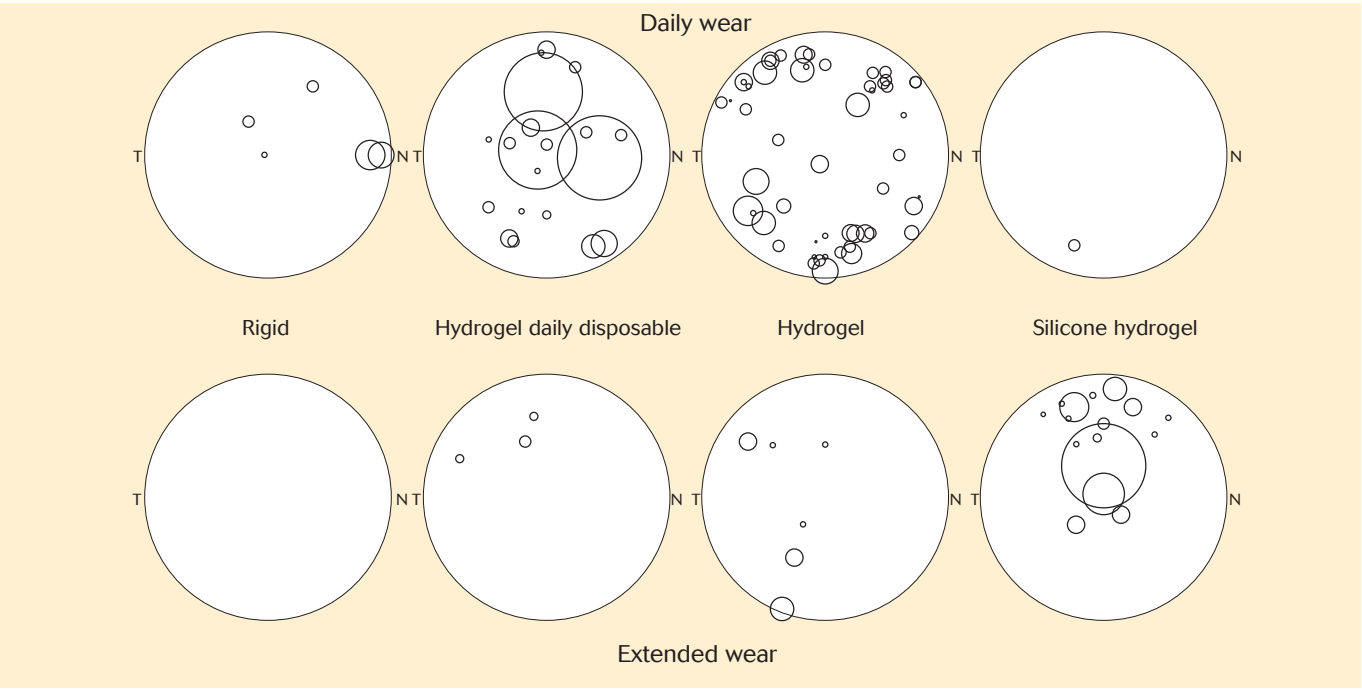


Fig. 26.17 Cartograms showing the size and location of infiltrates separately for the two wearing modalities and four lens types ('right eye only' representation as per Fig. 26.7). N, nasal; T, temporal. (Adapted from Efron N, Morgan PB, Hill EA, Raynor MK, Tullo AB. The size, location, and clinical severity of corneal infiltrative events associated with contact lens wear. Optom Vis Sci 2005;82:519–27.)

infectious, aetiology and, in that sense, may be considered a form of superior epithelial arcuate lesion. Gordon and Kracher[39] observed that 67% of patients using contact lenses on an extended-wear basis developed corneal infiltrates in the superior cornea, and a number of these patients (the exact number was not specified) were wearing early-generation silicone elastomer lenses, which had a high modulus of elasticity.

Although not statistically validated, the apparently random distribution of infiltrates recorded in patients using extended-wear hydrogel lenses[7] lends support to the previous hypothesis because these lenses have a lower modulus of elasticity, minimizing any mechanical insult; however, Suchecki et al.[25] reported a higher prevalence of infiltrates in the superior cornea of patients wearing hydrogel lenses on an extended-wear basis.

An assessment of central versus peripheral distribution of infiltrates[7] demonstrated that compared with an expected random distribution, a significantly higher proportion of infiltrates occur in the peripheral cornea of patients wearing reusable daily-wear hydrogel lenses ($\chi^2 = 11.8$; $p = 0.0006$) and in the central cornea of patients wearing daily disposable hydrogel lenses ($\chi^2 = 7.3$; $p = 0.007$). No such effect is observed for extended-wear silicone hydrogel lenses ($\chi^2 = 1.0$; $p = 0.33$). The disproportionately greater number of infiltrates occurring in the periphery of those wearing reusable daily-wear hydrogel lenses may be related to the typical methods adopted by patients for manually cleaning such soft lenses.

The two classic techniques used to clean contact lenses with solutions are to (a) place the lens on the palm of one hand and rub the lens in a circular motion with the index finger of the other hand and (b) rub the lens between the index finger and thumb.[40] In both cases, there is a tendency for the cleaning effect to be concentrated towards the centre of the lens, which leads to a higher concentration of deposits, such as denatured proteins, in the lens periphery compared with the more thoroughly cleaned lens centre.[41]

Lens deposits can compromise corneal integrity in a number of ways, such as the following: direct mechanical effects; harbouring environmental antigens and causing an immunological reaction in the adjacent cornea; or harbouring microorganisms and inducing an infection in the underlying cornea. Excess deposits in the lens periphery resulting in these forms of compromise in the peripheral cornea could account for the peripheral distribution of infiltrates observed in patients wearing daily-wear hydrogel lenses in the Manchester Keratitis Study.

A disproportionately greater number of infiltrates occur more towards the *centre* of the corneas of patients using daily-wear hydrogel daily disposable lenses.[7] As well, infiltrates occur *further* from the limbus with such lenses versus reusable daily-wear hydrogel lenses.[7] The reasons for these observations are unclear but may relate to patterns of lens contamination from the fingers of patients at the time of lens insertion. The typical method of removal of a lens from the blister pack is to place the index finger on the centre of the back surface of the lens and slide the lens out. In this way, the central part of an otherwise sterile single-use lens may become contaminated by the index finger, and the contaminants may then be transferred to the central cornea upon lens insertion, leading to a central CIE. This is different from removing a reusable soft lens from a lens case containing a disinfecting solution whereby any contaminants on the index finger and/or lens become disinfected. Mechanical characteristics of daily disposable lenses and consequent lens fitting behaviours may also play a role in the distribution of CIEs in patients wearing this lens type.

Depth of CIEs into the cornea

Jansen et al.[42] used anterior segment optical coherence tomography to determine the depth of infiltrates into the cornea, measured from the anterior corneal surface to the most posterior aspect of the infiltrate. The average depth recorded in six patients was between 170 and 230 μm. Given that the cornea is approximately 550 μm thick, the measurements of Jansen et al.[42] suggested that infiltrates penetrate to a depth of about 40% of the thickness of the cornea.

Incidence of keratitis

Epidemiological studies can be used to determine the incidence of keratitis among wearers of various types of contact lenses in the population. The findings of such studies are of considerable importance to practitioners as they define the overall magnitude of the problem. Incidence data can also be used to determine the risk of developing keratitis under defined conditions. Furthermore, such studies can help identify specific factors that influence this risk. Proper interpretation of the results of epidemiological studies can only be gained by considering the methodology that has been adopted in each case.

MULTI-SITE SURVEILLANCE STUDIES

To calculate the incidence of keratitis relating to contact lens wear, it is necessary to determine the number of cases of keratitis that occur over a defined period in a given population of lens wearers and the total number of persons in that population wearing contact lenses. The number of cases must be large enough to ensure statistical confidence in the results. A greater number of cases can be surveyed by increasing the duration of the surveillance period and/or increasing the size of the study population.

One approach to this question is to conduct a large-scale cohort study, whereby a defined population of lens wearers is tracked for a set period. This approach has been adopted by Schein et al.[20] In their prospective, cohort, post-market surveillance study, 131 practitioners were employed to track 4,999 patients over a period of 12 months. Schein et al.[20] were reliant upon complete case capture and full reporting compliance by these practitioners.

An alternative and more widely used approach is to track the number of cases of keratitis in an entire country or defined geographical region. This approach has been adopted in the studies of Poggio et al.,[14] Cheng et al.,[13] Lam et al.[17] and Stapleton et al.,[19] who surveyed five states of the USA, the Netherlands, Hong Kong and Australia and New Zealand, respectively. These authors were also reliant upon complete case capture and full reporting compliance by all eye care practitioners in the geographical regions they surveyed. Thus, Schein et al.,[20] Poggio et al.,[14] Cheng et al.,[13] Lam et al.[17] and Stapleton et al.[19] were reliant upon full cooperation from 131, 612, 379, 2,008 and 4,450 eye care practitioners, respectively. The large variance in these numbers in relation to the size of the geographical regions in the last four of these studies relates to the fact that Poggio et al.[14] and Cheng et al.[13] only surveyed ophthalmologists, whereas Lam et al.[17] and Stapleton et al.[19] surveyed both ophthalmologists and optometrists.

There are many confounding influences when conducting such multi-site studies, which serve to under-estimate the true incidence of keratitis: not all practitioners in the geographical region will agree to participate; individual practitioners cannot be guaranteed to have captured all cases of keratitis over the survey period; and not all practitioners will have reported their cases to the survey centre. In their evaluation of the surveillance approach, Keay et al.[43] observed that response rates as low as 58% can be expected from participating practitioners, although these authors demonstrated that this can be improved by following up with personalised e-mails and telephone calls. Notwithstanding the fact that such active follow-up can improve response rates, the extent to which such practices have impacted upon case capture rates in previously published studies[13,14,17,19,20] is unclear. Response rates in surveillance studies are probably influenced by such factors as the level of enthusiasm of each participant and the degree of individual personal commitment to the study.

The incidence figures for MK derived from the results of the studies considered earlier, together with those of the Manchester Keratitis Study,[10] are presented in Figure 26.18 for various lens types and wearing modalities. Considerable differences in incidence rates pertaining to given lens types are apparent; for example, the discrepancy between the highest and lowest reported incidence rates is about 10 times those of both rigid lenses and hydrogel extended-wear lenses. It is likely that the discrepancies between the incidence values for a given lens type relate, at least in part, to the different criteria adopted for MK by the various authors of those studies, as discussed previously.

SINGLE-SITE SURVEILLANCE STUDIES

The Manchester Keratitis Study[10] employed a number of unique and innovative strategies to circumvent the problems inherent in multi-site studies. The study was conducted in a single hospital location, which facilitated tight monitoring of the attending clinicians to ensure that all cases were captured over the survey period. The use of the clinical severity matrix[11] (described earlier) allowed the clinical characteristics of *all* CIEs (not just severe cases) presenting to the hospital to be documented, thus obviating the requirement to diagnose MK according to a clinical definition.

To determine the denominator of the incidence equation, Poggio et al.,[14] Cheng et al.[13] and Stapleton et al.[19] relied upon estimates of the number of contact lens wearers in the population from random telephone surveys. The use of telephone surveys is problematic because the recipients of such calls are more likely to give answers that they believe are 'correct', rather than the 'true' answer.[44] Furthermore, lens wearers cannot be relied upon to give accurate technical information as to the type of lenses they are wearing (e.g. hydrogel vs. silicone hydrogel, or spherical vs. toric design). The Manchester Keratitis Study[10] adopted a rigorous approach to the determination of population lens wearing demographics. Actual sales information obtained from the Association of Contact Lens Manufacturers in the United Kingdom – a robust and validated[45] data set – were used in combination with detailed contact lens prescribing data collated during the time of the survey.[46] When these data were applied to the hospital catchment population (calculated using well-established methodologies[47]), the total number of lens wearers in the population could be estimated accurately.[45]

As a result of the strategies outlined previously – and in particular the more complete case capture at a single-site – it is not surprising that the Manchester Keratitis Study[5] arrived at higher incidence values for severe (or microbial) keratitis than those found in multi-site studies. That single-site studies, such as the Manchester Keratitis Study,[5] or studies with a small number of sites (< 10),[10,48,49] result in higher incidence figures compared with studies using a large number of sites (> 200)[13,14,17,19,50] – albeit at the expense of larger confidence intervals – is illustrated by considering the incidence values for MK resulting from the extended wear of hydrogel contact lenses reported by groups adopting these different approaches (Fig. 26.19). Probably the most accurate estimate displayed in this figure is that of Holden et al.,[48] who conducted a prospective study in which all lens wearers were under the ongoing care of only two research centres, ensuring virtually 100% case capture.

Putting aside the small minority of extremely serious cases requiring hospital admission and/or intensive medical therapy, it was observed during the Manchester Keratitis Study[6] that there is little difference in the 'clinical journey' of patients suffering from symptomatic CIEs of all levels of severity. All patients had to take time off work (or time off from pursuits in which they would otherwise have been engaged); it was

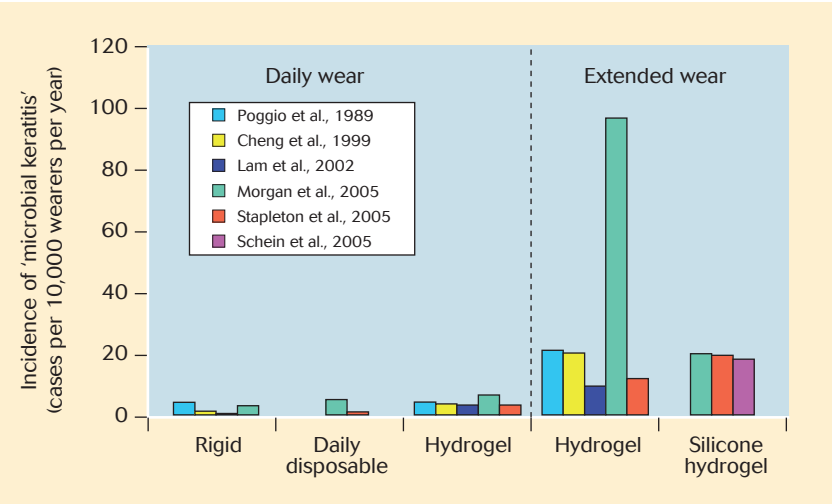


Fig. 26.18 Incidence of microbial keratitis (MK) reported by various authors. A few incidence values are missing because some authors did not determine the incidence of MK with all five lens types. (Adapted from Efron N, Morgan PB. Rethinking contact lens associated keratitis. Clin Exp Optom 2006;89:280–98.)

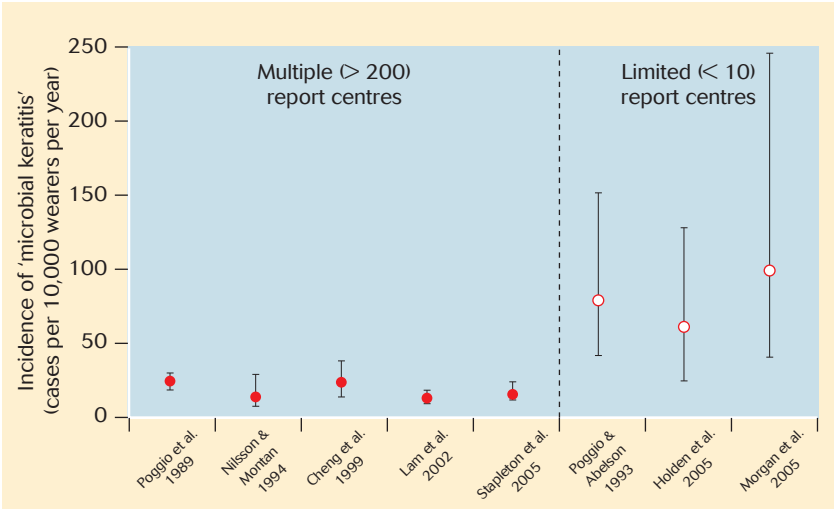


Fig. 26.19 Incidence and 95% confidence intervals reported for extended wear of hydrogel lenses, stratified according to studies with a small number of sites (10) versus studies using a large number of sites (200). Data from the Manchester Keratitis Study[5] are shown as in Morgan et al. (2005). (Adapted from Efron N, Morgan PB. Rethinking contact lens associated keratitis. Clin Exp Optom 2006;89:280–98.)

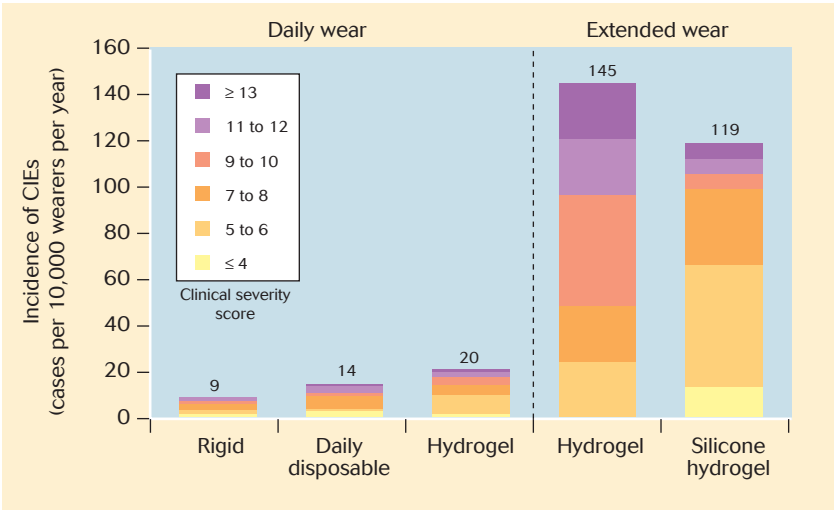


Fig. 26.20 Incidence of all CIEs as determined by the Manchester Keratitis Study, with colour banding indicating the distribution of clinical severity scores. (Adapted from Efron N, Morgan PB, Hill EA, Raynor MK, Tullo AB. Incidence and morbidity of hospital-presenting corneal infiltrative events associated with contact lens wear. Clin Exp Optom 2005;88:232–9.)

necessary to seek advice from a health care professional (which is often a hospital setting) and be subjected to an ophthalmic examination, sometimes involving corneal scraping; most patients were required to temporarily suspend lens wear and resort to alternative modes of vision correction (typically spectacle wear); patients often had to access various therapeutic or prophylactic topical and systemic medications, including analgesics to alleviate the pain, either on prescription from their attending clinician or as over-the-counter products; and patients had to bear some of the costs of medical care and therapeutics (depending on their welfare entitlements and/or medical health care cover). All of these factors probably served to heighten the anxiety of the patients, many of whom would have feared suffering from a potentially permanent loss of sight.

In view of the previous discussion, incidence data from the Manchester Keratitis Study are best presented with respect to CIEs of all levels of severity.[6] Previous studies have presented incidence figures only for severe (or microbial) keratitis. Figure 26.20 shows the incidence of CIEs, determined in the Manchester Keratitis Study,[6] for five key lens types/wearing modalities, stratified for severity using colour coding. For extended wear, there is no statistically significant difference between the incidence of CIEs for hydrogel versus silicone hydrogel lenses; however, CIEs occurring as a result of extended wear of hydrogel lenses tend to be more severe than those that occur with the extended wear of silicone hydrogel lenses ($p < 0.04$).[6] These observations suggested that increasing the level of corneal oxygenation does not lessen the likelihood of developing a CIE during extended wear, whereas greater levels of oxygen will serve to reduce the severity of a CIE should this occur, thus providing a strong rationale for fitting silicone hydrogel lenses, instead of hydrogel lenses, to patients wishing to wear lenses on an extended-wear basis.

When considering only severe cases, extended wear of conventional hydrogel lenses is associated with a five-fold greater incidence of CIEs compared with extended wear of silicone hydrogel lenses ($p < 0.04$).[10] Thus, irrespective of whether data from the Manchester Keratitis Study are presented as the incidence of all CIEs stratified by severity[6] or only severe CIEs,[10] the findings are consistent with predictions of reduced rates of severe keratitis with silicone hydrogel lenses based on reports of worldwide cases of lens-related infections[51] and the general clinical performance with this lens type.[51]

HOSPITAL SURVEYS OF ALL PRESENTING CONTACT LENS COMPLICATIONS

A number of surveys have been conducted over the past 25 years of all patients with contact lens–related complications presenting to hospital clinics. Although these surveys do not generate precise incidence figures, they do offer a perspective on the proportion of keratitis cases presented to such clinics in relation to all other presenting problems and how this proportion may have changed over time.

In 1992, Stapleton et al.[52] reported that of 1,104 patients with contact lens–related disorders presenting to an acute referral hospital eye clinic in the UK, 13.3% presented with 'sterile keratitis' (infiltrates) and 5.4% presented with 'presumed microbial keratitis'. In the extensive hospital-based surveys of contact lens complications conducted between 2009 and 2018 – carried out in China,[53] India,[54] Nepal,[55] Singapore,[56] the USA[57] and the UK[58] – various forms of keratitis were reported (Table 26.2). Differences in reported values among sites may relate more to the types of clinics (acute referral clinics or general contact lens clinics) and mode of data collection.

In reviewing the current literature, Bullimore[59] determined that the incidence of CIEs in children is no higher than in adults and that in the youngest age range of 8 to 11 years, considered in his review, suggested that it may be markedly lower.

Risks of keratitis

In the Manchester Keratitis Study, logistic regression analyses were performed to investigate the association between a range of risk factors and the occurrence CIEs.[9] Factors identified as being associated with an increased risk of development of a CIE included wearing modality/lens type (greatest risk for extended-wear hydrogel lenses of 7.1 vs. daily-wear hydrogel lenses); male gender (relative risk 1.4); smoking (1.4); the absence of relevant ocular (1.8) and general health (2.4) problems; and the late winter months (greatest risk in March (3.6) vs. July). The overall predictive value of these risk factors for a given individual was low.

Numerous authors have applied sophisticated statistical models to determine factors that contribute to an increased risk of developing keratitis. Some authors have attempted to determine risk relating to low-grade CIEs and severe MK as if they were separate entities; however, given the overlap between these entities, as discussed throughout this paper, such a distinction is artificial. The risks identified in all of these studies will essentially apply to all forms of keratitis, so such a distinction will not be made here.

MODIFIABLE VERSUS NON-MODIFIABLE RISKS OF KERATITIS

A useful approach to considering risk factors is to divide them into modifiable and non-modifiable risks. Such a distinction is not always clear, but in essence, a modifiable risk factor is a behaviour, attribute or feature that can be readily rectified by patients on advice from their practitioners. Non-modifiable risk factors are those that either cannot be readily changed or are impossible to change. A detailed analysis of all suggested risk factors is beyond the scope of this chapter, so a summary of modifiable and non-modifiable factors associated with an increased risk of keratitis is presented in Table 26.3.[2,9,13,14,17,19,22,60-86] As can be seem from this table, there is disagreement as to whether some of these factors pose a higher or lower risk of keratitis. This list is not exhaustive, but it highlights key associations identified to date. Specific factors found *not* to be associated with increased risk, as reported my many researchers, are not listed.

TABLE 26.2 Proportion of various forms of keratitis among hospital-presenting contact lens wearers, in relation to all presenting complications

Author	Country	Year	Population size studied	Retrospective or prospective	Proportion of keratitis events
Li et al.[53]	China	2018	141	Retrospective	BK – 5.7% AK – 5.0% CLARE – 2.1% IK – 3.6% CLPU – 4.3%
Sapkota et al.[55]	Nepal	2013	4,064	Retrospective	MK – 2% CLARE – 2% IK – 1% CLPU – 3%
Lee et al.[57]	USA	2012	1,369	Prospective	MK – 28.3% CIE – 26.7%
Teo et al.[56]	Singapore	2011	953	Prospective	MK – 25.6% CIE – 7.5%
Nagachandrika et al.[54]	India	2011	1,255	Retrospective	MK – 0.9% CLARE – 0.1% IK – 1.4% CLPU – 0.6% AIK – 0.1%
Radford et al.[58]	UK	2009	877	Prospective	CIE – 27.5% CLARE – 5.4%

AIK, asymptomatic infiltrative keratitis; AK, *Acanthamoeba* keratitis; BK, bacterial keratitis; CIE, corneal infiltrative event; CLARE, contact lens–associated acute red eye; CLPU, contact lens peripheral ulcer; IK, infiltrative keratitis; MK, microbial keratitis.

TABLE 26.3 Factors that carry an increased risk of keratitis

Modifiable risk factors	Non-modifiable risk factors
Sleeping in lenses[2,9,13,14,17,19,60,61]	Late winter months[9]
Longer periods, overnight use[22,62,63]	Warmer climate[64]
More days of lens wear per week[58]	Younger age (< 25 years)[65,66]
Poor hand hygiene[58]	Older age (> 50 years)[66]
Poor storage case hygiene[19]	Absence of compromised ocular health[9]
Care system non-compliance[67]	Absence of compromised general health[9]
Chlorine disinfecting systems[67]	Ametropia > ±5.00 D[65]
Multi-purpose disinfecting systems[68,69]	Lower socio-economic class[63]
Smoking[19,17,58,62]	Higher socio-economic class[19]
Reusable contact lenses[68]	Diabetes[62]
Internet contact lens purchase[19]	Less lens wearing experience[58,68]
Higher risk-taking propensity[70]	More lens wearing inexperience[19]
Swimming[71-73]	Males[9]
Overnight orthokeratology[74-77]	History of CIEs[69,78]
Silicone hydrogel material[2,58,68,79,80]	Bacterial bioburden[81-84]
	Limbal redness[85]
	Mucin balls[86]

CIE, corneal infiltrative event; D, diopter.

PUTTING THE RISK OF KERATITIS INTO A BROADER PERSPECTIVE

The risk of silicone hydrogel lens–related keratitis is about 1.5 to 16 times less risky than certain non-fatal disruptive occurrences in the general population and about the same as the risk of developing breast cancer.[87] Compared with other ocular conditions, the risk of MK with silicone hydrogel lenses is about the same as that of developing late-stage age-related macular degeneration or retinal detachment after cataract extraction on an annual basis; it is over 200 times greater than that of developing eye or orbit cancer; and it is about 7, 20 or greater than 30 times lower than the risk of proceeding to penetrating keratoplasty in keratoconus, developing nuclear cataract or experiencing a CIE during use of low-Dk extended-wear lenses, respectively. Although the risk of MK with extended wear of modern-day silicone hydrogel contact lenses has not changed since the 1980s, when put in perspective with other life risks, it is a relatively rare occurrence.[87]

Morbidity of keratitis

The key measure of morbidity in relation to the development of a CIE is whether this leads to any permanent vision loss or chronic damage to the cornea.

VISION LOSS

Measurement of vision is critical, for clinical and medico-legal reasons, during the acute phase of a CIE. Specifically, vision should always be measured at the time of initial presentation to the clinic and during the treatment phase. Visual acuity measures do not always provide a useful indication of morbidity because much of the vision loss during this period is related to ocular inflammation and oedema, which will largely resolve with treatment. To obtain a true measure of morbidity, it is necessary to assess vision long after such an event has resolved.

Edwards et al.[61] reported that delaying treatment by 49 to 72 hours had a 4.5 times (odds ratio; 95% confidence interval 1.4–14.9) greater risk of visual loss compared with seeking treatment early.

Attempts were made to contact the eye care practitioner of each contact lens wearer examined in the Manchester Keratitis Study[10] (with their consent) about 6 months after attending the hospital. The practitioner was asked to provide, from his or her own clinical records, measures of best corrected visual acuity (BCVA) in the affected eye of the hospital attendee, both before and about 6 months after the hospital visit.

Estimates of BCVA before and after hospital attendance were obtained from the eye care practitioners of 38 of the 118 patients suffering from a CIE.[6] The elapsed time between the hospital visit and the measurement of BCVA after the hospital visit was 173 ± 132 days (mean ± standard deviation). Estimates of BCVA were generally reported using Snellen's notation. The results of this analysis are displayed in Figure 26.21. Taking a change of two lines of BCVA measured in routine clinical practice as representing a significant change in vision,[88,89] it can be said that no patients in the Manchester Keratitis Study suffered significant vision loss (95% confidence interval 0–9.2%).[6]

The clinical severity scores of the sub-group of 38 patients in whom morbidity was assessed (7.7 ± 3.0) were identical with those of the 118 contact lens wearers who suffered from a CIE during the survey period (7.7 ± 2.9),[6] suggesting that the morbidity-assessment sub-group constituted a representative sample of all those who had suffered from a CIE. The finding that 0% (95% confidence interval 0–9.2%) of patients suffered clinically significant vision loss as a result of CIEs[6] is consistent with the analysis by Holden et al.[46] of patients suffering from severe keratitis.

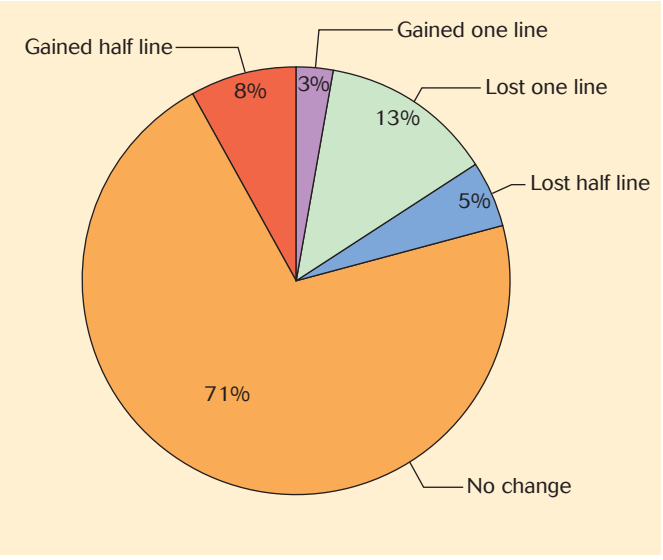


Fig. 26.21 Change in best corrected visual acuity (BCVA) 173 ± 132 days after visiting the hospital with a corneal infiltrative event (CIE), compared with BCVA prior to attending the hospital. (Adapted from Efron N, Morgan PB, Hill EA, Raynor MK, Tullo AB. Incidence and morbidity of hospital-presenting corneal infiltrative events associated with contact lens wear. Clin Exp Optom 2005;88:232–9.)

The reason for the low rate of vision loss after experiencing a CIE can be explained in terms of the size, density and location of any residual scar after such an event. A CIE can occur at any location of the cornea, but only those occurring within the pupillary area could leave a scar that is capable of directly interfering with vision. Only 13% of the CIEs documented in the Manchester Keratitis Study[7] fell within the central 4 mm zone of the cornea (Fig. 26.7). For the small proportion of CIEs that occur within the central corneal zone, the density of any residual scar will have a bearing on the degree to which it interferes with vision. However, it is possible that residual corneal scarring in the central or mid-peripheral cornea could still adversely affect the quality of vision, if not BCVA, by inducing glare caused by light scatter.

Data from the Manchester Keratitis Study[7] can be extrapolated to the population of lens wearers generally. Assuming that a CIE is the only potential cause of vision loss among contact lens wearers, and taking the 'worse case' scenario of the 95% confidence interval for vision loss (9.2% of CIE patients losing two or more lines of BCVA),[6] it can be calculated that up to 0.02% of all contact lens wearers will suffer vision loss per year. To put this finding into a broader perspective, it has been estimated[90-92] that 2% to 6% of patients suffer vision loss of two lines of BCVA or greater after laser refractive surgery. Assuming an average wearer uses contact lenses for 10 years, the risk of vision loss with contact lenses is at least 10 to 30 times lower than that with laser refractive surgery.

CHRONIC CORNEAL DAMAGE

In the Manchester Keratitis Study, the central corneas of both eyes of 13 subjects who had suffered a CIE 27 ± 4 months previously were examined by using slit lamp biomicroscopy, confocal microscopy and ultrasound pachometry.[8] Snellen visual acuity in both eyes was recorded. A questionnaire was administered to ascertain the type and extent of changes in contact lens wear and care since the CIE. Slit lamp biomicroscopy revealed the presence of a circular scar, approximately 1.5 mm in diameter, in the central cornea of the right eye of the patient who had suffered the most clinically severe CIE; no residual scar, or any other abnormality, was detected in any of the other 12 patients.

No significant difference between the two eyes was found with respect to basal epithelial cell density; anterior or posterior keratocyte density; endothelial cell density, polymegethism or pleomorphism; corneal thickness; or visual acuity. Anecdotally, however, markedly reduced pan-corneal cell counts, increased endothelial polymegethism and reduced corneal thickness were observed in the affected eye of the patient who had suffered the most clinically severe CIE.

After experiencing CIEs, many patients changed the lens type or brand, ceased to routinely sleep wearing lenses or wore lenses less often. These changes in lens-related behaviours seemed to be aimed at reducing the risk of a further occurrence. It can be concluded from these observations that low-severity CIEs generally do not compromise the long-term integrity of the cornea; however, more severe CIEs may be associated with chronic tissue morbidity.

CIEs are a disease continuum

CIEs should be considered as a continuous spectrum of ocular disease, rather than as a binomial division into two disease subtypes or as a polynomial division into three or more disease sub-types. We should, therefore, discontinue the use of misleading and confusing terms, such as CLPU, CLARE, IK, AI and AIK. Instead, we should simply use the terms CIE or MK, with the realization that they are overlapping conditions.

The term 'CIE' should be used to designate any contact lens–associated condition in which infiltrates appear in the cornea. An overall assessment of the level of severity of a CIE can be made with the assistance of a clinical severity matrix, such as that described by Aasuri et al.[11] and adopted in the Manchester Keratitis Study.[4-10] If a CIE becomes severe – for example, with a severity score greater than 8 – and presents with such features as severe pain, acute eye redness, anterior chamber flare, large deep ulcer, serous or mucopurulent discharge or hypopyon, then the condition can be designated as MK; that is, MK is a severe form of CIE.

This line of thinking has been endorsed by other prominent contact lens epidemiologists. For example, Szczotka-Flynn and Chalmers[93] noted: 'Efron and Morgan[5] have advanced the concept that all contact lens–related corneal infiltrates are 'CIEs,' including severe MK, and thus all should be graded on a continuous spectrum of disease severity rather than by aetiology. There is validity to this approach as it is impossible to clinically distinguish a single small focal infiltrate as a sterile lesion or an early onset infectious event, and thus all are typically initially treated with anti-microbial therapy. Therefore, the inciting aetiology may never be known. Clear statement of definitions for CIEs in published literature will help the reader understand which events are being analysed.'

General principles of clinical management

A detailed account of the clinical management of contact lens–associated MK is presented in Chapter 27. However, some general rules can be derived from the array of issues considered in this chapter. In view of the clinical uncertainties relating to the diagnosis of a CIE as resulting from replicating microorganisms versus some other sterile cause (e.g. mechanical, hypoxic, toxic or allergic aetiology), contact lens wear should be suspended, and therapeutic management initiated immediately, if the following three criteria are met:

a) the patient is wearing contact lenses;
b) the patient has presented complaining of ocular discomfort that is not resolving or is becoming progressively worse; and
c) a CIE is observed in the eye that the patient claims is uncomfortable.

This conservative approach allows clinical decisions to be made *without* reference to the flawed binomial or polynomial classification systems used previously.

The rationale for this approach can be appreciated with reference to Figure 26.16. Consider the scenario of a contact lens wearer presenting at 'time = 0' complaining of a sore eye, and on examination with a slit lamp biomicroscope, a CIE is observed in that sore eye. The patient reports that the eye soreness was first noticed about 12 hours ago (displayed on the horizontal *x*-axis) and has been getting progressively worse. The vertical *y*-axis in Figure 26.16 represents the clinical severity score, and in this example, the patient has crossed the 'discomfort threshold' (the threshold above which patients might be expected to take action and seek help) of an arbitrary score of 6. However, the attending clinician has no way of knowing at 'time = 0' whether this is 'patient A' or 'patient B'. If the clinician could magically look into the future, it would be apparent that if

this is patient A, the case involves a self-limiting CIE caused by a low-virulence pathogen and that medication is not required. If, however, this is patient B, the case involves a CIE caused by a highly virulent pathogen that will rapidly progress into a severe MK and which required intensive antibiotic therapy.

But the clinician cannot look into the future and cannot be sure if the individual is patient A or patient B. After suspending lens wear, the only options are to either 'prescribe now' or 'wait and see'. Of course, the latter approach is not an option at all. In the interest of the patient, anti-microbial agents should be prescribed immediately. It may be prudent to first perform corneal scraping and culture to determine the causative agent. If the CIE is thought to be a case of MK, a broad-spectrum antibiotic could be prescribed immediately. The regimen can be later modified if the culture is positive and the likely causative agent is identified.

CLINICAL CAVEATS

There may be some caveats to the management strategies outlined previously. For example, if the patient reports having had a sore eye for the previous few days but that it has become progressively *less* severe, then it may be prudent not to prescribe any medication because the condition might be resolving. Certainly, it would be necessary to monitor the patient carefully. Fluffy, white infiltrates and other associated signs and symptoms might suggest a viral epidemic keratoconjunctivitis that has occurred coincidentally with lens wear; in this case, therapeutic intervention is usually not required. The patient history might suggest that the sore eye was associated with a traumatic event, ruling out a microbial cause.

Another difficulty with the approach advocated here is that it necessarily represents 'over prescribing' because, clearly, not all symptomatic CIEs will have a microbial origin. Inappropriate prophylactic antibiotic therapy can either do nothing or, in the worst case, cause allergic or toxic reactions and facilitate the development of microbial resistance. However, these outcomes, albeit undesirable, represent the 'lesser of two evils', and in view of the absence of a reliable clinical means of diagnosing true microbial versus sterile keratitis, the interests of contact lens wearers suffering from symptomatic CIEs are best served by erring on the side of caution and initiating antimicrobial therapy immediately. The treatment regimen can be modified or withdrawn as further evidence is gathered (e.g. culture results from corneal scraping) and/or the severity of the CIE changes over time.

PROPHYLAXIS

Lens wear should be suspended if CIEs are observed in a contact lens wearer. If the condition is symptomatic, then the case should be treated as a presumed MK and managed accordingly (see Chapter 27).

Ozkan et al.[94] investigated whether prophylactic topical antibiotic instillation (tobramycin 0.3%) during continuous wear of silicone hydrogel lenses could reduce the incidence of CIEs. There was no difference in the incidence of CIEs in the test versus control groups, leading these authors to conclude that this prophylactic measure did not work.

Prognosis

Aquavella and DePaolis[95] noted that although the acute phase of an infiltrative event may only last for 2 days, the infiltrate itself may take much longer to resolve. Josephson and Caffery[28] suggested that there is a general correlation between severity and resolution time, such that more severe infiltrates take longer to resolve. Baum and Dabezies[96] reported that contact lens–induced peripheral ulcers and mid-peripheral infiltrates usually resolve within a week, whereas Sweeney et al.[1] reported that 1 to 3 weeks are needed for resolution.

Jansen et al.[42] used anterior segment optical coherence tomography to monitor the time course of resolution of CIEs in six patients who were wearing silicone hydrogel contact lenses. They reported that CIEs resolved in 9.9 $\pm$ 5.5 days.

Differential diagnosis

The primary differential diagnosis is to distinguish between CIEs – a benign self-limiting condition, versus MK – a progressive and potentially devastating ocular disease. The difficulties of making such a differential diagnosis early in the presentation of an infiltrative event has been discussed throughout this chapter.

Other conditions, such as old corneal scars, deep stromal opacities and certain dystrophies, can take on the appearance of CIEs. The primary differentiation is that CIEs are more superficial and transient, typically resolving within 10 days of ceasing lens wear. The other conditions referred to earlier tend to present in the deeper layers of the stroma and are chronic.

Conclusions

In this chapter, the difficulties inherent in attempting to classify CIEs using either binomial or polynomial approaches have been outlined. The clinical journey of patients suffering from a symptomatic CIE is a miserable one, irrespective of the level of severity, although it is recognised that a very severe case of MK can be an especially painful and distressing experience. This leads to the conclusion that clinical thinking around this topic should relate to all patients who experience a CIE; that is, attention should not be just concentrated on those who develop severe keratitis, as has been the case in the past.

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27 Microbial Keratitis

As explained in some detail in Chapter 26, microbial keratitis is a particular type of corneal infiltrative event (CIE) characterised by the fact that replicating microorganisms are the cause. Microbial keratitis can be 'self-limiting', whereby it develops to a certain level of severity and then subsides, perhaps only resulting in mild discomfort at the peak of its development. A case of microbial keratitis may be self-limiting because the causative microorganisms cease replicating, possibly as a result of some action taken by the lens wearer, such as removing the lenses or instilling eye drops.

If not treated early (or not self-limiting), microbial keratitis can be progressive and potentially devastating to the cornea. It is the most severe reaction which can occur in response to contact lens wear. The patient may suffer from considerable pain and must incur the discomfort, cost and inconvenience associated with the acute management of this condition. In very severe cases, the patient may suffer partial or complete loss of sight. In perhaps the most severe case microbial keratitis ever recorded,[1] the patient ended up with bilateral large, deep corneal ulcers and hypopyon. The right eye perforated spontaneously, and the patient developed secondary glaucoma and bilateral optic atrophy. All of this resulted in total bilateral blindness[1] (Fig. 27.1). Others have also reported cases of microbial keratitis leading to blindness resulting from continuous lens wear.[2,3]

Microbial keratitis is defined as an inflammation of corneal tissue caused by direct infection by microbial agents, such as a bacteria, fungi, protozoa and viruses. Bacterial, fungal and protozoan keratitis can be directly caused by contact lens wear, and these forms of keratitis will be considered separately throughout this chapter. Contact lens wearers may coincidentally contract viral infections, such as epidemic keratoconjunctivitis (which is non-ulcerative)[4] or herpes simplex keratitis (which is ulcerative),[5] but there is no reason to believe that contact lens wear itself is a contributing factor to the development of the infection.

The terms 'infectious keratitis' and 'microbial keratitis' are essentially synonymous. The term 'ulcerative keratitis' has also been used as a synonym for microbial keratitis; however, this usage is not always correct because a given case of microbial keratitis may not necessarily be ulcerative, and an ulcerative keratitis may not necessarily be microbial.

Signs and symptoms

BACTERIAL KERATITIS

An early symptom of bacterial keratitis is a foreign body sensation in the eye associated with an increasing desire to remove the lenses. In the case of an actual foreign body, or that of other causes of lens-related ocular discomfort, lens removal leads to immediate relief. Continuing or worsening discomfort after lens removal should lead a clinician to suspect microbial keratitis. Associated symptoms include pain, eye redness, swollen lids, increased lacrimation, photophobia, discharge and loss of vision[6] (Fig. 27.2).

Besides the obvious signs of eye redness and lacrimation, an area of infiltration will typically be observed at the site of infection[6] (Fig. 27.3). In the early stages, infiltrates may be confined primarily to the epithelium. As the disease progresses, the stroma becomes increasingly hazy, and the epithelium above the infiltration begins to break down, leading to corneal staining of the ulcer and surrounding cornea (Fig. 27.4). The appearance of bacterial keratitis in the early stages (Figs. 27.3 and 27.4) is indistinguishable from a so-called contact lens peripheral ulcer (CLPU) (see Chapter 26).

Conjunctival redness may be initially confined to the limbal and bulbar regions adjacent to the field of infection, providing an important clue to the clinician as to its location. This clue is soon lost as the condition advances and the eye becomes more inflamed with circumlimbal conjunctival redness (Fig. 27.2).

Bacterial keratitis can have a rapid and devastating time course. The initial focal ulcer (as shown in Figs. 27.3 and 27.4) can progress to form a swirling, circular, milky-white infiltrate (Fig. 27.5). Worsening of the condition will lead to the formation of a creamy, pussy ulcer (Fig. 27.6), anterior chamber flare, iritis and hypopyon. The time course from initial symptoms to the appearance in Figure 27.6 can be as rapid as 4 to 6 hours. A serous or mucopurulent discharge will be evident. If not properly treated, the stroma can melt away, leading to corneal perforation in a matter of days (Fig. 27.1). A grading scale for microbial keratitis is displayed in Appendix A; the sequence of grades also provides an illustration of the sequence of events as the keratitis increases in severity.

PROTOZOAN KERATITIS

The time course of keratitis due to amoebic protozoa is not as rapid as for bacterial keratitis; typical signs include corneal staining, pseudo-dendrites, epithelial and anterior stromal infiltrates, which may be focal or diffuse, and a classic radial keratoneuritis (Fig. 27.7) – the last being a circular formation of opacification which becomes apparent relatively early in the disease process. A fully developed corneal ulcer may take weeks to form. The pain associated with *Acanthamoeba* keratitis is so severe that it has been described as causing the patient to become almost suicidal. Figure 27.8 is an ocular thermogram of the face of patient suffering from contact lens–induced *Acanthamoeba* keratitis. As can be seen from the temperature scale to the right of this figure, the red and pink colouration around the right eye indicates higher temperatures, consistent with severe ocular inflammation.

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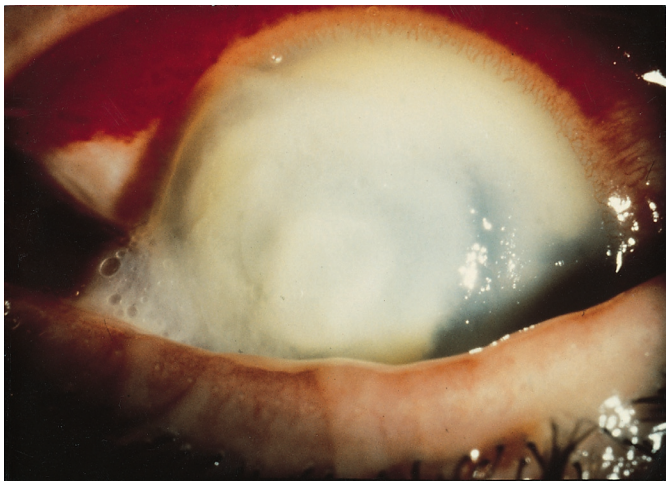


Fig. 27.1 Severe case of microbial keratitis, which eventually resulted in perforation, optic atrophy and permanent blindness. (Chalupa E, Swarbrick HA, Holden BA, Sjostrand J. Severe corneal infections associated with contact lens wear. Ophthalmology 1987;94:17–22.)



Fig. 27.2 Early stages of *Pseudomonas* keratitis, with limbal redness, increased lacrimation and swollen eyelids. A small white ulcer can be seen near the inferior pupil margin. (Courtesy Lyndon Jones, British Contact Lens Association Slide Collection.)

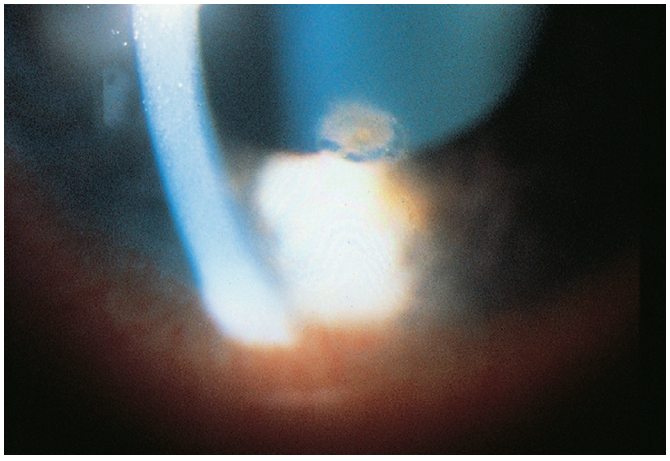


Fig. 27.3 Slit lamp photograph of the corneal ulcer depicted in Figure 27.2. (Courtesy Lyndon Jones, British Contact Lens Association Slide Collection.)

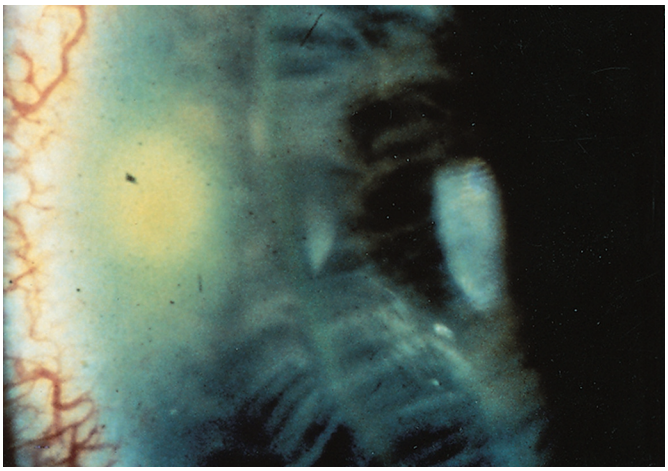


Fig. 27.4 Peripheral corneal ulcer in the early stages showing fluorescein staining of the ulcer and background fluorescence indicating diffusion of fluorescein into the stroma. (Courtesy Brien Holden Vision Institute.)

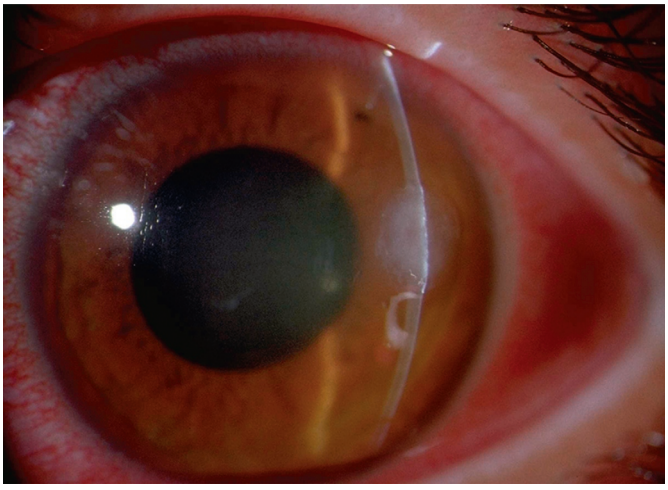


Fig. 27.5 Moderately advanced case of contact lens–induced microbial keratitis, displaying a swirling, circular, milky-white infiltrate. The intense limbal and bulbar redness indicates the active nature of the condition.

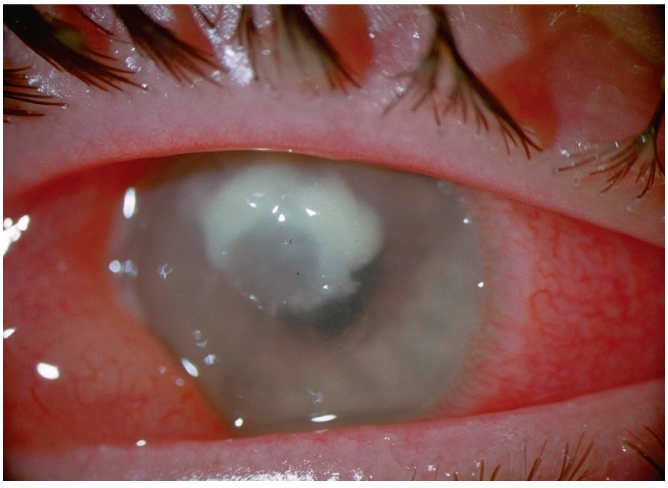


Fig. 27.6 Creamy, pussy ulcer in the advanced stage of a contact lens–induced microbial keratitis. (Courtesy Barry Weissman.)

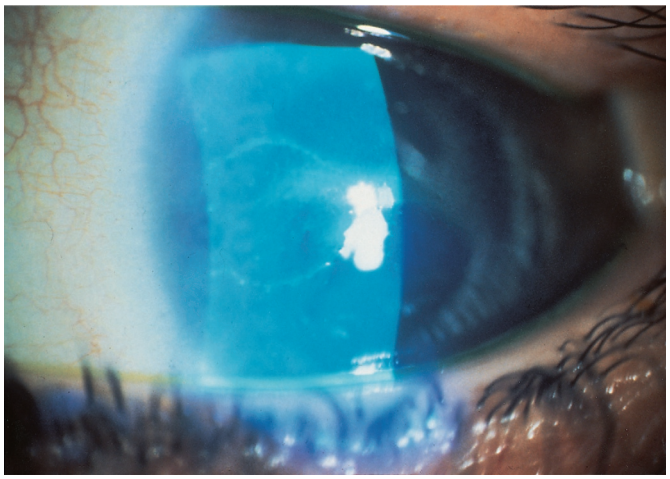


Fig. 27.7 Breakdown of the epithelium in the classic pattern of radial keratoneuritis in a patient with *Acanthamoeba* keratitis. (Courtesy Florence Malet, Bausch & Lomb Slide Collection.)

FUNGAL KERATITIS

Fungal keratitis also seems to develop over a more prolonged time course, in a similar manner to amoebic keratitis. Hu et al.[7] presented a case series of patients with contact lens–associated fungal keratitis and reported a key symptom common to all cases reviewed – a sharp pain on removal of the lens from the eye after experiencing initial discomfort. This was followed by increased tearing, redness and photosensitivity. Vision deteriorated over a period of days. The form of presentation varied. One patient showed a round central stromal infiltrate, about 5 mm in diameter, corresponding to a deep corneal ulcer. In another patient, slit lamp examination with fluorescein staining showed a 4 × 3 mm, multi-lobed, central corneal infiltrate with complete loss of the overlying epithelium. One day later, the infiltrate appeared fluffy. In a third patient, a central corneal ulcer was seen with a paracentral opacity. There was also significant conjunctival and scleral injection and grade 2 cell and flare in the anterior chamber.

Ng et al.[8] diagnosed 16 patients (17 eyes) with *Fusarium* keratitis associated with contact lens wear. One patient had bilateral involvement. Six patients had a central lesion; four had paraxial lesions; one had paraxial and peripheral lesions; and the rest had peripheral lesions.

Of the 66 patients with fungal keratitis examined by Khor et al.,[9] 30 had involvement of the right eye, 34 had involvement of the left eye, and two had bilateral eye involvement (68 infected eyes). Nine eyes (13.2%) had been treated with corticosteroid eye drops before the diagnosis of fungal keratitis. At presentation, the best-corrected Snellen visual acuity in the affected eye was 20/60 or better in 51 patients (75%), 20/80 to 20/200 in 11 patients (16.2%) and count fingers or worse in 6 patients (8.8%). Of the 68 eyes, 11 eyes (16.2%) had infiltrates which were described as central (involving the visual axis), 42 eyes (61.8%) had paracentral infiltrates, and 15 eyes (22.1%) had peripheral infiltrates. There were 25 eyes (36.8%) with classic fungal satellite lesions, five eyes (7.4%) with a ring infiltrate and 47 eyes (69.1%) with documented anterior chamber inflammation (consisting of anterior chamber cells or frank hypopyon) (Fig. 27.9).

Pathology

The hazy region of infiltration observed clinically in patients with microbial keratitis is presumed to be composed primarily of inflammatory cells but will also include the causative microorganisms, serum and proteins, as well as lipid which may leak from the limbal vessels.

HISTOPATHOLOGY

Sankaridurg et al.[10] developed an animal model (guinea pig) of endotoxin-mediated stromal infiltration. Histopathological examination of the affected regions of the stroma revealed focal or diffuse infiltration of polymorphonuclear leucocytes.

In an extraordinary study, Holden et al.[11] obtained biopsy samples of the cornea and conjunctiva of three patients suffering from low-grade contact lens–associated keratitis. All three

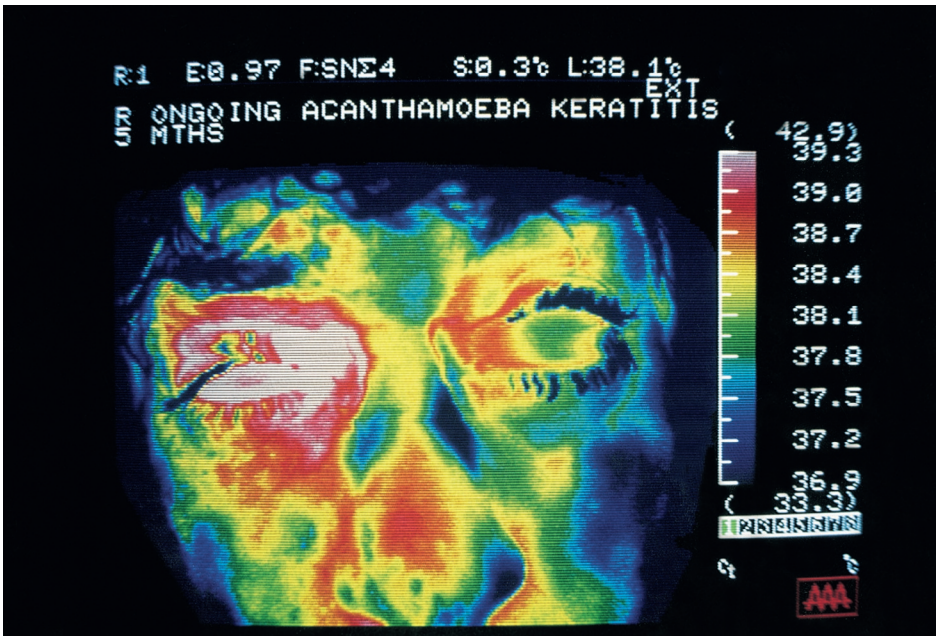


Fig. 27.8 Ocular thermogram of a patient with *Acanthamoeba* keratitis of the right eye, showing the increased temperature of the affected eye. (Courtesy Meng Poey Soh.)

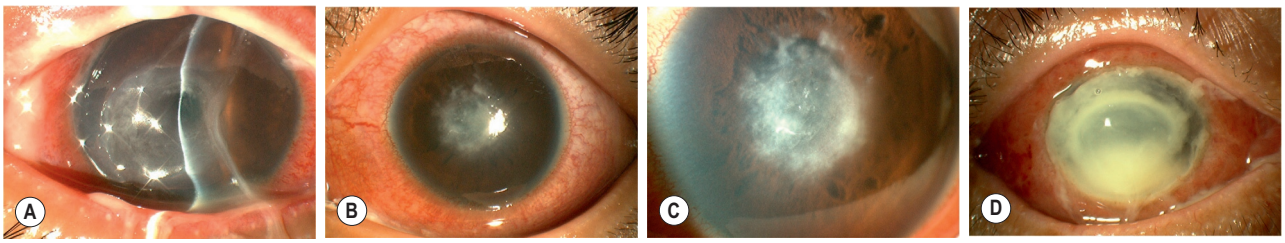


Fig. 27.9 Four cases of contact lens–associated *Fusarium* keratitis seen in Singapore. **(A)** Central stromal ring infiltrate, grade 2.3. **(B)** Central round infiltrate with indistinct feathery edges and satellite lesions, grade 2.8. **(C)** Central vertically oval ulcer with an inset ring infiltrate, indistinct feathery edges and small satellite lesions, grade 3.2. **(D)** Pan-corneal opacification with dense ring infiltrate and large hypopyon, grade 4.0. (Courtesy Donald Tan.)

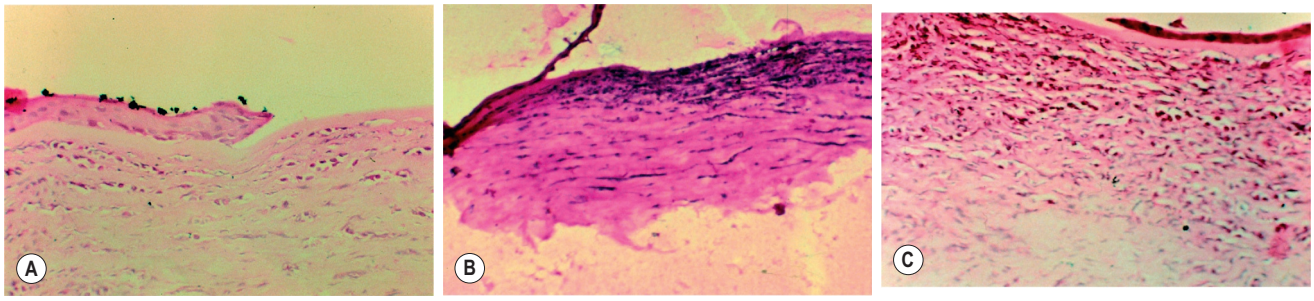


Fig. 27.10 Histological sections from patients suffering from a corneal infiltrative event. **(A)** Marked thinning of the epithelium. **(B)** Loss of Bowman's layer in the centre. **(C)** Infiltration of polymorphonuclear leucocytes into the stroma. (All haematoxylin and eosin stain.) (Chalupa E, Swarbrick HA, Holden BA, Sjostrand J. Severe corneal infections associated with contact lens wear. Ophthalmology 1987;94:17–22.)

patients were using extended-wear hydrogel contact lenses. The diameter of the three infiltrates ranged from 0.3 to 0.6 mm. Histopathological examination of the corneal sections revealed a focal area of epithelial loss surrounded by a severely attenuated epithelium in all three patients (Fig. 27.10A). Bowman's layer appeared to be intact and of normal thickness in two patients, but there was a localised area of loss in the other patient (Fig. 27.10B). The anterior corneal stroma was infiltrated with numerous polymorphonuclear leucocytes beneath the area of epithelial compromise (Fig. 27.10C). The conjunctival epithelium appeared normal, and diffuse inflammatory cell infiltration, predominantly with mononuclear cells, was observed in the conjunctival stroma.

ANTERIOR SEGMENT OPTICAL COHERENCE TOMOGRAPHY

Konstantopoulos et al.[12] demonstrated the utility of anterior segment optical coherence tomography for assessing the morphological characteristics of corneal pathological changes during the course of microbial keratitis. Seven patients (eyes) with suspected microbial keratitis underwent standard clinical examination and treatment based on slit lamp clinical examination findings. Anterior segment optical coherence tomography scanning was performed on presentation and at two follow-up appointments. All scans were carried out with the scanning beam passing through the centre of the infiltration and at a specific meridian. Examination was carried out by the same operator.

Corneal infiltration was imaged as a hyper-reflective area in the corneal stroma on high-resolution anterior segment optical coherence tomography scans. Retro-corneal pathological features and anterior chamber inflammatory cells could be imaged.

Corneal and infiltrate thickness could be measured with callipers in six cases. The depth of infiltrates into the cornea was measured as ranging from 180 to 590 μm (the latter measurement essentially representing full corneal thickness). In one case, corneal and infiltrate thicknesses could not be measured because of a thick inflammatory plaque attached to the endothelium. In this case, the width of the plaque was measured on serial scans. The authors concluded that anterior segment optical coherence tomography imaging provides a range of parameters which can be used to assess microbial keratitis and the treatment response objectively.[12]

Aetiology

Contact lens wear can alter normal flora in certain groups of contact lens wearers – including those who have used certain chemical disinfection systems, older contact lens wearers and persons who have discontinued contact lens wear.[13,14] However, studies of the microbiological environment of the eyes of contact lens wearers suggest that there is little correlation between the types of bacteria which contaminate lens care paraphernalia and ocular flora in corresponding patients. Thus, contamination alone cannot explain changes to normal ocular flora occurring during contact lens wear.

Wu et al.[15] demonstrated that post-lens tear fluid can lose anti-microbial activity over time during contact lens wear, supporting the idea that efficient tear exchange under a lens is critical for homeostasis. Thus, a well-fitting contact lens with good movement, is a basic, but important, strategy for minimizing the risk for microbial infection.

BACTERIAL KERATITIS

The spectrum of bacteria implicated in contact lens–associated microbial keratitis can be appreciated by considering the culture results from corneal scrapes taken from 25 of the patients surveyed in the Manchester Keratitis Study[16] (Table 27.1).

TABLE 27.1 Outcomes of cultures of corneal scrapes from the Manchester Keratitis Study

Patient code	Age	Gender	Wearing modality	Lens type	Clinical severity score	Culture outcome
82	26	F	Daily wear	Hydrogel	7	*Staphylococcus* spp.*
48	30	F	Extended wear	Silicone hydrogel	8	*Bacillus* spp.
36	32	M	Extended wear	Hydrogel daily disposable	9	No growth 5 days
58	40	M	Daily wear	Hydrogel	9	No growth 5 days
197	23	M	Daily wear	Hydrogel	9	No growth 5 days
205	34	M	Daily wear	Hydrogel	9	No growth 5 days
209	35	F	Extended wear	Hydrogel	9	No growth 5 days
362	83	F	Daily wear	Rigid	9	*Stenotrophomonas maltophilia*
364	23	F	Daily wear	Hydrogel daily disposable	9	No growth 5 days
44	61	M	Extended wear	Silicone hydrogel	10	*Propionibacterium acnes*
185	20	F	Daily wear	Hydrogel	10	Mixed coliforms
206	51	F	Daily wear	Hydrogel daily disposable	10	*Candida albicans*
369	30	F	Daily wear	Hydrogel	10	*Acinetobacter* spp.
92	24	F	Daily wear	Hydrogel	11	No growth 5 days
95	20	F	Extended wear	Hydrogel	11	*Staphylococcus* spp.*
195	31	M	Daily wear	Rigid	11	No growth 5 days
291	60	F	Extended wear	Silicone hydrogel	11	No growth 5 days
41	27	F	Daily wear	Hydrogel daily disposable	12	No growth 5 days
213	48	M	Daily wear	Hydrogel	12	Mixed coliforms
295	24	F	Daily wear	Hydrogel daily disposable	12	No growth 5 days
365	19	M	Daily wear	Hydrogel	12	No growth 5 days
372	21	M	Daily wear	Hydrogel	13	No growth 5 days
375	47	M	Daily wear	Hydrogel	14	*Pseudomonas* spp.
93	29	M	Extended wear	Hydrogel	16	*Pseudomonas* spp.
273	25	M	Extended wear	Silicone hydrogel	19	*Pseudomonas* spp.

After Morgan PB, Efron N, Hill EA, et al. Incidence of keratitis of varying severity among contact lens wearers. Br J Ophthalmol 2005;89:430–6.
*Coagulase negative.

A clinical decision was taken to execute corneal scraping in two of 80 cases which were classified by the scoring system to be non-severe keratitis, and bacterial growth was detected in both cases. A corneal scrape was performed in 23 of the 38 cases classified as severe keratitis; of these, 10 were culture-positive. This is equivalent to a culture-positive rate of 43%, which is consistent with that observed in other contact lens studies.[17-19] *Pseudomonas* species, which are generally considered the most virulent bacterial pathogen in contact lens–related keratitis,[20] were associated with the three highest clinical severity scores of the patients on whom corneal scraping was performed.

The bacterial species implicated in the vast majority of cases of bacterial keratitis, and certainly in the most severe cases, is *Pseudomonas aeruginosa*, a Gram-negative bacteria. Other Gram-negative bacterial species have been cultured from infected corneas at the same time, such as *Serratia*, *Enterobacter*, *Escherichia coli* and *Klebsiella*. Gram-positive bacterial species, such as *Staphylococcus aureus* and *Staphylococcus epidermis*, have less frequently been isolated from corneal ulcers in patients with microbial keratitis.

Gram-negative *Achromabacter*, *Stenotrophomonas* and *Delftia* have recently been identified as scaffold organisms in biofilm on contact lens cases and contact lenses of patients with keratitis.[21] In addition, *Elizabethkingia* forms biofilms on contact lens cases.[22] These four organisms have physiology similar to that of *Pseudomonas*; however, their virulence is lower, and their antibiotic resistance profiles are different from that of *Pseudomonas*.[22] The extent to which these organisms contribute to contact lens–associated microbial keratitis is yet to be clarified.[23]

Other bacterial species have been reported, but with less frequency. These include *Serratia marcescens*, a water-borne Gram-negative organism; *Nocardia*, a Gram-positive bacterium which causes an epithelial slow-progressing granulomatous appearance and can resemble adenovirus; and non-tuberculosis *Mycobacterium*, *M. cheloni* and *M. fortutim*.[21,24]

Pseudomonas aeruginosa

For infection to occur, contact lens wear must somehow compromise corneal defences against infection.[25,26] Research into this issue has focused on the question as to why this compromise favours infection with *Pseudomonas*, and for this reason, the following discussion will focus on this particular pathogen.[20]

Using cells removed from corneas by irrigation, Fleiszig et al.[27] found that extended wear of hydrogel lenses increases *Pseudomonas* adherence to human corneal epithelial cells (Fig. 27.11). It has also been demonstrated that *Pseudomonas* lipopolysaccharide is a major factor contributing to the ability of *Pseudomonas* to adhere to the cornea and to contact lenses[28] and that bacterial pili, which were previously reported to be major factors in *Pseudomonas* adherence, play only a minor role.[29]

A key to understanding the pathology of *Pseudomonas* infection is to understand why this bacterium does *not* adhere to the healthy cornea, whereas it is known to adhere readily to most surfaces, including inert surfaces, without the necessity for specific receptors. The answer lies in the natural protective layers of the corneal surface; specifically, the mucus layer of the tear film and the epithelial cell surface glycocalyx (which also contains mucin molecules and fibronectin) inhibit *Pseudomonas* adherence to the intact healthy corneal surface[30,31] (Fig. 27.12). The precise mechanism involves *Pseudomonas* binding to mucin molecules and competitive inhibition of bacterial adherence to the cornea. Furthermore, certain tear film components can bind *Pseudomonas*,[32] and the whole human

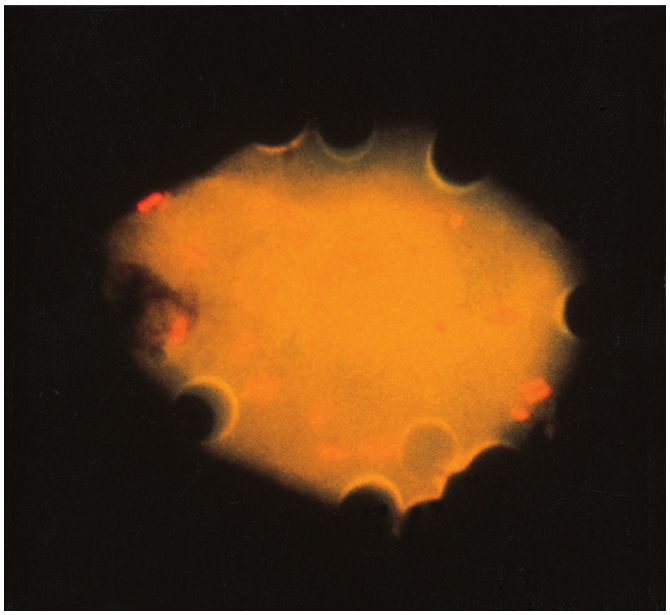


Fig. 27.11 In vitro preparation showing *Pseudomonas* bacteria (small orange rods) adherent to a human epithelial cell (orange). The semicircles at the edge of the cells are an artefact of the preparation mount. (Courtesy Suzanne Fleiszig.)

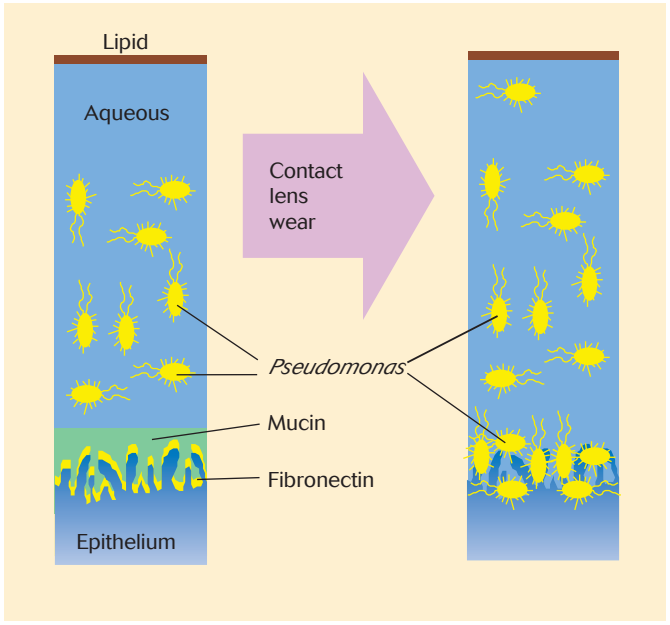


Fig. 27.12 Schematic diagram of the corneal surface. Left: *Pseudomonas* bacteria in the tear film are unable to attach to the epithelial surface because of the mucus and fibronectin layers. Right: contact lens wear depletes the protective layers and *Pseudomonas* attaches to the epithelium.

tear fluid can protect the corneal epithelium against *Pseudomonas* virulence mechanisms.[33,34]

Epithelial cell polarity determines the susceptibility of epithelial cells to *Pseudomonas* invasion and cytotoxicity.[35] Specifically, the basolateral cell surfaces (the sides and the bottoms of cells) are much more susceptible to infection than the apical cell membrane (the top surface of cells). This research indicates another way in which the intact healthy cornea is able to resist infection and why corneal surface injury predisposes to infection.

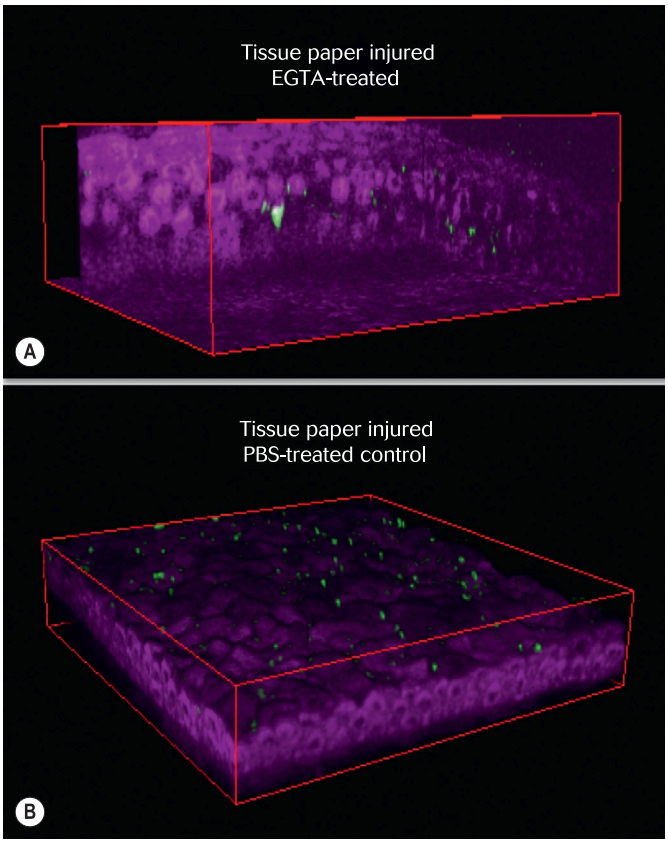


Fig. 27.13 Three-dimensional imaging of challenged mouse corneas. **(A)** Paper-injured cornea treated with ethylene glycol tetraacetic acid (EGTA) allows *Pseudomonas* (green dots) to penetrate. **(B)** Paper-injured cornea treated with control phosphate-buffered saline (PBS) solution results in *Pseudomonas* failing to penetrate. (Courtesy Suzanne Fleiszig.)

Surfactant protein D can contribute to the clearance of *Pseudomonas* from the healthy ocular surface and proteases can compromise that clearance.[36] Moreover, surfactant protein D degradation in vivo is a mechanism by which *Pseudomonas* proteases could contribute to virulence.[36]

In vitro and in vivo data show functional roles for epithelium-expressed anti-microbial peptides in normal corneal epithelial cell barrier function against *Pseudomonas*.[37] Tam et al.[38] used a suite of imaging technologies to enable three-dimensional and temporal sub-cellular localization and quantification of bacterial distribution within the murine cornea without the need for tissue processing or dissection. These authors demonstrated bacterial invasion of the cornea by using a mouse model (Fig. 27.13). The corneas were first blotted with lint-free tissue to allow *Pseudomonas* to attach to the epithelial surface, then ethylene glycol tetraacetic acid – a calcium chelator capable of disrupting calcium-dependent cell–cell junctions – was added. This allowed the bacteria to traverse the cornea. Treatment with a control solution (phosphate-buffered saline) resulted in the epithelial barriers remaining intact, preventing the bacteria from entering the cornea.

These methods demonstrated the importance of MyD88, a central adaptor protein for Toll-like receptor–mediated signalling, in protecting a multi-layered epithelium against both adhesion and traversal by *Pseudomonas* ex vivo and in vivo.[38]

It is now known that some strains of *Pseudomonas* invade corneal epithelial cells during corneal infection (Fig. 27.14).[39]

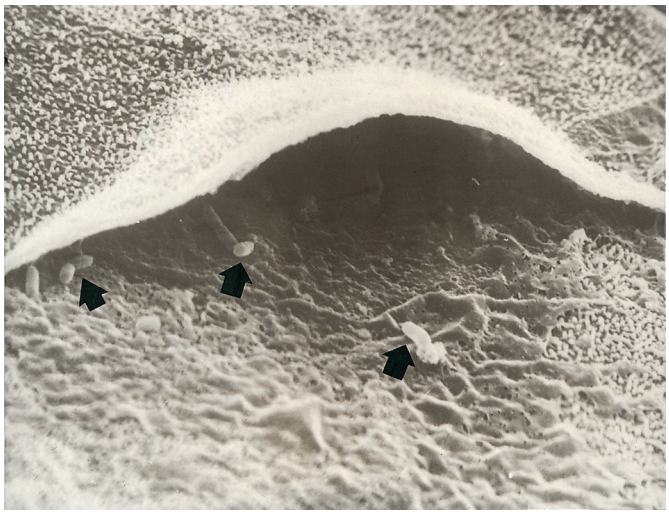


Fig. 27.14 Scanning electron micrograph of the cornea showing *Pseudomonas* bacteria (arrows) about to enter beneath an epithelial cell that has partially sloughed off. (Courtesy Suzanne Fleiszig.)

Previously, it was thought that this bacterium was an extracellular pathogen; that is, *Pseudomonas* resided only in extracellular compartments during disease. The significance of bacterial invasion of epithelial cells is that once the bacterium is inside a cell, it then has the potential to internally alter host cell function. Meanwhile, it is protected from factors of the host immune system and from most forms of antibiotic therapy – neither of which can enter epithelial cells. This finding has led to a flurry of new studies in the ophthalmic field and in research related to cystic fibrosis and other lung infections caused by *Pseudomonas*.[40] (*Pseudomonas* pneumonia is the leading cause of death in cystic fibrosis and has become one of the leading causes of death in patients with acquired immunodeficiency syndrome).

In vitro systems have been used to study *Pseudomonas* invasion of corneal epithelial cells, with use of whole cornea, cultured corneal cells and epithelial cells washed from human corneas by irrigation.[41] By using these systems, it has been demonstrated that bacterial uptake by cells is an active process involving the host cell cytoskeleton, that host cell signal transduction mechanisms is involved and that there is rapid replication of bacteria inside host cells. The lipopolysaccharide outer core has been found to be a major bacterial factor in *Pseudomonas* invasion of epithelial cells.[42] Real-time video microscopy has revealed that invasive *Pseudomonas* isolates induce the formation of membrane blebs in multiple epithelial cell types, which are exploited for intra-cellular replication and rapid real-time motility (Fig. 27.15).[43]

Another important discovery is that there are *two* types of *Pseudomonas* which cause clinical disease and that the

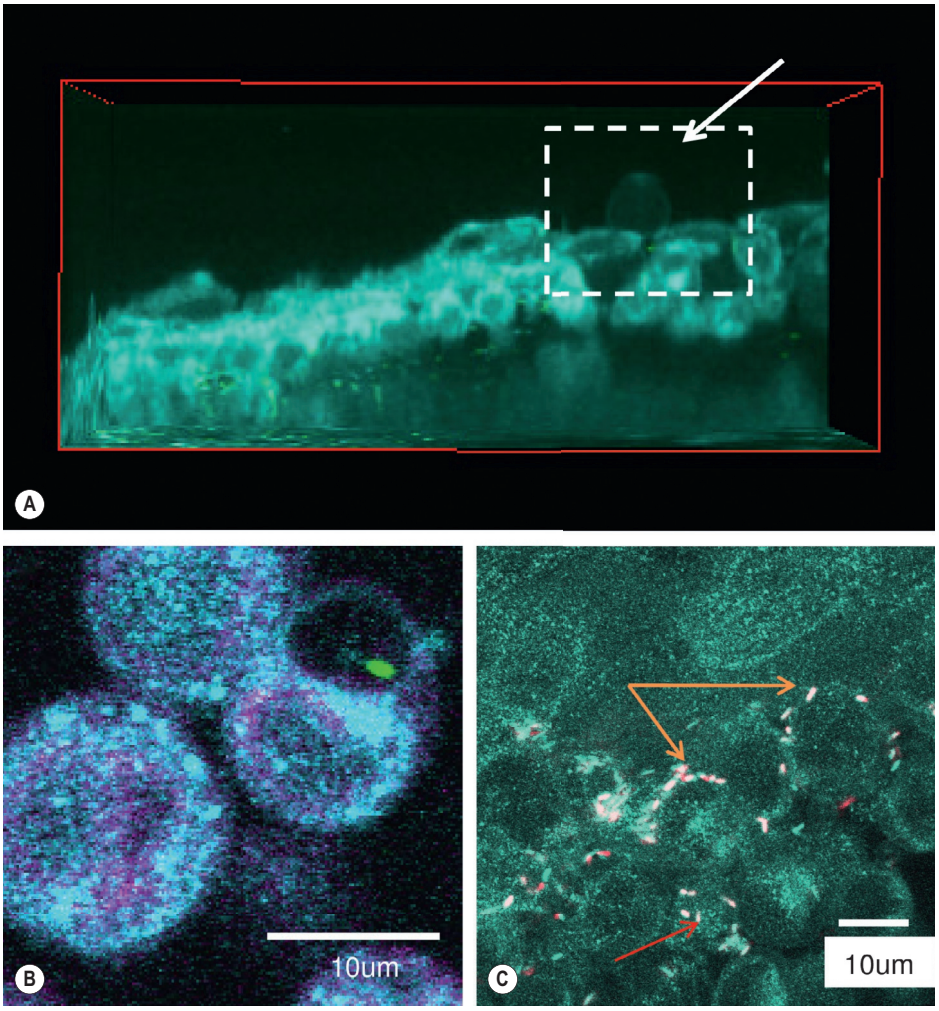


Fig. 27.15 Panels **(A)** and **(B)** show bacterial-induced membrane bleb formation ex vivo visualised as spherical membrane projections (arrow) extending away from the epithelial cells. A wide-field view of the epithelium is shown in **(A)**, and a higher magnification image revealing a bleb-confined bacterium is shown in **(B)**. In **(C)**, bacteria can be seen located between cells (orange arrows), where some were motile (fast-moving bacteria in red; slower-moving bacteria in white). Other bacteria in this image appear to be in the cytoplasm (red arrow). (Courtesy Suzanne Fleiszig.)

pathogenesis of the two types is entirely different.[44] One type invades corneal epithelial cells without killing the host cell and probably causes disease largely via the host immune response (invasive strains). The other type is cytotoxic for corneal and other epithelial cells; that is, these bacteria kill the host cell (cytotoxic strains).[45]

Genetic differences between these two types of *Pseudomonas* explain their different behaviours, and these differences lie in the *exsA* regulated pathway of the bacterial chromosome.[46] By using mutants which lack this pathway, it has been demonstrated that strains which were previously cytotoxic changed to the invasive phenotype.[47,48] These results probably explain much of the conflicting information in the earlier literature relating to the pathogenesis and treatment of *Pseudomonas* eye infections. These findings will also underpin new strategies to reduce the risk for contact lens–related infections and will assist in the development of new forms of drug therapy.

PROTOZOAN KERATITIS

Acanthamoeba is the only protozoan species known to be associated with contact lens infections. *Acanthamoeba* species are ubiquitous, unicellular, free-living, parasitic, amoebic protozoa which have chameleon-like tendencies in that they are able to transform from chemotherapeutically susceptible trophozoites into a resistant cystic form. The trophozoites are polygonal, measure 15 to 45 μm in diameter, are mobile and track in wavy lines when plated on agar. They derive nutrition from bacteria, yeast and other unicellular organisms. The cysts are double-walled and up to 16 μm in length. *Acanthamoeba* species are widely distributed in the natural environment and have been isolated from swimming pools, hot tubs, tap water, contact lens solutions, soil, dust, reservoirs, ice, the nasopharyngeal mucosa in healthy humans and even the air we breathe.[49]

When exposed to unfavourable environmental conditions, the trophozoites form into double-walled cysts. *Acanthamoeba* cysts are about 9 to 27 μm in diameter with a wrinkled outer wall (exocyst) and polyhedral inner wall (endocyst).[50] In cystic form, *Acanthamoeba* species are highly resistant to the immune response of the host and to harsh environments, including temperature extremes, changes in pH, standard chlorination of water and many anti-microbial agents.[51]

Risk factors for *Acanthamoeba* keratitis include contact lens wear, corneal trauma and exposure to contaminated water.

Various authors have demonstrated the utility of corneal confocal microscopy in the detection of *Acanthamoeba* keratitis associated with contact lens wear.[52-55] Confocal microscopy can readily image *Acanthamoeba* in cystic form and detect any consequent changes in the stroma, such as altered keratocyte reflectivity. It is uncertain whether *Acanthamoeba* trophozoites can be differentiated from the cytoplasm of epithelial cells or keratocytes; all published studies appear to be describing *Acanthamoeba* cysts.

Confocal microscopy is well tolerated by patients suffering from *Acanthamoeba* keratitis, who may otherwise be in a great deal of pain. Patients seem to experience no additional discomfort or adverse effects in the course of imaging the cornea, and there is no evidence of significant ocular trauma after the procedure. Nevertheless, a high degree of patient cooperation and steady fixation is required for successful imaging, and the procedure may be difficult to perform on children or extremely debilitated patients.

Images obtained from various layers of the cornea in a contact lens wearer with *Acanthamoeba* keratitis are shown in Figure 27.16. The two bright spots to the right of a highly reflective epithelial cell in Figure 27.16A probably represent *Acanthamoeba* cysts. The basal epithelial layer (Fig. 27.16B) and anterior stroma (Fig. 27.16C) are also infected. *Acanthamoeba* cysts are evident in the mid-stroma (Fig. 27.16D), but the keratocyte nuclei are less distinct, and the cytoplasm of the keratocytes appears to be much brighter than normal. The bright keratocyte nuclei in the posterior stroma (Fig. 27.16E) probably represent activated keratocytes. It is not possible to discern whether some of the bright shapes represent very bright keratocyte nuclei or *Acanthamoeba* cysts. Scattered debris of uncertain origin is evident just anterior to the endothelium (Fig. 27.16F). It is clear from these images that, in this case, the entire cornea has been affected by the *Acanthamoeba* infection.

Acanthamoeba cannot be reliably diagnosed from clinical findings alone and successful medical treatment depends on initiating therapy early in the disease process. The confocal microscope provides a significant advantage in diagnosing and managing *Acanthamoeba* keratitis because of its ability to image the parasite in the cornea in vivo during the early stages of the

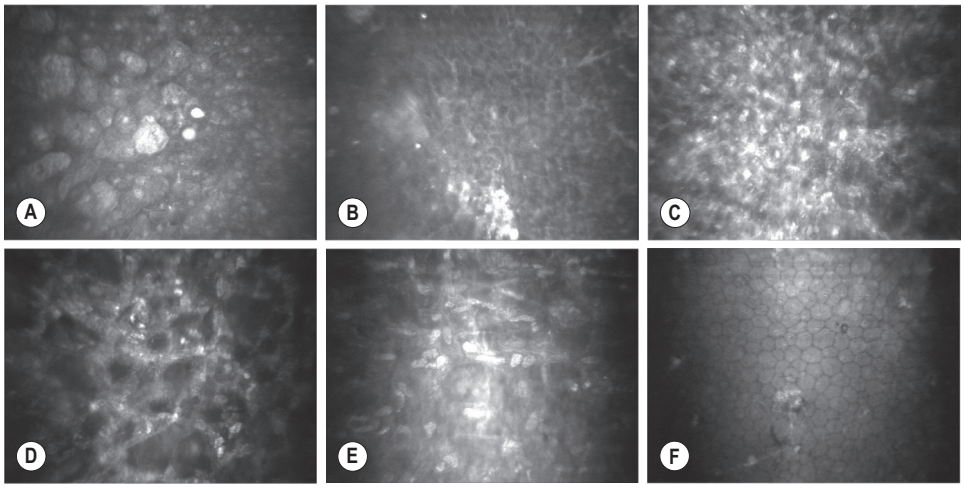


Fig. 27.16 *Acanthamoeba* keratitis. **(A)** Superficial cell layer of the epithelium. **(B)** Basal cell layer of the epithelium. **(C)** Anterior stroma. **(D)** Mid-stroma. **(E)** Posterior stroma. **(F)** Endothelium. Imaged with confocal microscope. (Courtesy Dimitra Makrynioti.)

infection, at least in cystic form. It is possible to image the *Acanthamoeba* cysts because of the enhanced lateral resolution of the confocal microscope (1 μm); such imaging is not possible with the slit lamp biomicroscope because of its more limited resolution (20–30 μm). In addition, the high-contrast 'optical sections' which comprise the confocal microscope images obviate the need for staining, and the capacity to image the cornea in real time offers the distinct advantage of facilitating an immediate clinical diagnosis.

Confocal microscopy is an inexpensive test to perform clinically once the cost of the instrument has been recovered. It also offers the potential for long-term savings by way of early diagnosis and, thus, earlier treatment and subsequent avoidance of penetrating keratoplasty procedures. Because this test is non-invasive, it can be performed even when there is a fairly low index of suspicion for this disease. Besides facilitating an initial diagnosis and monitoring of the response of the eye to treatment, confocal microscopy also can be used to check for recurrence after treatment has been discontinued or after penetrating keratoplasty.

In conclusion, the confocal microscope has quickly emerged as a fast, safe and sensitive diagnostic tool for the detection and diagnosis of *Acanthamoeba* keratitis, differential diagnosis from bacterial and fungal keratitis, determination of the level(s) of cornea affected, grading the severity of the condition, monitoring the progression of the disease and evaluating the efficacy of various treatment modalities.

FUNGAL KERATITIS

Of all possible forms of keratomycosis, the vast majority are caused by *Fusarium*, *Aspergillus* and *Candida*. *Fusarium* and *Aspergillus* are moulds (filamentary fungi), which produce feathery colonies joining together to produce hyphae. *Candida* is a yeast which produces pseudo-hyphae. Hyphae and pseudo-hyphae may form a branching network and may become quite dense (a mycelium). Hyphae may contain internal cross walls, called *septa*, which divide the hyphae into separate cells. Such structures are easily detected by using confocal microscopy.[55]

Parmar et al.[55] demonstrated the potential for confocal microscopy to aid in the differential diagnosis of *Acanthamoeba* keratitis and fungal keratitis. Of 63 cases of suspected *Acanthamoeba* keratitis examined with confocal microscopy, fungal hyphae were observed in two patients, one of whom was positive for both *Acanthamoeba* and a fungus.

Before the worldwide outbreak of contact lens–associated *Fusarium* keratitis in the mid-2000s, fungal keratitis was considered a rare complication of contact lens wear. Indeed, no fungal organisms were recovered in the epidemiological studies of contact lens–related keratitis by Cheng et al.[18] Morgan et al.,[16] Stapleton et al.[19] and Lam et al.[56] reported only one case of contact lens–related fungal keratitis (*Penicillium* sp.).

The outbreak of *Fusarium* keratitis referred to earlier occurred among patients using a particular brand of now-discontinued contact lens disinfecting solution (ReNu with MoistureLoc, Bausch & Lomb, Rochester, New York, USA). Confocal microscopy greatly assisted in the diagnosis and characterization of these infections.[57-59] Alfonso et al.[57] used confocal microscopy to examine five patients with suspected contact lens–associated *Fusarium* keratitis, and in all cases, hyphal elements were observed. Four of these patients had corneal smear analysis performed, and only two had positive results on culture, leading Alfonso et al.[57] to conclude that confocal microscopy is a valuable aid, in addition to microbial culture, to establish the diagnosis of such conditions promptly and to guide initial specific anti-fungal therapy.

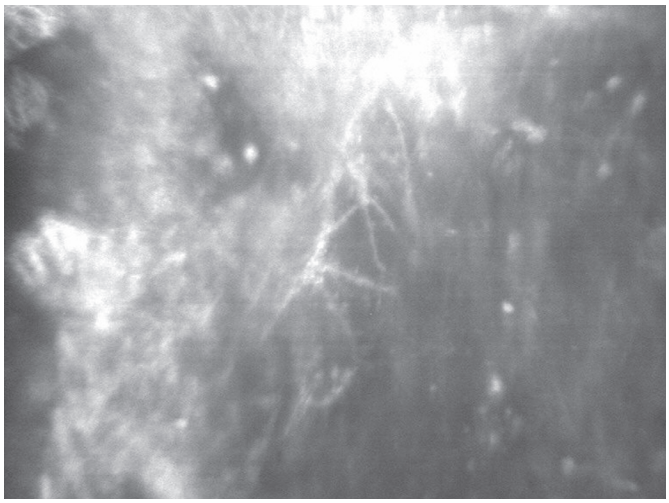


Fig. 27.17 *Fusarium* keratitis imaged using confocal microscopy. Evidence of fungal growth in the stroma is confirmed by the presence of branching hyphal elements. (Courtesy Eduardo Alfonso.)

Figure 27.17 is a confocal microscopy image of a contact lens wearer suffering from *Fusarium* keratitis. The hyphae appear as a crisscrossing mass of tubular-like elements and appear to have a consistent diameter of about 7 to 10 μm. Although not shown in Figure 27.17, septal divides can sometimes be seen as short bright lines crossing the hyphae at regular intervals. The appearance of filamentous structures in the stroma of a patient with *Fusarium* keratitis was demonstrated to be morphologically similar to those imaged from a culture plate of *Fusarium* obtained from corneal scraping in the same patient.[60]

Management

GENERAL ADVICE

As discussed in Chapter 26, abundant evidence of the various risk factors relating to the development of keratitis is now available. The key risk factor is overnight lens wear. Patients should be advised that although sleeping with lenses on carries a far greater risk for microbial keratitis compared with use of daily-wear lenses, the incidence is still very small. It is up to the patient to weigh the risks versus the benefits of extended lens wear. As a comparison, Holden et al.[61] pointed out that the incidence of vision loss of two or more lines of best corrected visual acuity is between 306 and 871 cases per 10,000 patients per year undergoing laser-assisted in situ keratomileusis (LASIK), versus only 0.8 cases per 10,000 patients per year wearing extended-wear hydrogel contact lenses.

Because of the potentially devastating effects of microbial keratitis, any case of contact lens–related ocular pain that persists after lens removal should be treated with suspicion. Certainly, all patients should be advised to remove their lenses if they have a sore red eye and to see their practitioner or seek medical attention if the pain persists or worsens in the first few hours after lens removal.

Patients travelling to warm environments should be warned of the possible increased risk for developing microbial keratitis.

The importance of complying with a full care regimen must be emphasised. Lens wearers should be advised to avoid allowing their contact lenses or care systems to come into contact with water. It is also advisable to warn patients to wear goggles when swimming because of the possibility of an increased risk of developing microbial keratitis.

Patients with diabetes should be warned of the increased risk for infection because of their metabolic condition,[17] but at the same time, they should be informed that the incidence of microbial keratitis among contact lens wearers with diabetes is still very low.

OCULAR EXAMINATION

A contact lens–wearing patient presenting with a sore red eye should be examined on an urgent basis, and a tentative diagnosis must be made as to whether the condition is likely to be microbial keratitis. Any case presenting with a combination of (a) contact lens wear, (b) ocular discomfort and (c) presence of corneal infiltrates should be assumed to be microbial keratitis and should be managed and treated accordingly until proven otherwise.

MEDICAL TREATMENT

In the case of a suspected or confirmed microbial keratitis, corneal scraping should be performed to determine if the condition is infectious and to possibly identify the offending microorganism.

The scraping protocol, generally, is to inoculate specimen collection paraphernalia in the clinic. Samples are taken from the leading edge and/or base of the lesion with a 26-gauge needle or a D15 blade. Two glass slides are generally smeared with the scraping material as the initial samples, which will be investigated in the microbiology laboratory using established staining techniques. Morphological features of the organism, such as rod or coccal shape, fungal hyphae or *Acanthamoeba* cysts, can also be visualised. Other samples, collected with a sterile swab during corneal scraping, can be taken for molecular testing, such as polymerase chain reaction test.[23]

Corneal confocal microscopy can also help differentiate between bacterial, protozoan or fungal infection. Once the nature of the causative organism has been determined with some degree of confidence, the following therapies may be introduced.

Bacterial keratitis

Broad-spectrum antibiotics should be instilled while the result of the corneal scraping is awaited because such episodes are best presumed to be infectious unless proven otherwise. Two approaches can be adopted:

- *Dual therapy* – involving a combination of two fortified antibiotics to cover common Gram-positive and Gram-negative pathogens, in the form of an aminoglycoside (tobramycin or gentamicin) and a cephalosporin (cephazolin)
- *Monotherapy* – with a fluoroquinolone, such as ciprofloxacin 0.3% or ofloxacin 0.3%[62]

Unfortunately, the results of scrapings are often equivocal because (a) antibiotics may have been instilled as a necessary precautionary measure before hospitalization; (b) numerous microorganisms may be isolated, making it difficult to identify the true culprit; and (c) the culture result may, by chance, be a false-negative one. Martins et al.[63] claimed that contact lens cultures may identify the causative organisms in most cases of contact lens–related microbial keratitis.

Specific fortified topical antibiotics, such as gentamicin and cephazolin, may be prescribed if the causative organism is positively identified. These agents are initially instilled at hourly intervals around the clock. The frequency can be reduced to 2-hourly administrations during the waking hours if the response is favourable. Continuing improvement should allow for substituting fortified drops with weaker commercial preparations, which are then tapered and eventually discontinued. Oral ciprofloxacin may also be indicated to prevent contiguous spread to the sclera.[62] Antibiotics can be delivered via subconjunctival injection or even intravenously if corneal perforation is a possibility.

Chloramphenicol is a broad-spectrum bacteriostatic agent which is used to treat many eye infections. However, *Pseudomonas aeruginosa* is intrinsically resistant to this drug. Chloramphenicol is therefore contraindicated in contact lens–associated infections because of *Pseudomonas aeruginosa* being the causative organism in a high proportion of cases.

During the early phase of bacterial keratitis, steroids are generally not prescribed (especially if the ulcer is culture-positive) because these drugs inhibit epithelial metabolism and retard the re-epithelialization and other tissue repair activities. Steroids may be prescribed, but with extreme caution, in the late healing phase to dampen the host response. A typical regime would introduce steroids on day 3 after 2 days of intense antibiotic therapy. The schedule of steroids, concurrent with antibiotics, might be four times per day for 1 week, twice a day for 1 week and once a day for 1 week and finally cessation. Tapering steroids is essential to avoid a rebound effect.

Protozoan keratitis

Successful treatment of *Acanthamoeba* keratitis is best achieved by prompt diagnosis. Early signs of this condition tend to be rather non-specific, and *Acanthamoeba* keratitis is frequently misdiagnosed as herpes simplex or *Pseudomonas* keratitis. Furthermore, current methods of diagnosis – besides confocal microscopy, which is not widely deployed – are unreliable and usually have a fairly high rate of false-negative results. Current diagnostic methods include corneal culture and stromal biopsy. Because these methods are invasive, they are often deferred until a high index of suspicion for the disease arises and are resorted to only when there has been no response to treatments for bacterial, viral and/or fungal keratitis.[51]

A combination of propamidine isethionate 0.1% (Brolene) and polyhexamethylene biguanide 0.02% drops is well tolerated, non-toxic and largely effective against *Acanthamoeba* species. Alternatively, a combination of Brolene and neomycin or a fluoroquinolone with chlorhexidine may give good results.[64] Topical steroids can be used to control persistent inflammation but should be terminated before cessation of anti-amoeba therapy.[62]

Kumar and Lloyd[64] pointed out that the encysted stage in the life cycle of *Acanthamoeba* species appears to cause the intractable problems and that many biocides are ineffective in killing the highly resistant cysts. Immunological methods are being investigated as a form of prevention, and oral immunization of animals has been successful in the prevention of *Acanthamoeba* keratitis by inducing immunity before infection occurs.[64] However, it is unlikely that immunization will be used to reduce of the incidence of contact lens–induced *Acanthamoeba* infection in humans.

Fungal keratitis

Fusarium keratitis associated with contact lens wear has been successfully treated with frequently alternating (hourly) natamycin (5%) and amphotericin B (0.15%) anti-fungal eye drops.[7,65,66] Topical natamycin can be supplemented with oral voriconazole, although the capacity of this approach to improve outcomes has been questioned.[67] For example, Proenca-Pina et al.[68] described the clinical course of a case of *Fusarium* keratitis which failed to respond to systemic and local voriconazole treatment and progressed to severe keratitis with endophthalmitis, requiring early therapeutic keratoplasty. After 8 months of follow-up, vision recovered to 6/15.

Chlorhexidine, an antiseptic used commonly for the treatment of *Acanthamoeba* keratitis,[69] is well tolerated[70] and can be used as an alternative to natamycin.

For yeast infections, such as with *Candida*, which is most common in ocular surface disease and immunosuppressed patients, topical amphotericin B is recommended.[71] Echinocandins (e.g. caspofugin and micafugin) can be added.[71] There is some evidence that fluoroquinolones may have a synergistic effect with amphotericin.[72] Often, multiple agents are used to offer maximum coverage.[71]

Additional medical strategies

Numerous other medical strategies may be used, depending on circumstances; in summary, these are:

- mydriatics – (e.g. atropine) to prevent posterior synechia;
- cycloplegics – to reduce pain from ciliary spasm (atropine also has a cycloplegic effect) and stabilise the blood-aqueous barrier;
- collagenase inhibitors – to minimise stromal melting;
- non-steroidal anti-inflammatory agents – to reduce inflammation and limit the infiltrative response;
- analgesics – to alleviate pain;
- tissue adhesives – are applied when the stroma has become extremely thin or perforated;
- debridement – to enhance the penetration of drugs into the eye; and
- bandage lens – to assist in re-epithelialization.

Surgical interventions include penetrating graft, which may need to be performed in the case of large perforations or non-healing deep central ulceration; lamellar graft; or double-layered amniotic membrane transplantation.[73]

Prognosis

The prognosis for recovery from microbial keratitis is variable and depends largely on the speed and efficacy of treatment. The prognosis is good if lenses are removed by the patient as soon as a problem is recognised; immediate advice is sought; a correct diagnosis is made; and prompt, appropriate and aggressive therapeutic measures are enforced, and the patient may ultimately be left with only a minor scar, which does not interfere with vision. A delay in treatment and the use of inappropriate medication can result in total vision loss.[1,2]

Keay et al.[74] examined factors influencing the severity of soft contact lens–related microbial keratitis in a series of 297 cases. Mean treatment costs were Aust $760 and indirect costs were Aust $468. Patients were symptomatic for 7 days, and vision loss of two or more lines of acuity occurred in 14.3% of cases. Cases with pathogenic causative organisms (66 of 297; 22%) were 11.4 times more likely to result in vision loss, had longer duration of symptoms (21 vs. 6 days, $p < 0.001$) and incurred higher costs. Delays of greater than 12 hours before treatment increased the likelihood of vision loss ($p = 0.048$), disease duration ($p = 0.004$) and associated costs ($p = 0.009$). Remoteness increased the risk for vision loss (odds ratio 5.1), and individuals older than 28 years of age had longer disease duration ($p = 0.02$). In overnight wear and after adjustment for culture result and treatment delays, silicone hydrogel lens wearers had slightly shorter disease duration (4 vs. 7 days, $p = 0.02$) but a rate of vision loss and cost similar to those of hydrogel wearers.

Bourcier et al.[75] noted that out of 300 cases of contact lens–induced microbial keratitis, 99% of ulcers resolved with treatment, but only 60% of patients had visual acuity better than the level at admission, and 5% had a very poor visual outcome.

In the case of *Staphylococcus* keratitis and *Streptococcus* keratitis, improvement in the condition may not be apparent until 24 to 48 hours after therapy has commenced. The microorganisms are generally eradicated from the cornea within 7 to 10 days.

Pseudomonas infections may appear to worsen slightly during the first 24 hours after medication has commenced. The condition will gradually improve thereafter, with the microorganism persisting for 14 days or longer.

Acanthamoeba keratitis has a slow time course of recovery. The condition may progress over many months, with periods of apparent improvement followed by regression. Patients are inevitably left with superficial nebulae corresponding to the site of infection (Fig. 27.18). Recurrence is common if treatment is stopped prematurely.[64]

Fungal keratitis can have a poor prognosis, if not detected and treated early. As can be seen from Table 27.2,[9,76-80] keratoplasty was required in a significant proportion of cases of confirmed *Fusarium* keratitis. This analysis suggests that, overall, 28% of patients developing *Fusarium* keratitis may end up requiring keratoplasty.

Figure 27.19 shows a severe case of contact lens–associated *Fusarium* keratitis, with dense infiltration and ulceration superiorly, hazy cornea, mucopurulent discharge and severe hyperaemia. In this case, the lesion progressed to perforation. The eye was saved with a therapeutic keratoplasty but glaucoma developed later, necessitating glaucoma surgery.

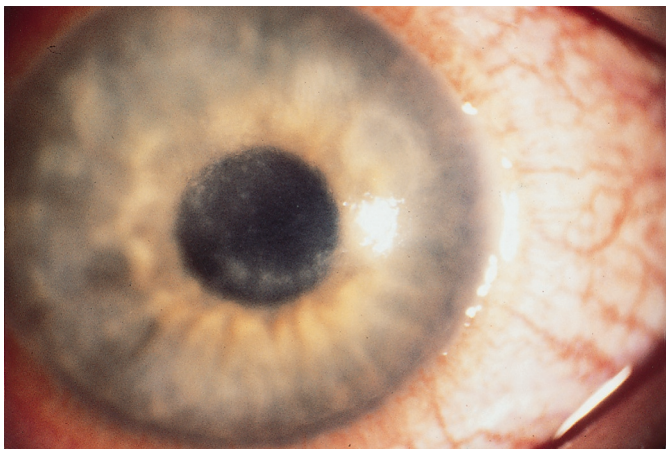


Fig. 27.18 Residual scar formation during the late healing phase of a patient suffering from *Acanthamoeba* keratitis. (Courtesy Andrew Tullo.)

TABLE 27.2 Cases of contact lens–associated *Fusarium* keratitis requiring keratoplasty

First author	Year of publication	Country	Cases (n)	Keratoplasty required (n)	Keratoplasty required (%)
Khor[9]	2006	Singapore	68	5	7
Chang[76]	2006	USA	164	55	34
Rao[77]	2007	Hong Kong	12	3	25
Gorscak[78]	2007	USA	15	6	40
Kaufmann[79]	2008	Switzerland	6	5	83
Gaujoux[80]	2008	France	17	5	29
Total	–	–	282	79	28

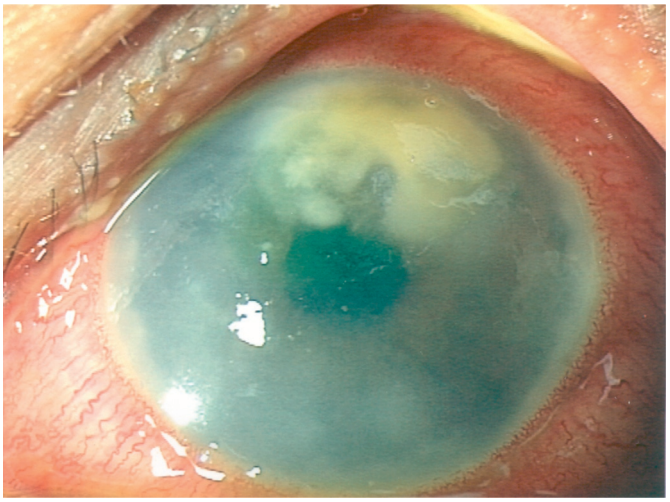


Fig. 27.19 Severe *Fusarium* keratitis. (Courtesy Philip Lam.)

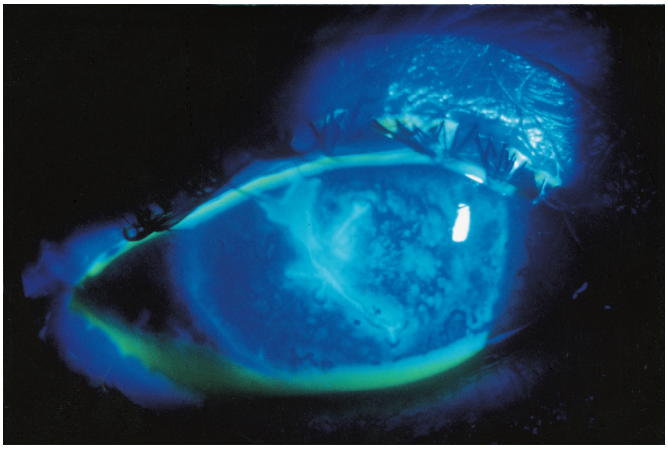


Fig. 27.20 Dendritic pattern of corneal ulceration in a contact lens wearer who had contracted herpes keratitis. The patient was human immunodeficiency virus (HIV) positive. (Courtesy F J Palomar-Mascaro, Bausch & Lomb Slide Collection.)

Hu et al.[7] reported that in patients who responded well to therapy, the time to cure, defined as the time to regaining baseline visual acuity in the affected eye after initiation of anti-fungal therapy, was approximately 4 weeks.

Differential diagnosis

The approach to diagnosis of microbial keratitis has shifted substantially in recent years. The previous approach was to attempt to differentially diagnose microbial keratitis from sterile keratitis, and if the patient was deemed to have a sterile keratitis, then a 'wait and see' approach was adopted.

However, in light of the Manchester Keratitis Study (see Chapter 26), thinking has shifted substantially. Because microbial keratitis is indistinguishable from a sterile self-limiting CIE ('sterile keratitis'), all cases of contact lens wearers presenting with ocular discomfort and the presence of infiltrates in the affected eye should be treated as potential microbial keratitis until proven otherwise. It is only possible to distinguish between microbial keratitis and sterile self-limiting CIEs after the full natural course of the keratitis has occurred, that is, 'after the fact'. Of course, such an approach is untenable in clinical practice. It is essential to err on the side of caution because any CIE can quickly progress to full-blown corneal ulceration.

Acanthamoeba keratitis can take on a clinical appearance similar to that of herpetic keratitis[81] and, to a lesser extent, that of *Pseudomonas* keratitis. In the advanced stages of these conditions, the clinical geographical distribution of the ulcers across the cornea indicates the likely cause; a classic dendritic form of ulceration is evident in herpetic keratitis (Fig. 27.20), whereas in *Acanthamoeba*, the ulcer takes on a circular pattern (Fig. 27.7).

It is possible for *Acanthamoeba* keratitis and *Fusarium* keratitis to occur concurrently in the same patient, although this is rare.[82]

The ultimate differential diagnosis will be achieved on the basis of the results of cultures, smear tests, tissue staining and confocal microscopy whereby the offending organism can be identified; however, the results of such tests cannot always be relied upon for reasons explained earlier. Judgements must often therefore be based on clinical evaluation of the presenting signs and symptoms, the pattern of disease progression and the responsiveness of the condition to various treatment alternatives.

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28 Corneal Warpage

Because contact lenses are in direct contact with the eye, it stands to reason that physical forces can act to change the shape of both the lens and the eye. Indeed, both types of change have been documented and both can have important clinical sequelae. This chapter shall concentrate on changes in ocular shape induced by contact lens wear. Primary consideration will be given to *corneal* shape changes because these are critical to vision and lens-fitting techniques. However, contact lenses can also alter the surface topography of the conjunctiva (e.g. indentation rings) and the form of the upper lid (e.g. rigid lens–induced ptosis).

Consideration will be given to the various manifestations of contact lens–induced changes in corneal topography. The chapter title 'Corneal warpage' is adopted because this term has been used consistently in the literature for the past 40 years[1-4] to imply contact lens–induced shape change. The term 'warpage' has the connotation of gross distortion, and this term was no doubt deliberately chosen by the early workers in this field[1] to describe the gross changes in corneal topography that could be induced by scleral or polymethyl methacrylate (PMMA) lenses.

Although rigid lenses made from PMMA are rarely fitted today, evidence of corneal shape change resulting from PMMA lens wear represent a 'worse case scenario' in view of their high modulus and lack of oxygen permeability. As such, studies of corneal warpage in response to PMMA lens wear provide important lessons in respect of the extent to which corneal shape can be modified by contact lens wear. For this reason, examples of PMMA-induced corneal warpage will be considered through this chapter. A severe case of rigid lens corneal warpage is shown in Figure 28.1. Interestingly, some authors[5,6] have used the term 'warpage' to describe corneal shape changes in hydrogel lens wearers.

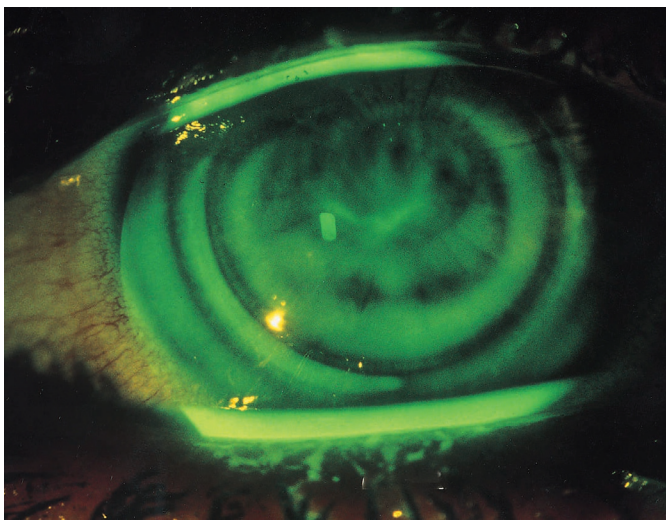


Fig. 28.1 Severe case of corneal warpage in a keratoconic eye seen here with the aid of fluorescein after removal of an ill-fitting hybrid rigid centre–soft surround lens. (Courtesy Russell Lowe, Bausch & Lomb Slide Collection.)

A myriad of terms have been coined by various authors to describe different phenomena relating to lens-induced corneal shape change; these include 'deformation', 'distortion', 'warpage', 'indentation', 'steepening', 'flattening', 'sphericalization', 'imprinting' and 'wrinkling'. These terms are generally self-explanatory and shall be used when discussing specific forms of corneal shape change. Wrinkling is a change that seems to occur in the epithelium and anterior stroma and, as such, was dealt with in Chapter 21 ('Epithelial wrinkling').

Although most contact lens–induced corneal shape changes are unintentional, one must not overlook the fact that some clinicians have fitted lenses with the deliberate intention of inducing or arresting corneal shape change; the three best-known practices, which have attracted considerable controversy, are:

- cone compression in keratoconus – with the aim of flattening the cone with apical bearing to halt or slow its progression;
- orthokeratology – with the aim of flattening the cornea to reduce myopia; and
- myopia control – with the aim of preventing the development of myopia or arresting the progression of myopia with reverse-geometry (orthokeratology) rigid lenses.

These concepts, in respect of the induced corneal shape changes, will also be reviewed briefly towards the end of this chapter.

Incidence

The incidence of corneal shape change caused by various categories of lens wear is well known. Finnemore and Korb[7] reported that 98% of PMMA lens wearers develop central corneal clouding (CCC), which will inevitably cause some degree of corneal steepening. More generalised distortion, or 'warpage', was noted in 30% of PMMA lens wearers by Rengstorff.[8]

When assessed using conventional keratometric techniques, current-generation rigid lenses of low to medium oxygen transmissibility (Dk/t) induce little or no change in overall corneal shape during daily wear[9] or extended wear.[10,11] Similarly, keratometry fails to highlight significant corneal shape changes in daily wear[12,13] and extended wear[14] of hydrogel lenses.

Corneal topography mapping techniques have revealed that all forms of contact lens wear are capable of inducing small but statistically significant changes in corneal topography.[15-18] Ruiz-Montenegro et al.[15] reported the prevalence of abnormalities in corneal shape to be 8% in a control group of non–contact lens wearers versus 75% in PMMA lens wearers, 57% in daily rigid lens wearers, 31% in daily soft lens wearers and 23% in extended hydrogel lens wearers. These authors attached some

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clinical significance to their findings because (a) decreases in best corrected visual acuities (BCVAs) of up to one line of Snellen's acuity were noted in many of the PMMA and rigid lens wearers; and (b) correlations were noted between lens decentration and corneal shape change.

Wang et al.[18] prospectively studied the eyes of 165 consecutive contact lens–wearing patients evaluated for keratorefractive surgery. Significant contact lens–induced corneal warpage was detected by corneal topography in 20 eyes of 11 patients, representing an overall prevalence of corneal warpage of 12% among this cohort of contact lens wearers.

The results of studies investigating corneal shape changes with silicone hydrogel lenses are equivocal. Various authors failed to observe corneal curvature changes in patients wearing low-modulus[19-21] and high-modulus[19,20] silicone hydrogel lenses during observation periods ranging from 1 to 18 months.

However, Dumbleton et al.[22] observed a small degree of central corneal flattening in both major meridians of 0.35 diopter (D) in patients wearing high-modulus silicone hydrogel lenses over a 9-month period. Gonzalez-Meijome et al.[16] noted a similar phenomenon in silicone hydrogel lens wearers over a 12-month wearing period; specifically, they observed an almost homogeneous increase in corneal radius of curvature for all corneal locations, being statistically significant for the 4-mm cord diameter area. Figure 28.2 shows an example of this phenomenon, where a person with high myopia wore a high-modulus silicone hydrogel lens for 30-day continuous wear, and 3 months after entering this mode of wear, central corneal flattening and 1.00 D of decreased myopia were detected.

Maldonado-Codina et al.[23] noted that over a 12-month period of continuous wear, corneal curvature of subjects wearing high-Dk rigid lenses (Z-alpha; Menicon Co. Ltd., Nagoya, Japan) became flatter by 0.13 mm compared with 0.04 mm for subjects wearing high-Dk silicone hydrogel lenses (Focus Night & Day, Ciba Vision, Duluth, Georgia, USA) ($F = 14.7$; $p = 0.0003$). The refractive findings in subjects wearing these lenses mirrored the corneal curvature changes.

Lens binding is known to occur with daily and extended wear of rigid lenses, the clinical evidence of which is an indentation of the cornea that can be seen in white light and with the aid of fluorescein. As indicated by subject reports, lens binding occurred in 29% of patients using daily-wear rigid lenses[9] and 50% of those using extended-wear rigid lenses,[10] respectively.

Tyagi et al.[24] investigated changes in anterior and posterior corneal topography after short-term use of rigid contact lenses in 14 participants who wore 9.5-mm-diameter PMMA lenses, 9.5-mm-diameter rigid lenses, 10.5-mm-diameter rigid lenses and soft silicone hydrogel lenses for 8-hour periods. The PMMA lenses caused flattening in both the central (0.09 ± 0.05 mm, $p < 0.001$) and peripheral (0.04 ± 0.03 mm, $p = 0.006$) cornea, whereas the rigid and silicone hydrogel lenses caused no significant changes.

Vincent et al.[25] examined the influence of short-term (3 hours) mini-scleral contact lens wear on corneal shape using Scheimpflug imaging on 10 young (mean 27 years) healthy participants. Small but significant anterior corneal flattening was observed immediately after lens removal (overall mean 0.02 ± 0.03mm, $p < 0.001$), which returned to baseline levels 3 hours after lens removal. During the 3-hour recovery period, significant posterior surface flattening (0.03 ± 0.02 mm) was also observed ($p < 0.01$). An increase in lower-order corneal astigmatism Z(2,2) was noted after lens wear. In a separate experiment, Vincent et al.[26] observed posterior corneal topography to remain stable after 8 hours of mini-scleral contact lens wear (-0.01 ± 0.07 mm steepening over the central 6 mm, $p = 0.60$).

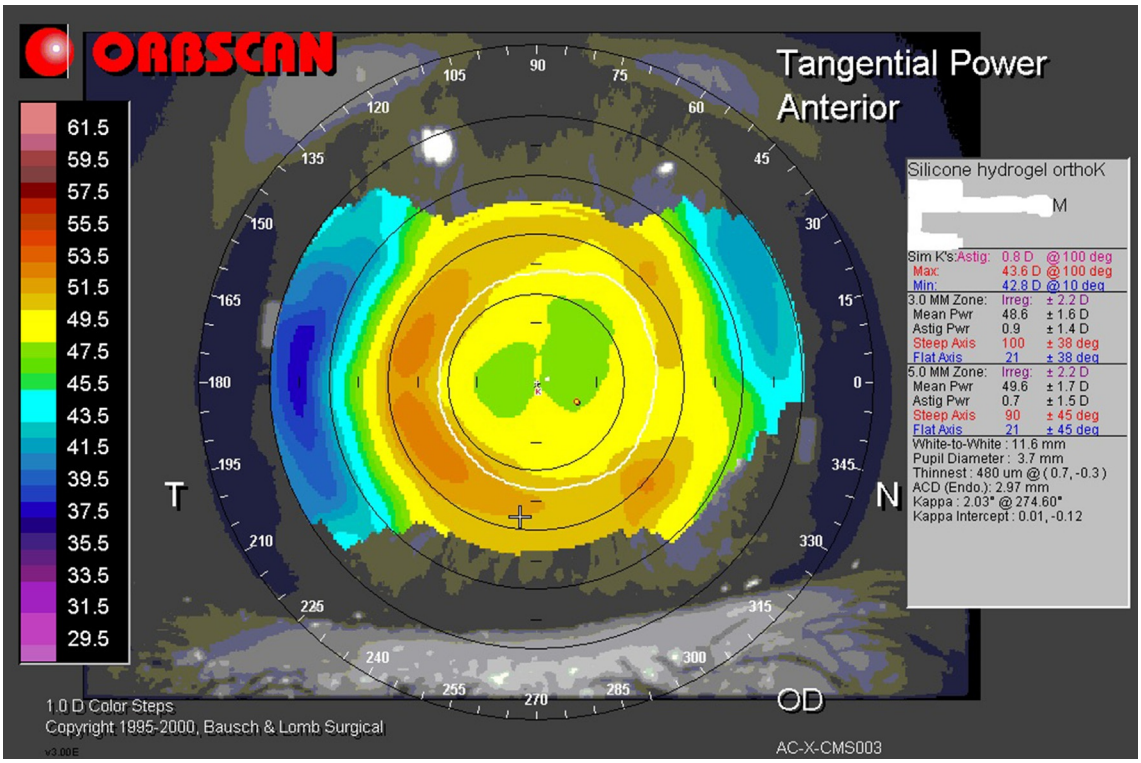


Fig. 28.2 Oblate corneal shape induced unintentionally in a lotrafilcon A extended-wear contact lens user. (Courtesy Loretta Szczotka-Flynn.)

Most other forms of lens-induced corneal shape change are either rare or are known to be associated with specific types of poorly designed or ill-fitting lenses.[27] Phillips[28] suggested that some patients may be prone to corneal warpage because of previous adverse lens wearing experiences or because of a hereditary predisposition to keratoconus. It is not possible to assign specific incidence figures to such rare phenomena.

Signs and symptoms

The clinical presentation of lens-induced corneal shape change – characterised by time course and precise topographical alterations – can manifest in a variety of forms and will depend primarily on the material, design and fit of the lens. In general, adverse signs and symptoms of corneal shape change include reduced and variable vision, changes in refraction and monocular diplopia.[29] The specific effects of lens-induced shape change shall be considered in the context of the various forms of topographical alterations that have been described.

CHANGE IN OVERALL CURVATURE

Much of the earlier literature concentrated on overall changes in curvature, that is, steepening or flattening of the anterior corneal surface as measured by keratometry. Results have been expressed as changes in corneal curvature (in millimetres), surface corneal power (in dioptres) or refraction (in dioptres).

CCC often occurred during the initial period of adaptation to PMMA lens wear and was generally associated with a myopic shift (see 'Aetiology'). Thus, patients newly fitted with PMMA lenses would complain of hazy vision because of the excess oedema and resultant reduced vision upon removing their lenses and putting on spectacles. Some patients would complain of mild ocular discomfort, but this probably relates more to the underlying cause (excessive oedema) rather than to the actual change in corneal shape.

This problem of blurred vision with spectacles after contact lens wear was termed 'spectacle blur',[30] and this posed a significant clinical problem because many patients could only wear PMMA lenses for a limited period and needed to wear spectacles at the end of the lens-wearing period.

As the patient adapts and the central corneal oedema subsides, there is a reversal of the induced myopia and the corneal curvature and refraction return to pre-fitting levels. After 12 months of PMMA lens wear, the cornea often displays central flattening, resulting in a hyperopic creep, or reduction in myopia.

Rigid lenses can also induce changes in overall curvature, whereby the extent of change is inversely proportional to the Dk/t and flexibility of the lens. The higher the Dk/t and the more flexible the lens, the less likely are lens-induced changes, assuming a well-fitting lens. Changes in corneal curvature of more than 0.25 D can apparently occur with high-modulus silicone hydrogel lenses[22] but are rare with flexible rigid lenses, low-modulus silicone hydrogel lenses and conventional low-Dk hydrogel lenses.

Clinical evaluation of corneal curvature has traditionally been achieved by using the optical keratometer. This instrument is still of limited use in clinical practice and can generally be relied upon to detect overall compromise to corneal shape. The difficulty arises when attempting to assess asymmetrical or localised regions of corneal distortion because most keratometers are based on an optical configuration that relies upon corneal reflections emanating from a 3-mm-diameter circle on the corneal surface. Thus, localised swelling entirely within or outside this 'circle' will go undetected.

CHANGE IN CORNEAL SYMMETRY

Numerous corneal topography instruments are currently available, and all have computerised algorithms for quantifying the degree of irregularity of corneal surface shape. Ruiz-Montenegro et al.[15] used a corneal topography device which computes a function known as the *Surface Asymmetry Index* (SAI). Specifically, the SAI provides a quantitative measure of the radial symmetry of the four central videokeratoscope mires surrounding the vertex of the cornea. The higher the degree of central corneal symmetry, the lower is the SAI. A high degree of central radial symmetry is characteristic of normal corneas.

Ruiz-Montenegro et al.[15] reported SAI mean values (± standard error of mean) associated with the following forms of lens wear:

- non-lens-wearing controls – 0.35 ± 0.03
- PMMA – 0.86 ± 0.22
- daily-wear rigid – 0.48 ± 0.09
- daily-wear hydrogel – 0.48 ± 0.11
- extended-wear hydrogel – 0.46 ± 0.08

The SAI was statistically significantly greater than the control group for all forms of lens wear except for daily-wear hydrogel lenses.

The clinical significance of this finding was highlighted by the fact that the authors observed a correlation between the nature of corneal deformation and the fit of the lens. For example, a superior riding rigid lens was associated with superior flattening, thus explaining the increase in SAI in that case. Such correlations were only observed in PMMA and rigid lens wearers, and an example is depicted in Figure 28.3.

Obvious corneal asymmetry can be detected by using a keratometer whereby the mires will not be perfectly circular; that is, they make take on an elliptical, pear or egg-shaped appearance. A sequence of progressively increasing levels of keratometer mire distortion is shown in Appendix A; this can be used as a grading scale for recording the level of severity of lens-induced corneal distortion when using a keratometer.

CHANGE IN CORNEAL REGULARITY

In addition to SAI, the instrument used by Ruiz-Montenegro et al.[15] also computes a function known as the *Surface Regularity Index* (SRI). The SRI is a quantitative measure of central and paracentral corneal irregularity derived from the summation of fluctuations in corneal power that occur along semi-meridians of the 10 central photokeratoscope mires. The more regular the anterior surface of the central cornea, the lower is the SRI. The SRI is highly correlated with BCVA.

Ruiz-Montenegro et al.[15] reported SRI mean values (± standard error of mean) associated with the following forms of lens wear:

- non-lens-wearing controls – 0.41 ± 0.04
- PMMA –1.17 ± 0.34
- daily-wear rigid – 0.93 ± 0.18
- daily-wear hydrogel – 0.52 ± 0.08
- extended-wear hydrogel – 0.51 ± 0.06

The SRI was statistically significantly greater than the control group for PMMA and daily rigid lens wear but not for daily or extended soft lens wear.

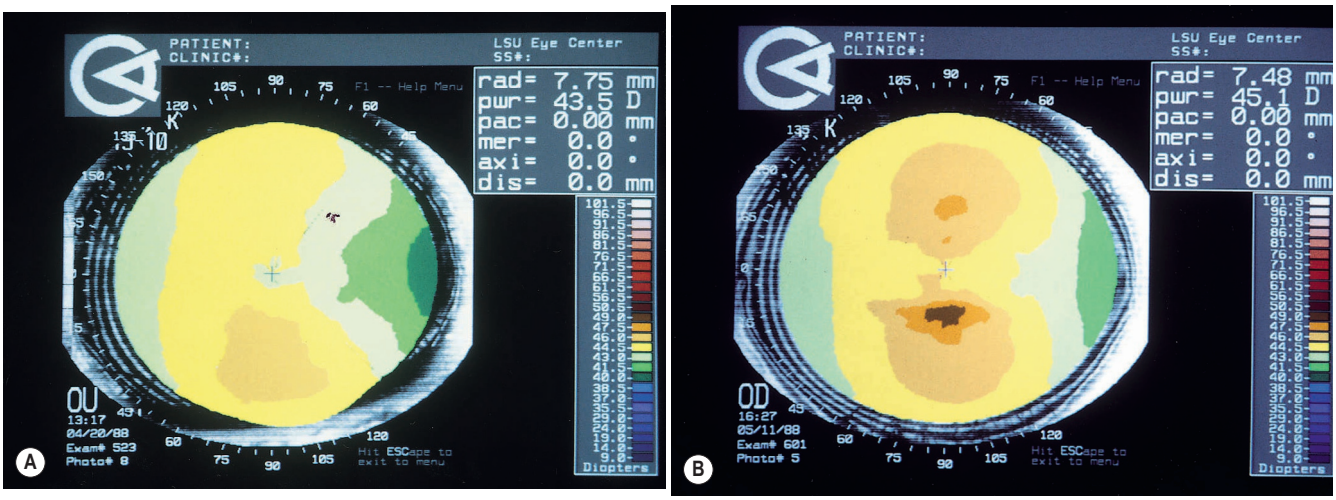


Fig. 28.3 **(A)** Corneal topographic map of cornea immediately after removal of a high-riding polymethyl methacrylate (PMMA) lens. Note superior corneal flattening. **(B)** Same cornea depicted in **(A)** 3 weeks after lens removal. The cornea has recovered normal with-the-rule astigmatism. (Courtesy Stephen Klyce.)

The clinical significance of changes in SRI was confirmed by the observation of the authors of an association in PMMA and rigid lens wearers whereby a decrease in BCVA occurred in patients displaying an increased SRI. The patients did not suffer significant discomfort.

A keratometer can detect gross corneal irregularity in the form of lack of clarity of the mires; that is, various sections of the mires will appear to be more in focus than others, and the circular mire lines may not appear to be perfectly smooth. Of course, such an assessment will only relate to the 3-mm-diameter ring of corneal surface that a keratometer samples optically.

Other inexpensive instruments, such as the Placido disc and Klein keratoscope, can provide a similar assessment to that offered by the keratometer, but over a wider expanse of cornea. Needless to say, corneal topography instruments offer distinct advantages over traditional instruments in terms of the extent of corneal coverage, sensitivity, accuracy, objectivity, computational power and data presentation.

CHANGE IN CORNEAL ASPHERICITY

Maeda et al.[31] used a corneal topography device to develop an indicator of the asphericity of the central cornea, which they termed the 'corneal asphericity index' (CAI). These authors[31] used the CAI to evaluate both normal corneas and corneas with rigid lens–induced warpage. The CAI (mean ± standard deviation) for the 22 control corneas was 0.33 ± 0.26, which indicates that the normal central cornea has a prolate shape. The average CAI for the 24 corneas with rigid lens–induced warpage was significantly lower (−0.15 ± 0.36). These data suggest that some corneas have abnormal asphericity in the central cornea when warpage occurs with rigid lenses.

CORNEO-SCLERAL LIMBAL CHANGES

Consejo et al.[32] assessed whether short-term soft contact lens wear alters the anterior eye surface. Twenty-two neophyte subjects wore soft contact lenses for a period of 5 hours. Topography-based corneo-scleral limbal radius estimates were derived from height measurements acquired with a corneo-scleral profilometer, and other ocular dimensions were determined by using an optical coherence topography-assisted biometer. Short-term soft contact lens wear was found to significantly modify corneo-scleral limbal radius (130 ± 74 mm, $p < 0.001$). In contrast, the white-to-white diameter and corneal curvature radius were not modified. Anterior chamber depth and central corneal thickness were significantly affected. Limbal radius increment was reversed 3 hours after lens removal for 68% of the subjects, but the time course of this reversal was not uniform.

LENS-INDUCED WARPAGE IN KERATOCONUS

Szczotka et al.[33] evaluated 205 patients with keratoconus by using a corneal topography apparatus for both qualitative corneal topographic patterns and quantitative indices. Fifty-six patients were non–contact lens wearers, 130 wore PMMA or rigid lenses and 19 wore hydrogel lenses. Data from the keratoconus patients were also compared with that for a control group comprising normal individuals with no history of contact lens wear.

All three keratoconus groups had a significantly increased frequency of an asymmetrical bowtie/skewed radial axes (AB/SRAX) pattern compared with normal controls. Differences among the videokeratography patterns for the patients with keratoconus included a significant shift from the AB/SRAX videokeratographic pattern to the irregular videokeratographic pattern in the PMMA/rigid lens sub-group and an increased frequency of the irregular pattern in the hydrogel lens group versus the no-lens group. Additional differences between the PMMA/rigid contact lens and no-lens keratoconus groups included increased values for the quantitative indices of SAI, SRI, SIM-K, and central K in the PMMA/rigid lens group.

CORNEAL INDENTATION

Rigid lenses can adhere to the cornea during open-eye[9] or closed-eye[10,34] wear. Adherence can occur at any time of the day in open-eye wear but is characteristically noticed

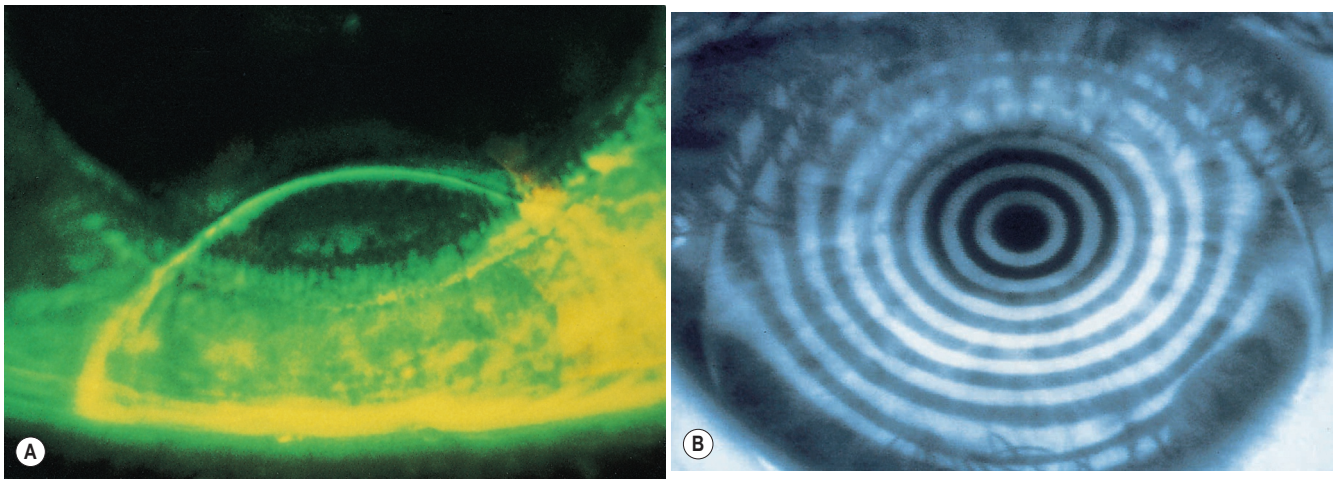


Fig. 28.4 **(A)** Corneal and conjunctival imprint of an inferiorly mislocated bound rigid lens viewed with fluorescein immediately after lens removal. **(B)** Superior arcuate imprint observed in unprocessed mires of a corneal topographer after lens removal. (A, Courtesy Donna LaHood, Bausch & Lomb Slide Collection. B, Courtesy Craig Woods, Bausch & Lomb Slide Collection.)

immediately upon eye opening after overnight wear. In the latter case, the lens usually begins to move freely after a few blinks; persistent binding for more than a few minutes is considered problematic. Indentation rings can also be caused by silicone elastomer lenses.[35]

Upon removal of a bound lens, an impression of the lens edge is usually evident on the cornea. Slit lamp examination with fluorescein reveals the presence of an annular indentation in the cornea (Fig. 28.4A), mild punctate keratitis primarily outside the lens edge and dense corneal desiccation inside the lens edge. An imprint from the bound edge after lens removal is clearly visible in Figure 28.4B, which is an unprocessed image of videokeratoscope rings. Lens binding is usually asymptomatic but can be mildly uncomfortable.

Pathology

All known forms of contact lens–induced changes to corneal topography can be explained in terms of three underlying pathological mechanisms – (a) physical pressure on the cornea exerted either by the lens and/or eyelids, (b) contact lens–induced oedema and (c) mucus binding beneath rigid lenses. The relative contributions of these factors vary in accordance with the type of topographical alteration.

CHANGE IN OVERALL CURVATURE

A comprehensive explanation of corneal shape change during PMMA lens wear has been provided by the classic analysis of Carney[36] – an analysis that can be extrapolated from PMMA lens wear to explain virtually all cases of overall corneal shape change with rigid and soft lens wear.

Carney[36] observed corneal shape changes induced by PMMA lenses in normal atmospheric conditions (21% oxygen) and in artificial conditions ranging from 0% oxygen (anoxia) to 100% oxygen. He demonstrated convincingly that corneal shape change during PMMA lens wear could be attributed to a combination of lens-induced oedema caused by hypoxia and physical pressure from the lens. The precise distribution of these two influences can explain the various forms of topographical changes observed with all forms of lens wear (see 'Aetiology').

CHANGE IN SAI, SRI AND CAI

The pathological processes that explain corneal shape changes characterised by SAI, SRI and CAI are difficult to elucidate because research has not been conducted to differentiate mechanisms that underlie changes in corneal symmetry, regularity and asphericity. In the absence of other explanatory mechanisms, one can only conclude that surface asymmetry, irregularity and asphericity are caused by differing contributions of the two key factors identified earlier – physical pressure by the lens/lids and lens-induced hypoxia.

It may also be true that individual differences in corneal rigidity could be a governing factor.[28] Ruiz-Montenegro et al.[15] noted that much of the variance in their data could be attributed to a small number of patients displaying large alterations in SAI and SRI. The implication here is that some patients who have 'softer' or more pliable corneas and some who have a hereditary predisposition to keratoconus[28] will be more susceptible to lens-induced shape changes and that recovery will be slower in such patients.

LENS-INDUCED WARPAGE IN KERATOCONUS

The mechanical stability of the cornea is compromised in keratoconus.[37] The biomechanical alterations may be introduced by increased sliding of collagen fibres as a result of reduced attachment to Bowman's layer and altered synthesis of the matrix substance.[38] Biochemical studies of keratoconic corneas have shown an increase in collagenolysis, an increase in the number of reducible collagen cross-links, the formation of proteoglycan bridges along and between corneal collagen fibrils and an apparent loss of keratin sulphate. All of these changes could interfere with corneal strength,[39] thus rendering the keratoconic cornea to be more susceptible to contact lens–induced warpage.

Alipour et al.[40] evaluated the differences in biomechanical properties between contact lens–induced corneal warpage and normal and keratoconic eyes. The authors examined 94 eyes of 47 patients with suspected warpage and 46 eyes of 23 patients with keratoconus. Cases of suspected warpage were monitored until a definite diagnosis was made (warpage, normal or keratoconus). Contact lens–related corneal warpage was found in 44 eyes of 22 patients. A diagnosis of 'non-warpage normal eyes'

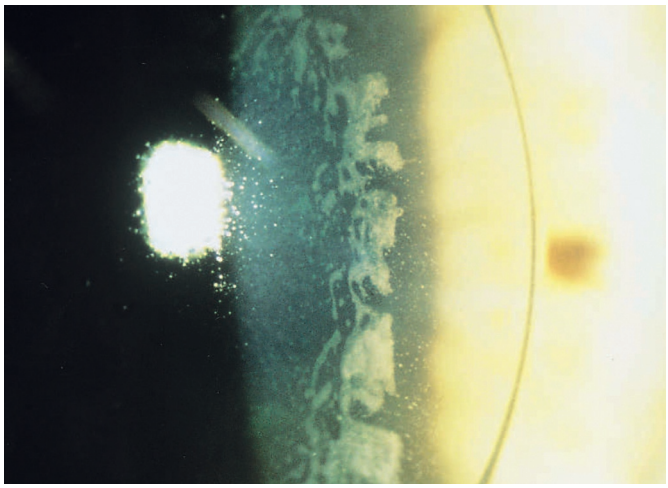


Fig. 28.5 Build-up of mucus and debris beneath a bound rigid lens pictured here 2.5 hours after waking. (Courtesy Robert Terry, Bausch & Lomb Slide Collection.)

was made in 46 eyes of 23 people. The authors included 46 eyes of 23 patients with known keratoconus for comparison. The biomechanical properties (corneal resistance factor and corneal hysteresis) were different, with the highest value found in the warpage group followed by normal and keratoconus groups. Corneal resistance factor was 10.08 ± 1.75, 9.23 ± 1.22 and 7.38 ± 2.14 and corneal hysteresis was 10.21 ± 1.57, 9.59 ± 1.21 and 8.69 ± 2.34 in the warpage, normal and keratoconus groups, respectively. These authors concluded that corneal biomechanics may be different in people who develop contact lens–induced warpage.

CORNEAL INDENTATION

Indentation associated with lens binding appears to be more related to physical pressure and less to the effects of hypoxia. In the case of overnight wear, mucus accumulation beneath the lens is a feature of lens binding (Fig. 28.5), the aetiological significance of which shall be considered in the next section.[41]

Aetiology

Theoretical and experimental analyses have been undertaken to explain the aetiology of lens-induced corneal shape changes. These shall be considered with respect to the various forms of shape changes described earlier.

CHANGE IN OVERALL CURVATURE

The typical pattern of refractive change during PMMA lens wear – an initial myopic shift during adaptation followed by a recovery over 3 to 6 months and subsequent myopia reduction – can be explained by using the Carney model.[36] A centrally fitting PMMA lens will induce hypoxia beneath the lens, resulting in oedema in the corresponding central region of the cornea. This phenomenon, known as *central corneal clouding* (CCC) (see Figs. 22.1 and 22.13), is characterised by an increased curvature of the central cornea as the stroma in that region thickens, resulting in a myopic shift. A moderate increase in corneal thickness of 2% over a 4 mm-wide central zone will increase corneal surface power by about 1.75 D.

After the initial adaptation (subsequent to possible lens refits to provide more movement), the hypoxia will be alleviated, and the cornea may return to its original shape. Another influence would be occurring concurrently – a progressive overall flattening of the cornea resulting from the constant bearing of the lens against the corneal apex. This flattening would lead to a hyperopic shift in refraction, which would presumably have been masked by the initial marked apical steepening caused by hypoxia during the adaptive phase described earlier.

Although the explanation provided earlier cannot be considered definitive, the following general principles can be applied to explain lens-induced corneal shape change: (a) local lens induced hypoxia causing localised oedema, corneal swelling and myopic shift; and (b) overall lens bearing causing corneal flattening and a hyperopic shift. An additional but less likely influence is that of a steep lens moulding the cornea into a more curved shape, thereby inducing a myopic shift.[42]

It can be presumed that rigid lenses of higher oxygen performance will influence corneal shape more by way of physical bearing than hypoxic oedema. Certainly, there will be an increasing shift in favour of physical bearing and against hypoxic oedema, as aetiological factors in lens-induced shape change, as rigid lens Dk/t increases. Gleason et al.[43] reported that 9.6% of patients wearing hyper-permeable rigid lenses (Dk = 163) who successfully completed a 1-year prospective clinical trial demonstrated mean keratometric changes of 0.57 D in the horizontal meridian and 0.73 D in the vertical meridian.

The slight corneal flattening observed in patients wearing silicone hydrogel lenses[16,22,23] is associated with a progressive thinning effect for the central cornea, which can remain for up to 3 months after discontinuing lens wear.[16] According to Gonzalez-Meijome et al.,[16] the mid-peripheral and peripheral areas did not display such a thinning effect during continuous wear. The overall effect seems to be a result of mechanical pressure induced by these silicone hydrogel materials, which are characterised by a relatively high modulus of elasticity.

Tyagi et al.[44] investigated the influence of soft contact lenses on regional variations in corneal thickness and shape while taking account of natural diurnal variations in these corneal parameters. Twelve young, healthy subjects wore four different types of soft contact lenses on 4 different days. The lenses were of two different materials (silicone hydrogel or hydrogel), designs (spherical or toric) and powers (+3.00 or −7.00 D). Corneal thickness and topography measurements were taken before and after 8 hours of lens wear and on 2 days without lens wear by using the Pentacam HR system. The hydrogel toric contact lens caused the greatest level of corneal thickening in the central (20.3 ± 10.0 μm) and peripheral (24.1 ± 9.1 μm) cornea ($p < 0.001$), with an obvious regional swelling of the cornea beneath the stabilizing zones. The anterior corneal surface generally showed slight flattening. All contact lenses resulted in central posterior corneal steepening, and this was weakly correlated with central corneal swelling ($p = 0.03$) and peripheral corneal swelling ($p = 0.01$). The authors noted that the magnitude of corneal swelling induced by the contact lenses over the 8 hours of wear was less than the natural diurnal thinning of the cornea over this same period.

CHANGE IN SAI, SRI AND CAI

The data of Ruiz-Montenegro et al.[15] have provided quantitative proof that rigid lenses disturb corneal symmetry and regularity

less compared with PMMA lenses and that hydrogel lenses least affect the SAI and the SRI. This can only be presumed to be attributed to less physical deformation by softer lenses and less lens-induced hypoxic oedema with rigid and soft lenses.

A likely cause of increased SAI in rigid lens wearers could be physical pressure from a lens that is constantly tending to decentre in a predictable manner. Ruiz-Montenegro et al.[15] and Wilson et al.[27] noted a correlation between lens decentration and corneal topographic change. The precise cause of the increased SRI cannot be easily explained in terms of improper lens fitting. Changes in the CAI may be related more to symmetrical lens moulding effect.

Further experimentation along the lines of the studies of Carney[36] would be required to provide a full explanation of the specific aetiology of lens-induced changes to SAI, SRI and CAI.

LENS-INDUCED WARPAGE IN KERATOCONUS

Szczotka et al.[33] concluded that the increased frequency of qualitative and quantitative corneal irregularity in patients with keratoconus wearing rigid lenses may reflect a true mechanical effect of contact lens wear; however, these authors could not reject the possibility that this finding may also reflect an advanced disease state in these patients limiting them to rigid lens wear.

CORNEAL INDENTATION

Binding of rigid lenses to the cornea during overnight wear has been explained by Swarbrick and Holden.[34] Thinning of the post-lens tear film during sleep leaves a very thin, highly viscous layer of mucus-rich tears between the lens and the cornea, acting as a form of glue to bind the lens to the cornea. This tear film thinning is caused by constant lid pressure against the lens during eye closure.

Upon eye opening, the shear force imparted by the eyelid may be insufficient to initiate lens movement, and the lens will remain bound until the mucus film is diluted by the gradual penetration of aqueous tears. Evidence for this theory comes from clinical observations of fluorescein movement under rigid lenses as the lens becomes unstuck[41] (Fig. 28.6).

Rigid lens binding during open-eye lens wear occurs less frequently and may be partially explained by mucus-mediated adhesion. Another possibility is that in the course of moving around the cornea and being intermittently compressed by the lids, a rigid lens may assume a position whereby a slight negative pressure is created beneath the lens. This could create a mild suction that temporarily holds the lens in place and results in corneal indentation due to the mild pressure of a static lens edge.

Rae and Huff[35] studied silicone elastomer lens binding in vitro to determine what factors may influence its development on the cornea or corneo-sclera. Lens binding to corneas was not influenced by corneal toricity (0–20 D), corneal fitting relationship (2.00 D steep to 4.00 D flat), mucin (2% or 5%) in the tear-bath or trans-corneal pressure (11–22 mmHg). In isolated corneas or in whole eyes, transient intra-ocular pressure changes did not influence keratometry readings, ruling these out as potential mechanisms for corneal binding during sleep. Corneo-scleral preparations were also examined to simulate a de-centred lens.

Corneo-scleral binding occurred with a significantly greater frequency than corneal binding and was not influenced by corneal toricity, corneal fitting relationship (up to 0.5 mm steeper than K) or mucin concentration. Unlike the final stages of clinical lens adhesion, the binding observed by Rae and Huff[35] permitted lateral lens movement and occurred without leaving an indentation ring. These findings may suggest that the system models the initiation of corneo-scleral binding, involving decentration and suction onto the corneo-scleral junction. Rae and Huff[35] concluded that corneal binding could not be explained by a chemical attraction between the silicone elastomer lens surface and the cornea, with or without mucin interaction, and must be accounted for by other factors found in vivo.

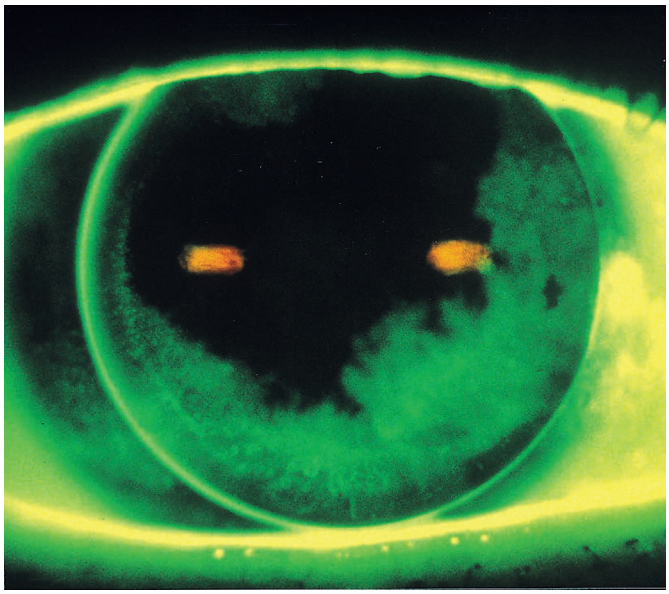


Fig. 28.6 Gradual penetration of fluorescein beneath a bound lens as the mucus adhesion breaks down. (Courtesy Patrick Caroline, Bausch & Lomb Slide Collection.)

Patient management

Because PMMA lenses are rarely fitted today, the difficult fitting problems encountered with such lenses are only of historical interest. However, as has been revealed previously, rigid lenses can induce clinically significant changes in corneal topography, which may be especially evident in patients with higher-power prescriptions requiring thicker lenses. Such lenses will impart greater physical and hypoxic stress on the cornea compared with thinner lenses made of the same material. Of course, in any case of contact lens–induced corneal shape change, refitting into soft lenses will usually provide a cure because soft lenses are known to have little or no effect on corneal topography.

CHANGE IN OVERALL CURVATURE

Refractive instability in patients wearing rigid lenses is a possible sign of lens-induced corneal shape change. Of course, other possible causes of refractive instability, such as unstable diabetes or advancing keratoconus, must be ruled out. Once other possibilities have been ruled out, the direction of refractive change may provide a clue as to the likely cause. A myopic shift suggests increased corneal curvature that could be caused by a steeply fitting lens or central hypoxic oedema. A hyperopic shift suggests a flat lens fit and excessive central lens bearing.

Although it is not always possible to determine the precise cause of a shift in refraction, a solution to the problem can be based on the principle that a well-fitting lens of high oxygen performance will induce minimum corneal shape change.

If the clinical decision has been made that the present lens is unacceptable, then a new lens must be fitted. Three basic approaches have been suggested for refitting rigid lens wearers suffering from corneal shape changes. These are as follows:

- *Sudden discontinuation* – the patient is advised to cease lens wear for an extended period (perhaps many weeks). The theory behind this approach is that the cornea is allowed to recover completely in the total absence of the influence of lenses.[45]
- *De-adaptation* – the patient is advised to continue wearing lenses but wearing time is gradually reduced to zero. The cornea is then monitored and lenses are refitted when stability has been reached.[46]
- *Immediate refit* – the patient is immediately refitted with lenses of superior design and higher Dk/t, so that recovery will occur more gradually during wear of the replacement lenses.[45,47]

Sudden discontinuation is not considered to be a viable technique for two reasons. First, patients who discontinue in this way, especially after PMMA lens wear, show excessive and unpredictable fluctuations in refractive state and corneal curvature.[48] In addition, permanent corneal distortion has been noted in some patients after sudden discontinuation of PMMA lens wear.[1] Second, this procedure is disconcerting to patients who must endure the wild refractive changes and suffer the inconvenience of not wearing lenses for some time.

De-adaptation is a compromise between the patient management techniques of 'sudden discontinuation' and 'immediate refit'. The preferred technique is 'immediate refit'.[45,47,49] The aim is to refit the patient with a lens of better fit and higher Dk/t. It is beyond the scope of this chapter to provide a full set of guidelines for achieving a superior rigid lens fit. Suffice to say that a thin, large-diameter, aspheric, back-surface-alignment fit often gives the best results.

Immediate refitting of rigid materials in long-term PMMA contact lens wearers was the aim of a study by Novo et al.[50] Six eyes with contact lens–induced corneal warpage from PMMA contact lenses were assessed. Six months after refitting, the SRI diminished by 0.51 ± 0.32 and the SAI improved by 0.32 ± 0.26. These authors[50] concluded that immediate refitting of rigid materials of similar design and fit in long-term PMMA contact lens wearers allows for attaining a slightly more regular and symmetrical central corneal shape, resulting in improved spectacle-corrected visual acuity.

During rigid lens wear, the tear layer may mask any deleterious effects on vision arising from corneal distortion. Thus, patients will be satisfied because they can continue to wear lenses, and vision will be adequate. Furthermore, patients should be advised that their new lenses will be more flexible and less scratch-resistant and that greater caution will be required when cleaning and handling lenses.

If supplementary spectacles are to be prescribed, it is obviously preferable to delay this until there has been a stabilization of corneal shape. This could take 3 weeks after the lens refit, although a longer period should be allowed if the corneal distortion that prompted the refit was particularly severe.[45]

CHANGE IN SAI, SRI AND CAI

Gross changes in corneal asymmetry may be attributed to rigid lens decentration, with corneal flattening in the region of the decentred lens. Refitting a lens with good centration should solve the problem; this may involve fitting a larger-diameter lens and avoiding excessive central bearing. Changes in corneal asphericity are presumably caused by an overall symmetrical moulding effect.

The exact cause of excessive lens-induced corneal surface irregularity may be difficult to ascertain. If vision has dropped by more than one line of Snellen acuity, then refitting with a large diameter lens of high Dk/t may allow the cornea to recover to a more normal topographical form.

Ruiz-Montenegro et al.[15] stated that they do not have their patients routinely discontinue contact lens wear if they are asymptomatic and have mild alterations to the SAI and/or the SRI, even if the changes are associated with a small decrease in BCVA.

LENS-INDUCED WARPAGE IN KERATOCONUS

Lens-induced warpage in patients with keratoconus can be avoided by fitting lenses with a lower modulus of elasticity and/or adopting an apical clearance fitting philosophy. A potential disadvantage of apical clearance is that the cone may progress more quickly compared with an apical touch fit. Clearly, these competing factors will need to be weighed when deciding on the appropriate strategy for a given patient.

CORNEAL INDENTATION

Although there is little doubt that mucus adhesion is the principle mechanism of binding of a rigid lens to the cornea,[41] the literature is full of ambiguous and often contradictory opinions as to lens fitting strategies for avoiding this problem. A review of the pertinent literature by Woods and Efron[51] produced a list of the various suggested strategies, which include flatten base curve, steepen base curve, increase centre thickness, reduce centre thickness, reduce back optical zone diameter, reduce total diameter, increase axial edge lift, increase edge band width, use an aspheric design and prescribe lubricants.

It has been suggested that rigid lens binding may be, in some way, related to long-term deposit formation and lens surface modification. This theory is derived from research which shows that the incidence of rigid lens binding in extended wear can be reduced by regular lens replacement.[51] Interestingly, lens binding was not alleviated in daily wear of rigid lenses by regularly replacing lenses.[51]

Swarbrick and Holden[52] observed that rigid lens binding is a patient-dependent phenomenon. Their analysis did not reveal patient attributes that would allow a clinician to predict whether a given patient is likely to display binding. Nevertheless, the observation of patient dependence is useful as it serves to alert clinicians to the fact that binding is likely to recur in a given patient unless some remedial action is taken.

Significant changes to lens design could be attempted to alleviate further occurrences of binding in a given patient, although it must be recognised that this can only be effected using a systematic 'trial and error' approach in the absence of definitive guidelines in the literature.

Because lens binding is a problem that relates specifically to rigid lenses, refitting with soft lenses is an obvious solution to this problem.

Prognosis

The prognosis for recovery of normal corneal topography is highly variable and dependent upon the magnitude and duration of the lens-induced deformation forces. Although the time course of recovery from physical forces on the cornea may be difficult to predict, recovery from chronic lens-induced oedema is known to occur within 7 days of cessation of lens wear.[53]

From a patient management perspective, knowledge of the rate of recovery from lens-induced shape changes are of particular relevance to patients who are currently wearing rigid contact lenses and are considering either being refitted with soft lenses or undergoing refractive surgery. It is essential that any lens-induced shape change be allowed to subside before refractive surgery is performed.

CHANGE IN OVERALL CURVATURE

Dramatic changes in corneal curvature after cessation of long-term PMMA lens wear have been documented by Rengstorff.[48] There is an initial reduction in myopia over the first 3 days, averaging 1.32 D, followed by a gradual return to baseline over the next 3 weeks. The extent and duration of these changes correlate with the length of time that the PMMA lenses are worn. In general, the refractive changes occur in parallel with corneal shape changes.

Bennett and Tomlinson[45] observed that the pattern of corneal recovery after PMMA lens wear is the same irrespective of whether the 'sudden discontinuation' strategy or the 'immediate refit' strategy is adopted. Because vision is better and more stable when adopting the 'immediate refit' strategy, this procedure is favoured by the authors.

The prognosis of recovery from severe corneal warpage is not good. Hartstein[1] reported 12 cases of contact lens–induced corneal warpage that were deemed to be permanent. Morgan[54] reported that in 74 cases of severe PMMA-induced corneal warpage, only half of the corneas displayed satisfactory resolution within 3 months of cessation of lens wear. Wilson et al.[3] advise that rigid lens–induced corneal warpage can take 5 to 8 months to be fully resolved.

Calossi et al.[55] described a case of corneal warpage caused by 14 years of rigid lens wear. The patient was refitted with daily-wear high-water-content soft contact lenses. Significant changes in both refraction and keratometry were observed after the refitting; computerised videokeratography showed that the corneal contour of both eyes had normalised after about 6 months. This case serves to illustrate that it is possible to re-establish a normal cornea, without completely suspending contact lens wear, by changing from a rigid to a soft material, but the rate of recovery can be protracted.

Wang et al.[18] evaluated the resolution of contact lens–induced corneal warpage before kerato-refractive surgery. In the 12% of patients who demonstrated lens-associated warpage, the mean duration of prior contact lens wear was 21.2 years (range 10–30 years); lens use included daily-wear hydrogel (n = 2), extended-wear hydrogel (n = 6), toric (n = 4) and rigid (n = 8) lenses. Up to 3.00 D refractive and 2.50 D keratometric shifts, accompanied by significant topography pattern differences, were observed. The average recovery time for stabilization of refraction, keratometry (change within ± 0.5D) and topography pattern was 7.8 ± 6.7 weeks (range 1–20 weeks). Recovery rates differed between the lens types; these were:

- hydrogel extended wear –11.6 ± 8.5 weeks;
- hydrogel toric lens – 5.5 ± 4.9 weeks;
- hydrogel daily-wear – 2.5 ± 2.1 weeks; and
- rigid lens – 8.8 ± 6.8 weeks.

On the basis of these findings, Wang et al.[18] suggested that to optimise the quality and predictability of kerato-refractive procedures, an appropriate waiting period is necessary for contact lens–induced corneal warpage to stabilise. They recommended that resolution of corneal warpage be documented by stable serial manifested refractions, keratometry and corneal topographic patterns before scheduling former lens-wearing patients for kerato-refractive surgery.

On the basis of the findings of a retrospective analysis of 45 soft lens wearers and 45 non–contact lens wearing controls, Lloyd McKernan et al.[56] concluded that 2 weeks cessation of soft lens wear is sufficient for resolution of lens-induced corneal curvature changes.

Figure 28.7A shows the corneal topography of a patient after sleeping wearing high-water-content hydrogel lenses on a

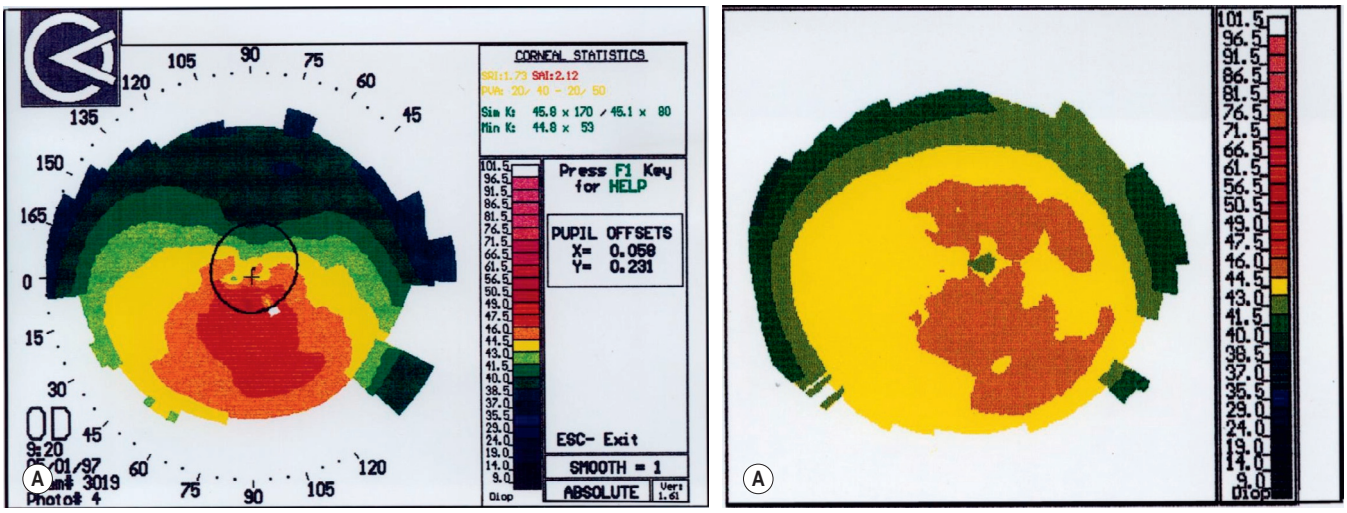


Fig. 28.7 **(A)** Pseudo-keratoconus pattern caused by soft lens–induced hypoxia. **(B)** Same eye as represented in **(A)** after 3 weeks without lens wear; note the resolution of corneal distortion. (Courtesy Loretta Szczotka-Flynn.)

weekly basis for 6 months. The inferior steepening, which mimics keratoconus, is notable. After discontinuing all lens wear, topography returned to normal in 3 weeks (Fig. 28.7B).

CHANGE IN SAI, SRI AND CAI

The patterns of recovery of corneas that have been rendered asymmetrical, irregular or aspheric as detected by videokeratoscopy are likely to be similar to those described earlier relating to changes in overall curvature. That is, taking the sum of the mean and standard deviation of the data of Wang et al.,[18] recovery is likely to occur within about 16 weeks for rigid lenses, 21 weeks for hydrogel extended-wear lenses and 5 weeks for hydrogel daily-wear lenses.

LENS-INDUCED WARPAGE IN KERATOCONUS

As Szczotka et al.[33] observed, it is difficult to dissociate the warpage effects of rigid lenses from the diseased state of keratoconus; nevertheless, an appreciation of the overall prognosis for keratoconic lens wearers can be gained by considering the success rate of contact lens fitting and rate of progression to keratoplasty. Such a study was undertaken by Smiddy et al.[57] in relation to 115 consecutive patients with keratoconus who had been referred for keratoplasty after previous contact lens fittings had no longer been successful. Of 190 non-operated eyes that needed to be fitted with contact lenses, 165 eyes (87%) could be fitted. Of these, 51 eyes (31%) ultimately needed keratoplasty after an average of 38 months of lens wear, and 114 eyes (69%) did not require keratoplasty over an average follow-up interval of 63 months of wearing contact lenses.

CORNEAL INDENTATION

In relation to a specific binding episode (with associated corneal indentation), prognosis for recovery is good. Swarbrick and Holden[52] reported that 25% of all lenses bound on eye opening were mobile within 10 minutes and that 50% were mobile within 30 minutes; however, 40% were still bound 60 minutes later. All lenses could eventually be freed by gentle manipulation of the lens through the lids. In almost two-thirds of the cases where lenses had been assessed as bound on eye opening, clinical signs of binding were apparent 2 hours after eye opening.[52] All signs of binding disappear within 24 hours in the absence of lens wear.

The prognosis for avoiding future episodes of rigid lens binding is not good given that binding is a patient-dependent phenomenon. A satisfactory prognosis can only be achieved in such patients if significant changes are made to lens design or type.

Differential diagnosis

It is generally possible to differentiate vision loss caused by corneal shape change from that resulting from other causes by reconciling refractive shifts with changes in corneal curvature. Although this relationship generally holds true, it is important to recognise that other factors, such as localised oedema and changes to other refractive components of the eye, can alter refractive status.

Contact lens–induced corneal warpage can take on a very similar clinical appearance to keratoconus[6] (Fig. 28.8). The key differentiating features of these two conditions in advanced

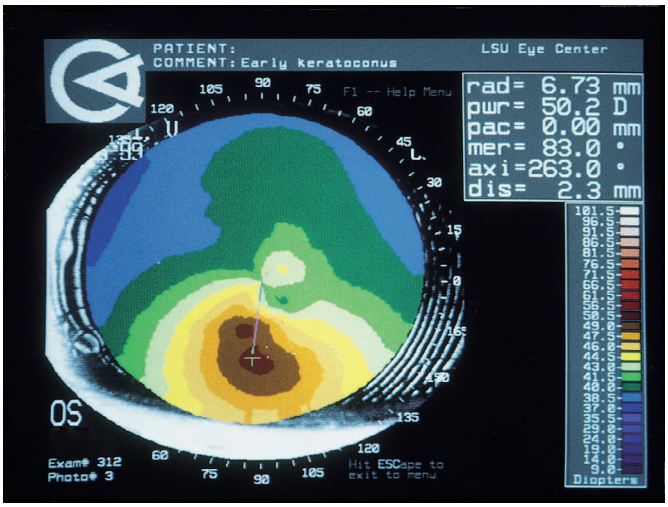


Fig. 28.8 Early keratoconus, which takes on a similar appearance to corneal warpage induced by a high-riding rigid lens (compare this image with Figure 28.3A). (Courtesy Stephen Klyce.)

cases are that patients with keratoconus often display corneal thinning, Vogt's striae, Fleischer ring and progressive corneal steepening (cone development), whereas lens-induced corneal warpage recovers after cessation of lens wear and is not associated with clinically detectable corneal thinning, striae and ring pathology.

In the early stages of keratoconus, however, differentiation from mild lens-induced corneal warpage can be difficult. Lebow and Grohe[58] pointed out that superior corneal flattening associated with inferior corneal steepening is a videokeratoscopic topography pattern that usually describes both keratoconus and contact lens–induced warpage. To differentiate these two conditions topographically, these authors[58] analysed 10 different corneal topographic shape variables and found that three unique measurements of corneal geometry – shape factor, irregularity and apical toricity – could be used to differentiate between these two conditions with a high degree of accuracy and specificity. A similar approach has been described by Smolek et al.[59]

Schallhorn et al.[60] sought to distinguish between corneal ectasia and contact lens–related warpage by characteristic patterns on corneal topography and optical coherence tomography epithelial thickness maps. Twenty-one eyes with keratoconus, six eyes with forme fruste keratoconus (better eye of asymmetric keratoconus) and 15 eyes with contact lens–related warpage were identified. The keratoconus and forme fruste keratoconus eyes had coincident topographic steepening with epithelial thinning. The locations of minimum epithelial thickness and maximum axial power agreed in 90% of the keratoconic eyes, whereas the minimum epithelial thickness and maximum mean power agreed in 95% of them. Conversely, the warpage eyes had coincident topographic steepening with epithelial thickening and normal pachometry maps. The locations of maximum epithelial thickness and maximum axial power agreed in 93% of the warpage eyes, and the maximum epithelial thickness and maximum mean power agreed in all warpage eyes. The authors concluded that epithelial thickness maps and corneal topographic maps are powerful synergistic tools in evaluating eyes with abnormal topography and can help differentiate between keratoconus and non-ectatic conditions.

Suggestions that rigid contact lens wear can induce keratoconus[61] have been dismissed because of lack of sound evidence. Any association between keratoconus and rigid lens wear is almost certainly coincidental rather than causative.

Intentional corneal moulding

Brief mention needs to be made of two clinical approaches that attempt to use the known corneal moulding properties of rigid lenses for the purpose of re-shaping the cornea.

CONE COMPRESSION IN KERATOCONUS

Confirmed cases of keratoconus are almost always fitted with rigid lenses so as to neutralise corneal distortions and provide satisfactory vision. A variety of fitting philosophies can be adopted to fit the keratoconic eye, including apical bearing, apical clearance, three-point-touch and lid attachment procedures. The theory behind the first of these – apical bearing – is that constant bearing on the cone will arrest or slow the progression of the cone. Both scleral and rigid lenses have been used historically for this reason (Fig. 28.9A).

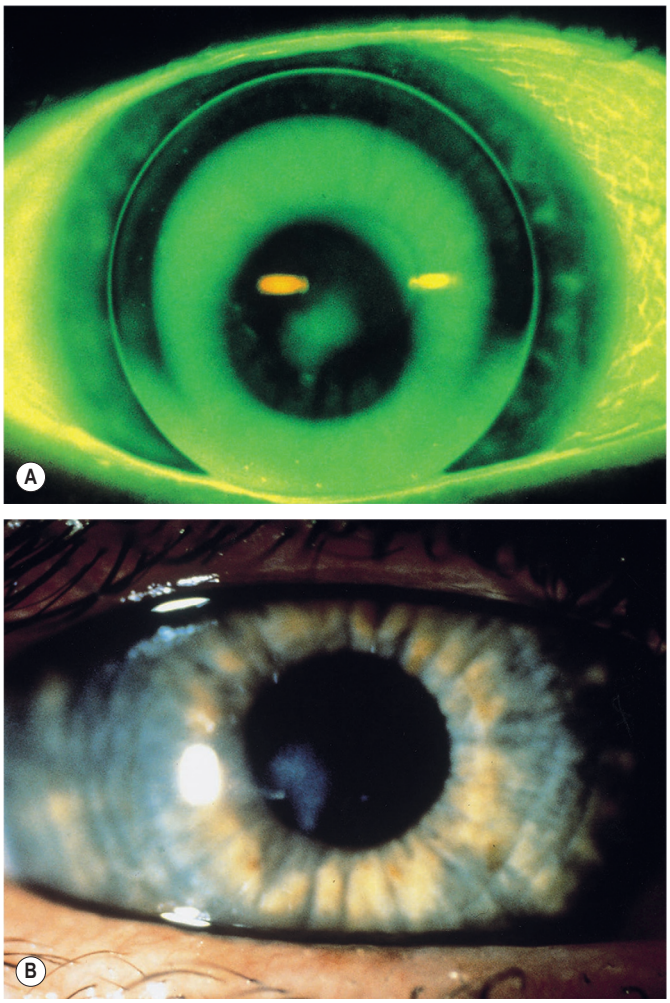


Fig. 28.9 **(A)** Rigid lens fitted to a keratoconic eye, with the fluorescein pattern indicating central and mid-peripheral bearing. **(B)** Same eye as depicted in **(A)**, pictured here in white light and revealing central corneal scarring induced by the apical lens bearing. (Courtesy Meredith Reyes, Bausch & Lomb Slide Collection.)

Korb et al.[62] warned that an apical bearing lens fit can result in scarring of the apex of the cone (Fig. 28.9B). Furthermore, Ruben and Trodd[63] demonstrated that there was no difference in the rate of progression of keratoconus in lens-wearing versus non-lens-wearing groups. Despite these observations, the apical bearing technique appears to have been historically favoured by 88% of practitioners based on the results of a national survey in the USA among 1,209 patients with keratoconus wearing rigid lenses.[64]

ORTHOKERATOLOGY

Orthokeratology is a term used to describe the clinical procedure of deliberately fitting flat, spherical rigid lenses in such a manner that the cornea is moulded into a new shape (essentially 'flattened'), with the aim of reducing the level of myopia. It is a technique that has been evolving since the 1960s. More recent iterations of orthokeratology employ the practice of fitting reverse-geometry lenses, which create heavy central and outer-peripheral bearing upon the cornea (Fig. 28.10). Orthokeratology lenses can be made of high-oxygen-permeability materials, permitting the wearing of orthokeratology lenses on an overnight basis (i.e. overnight orthokeratology[65]).

The advent and acceptance of kerato-refractive surgery for the correction of refractive errors has ensured that interest in other non-surgical approaches, such as orthokeratology, has remained relevant. The resurgence of orthokeratology as a viable alternative to refractive surgery or, indeed, to traditional contact lens or spectacle corrections is a consequence of three developments:

- the availability of new lens designs, particularly reverse geometry lenses, and the ability to design and manufacture lenses to produce a specific tear layer thickness profile;
- the availability of corneal topography devices to assist with contact lens design and to evaluate corneal shape changes; and
- the availability of new high-oxygen permeable materials, allowing overnight lens wear.

Orthokeratology lenses for myopia and hyperopia can induce significant structural and optical changes in as little as 15 minutes.[66] The cornea, particularly the epithelium, is

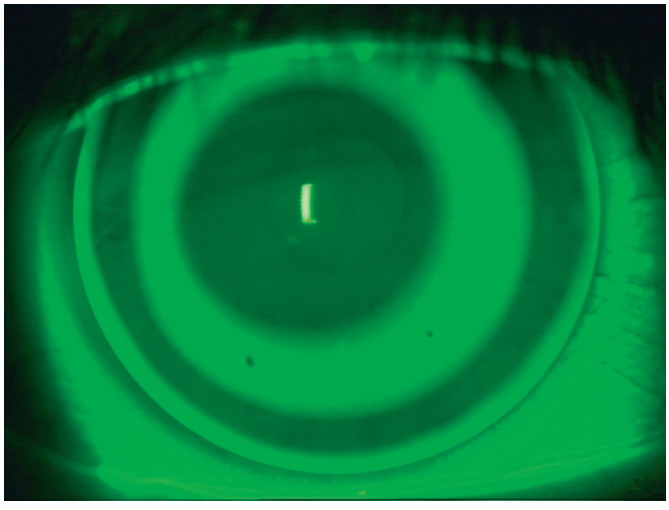


Fig. 28.10 Fluorescein pattern for a correctly fitted reverse-geometry lens. (Courtesy Ruth Cornish, Bausch & Lomb Slide Collection.)

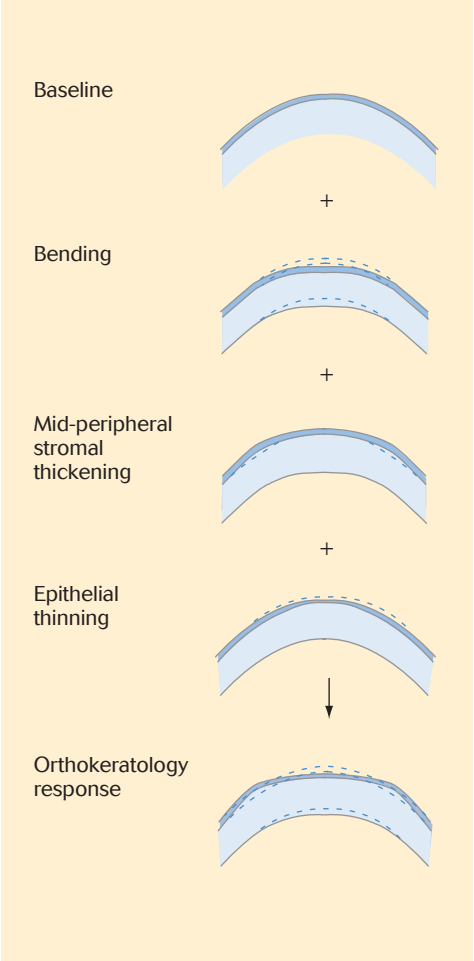


Fig. 28.11 The change from baseline corneal shape and thickness resulting from a reverse-geometry lens in the process of orthokeratology can be modelled as a result of the composite effects of bending, mid-peripheral stromal thickening and central epithelial thinning. (Adapted from Carney LG. Orthokeratology. In: Efron N, editor. Contact Lens Practice. Second ed. Oxford: Butterworth Heinemann Elsevier; 2010. p. 332–8.)

remarkably malleable, with rapid steepening and flattening possible in little time.[66] The average magnitude of the refractive change using orthokeratology lenses is only about 1.75 D[65,67] and is subject to significant individual variability.

The issue of predictability of orthokeratology-induced corneal shape changes still remains unresolved. The corneal changes are not permanent, with significant regression occurring over a few hours.[65] Ongoing use of contact lenses (sometimes referred to as 'retainer lenses'), whether for overnight wear or daily wear, is still needed to sustain the refractive changes. Questions have been raised about the scientific rigor studies relating to current orthokeratology practices,[68] especially in relation to a lack of appropriate masking, randomization and experimental control.

The corneal curvature changes in orthokeratology appear to result from a combination of short-term corneal moulding and a longer-term redistribution of anterior corneal tissue.[69,70] It has also been suggested that the tear reservoir generated by the steeper secondary curves leads to pressure changes that are responsible for the corneal tissue redistribution[70,71] (Fig. 28.11).

Despite the relative safety of overnight orthokeratology with respect to reversible and non-sight-threatening adverse events, there have been reports of complications, such as recurrent lens binding and central island formation.[72] There also appears to be an increased risk for microbial keratitis resulting from overnight lens wear with reverse-geometry lenses,[73-79] necessitating a careful risk/benefit analysis for each patient contemplating this procedure.

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29 Endothelial Bedewing

Eye care practitioners from time to time will observe deposits, such as keratic precipitates, on the endothelial surface. These may be benign or may be associated with a broad range of uveal responses. In 1979, McMonnies and Zantos[1] described the appearance of endothelial deposits of uncertain origin in patients who were intolerant to contact lens wear (Fig. 29.1). They described this condition as 'endothelial bedewing'. This condition was further discussed soon thereafter by Zantos and Holden[2]; however, since then, this topic has received little attention in the literature.

As will be discussed in this chapter, it is not at all clear that endothelial bedewing is *induced* by contact lens wear; however, there appears to be an *association* between lens wear and endothelial bedewing. This association is worth considering because specific management strategies need to be employed to solve the problem.

Incidence

Deposits or pigment spots on the endothelium (or on the anterior lens capsule) are commonly observed during routine slit lamp examination of all patients. These are often benign and do not affect vision, except in rare cases.[3]

Hickson and Papas[4] conducted an extensive biomicroscopic examination on 70 normal, asymptomatic, consecutively presenting, non–contact lens wearers and found that 20% of the sample displayed endothelial bedewing. The authors concluded that endothelial bedewing could occur idiopathically in non-lens-wearing eyes.

McMonnies and Zantos[1] reported seeing 25 patients with endothelial bedewing associated with contact lens intolerance over a 9-month period, suggesting that this condition is not uncommon. However, it is important to recognise that these observations were made some time ago, when the contact lens market was dominated by soft contact lenses, which were replaced infrequently, made of materials of low oxygen transmissibility (primarily hydroxyethyl methacrylate), and maintained using relatively unsophisticated lens care systems. At that time, contact lenses in general were associated with a higher prevalence of adverse reactions – relating to spoiled lenses and mildly toxic solution preservatives – compared with the present-day situation.

Surveys conducted between 1992 and 2018 of contact lens complications among patients presenting to large clinics or hospital eye departments – carried out in China,[5] India,[6] Japan,[7] Nepal,[8] Singapore,[9] the USA[10] and the UK[11,12] – have failed to report any form of endothelial dysfunction. It is, therefore, not possible to deduce the prevalence of contact lens–associated endothelial bedewing in modern-day contact lens practice.

Signs and symptoms

Contact lens–associated endothelial bedewing is characterised by the appearance of small inclusions on the endothelial surface, which are most easily seen in the region of the inferior central cornea near to or immediately below the inferior pupil margin. The area of bedewing can vary in shape. For example, endothelial bedewing may appear as an oval cluster of inclusions or a less discrete dispersed formation. The condition is usually bilateral.[1]

The preferred slit lamp observation technique is marginal retro-illumination, where the attention of the observer is directed to the region of the cornea in front of the border between the brightly illuminated iris and the dark pupil. With this technique, the particles or inclusions are seen as small discrete circular optically translucent entities. Most cells appear to display an optical phenomenon known as 'reversed illumination' whereby the distribution of light within the cell is the opposite of the background distribution of light (Fig. 29.2). However,

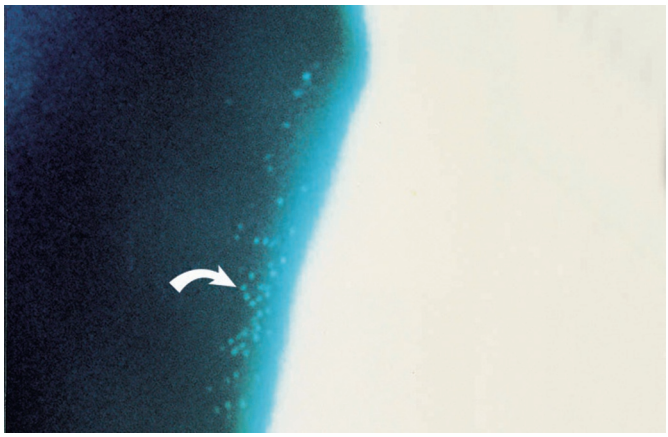


Fig. 29.1 Endothelial bedewing observed using marginal retro-illumination (arrow). (Courtesy Steve Zantos, Brien Holden Vision Institute.)

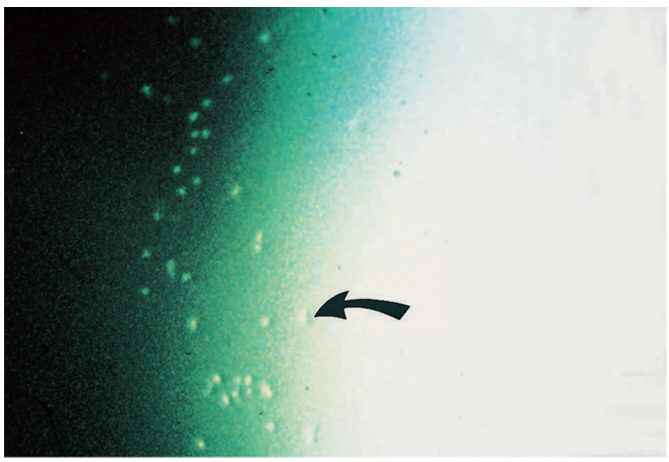


Fig. 29.2 Endothelial bedewing observed at high magnification. In this case the individual cells are displaying 'reversed illumination' (arrow). (Courtesy Charles McMonnies.)

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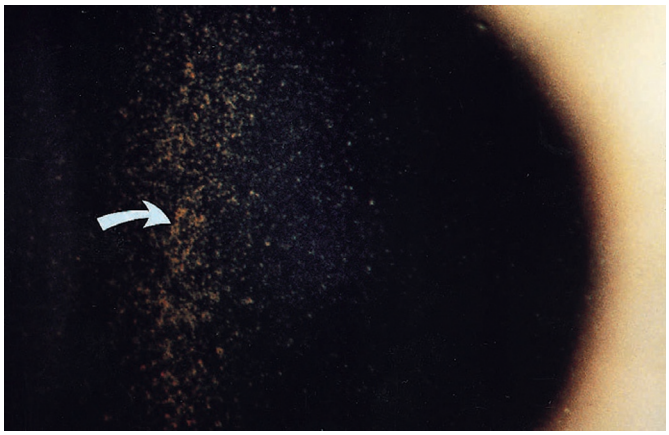


Fig. 29.3 Pigment dispersion observed using indirect retro-illumination (arrow). (Courtesy Ronald Stevenson, British Contact Lens Association Slide Collection.)

in some cases of endothelial bedewing, the inclusions can also display unreversed illumination. The optical basis for these characteristic forms of illumination has been discussed in Chapter 19.

When viewed in direct illumination, endothelial bedewing can appear as fine, white precipitates or as an orange/brown dusting of cells. Coloured particles are likely to be cellular debris (see 'Pathology'), and their actual colour can give a clue to the length of time they have been present. Newly deposited cells are often whitish in colour, but these become pigmented over time.

Figure 29.3 is a slit lamp photograph of the right eye of a 35-year-old male referred for assessment of suitability for contact lenses to correct myopia. An extensive 'dusting' of brown pigment can be observed in a spindle shape characteristic of pigment dispersion syndrome (the so-called Krukenberg spindle).

There appears to be no fixed pattern of associated signs. Among their detailed case reports of three patients, McMonnies and Zantos[1] noted the following signs (in addition to bedewing): conjunctival redness, epithelial erosion, epithelial oedema and reduced corneal transparency. There were no cases of flare in the anterior chamber.

The main associated feature of endothelial bedewing is either total or partial intolerance to lens wear. Some patients may present after having recently abandoned lens wear. Patients may also complain of 'fogging' of vision or stinging. It should be noted, however, that the association between bedewing and lens intolerance is not obligatory; McMonnies and Zantos[1] observed two cases of endothelial bedewing in successful lens wearers.

Mackie[13] described a condition which he named 'total endothelial bedewing'. According to Mackie, this acute phenomenon occurs in hydrogel lens wearers. Patients usually present complaining of blurred vision. The condition resolves rapidly (within 2 days of lens removal) and does not recur. It is unclear whether Mackie was observing the same phenomenon as that reported by McMonnies and Zantos.[1]

Brooks et al.[14] examined the posterior surface of the endothelium by using the 'relief mode' of an endothelial specular microscope and observed numerous deposits, including red blood cells, white blood cells, keratic precipitates, pigment granules and pseudo-exfoliative keratic precipitates. Using corneal confocal microscopy, Bastion and Mohamad[15] observed small white dots throughout the corneas of 56 soft contact lens wearers. In one patient, these were observed at the level of the endothelium.

Pathology

McMonnies and Zantos[1] originally surmised that the bedewing particles were either droplets of clear fluid (oedema) within the endothelial cells or inflammatory cells, such as leucocytes or macrophages, resting on the posterior surface of the endothelium. Particles displaying a 'reversed illumination' optical appearance are likely to be inflammatory cells. The reason for this is that 'reversed illumination' indicates the presence of material of higher refractive index within the entity displaying this appearance compared with the refractive index of the medium surrounding that entity. The material of higher refractive index acts as a converging refractor causing a crossing over of the light rays. The cytoplasm, organelles and nucleus of an inflammatory cell resting on the endothelial surface would be of a higher refractive index than the surrounding clear aqueous humour, giving rise to reversed illumination. An inflammatory cell embedded within the endothelium would probably not display reversed illumination in view of the lack of a significant refractive index difference between the inflammatory cell and the surrounding endothelial cells.

Fluid droplets lying within the endothelium would be of a lower refractive index compared with the surrounding cytoplasm, organelles and nucleus of an endothelial cell and would therefore be expected to display 'un-reversed illumination' whereby the distribution of light within the particles is the same as the background distribution of light. Fluid drops on the surface of the endothelium would be surrounded by aqueous humour and thus would be unlikely to display such optical characteristics as a result of lack of refractive index difference between the fluid drop and the aqueous.

Bergmanson and Weissman[16] described an additional feature of endothelial bedewing – that inflammatory cells start off on the endothelial surface but eventually become subsumed or engulfed by the endothelium and end up residing between adjacent endothelial cells and sealed off from the anterior chamber by zonula occludens. These authors provided convincing electron micrographic evidence to support this hypothesis. As described earlier, such engulfed inflammatory cells would be expected to produce a less pronounced appearance of reversed illumination because of the lower refractive index difference between the contents of the engulfed cell and the surrounding endothelial cells. It is likely that inflammatory cells observed in endothelial bedewing lie on the endothelium in the first instance, and some may become subsumed into the endothelium later.

Bergmanson[17] also provided evidence of fluid drops forming within the endothelium. Figure 29.4 is an electron micrograph of the endothelium after daily wear of an aphakic hydrogel lens in a 66-year-old person. In this instance, an inter-cellular oedematous space (indicated by the asterisk in the figure) has formed *between* adjacent endothelial cells.

Whatever the location of the bedewing (on or within the endothelium), the fact that most inclusions display reversed illumination suggests that these are of inflammatory origin, which, in turn, suggests that some forms of endothelial bedewing may have an inflammatory basis (see 'Aetiology'). Figure 29.5 is a schematic representation of endothelial bedewing.

On the assumption that endothelial bedewing can represent a mild inflammatory uveal response, the origin of the

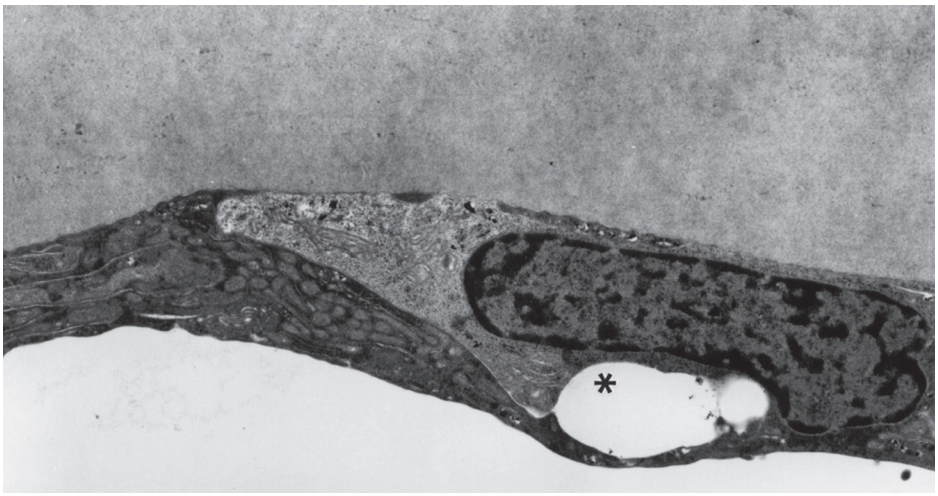


Fig. 29.4 Electron micrograph of fluid inclusion (asterisk) between adjacent endothelial cells. (Bergmanson JPG. Light and electron microscopy. In: Efron N, editor. The Cornea: Its Examination in Contact Lens Practice. Oxford: Butterworth-Heinemann; 2001. p. 136–77.)

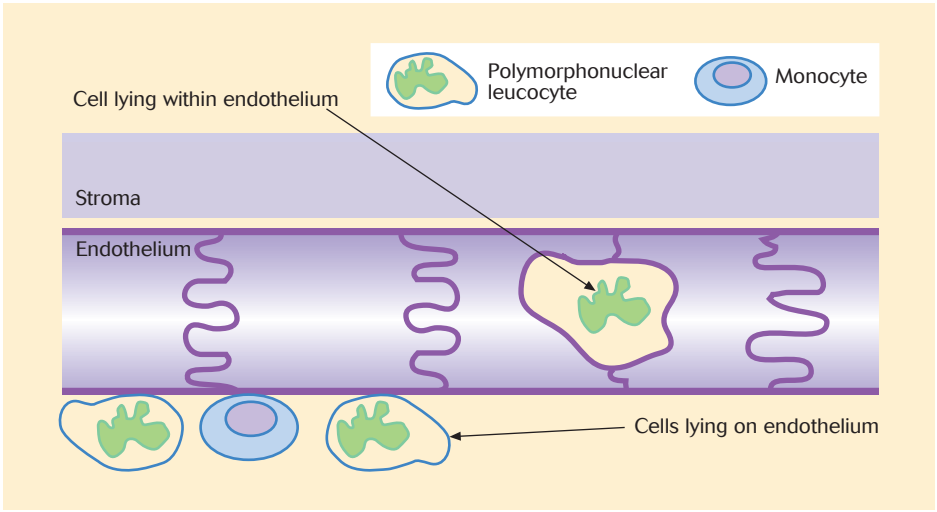


Fig. 29.5 Endothelial bedewing in the form of inflammatory cells lying on and within the endothelium.

inflammatory cells is likely to be the iris and/or ciliary body. During inflammation, vascular permeability is increased and inflammatory cells leave vessels in the iris and ciliary body and float around in the aqueous until they come to rest on the endothelial surface. One would therefore expect to occasionally observe mild aqueous flare in patients with endothelial bedewing, but this does not appear to have been reported.

Aetiology

The appearance and characteristic distribution of endothelial bedewing and the associated signs and symptoms of eye redness, stinging and blurred vision (besides lens intolerance) strongly suggest that the syndrome of endothelial bedewing can represent a mild anterior uveal inflammation. Although it is clear that contact lenses can induce a variety of inflammatory responses of the ocular surface tissues, it is less certain that contact lenses can induce a uveal inflammation.

Contact lens wear is thought to be intrinsically inflammatory,[18] and this could lead to a more frank inflammatory episode with an appropriate trigger. In most body tissues, hypoxia can lead to the release of inflammatory mediators, such as prostaglandins, which can, in turn, cause inflammation. One possible mechanism is depicted in Figure 29.6. In this model, hypoxia induces the release of prostaglandins from corneal tissue, and the prostaglandins diffuse into the aqueous humour and eventually enter the tissue of the iris. A mild inflammatory response is initiated, and inflammatory cells are released into the aqueous; these eventually come to rest on the endothelial surface.

Efron et al.[19] examined whether contact lens–induced corneal oedema was at least part inflammatory by measuring the level of oedema in response to contact lens wear in a group of individuals who took prostaglandin inhibitor drugs before lens wear. There was no difference between the level of oedema in this group versus that in a control subjects who did not take prostaglandin inhibitor drugs, leading to a rejection of the hypothesis that contact lens–induced corneal oedema has an inflammatory component. Nevertheless, a sequelae of events similar to that depicted in Figure 29.6 and described earlier is possible, perhaps with a family of inflammatory mediators other than prostaglandins.

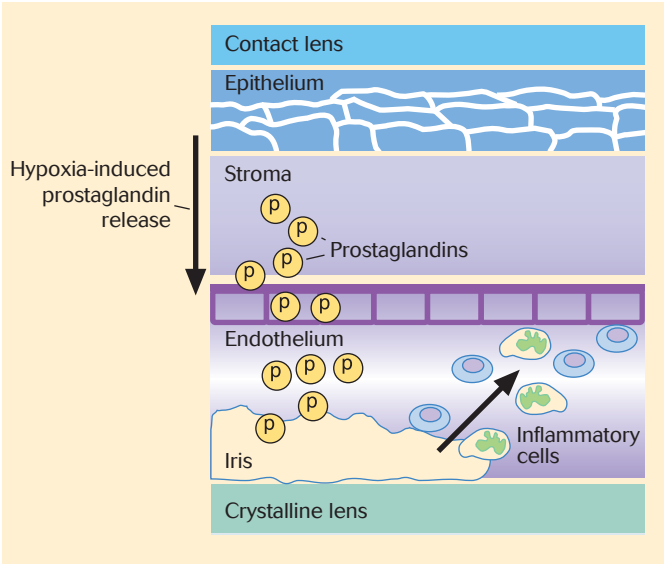


Fig. 29.6 Possible aetiology of endothelial bedewing.

It may well be the case that instead of contact lenses inducing a mild uveal response of which endothelial bedewing is a sign, the converse is true; that is, a patient may develop a mild anterior uveal response for reasons unrelated to lens wear, but the mild inflammatory status of the eye *causes* lens intolerance. Indeed, the latter explanation is the more likely scenario. Whatever the causation, it is important that clinicians are aware of the association so that appropriate management strategies can be put in place.

Patient management

As alluded to earlier, patients suffering from endothelial bedewing will have already devised strategies for alleviating the symptoms before they present to the clinic – namely, reducing wearing time or ceasing lens wear. Simply put, this is a condition that is managed by symptomatology rather than by signs. Wearing time should be reduced to a level that represents the balance between the need of the patient to wear lenses for a desired length of time each day and the level of discomfort that can be tolerated. If hypoxia is deemed to be the trigger behind an inflammatory response leading to the development of endothelial bedewing, then strategies to alleviate hypoxia, such as fitting more highly oxygen transmissible lenses, should be employed.

The presence of inflammatory cells on the endothelial surface should be viewed with caution by clinicians, who need to consider a variety of possible causes. Certainly, all forms of uveitis should be considered a possibility, and tests should be conducted to exclude such possibilities (see 'Differential diagnosis').

In all cases of endothelial bedewing, intra-ocular pressures should be measured as there is a possibility that some inflammatory cells may have migrated into the anterior angle, creating a blockage of aqueous outflow. Gonioscopy is also indicated, especially if intra-ocular pressure is elevated.

Prognosis

The pattern of recovery from endothelial bedewing is variable. McMonnies and Zantos[1] reported that in some cases the bedewing completely disappeared within 4 months, and in other cases, it changed little over many months. These authors also reported that lens intolerance persisted for many months in some patients even after the bedewing had disappeared.

Differential diagnosis

Various anomalies of the endothelium can potentially be confused with endothelial bedewing. Corneal guttata are focal accumulations of collagen on the posterior surface of Descemet's membrane that lead to localised bulging of the endothelial surface. This, in turn, leads to the appearance of darks spots in the endothelial mosaic when viewed using specular reflection.

Nakashima et al.[20] reported the presence of corneal pseudo-guttata in 44 out of 3,521 patients presenting consecutively to a local eye clinic. Of these patients, 16 were suffering from contact lens–induced keratitis. The authors concluded that corneal pseudo-guttata is commonly found in cases with corneal infiltration and inflammation. They noted that corneal pseudo-guttata is reversible and resolves completely without any damage to the corneal endothelial cells.

Contact lens–induced endothelial blebs, which are caused by localised endothelial cell oedema, can take on an identical appearance (see Chapter 30) (Fig. 29.7). Differential diagnosis is achieved by viewing the cornea under marginal retro-illumination, thus confirming the presence of the reversed or un-reversed illumination appearance of bedewing. Guttata and blebs do not display these optical phenomena.

When the cornea is viewed using marginal retro-illumination, bedewing can take on an appearance that is identical to either epithelial microcysts or vacuoles/bullae. The procedure for differentiating between these two conditions is to view the cornea by using a fine optical section at high magnification. At the very least, the depth of the pathology in the cornea can be determined (i.e. at the level of the epithelium or endothelium). If the endothelial bedewing is of the form whereby the cells are resting on the surface of the endothelium, then these will be observed as fine spots on the posterior corneal surface. If the bedewing cells have been engulfed into the endothelium, they may not be visible. Similarly, epithelial microcysts will not be observed in optic section. Thus, the appearance of spots on the endothelium when observed in optic section confirms the

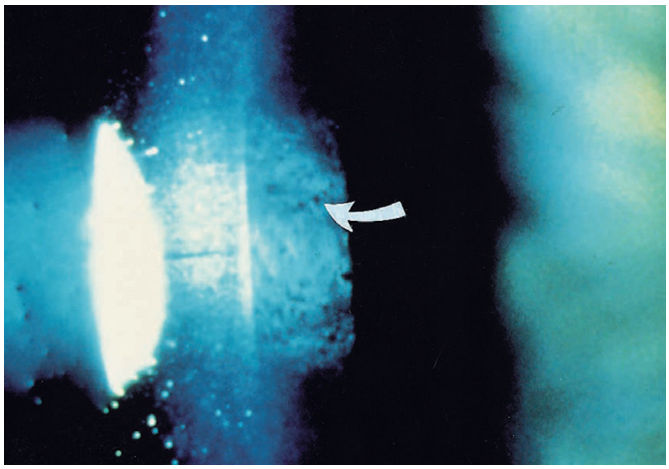


Fig. 29.7 Contact lens–induced endothelial blebs (arrow). (Courtesy Steve Zantos, Brien Holden Vision Institute.)

TABLE 29.1 Comparison of contact lens–associated endothelial bedewing and Fuch's heterochromic cyclitis

Feature	Contact lens–associated endothelial bedewing	Fuch's heterochromic cyclitis
Age of onset	Any age	Less than 45 years
Gender	No preference	No preference
Associated factors	Contact lens wear	Vitreous opacities 'Smudging' of iris crypts Iris pigment loss Iris atrophy
Symptoms	Intolerance to lens wear 'Fogging' of vision Stinging	Blurred vision
Signs	Conjunctival redness Epithelial erosion Epithelial oedema Reduced corneal transparency	Faint anterior chamber flare
Cells	White or pigmented precipitates form at inferior cornea	Only white precipitates scattered diffusely over cornea
Laterality	Usually bilateral	Usually unilateral
Secondary complications	Glaucoma	Glaucoma Cataract

diagnosis of a cellular form of endothelial bedewing, whereas the absence of spots does not assist in differential diagnosis.

The associated signs will assist in the differential diagnosis of endothelial bedewing versus epithelial microcysts. The latter is typically associated with extended hydrogel lens wear and symptoms are minimal or absent. However, endothelial bedewing is associated with stinging, eye redness, corneal clouding and lens intolerance.

The possibility that the patient is suffering from a form of uveitis that has occurred coincidentally with lens wear must be considered. The signs and symptoms associated with endothelial bedewing can closely mimic some of the mild manifestations of uveitis, such as Fuch's heterochromic cyclitis. Table 29.1 compares the signs and symptoms of endothelial bedewing and Fuch's heterochromic cyclitis as a guide to differential diagnosis.

If a uveitis of any sort is suspected – including an intractable case of endothelial bedewing associated with indicators of active pathology such as a red irritable eye and/or anterior chamber flare – therapeutic interventions may be required. These might include the prescription of corticosteroids to dampen the inflammatory response, mydriatics to prevent the formation of posterior synechiae and analgesics to reduce the pain. If uveitis is confirmed in a contact lens wearer, lens wear should be ceased until the condition has fully resolved.

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30 Endothelial Blebs

Before 1977, it was thought that contact lenses could only affect the cornea by direct mechanical influence or oxygen deprivation. Because the endothelium is located on the posterior surface of the cornea and is known to obtain all of its required oxygen from that dissolved in the aqueous humor,[1] this tissue layer was thought to be immune to the effects of contact lenses.

The first clue that contact lenses could alter corneal endothelium came from Zantos and Holden,[2] who noted that the endothelial mosaic undergoes a dramatic alteration in appearance within minutes of inserting a contact lens. Specifically, they reported observing a number of black, non-reflecting areas in the endothelial mosaic – which they called *blebs* – and an apparent increase in the separation between cells. These changes can be observed under high magnification (×40) using the slit lamp biomicroscope (Fig. 30.1).

The contact lens fraternity remained sceptical for some time, and it was not until (a) the appearance of blebs was verified independently[3] and (b) reports of contact lens–induced endothelial polymegethism were published by Schoessler and Woloschak,[4,5] in the early 1980s, that serious research commenced into understanding the endothelial response to lens wear.

Prevalence

The prevalence of endothelial blebs is thought to be essentially 100% among contact lens wearers[2]; that is, blebs can be observed in all patients – even those wearing highly oxygen transmissible lenses – within 10 minutes of lens insertion. There is a large variation in the intensity of the response between lens types and patients.[2,6,7] Asian subjects have a significantly higher degree of endothelial bleb formation compared with the non-Asian population for closed-eye lens wear.[8]

Signs and symptoms

The black, non-reflecting areas observed in the endothelial mosaic correspond to the position of individual cells or groups of cells. The initial impression one gains is that cells have 'fallen off' the posterior surface of the cornea, leaving behind gaps or black holes.[2] In corneas displaying a marked blebbing response, it also appears as if all endothelial cells throughout the field of view have become more separated and the endothelial surface takes on a more textured and three-dimensional appearance.[2]

The 'bleb response' displays a characteristic time course (Fig. 30.2). Blebs can be observed within 10 minutes of lens insertion. The number of blebs peaks in 20 to 30 minutes and then subsides to a low level after about 45 to 60 minutes. A low-level bleb response can be observed throughout the remainder of the wearing period.[2]

Hydrogel lenses cause a greater bleb response compared with well-fitting rigid lenses. Lenses of greater average thickness induce a greater response compared with thinner lenses. However, the design and fit of hydrogel lenses have little effect on the bleb response.[6] Ohya et al.[7] observed that blebs are confined to the central regions of the cornea beneath rigid lenses but that they occur throughout the cornea with soft lenses; that is, blebs are seen in all corneal areas covered by contact lenses.

Williams and Holden[9] observed two additional endothelial phenomena in patients wearing soft lenses on an extended-wear basis. First, there appears to be an increase in the number of blebs in the late evening, before going to sleep. Second, the overall magnitude of the bleb response can be seen to decrease over

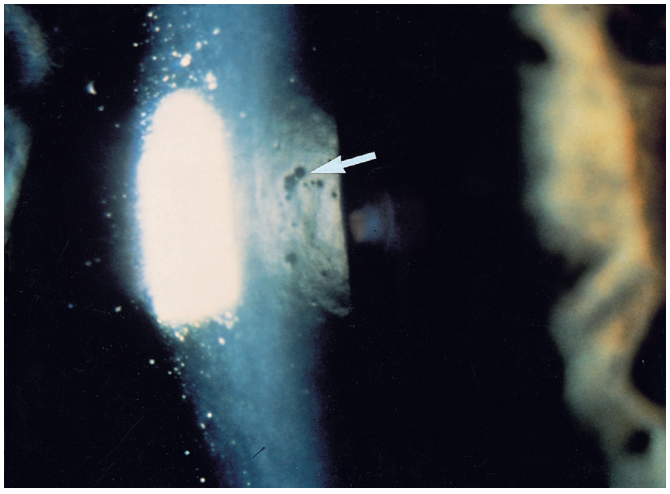


Fig. 30.1 Contact lens–induced blebs (arrow) in the endothelial mosaic observed in specular reflection with the slit lamp biomicroscope. (Courtesy Arthur Ho, Brien Holden Vision Institute.)

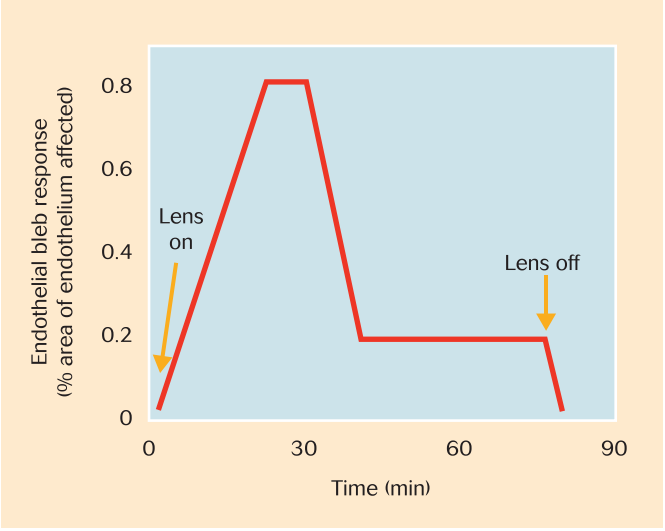


Fig. 30.2 Time course of appearance and resolution of contact lens–induced endothelial blebs.

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the initial 8 days of extended wear. Furthermore, Bruce and Brennan[10] noted that the overall bleb response was reduced by approximately 50% after 4 months of soft lens extended wear compared with baseline values. These observations suggest that some form of short-term[9] and long-term[9,10] adaptation of the endothelium takes place.

Brennan et al.[11] evaluated the corneal endothelial bleb response to wear of silicone hydrogel lenses (Acuvue Oaysis, Acuvue Advance and Focus Night & Day) and a conventional hydrogel lens (SofLens 38) in eyes of East Asian subjects. SofLens 38 produced a mean percentage area of blebs of 8% under closed-eye conditions, which was significantly greater than that produced by Acuvue Oaysis (1.6%). Both Acuvue Advance and Focus Night & Day produced a mean percentage bleb area of 0.4% under open-eye conditions. Acuvue Oaysis and Focus Night & Day produced statistically similar mean percentage bleb areas of 1.7% and 2%, respectively. The authors concluded that the similarity of the bleb responses induced by the silicone-hydrogel lenses under the tested wearing conditions is consistent with the proposition that increases in oxygen transmissibility (Dk/t) above a certain level will produce minimal change in corneal physiological conditions compared with that when no lens is worn.

Inagaki et al.[12] compared the time course of endothelial bleb formation and disappearance between contact lenses of low Dk/t (rigid 16, soft 15), medium Dk/t (rigid 49, soft 49) and high Dk/t (rigid 181, soft 175). Twenty subjects kept their eyes closed for 20 minutes after putting on each test lens. Starting just after eye opening, the eyes were examined for blebs every 5 minutes by specular microscopy, and the percentage area of the blebs was calculated. As controls, the same eyes were also examined without contact lens wear. The percentage area of the blebs just after eye opening and during a 55-minute 'recovery' period are shown in Figures 30.3A, B and C for low-, medium- and high-Dk/t lenses, respectively. No difference was observed between rigid and soft lenses of similar Dk/t values in the medium and high categories. However, for low-Dk/t lenses, rigid lenses appear to have a lower effect on the corneal endothelium compared with soft lenses.

Despite their stunning clinical appearance, blebs are asymptomatic and thought to be of little clinical significance. They are, however, of great interest to physiologists who are endeavouring to understand the workings of the cornea.

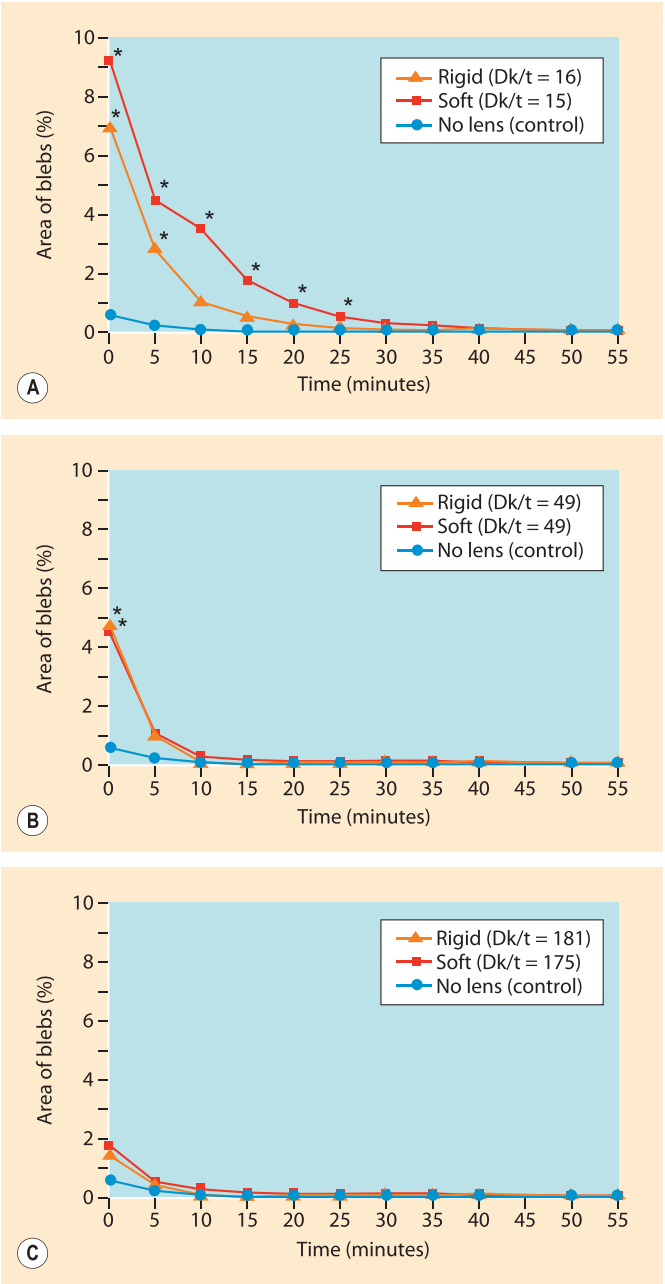


Fig. 30.3 Mean percentage area of the blebs over time following 20 minutes of closed-eye lens wear (or no lens wear) for **(A)** low-, **(B)** medium- and **(C)** high-Dk/t lenses. Asterisks represent significant difference from control eye ($p < 0.05$). (Adapted from Inagaki Y, Akahori A, Sugimoto K, et al. Comparison of corneal endothelial bleb formation and disappearance processes between rigid gas-permeable and soft contact lenses in three classes of Dk/t. Eye Contact Lens 2003;29:234–7.)

Pathology

ELECTRON MICROSCOPY

Histological studies of the endothelial bleb response were conducted by Vannas et al.,[13] who used (a) corneas from eyes that were enucleated (because of melanomas) and (b) corneas of beating-heart, brain-dead cadavers. The 'blebbed' endothelium displayed oedema of the nuclear area of cells, intra-cellular fluid vacuoles and fluid spaces between cells. Thus, endothelial blebs appear to be the result of a local oedema phenomenon, whereby the posterior surface of the 'blebbed' endothelial cell is bulged towards the aqueous. The endothelial cell bulges in the posterior direction because this represents the path of least resistance; that is, compared with the aqueous humour, the posterior stromal surface (Descemet's membrane) provides much greater resistance to endothelial cell swelling.

SLIT LAMP BIOMICROSCOPY

A simple optical model can be constructed to explain the appearance of blebs as seen with the slit lamp biomicroscope (Fig. 30.4). When the endothelium is viewed under specular reflection, light rays reflect from the tissue plane corresponding to the interface between the posterior surface of the endothelium and the aqueous humour. This interface acts as the reflective surface because it represents a significant change in tissue refractive index. The light rays that are reflected

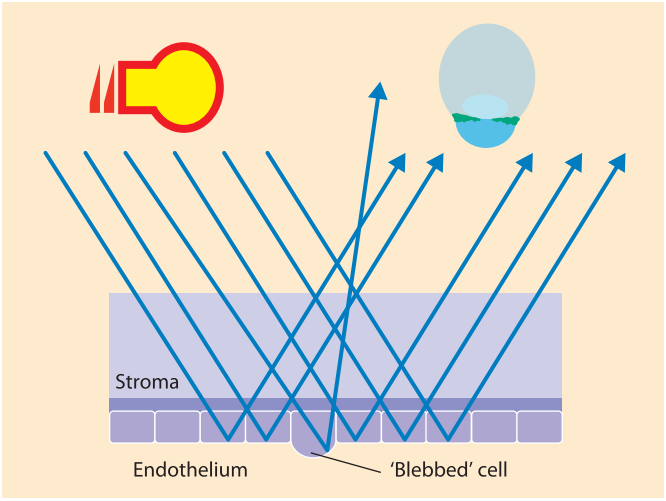


Fig. 30.4 Optical theory explaining the appearance of contact lens–induced endothelial blebs when viewed in specular reflection with the slit lamp biomicroscope.

from this interface give rise to an observed image of an essentially flat (or slightly undulating) mosaic of largely hexagonal endothelial cells.

Light rays which strike 'blebbed' endothelial cells will be deflected away from the observation path, leaving a corresponding area of darkness. Thus, an endothelial bleb is simply an individual endothelial cell (or group of adjacent cells) that has become swollen and bulged in the direction of the aqueous humour, giving rise to the compelling optical illusion that the cell (or cells) has disappeared.

CONFOCAL MICROSCOPY

The confocal microscope has been used to observe the endothelial bleb response at very high magnification (×680).[14,15] Kaufman et al.[14] observed the corneas of three patients wearing high-water-content hydrogel contact lens for the first time. In one patient, endothelial changes consisting of irregularly shaped, round or oval, dark regions were observed within the endothelial mosaic. These changes were most evident 20 minutes after lens insertion, and by 30 minutes, the changes were fewer and less prominent. Kaufman et al.[14] suggested that their results confirmed the 'localised oedema' theory of endothelial bleb formation.

Efron et al.[15] obtained images from each eye of 15 normal subjects (age range 19–36 years; mean 26 ± 6 years) before and after 20 minutes wear of a +5.50 diopter (D) 58%-water-content hydrogel lens in one eye. The extent of the bleb response was graded by using the grading scales shown in Appendix A of this book (see 'Observation and grading'); the images were also assessed qualitatively. After 20 minutes of lens wear, the mean bleb response in the lens-wearing eye was grade 1.0 (range 0.0–3.2). Two subjects did not display blebs. No blebs were observed in the non-lens-wearing eyes. Individual blebbed cells comprising of a bright central spot, surrounded by a darker annulus, were observed in the endothelium of most subjects.

In one subject, the endothelium was imaged at baseline and over a time sequence of 5, 10, 15 and 20 minutes of lens wear (Fig. 30.5). The time sequence reveals the initial appearance

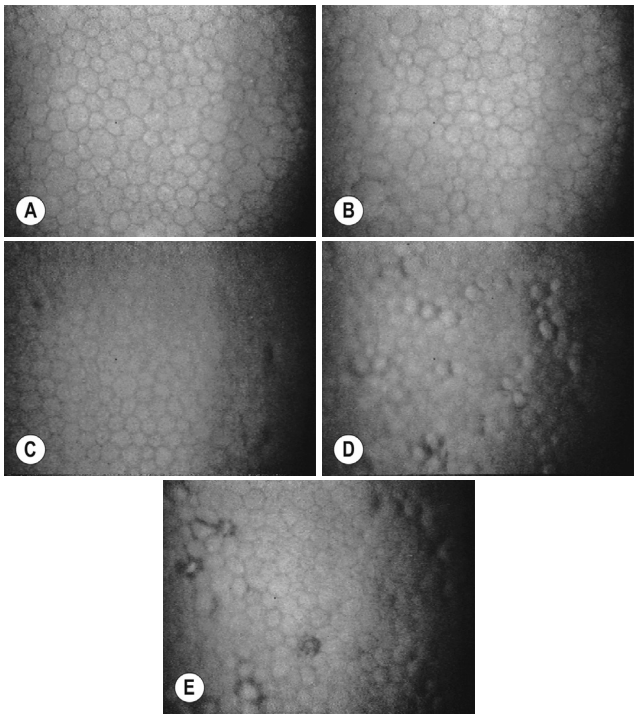


Fig. 30.5 **(A–E)** Confocal microscope images of the development of endothelial blebs over a 20-minute period. (Courtesy Haliza Mutalib.)

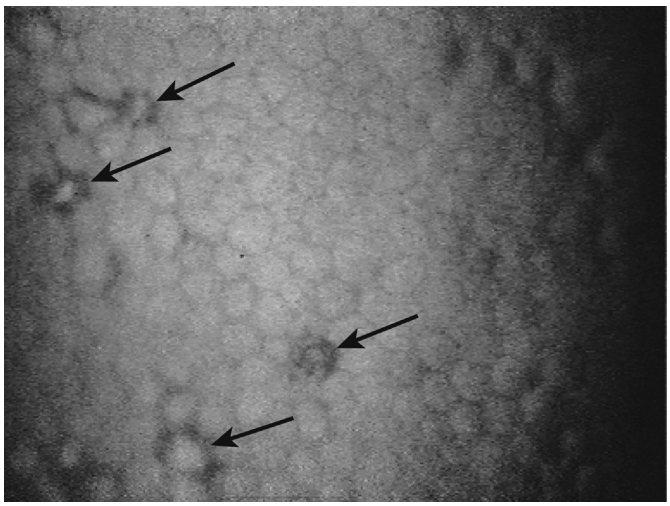


Fig. 30.6 Enlargement of a confocal microscope image of blebs (arrows), each showing a bright centre surrounded by a thick, dark annulus. The surrounding unaffected endothelium reflects brightly. (Courtesy Haliza Mutalib.)

of a dark border, which broadens into a thick, dark annulus after 15 to 20 minutes of lens wear (Fig. 30.6).

The appearance of endothelial blebs using confocal microscopy (Fig. 30.6) can be explained with an optical model. This model employs normal light reflection because light rays pass to and from the endothelium through the confocal microscope objective lens via a pathway of light directly towards and away from the cornea, perpendicular to its surface. This is different from specular microscopy using the slit lamp biomicroscope whereby angular light reflection is employed to observe the endothelium (Fig. 30.7).

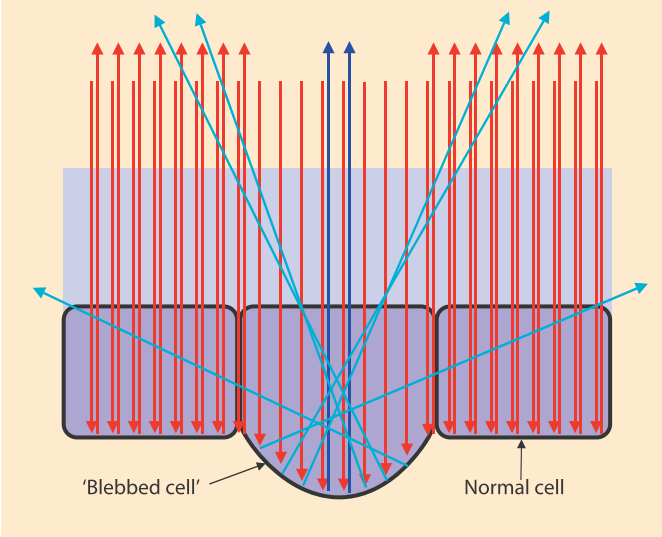


Fig. 30.7 Optical theory explaining the appearance of contact lens–induced endothelial blebs when viewed in normal reflection with the confocal microscope.

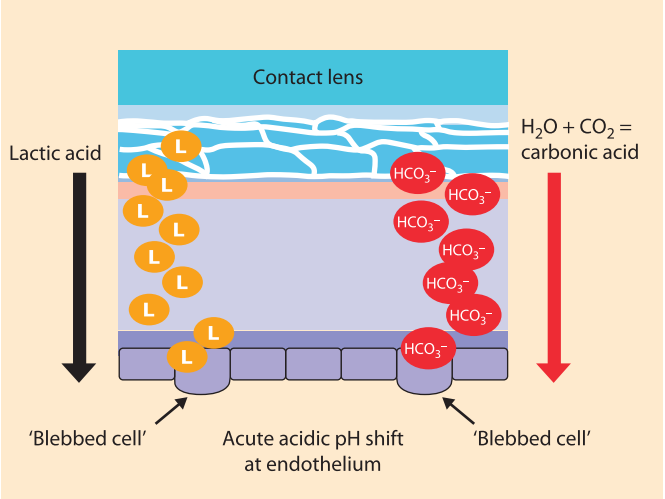


Fig. 30.8 Aetiology of contact lens–induced endothelial blebs.

The model illustrates a single 'blebbed' cell flanked on either side by a normal 'non-blebbed' cell. It can be seen from the confocal model that light is normally reflected from the flat surface 'non-blebbed' cells and the apex of the blebbed endothelial cell, all of which will appear bright. The sloping sides of the blebbed cell reflect light away from the objective and thus appear dark. This model therefore explains the confocal appearance of a blebbed cell as having a dark annulus surrounding a bright central spot (see Figure 30.6). These observations are consistent with the prevailing theory that blebs represent swelling of individual endothelial cells in the posterior (aqueous) direction.

Aetiology

The aetiology of endothelial blebs has been explained by Holden et al.[16] These authors attempted to induce blebs by using a variety of stimulus conditions and concluded that one physiological factor common to all successful attempts to form blebs was a local acidic pH change at the endothelium.

Two separate factors induce an acidic shift in the cornea during contact lens wear: (a) an increase in carbonic acid caused by retardation of carbon dioxide efflux (hypercapnia)[17] by a contact lens and (b) increased levels of lactic acid as a result of lens-induced oxygen deprivation (hypoxia)[17] and the consequent increase in anaerobic metabolism (Fig. 30.8). When silicone elastomer contact lenses are worn, such metabolic changes do not take place because of the extremely high oxygen permeability of such lenses.

Endothelial blebs are not observed in the contralateral eye when induced by lens wear in the ipsilateral eye,[18] and they are observed in graft corneas,[19] thus precluding the possibility of central neural control of this phenomenon. Furthermore, contact lens–induced endothelial blebs are unaffected by prostaglandin inhibitor drugs, precluding an inflammatory basis for the response.[20]

Bonanno and Polse[21] confirmed by using direct measurement that contact lens–induced hypoxia and hypercapnia result in an acidic shift in the cornea, and these authors noted that the extent of acidosis that they measured is in the range where endothelial function may be affected. Furthermore, the time course of the appearance of blebs after lens insertion and resolution after lens removal is consistent with the time course of corneal pH change as measured by Bonanno and Polse.[21]

The cornea becomes hypoxic and hypercapnic during sleep, so it would be expected that the consequent acidic changes would induce blebs. Various authors[6,22] have confirmed that there is a diurnal variation in the endothelial bleb response whereby more blebs can be observed immediately upon awakening from sleep.

The question arises as to the precise mechanism by which acidosis causes endothelial cells to swell. All cells in the human body function optimally when surrounded by extracellular fluid that is maintained within an acceptable range of pH, temperature, tonicity, ion balance and so on. The carbonic acid and lactic acid may alter the physiological status of the environment surrounding the endothelial cells by shifting pH in the acidic direction. This may induce changes in membrane permeability and/or membrane pump activity, resulting in a net movement of water into endothelial cells. The resultant cellular oedema is observed as 'blebbing'.

Observation and grading

The corneal endothelium can be viewed by specular reflection using a slit lamp biomicroscope at ×40 magnification. To observe the endothelium by using this technique, the angle between the illumination and observation systems must be symmetrical about a plane extending normally from the cornea and will typically be between 75° and 90°. The endothelial mosaic can be seen adjacent to a bright reflex from the corneal surface (see Fig. 30.1). With use of this technique, only the mid-peripheral nasal or temporal endothelium can be viewed; this does not pose a problem because changes in these regions are representative of changes elsewhere in the cornea.[9]

Although individual endothelial cells can only just be resolved at ×40 magnification, blebs have a stark appearance and are easily recognizable. A variety of sophisticated automated specular endothelial microscopes are available for

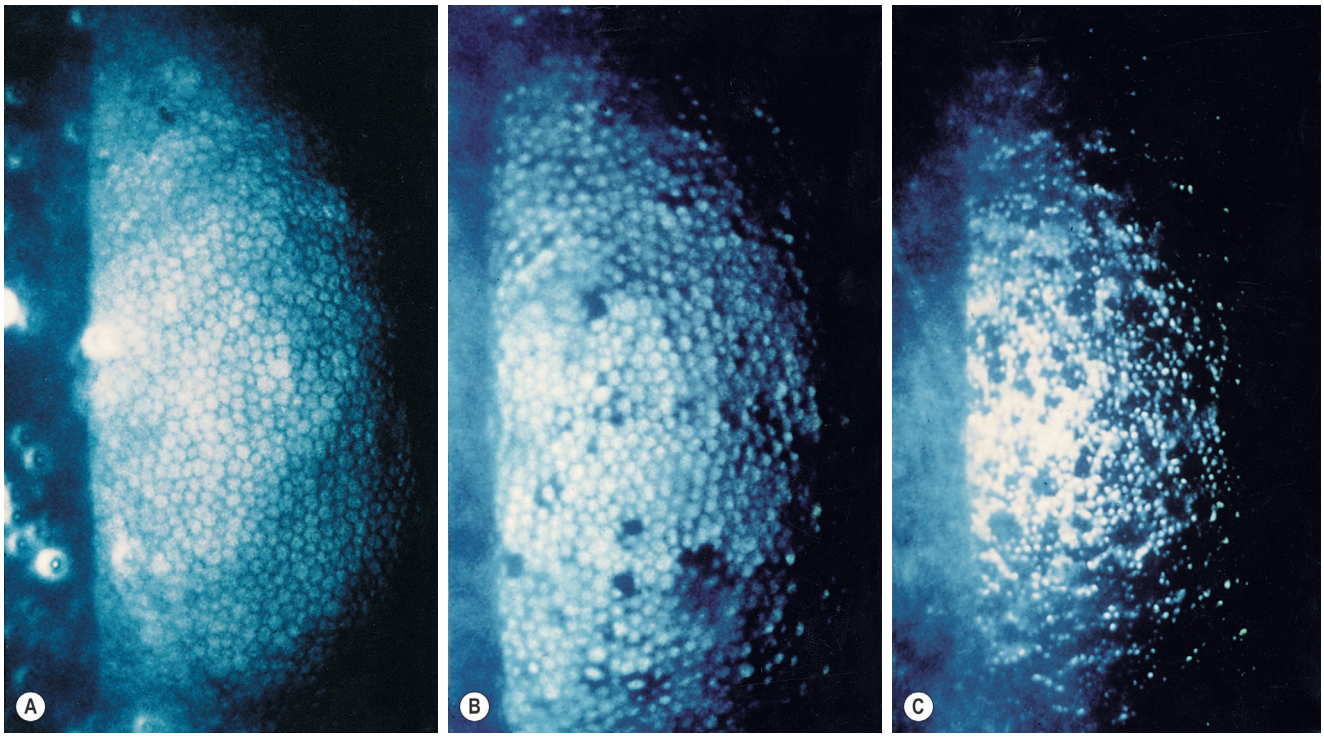


Fig. 30.9 High-magnification slit lamp photographs of contact lens–induced endothelial blebs: **(A)** grade 0; **(B)** grade 2; and **(C)** Grade 4. (A, Courtesy Steve Zantos, Brien Holden Vision Institute. B, Courtesy Lewis Williams, Brien Holden Vision Institute. C, Courtesy Brien Holden, Brien Holden Vision Institute.)

viewing the endothelium[23]; these instruments offer higher magnification and superior resolution compared with slit lamp observation. As discussed previously, the confocal microscope provides an even higher level of magnification, which allows detailed examination of individual cells. Endothelial specular microscopes[7,8] and confocal microscopes[14,15] are invaluable as research tools when it is necessary to quantify endothelial changes and understand the pathology of this phenomenon; however, a general appraisal of the endothelial bleb response can still be obtained satisfactorily with a good-quality, high-magnification slit lamp.[2]

The extent of endothelial bleb formation can be graded by using the grading scale for this response provided in Appendix A; however, the usual connotation that is associated with contact lens grading scales concerning the urgency for clinical action (see Chapter 2) does not apply here because contact lens–induced endothelial blebs are thought to be innocuous, irrespective of the level of severity of blebbing. The 0-to-4 scale of the bleb response shown in Appendix A can be considered as being approximately linear. High-magnification slit lamp photographs of endothelial blebbing of grades 0 (normal), 2 (slight) and 4 (severe) are shown in Figure 30.9.

Management

Although the phenomenon of endothelial blebs is of immense interest from a physiological standpoint, there are no readily apparent clinical ramifications. The bleb response occurs to a greater or lesser degree in most patients and displays a characteristic time course. It is not known whether a propensity for the endothelium of a patient to exhibit blebbing is a positive or negative attribute.

Williams[6] surmised that the severity of an endothelial bleb response is reduced in patients displaying increased levels of endothelial polymegethism, which could partially explain the apparent long-term adaptation of the bleb response. Specifically, a low-level bleb response has been interpreted as an indication that the endothelium has lost its capacity to respond to changes in its immediate environment; that is, the endothelium has become ‘exhausted’.

Theoretically, the bleb response can be used as a relative measure of the combined impact of contact lens–induced hypoxia and hypercapnia on the cornea of a given patient. That is to say, in a given patient, a lens with lower average oxygen transmissibility will induce a more severe bleb response.[6] This concept has been explored experimentally.[7,8] Ohya et al.[7] observed the time course, frequency and location of endothelial blebs in 11 eyes of nine contact lens–wearing patients. Eight types of contact lenses with varying Dk/t were used. The authors demonstrated an inverse correlation between the number of blebs and the Dk/t of the contact lens. In addition, Hamano et al.[8] demonstrated a significantly higher degree of bleb formation with lenses of lower Dk/t values.

The results outlined earlier imply that a comparison of the severity of the bleb response could have clinical utility in comparing lenses or in selecting lenses of optimal gas transmission characteristics. For example, Szczotka-Flynn et al.[24] used the bleb response to demonstrate equivalence of physiological impact of hydrogel and silicone hydrogel lenses.

However, Bruce and Brennan[25] suggested that the bleb response is of little use for the longitudinal monitoring of patients wearing a given lens type, in view of the lack of variability in the magnitude of its response relative to its test–retest reliability.

Prognosis

The prognosis for recovery from endothelial blebs is excellent. After removal of a contact lens, blebs disappear within 45 minutes.[2,7,12] Blebs will reappear when lens wear is re-introduced and resolve when lenses are removed, but in any event, blebs are harmless.

Differential diagnosis

Primary chronic corneal disorders, such as Fuch's endothelial dystrophy, are often characterised by the presence of guttata, which appear as small shallow depressions in the endothelial mosaic in the early stages of the disease process and as distinct black holes in advanced cases.[26] In patients with guttae caused by dystrophy, extensive confluent areas of blebbing may be apparent (Fig. 30.10). Such confluence is not observed in contact lens–induced blebbing. The key distinction between guttae related to corneal dystrophy and contact lens–induced blebs is simply the permanence of guttae and the transience of blebs.

Brooks et al.[27] pointed out that in addition to being a contact lens–induced effect, blebs may also be seen in a wide variety of pathological conditions, including superficial keratopathies, deep keratopathies, anterior uveitis and contusion injury. These blebs vary in size in different conditions and are often transient.[28] They also have a different appearance from contact lens–induced blebs in that the areas of darkness are more diffuse, and there is no apparent separation of cells throughout the field.[28] Blebs have also been observed in clear corneal grafts fitted with hydrogel lenses.[19]

Interestingly, transient phenomena that closely resemble endothelial blebs have been observed in patients with acute superficial eye disorders. Specifically, Zantos and Holden[29] noted such transient endothelial changes in cases of acute 'red eye' associated with extended contact lens wear; these formations have exactly the same appearance as contact lens–induced blebs, but are different in that they persisted for many days after cessation of lens wear.

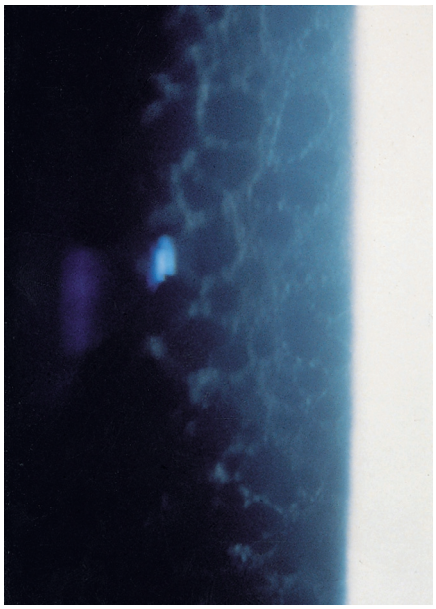


Fig. 30.10 Corneal dystrophy depicting severe guttate changes. (Courtesy Charline Gauthier, Bausch & Lomb Slide Collection.)

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31 Endothelial Cell Redistribution

Concern that contact lenses may be *adversely* affecting the corneal endothelium has resulted in endothelial examination becoming a routine procedure during biomicroscopic examination of the cornea of contact lens wearers (Fig. 31.1). This concern can be traced back to the original observation by Zantos and Holden[1] in 1979 of acute transient changes ('blebs') in the corneal endothelium associated with contact lens wear (see Chapter 30). This discovery gave the first clue to researchers and clinicians that the corneal endothelium was susceptible to short-term alterations in the physiological environment at the ocular surface.

Attention has also been directed towards the chronic endothelial changes induced by contact lenses; these include an *apparent* endothelial cell loss and changes in cell size/shape. This chapter will address the controversial question as to whether contact lens wear results in endothelial cell loss (Fig. 31.2). The issue of contact lens–induced alterations to cell shape and size is dealt with in Chapter 32.

There are differing opinions as to whether observable changes in the endothelium are of any real clinical significance; nevertheless, practitioners ought to be able to examine and assess the integrity of the endothelium and should be prepared to interpret any changes observed in the context of the various theories concerning corneal endothelial structure and function.

Normal endothelial cell density

The corneal endothelium is a monolayer of approximately half a million cells (at birth) that constitutes the posterior corneal surface. Anteriorly, the endothelium is in apposition with a basement membrane that is formed by secretions from the endothelium itself. The basement membrane is known as the 'posterior limiting lamina' (or 'Descemet's membrane'). The anterior surface of the endothelial cell is known as the *basal surface*. The posterior (apical) surface of the endothelium is in direct contact with the aqueous humour.

Upon examination with the slit lamp biomicroscope, the endothelium can be observed using specular reflection. In the normal endothelium of an infant, all cells are approximately the same size and have a characteristic hexagonal shape. These features can only just be resolved by using a good-quality slit lamp biomicroscope at the highest magnification (×40) (Fig. 31.1).

The convention that has been universally adopted for denoting the number of endothelial cells in the human cornea is to present the *endothelial cell density*, expressed as the number of cells per square millimetre. In the normal eye, endothelial cell density decreases from approximately 4,400 cells/mm^2 at birth to 2,200 cells/mm^2 at age 80 years[2,3] (Fig. 31.3). Obviously, any change in cell density thought to be attributed to contact lens wear must be considered in the context of this normal age-related change.

Signs and symptoms

Early workers,[4-7] all using different experimental methodologies, observed various degrees of endothelial polymegethism (see Chapter 32) in long-term contact lens wearers but failed to find evidence of a loss of endothelial cells. However, subsequent studies have challenged this notion.

Dada et al.[8] examined the effects of long-term daily wear of polymethyl methacrylate (PMMA) lenses on the corneal endothelium in eight patients who had been prescribed lenses in one

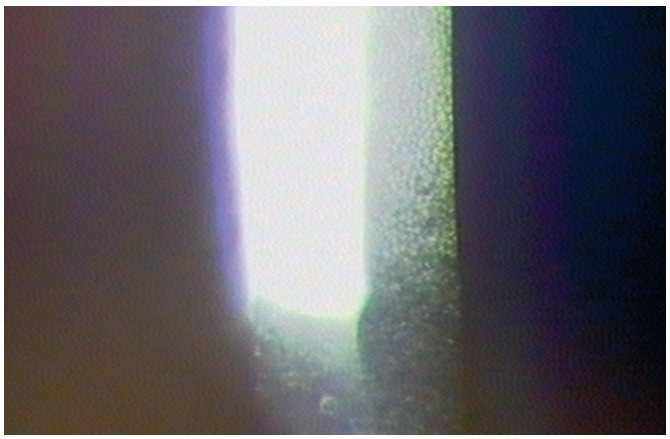


Fig. 31.1 High-magnification slit lamp biomicroscope photograph of a normal corneal endothelium seen in specular reflection. (Courtesy Carole Maldonado-Codina.)

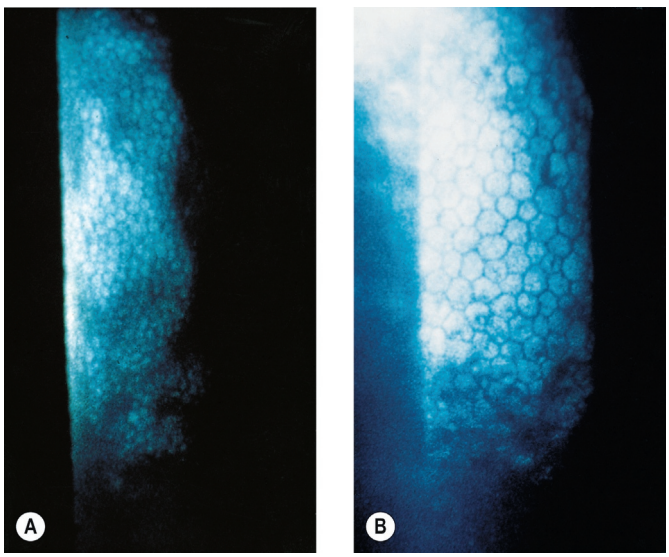


Fig. 31.2 Very-high-magnification slit lamp biomicroscope photographs of **(A)** high and **(B)** low endothelial cell density.

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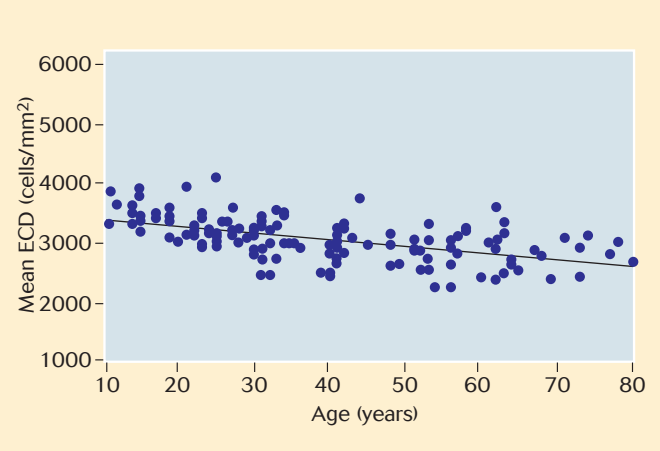


Fig. 31.3 Relation between endothelial cell density and age. (Adapted from Hollingsworth J, Perez-Gomez I, Mutalib HA, Efron N. A population study of the normal cornea using an in vivo, slit-scanning confocal microscope. Optom Vis Sci 2001;78:706–11.)

eye only. A significant reduction in cell density was observed in the lens-wearing eyes.

MacRae et al.[9] examined 162 PMMA contact lens wearers and age-matched controls; 81 subjects had worn contact lenses for more than 20 years. These authors[9] found that although the mean endothelial cell density in the PMMA lens–wearing group was not different from that in controls, a significantly greater percentage of lens wearers (9 (11%) of 81 patients) had cell densities less than 2,000 cells/mm^2 compared with controls (2 (2.5%) of 81 patients); that is, these authors noted a sub-group of PMMA contact lens wearers who were more susceptible to reduced endothelial cell densities with long-term contact lens use.

Setala et al.[10] made observations similar to those of MacRae et al.[9] These authors[10] used a specular microscope to examine the endothelia of 101 subjects wearing soft lenses and PMMA lenses with wearing experience of 10 years or greater and that of 50 matched control subjects. The mean corneal endothelial cell density of the lens wearers (2,846 cells/mm^2) was statistically significantly less than that of the control eyes (2,940 cells/mm^2). The mean endothelial cell density of the eyes exposed to lens wear for greater than 25 years (30 eyes) was 2,575 cells/mm^2, and very low densities ($<$ 2,000 cells/mm^2) were observed in 16 eyes of the lens-wearing group (8%). Cell densities less than 2,500 cells/mm^2 were observed in a total of 41 eyes (20%) in the lens-wearing group, whereas in the control group (100 eyes), all of the subjects, except one, had cell densities of more than 2,500 cells/mm^2 in both eyes.

McMahon et al.[11] reported that a group of 16 long-term PMMA lens wearers had an endothelial cell density (2,147 cells/mm^2) that was statistically significantly less than that of a matched control group of non–lens wearers (2,865 cells/mm^2). Hollingsworth and Efron[12] reported that endothelial cell density was unaffected by rigid gas permeable lens wear ($p = 0.36$)

The effect on endothelial cell density of the duration of soft contact lens–wearing periods was explored by Lee et al.[13] These authors divided 90 soft contact lens wearers into three equal groups: (a) short-term users ($<$ 5 years of lens wear), (b) intermediate-term users, (6–10 years of lens war) and (c) long-term users ($>$ 10 years of lens wear). Thirty non–contact lens wearers were included as controls. All eyes were examined with a specular microscope. The authors found that soft contact lens wear was significantly correlated with decreasing corneal endothelial cell densities with time.

Suzuki and Okamura[14] reported that mean endothelial cell area increased by only 3% (i.e. endothelial cell density decreased) among 78 patients wearing disposable soft contact lenses. Chang et al.[15] did not detect a change in endothelial cell density in 76 daily soft lens wearers who had been wearing lenses for at least 5 years. Yagmur et al.[16] compared the endothelium of 71 contact lens wearers with myopia to 71 non–contact lens wearing controls. Endothelial cellular density in lens wearers (2,611.2 $\pm$ 298.4 cells/mm^2) was not significantly different from that of control subjects (2,643 $\pm$ 218.2 cells/mm^2).

Doughty et al.[17] examined the endothelia of 18 patients who had been wearing hydrogel lenses for 5.5 years (range 3–9 years). The patients were re-fitted with silicone hydrogel lenses (Focus Night & Day) for continuous wear over 30 days and nights and were assessed immediately before and 6 months after the re-fitting, with lens replacement every 30 days. The mean endothelial cell area increased slightly from 358 to 363 μm^2 ($p = 0.701$), indicating a lower cell density.

Doughty[18] also examined one eye of each of 46 subjects who had been wearing rigid lenses for 6.0 $\pm$ 1.6 years (range 3–9 years), using a non-contact specular microscope. The group cell area value was 401 $\pm$ 42 μm^2 to give an estimated endothelial cell density of 2,520 $\pm$ 273 cells/mm^2. These values were not significantly different from values derived from a historical database.

Sanchis-Gimeno et al.[19] studied the differences in endothelial cell density in a pair of 31-year-old monozygotic female twins; one had been wearing contact lenses for the past 15 years and the other had never worn contact lenses. Lower central corneal endothelial cell densities were found in both eyes of the monozygotic contact lens–wearing twin.

None of the reports highlighted here reported any adverse effects of altered endothelial cell density in lens wearers.

Leem et al.[20] found that central endothelial cell density was lower in subjects with diabetes versus control subjects without diabetes. They also observed lower central endothelial cell densities in contact lens wearers with diabetes versus patients with diabetes who did not wear contact lenses. These data suggest that diabetes exacerbates endothelial cell redistribution. However, O'Donnell and Efron[21] found that endothelial cell characteristics were similar for a group of patients with diabetes (type 1, $n = 26$; type 2, $n = 4$) who wore soft contact lenses versus a group of age-matched control subjects without diabetes who were also contact lens wearers ($p > 0.05$).

Pathology

Perhaps an initial interpretation of a reduced endothelial cell density is that there are fewer cells on the posterior corneal surface because the cells suffer apoptosis or somehow become dislodged. It is known that intra-ocular surgery can cause endothelial cells to dislodge as a result of direct trauma to the endothelium,[22,23] but this effect could not be happening with soft lenses.

One possible explanation for the apparent contact lens–induced endothelial cell loss has been provided by Wiffen et al.,[24] who compared central and peripheral corneal endothelial cell densities in normal subjects and long-term contact lens wearers. Specifically, endothelial cell density was measured by

contact specular microscopy in the corneal centre and temporal periphery of both eyes of 43 long-term contact lens wearers and in 84 normal subjects who had never worn contact lenses. The latter group included 43 age- and gender-matched controls for the contact lens wearers. Central cell density (2,723 ± 366 cells/mm^2) was significantly higher than peripheral cell density (2,646 ± 394 cells/mm^2) for the normal group but not for the contact lens wear group (2,855 ± 428 cells/mm^2 central; 2,844 ± 494 cells/mm^2 peripheral). On the basis of their results, Wiffen et al.[24] suggested that contact lens wear causes a mild redistribution of endothelial cells from the central to the peripheral cornea.

The observation of Wiffen et al. of cell redistribution from the centre to the periphery of the cornea could explain the apparent loss of cells reported elsewhere.[24] Invariably, authors who have reported lens-induced endothelial cell loss would have only examined the central corneal endothelium and would have been unaware of any *increase* in cell density in the corneal mid-periphery caused by endothelial cell redistribution; that is, although there is no actual endothelial cell loss, there is a reduction in endothelial cell density in the central region of the cornea, which is counterbalanced by a commensurate increase in cell density in the corneal mid-periphery (which other researchers have inadvertently ignored). The overall endothelial cell population of the cornea is therefore unaffected by contact lens wear.

Figure 31.4 is a schematic diagram illustrating the endothelial cell redistribution theory of Wiffen et al.[24] Because gaps are not observed between cells in endothelia with reduced cell densities, the cell redistribution must involve a spreading out and perhaps thinning of central cells, and a 'bunching up' of more peripheral cells.

The theory of Wiffen et al.[24] has been subsequently confirmed by Doughty and Aakre,[25] who observed a mean central and mid-peripheral endothelial cell density of 2,747 and 2,954 cells/mm^2, respectively, among 104 contact lens wearers with myopia. They noted a net ratio of mid-peripheral endothelial cell density of 1.0768:1 ($p < 0.001$). This ratio correlated to the years of soft contact lens wear, with a linear regression analysis indicating a modest but statistically significant effect ($p = 0.008$).

Efron et al.[26] did not find evidence of a change in endothelial cell density on a group of patients who had recently suffered from a contact lens–associated[12] corneal infiltrative event.

Aetiology

The reason for the apparent re-distribution of endothelial cells from the centre to the periphery of the cornea is unclear. It may represent some form of physiological adaptation to lens wear. Wiffen et al.[24] suggested that central lens-induced hypoxia may be the driving force. If this phenomenon is linked to contact lens–induced polymegethism, then the corneal acidosis – which is thought to be responsible for that effect (see Chapter 32) – may also play a role in endothelial cell redistribution.

Observation and grading

The corneal endothelium can be viewed by specular reflection by using a variety of instruments, such as contact or non-contact specular microscopes, confocal microscopes or slit lamp biomicroscopes. To observe the endothelium with the use of the slit lamp biomicroscope, a magnification of at least ×40 must be used, and the angle between the illumination and observation systems should be symmetrical about a plane extending normally from the cornea, typically being 75° to 90°. The endothelial mosaic can be seen adjacent to a bright reflex from the corneal surface. With use of this technique, only the mid-peripheral nasal or temporal endothelium can be viewed; this does not pose a problem if the same approximate area is observed each time for comparative purposes (e.g. assessing changes in a patient over time).

The observation of individual endothelial cells is at the very limit of resolution when using a slit lamp biomicroscope at the typical maximum ×40 magnification. Even with the assistance

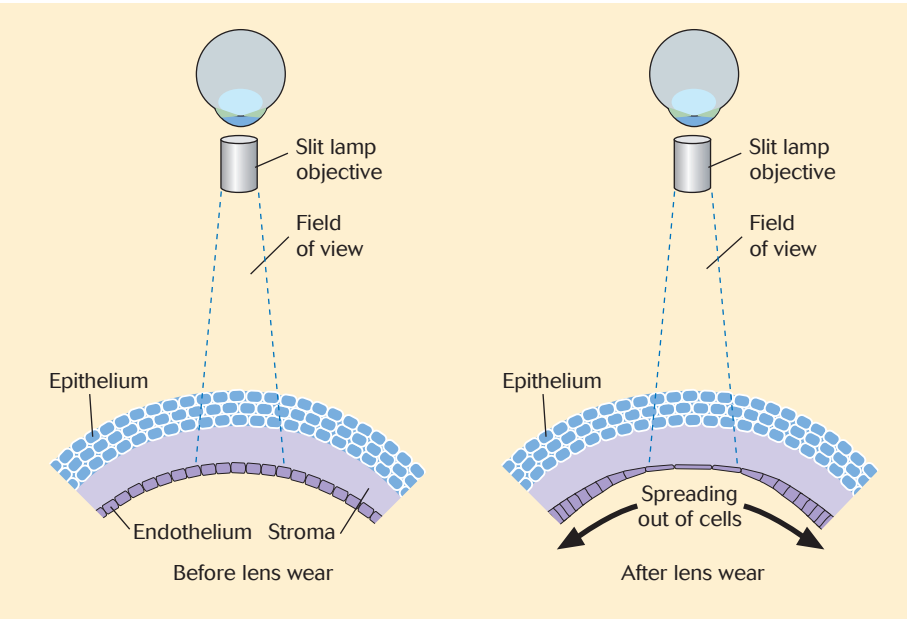


Fig. 31.4 Cell redistribution theory to explain the contact lens–induced reduction in endothelial cell density of the central corneal endothelium. In this schematic, seven cells are counted in the field of view of the central endothelium before lens wear, versus only three cells after lens wear, giving the false impression of contact lens–induced endothelial cell loss (The total number of endothelial cells remains unchanged).



Fig. 31.5 Automated analysis of endothelial morphology using the image analysis software of the Topcon SP-1P Specular Microscope. (Courtesy Topcon Corporation.)

of a graduated eyepiece graticule or a reference grading scale, endothelial cell density is difficult to estimate and often impossible to determine in the presence of normal involuntary micronystagmoid and vibratory eye movements.

The endothelium can be effectively examined in the clinic with the aid of an automatic non-contact specular microscope. Such instruments incorporate sophisticated digital video image-capture and computer image-analysis technology.[27] For example, the Topcon Specular Microscope SP-1P (see Figure 1.17) incorporates a 'panorama' function which takes separate images in the central, nasal and temporal corneal areas and combines these to create a larger area for the observation and analysis of endothelial cells. Built-in software calculates the minimum, maximum and average cell sizes, cell density, standard deviation, coefficient of variation of cell size and hexagonal cell ratio (Fig. 31.5).

Modern confocal microscopes also come equipped with automated endothelial analysis software. A suitable image of the endothelium is captured and digitised. A region of interest is then defined by electronically interposing a square border onto the image displayed on a computer screen. The image is automatically enhanced to sharpen the cell borders, and the cells are automatically traced. Any gaps can be closed manually. Various parameters can then be calculated and presented graphically (Fig. 31.6).

Management

Studies of changes in endothelial cell density in response to ophthalmic surgery suggest that a lower limit of 400 to 700 cells/mm^2 is required for the maintenance of corneal health and transparency[28]; below this value, the endothelium will decompensate, and the cornea will become oedematous. Such low endothelial cell densities are rarely, if ever, seen among contact lens wearers. For example, only 11% and 8% of long-term contact lens wearers examined by MacRae et al.[9] and Setala et al.,[10] respectively, had endothelial cell densities less than 2,000 cells/mm^2.

On the assumption that a reduced endothelial cell density in the central cornea is a result of a mild cell redistribution, rather than actual cell loss, this phenomenon may not really need to be managed. However, in a more conservative approach, it is assumed that any change induced by an external influence, such as contact lens wear, is potentially adverse, and preventative or remedial measures should be adopted. By this reasoning, any measures to minimise the known physiological effects of lens wear, such as fitting lenses of superior oxygen transmissibility or lenses that have a reduced physical effect on the eye, could be adopted.

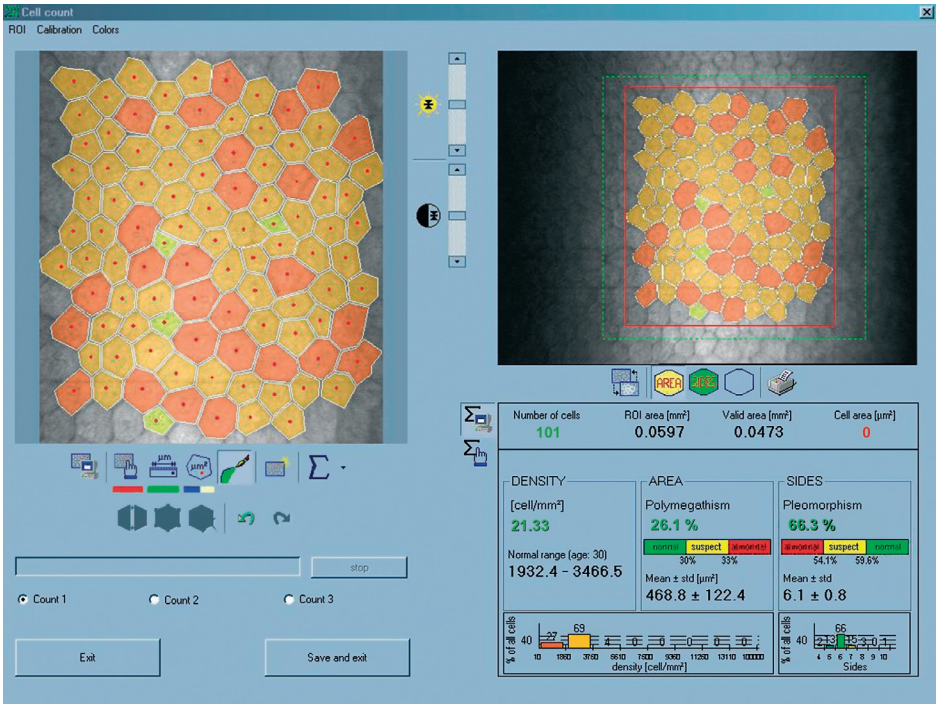


Fig. 31.6 Automated analysis of endothelial morphology using the image analysis software of the Nidek Confoscan 4 Corneal Confocal Microscope. (Courtesy Inma Perez-Gomez.)

Prognosis

Information relating to the recovery from lens-induced central endothelial cell redistribution has not been reported in the literature. However, Wiffen et al.[24] believed that such a redistribution may reverse itself when contact lens wear is discontinued. They base this belief on studies[29,30] which measured central and peripheral cell density in patients who discontinued contact lens wear in conjunction with excimer laser photorefractive keratectomy. Both studies[29,30] found significant increases in central cell density and significant decreases in peripheral cell density. Another investigation[31] showed an increase in central cell density after excimer laser-assisted in situ keratomileusis (LASIK) in contact lens wearers, but not in patients who had not worn contact lenses. These observations suggest that the prognosis for recovery of lens-induced central endothelial cell redistribution may be reasonably good.

Differential diagnosis

Any suspected reduction of endothelial cell density must be differentiated from the effects of ageing,[2,3,32,33] intra-ocular surgery,[22,23] eye disease[34] or systemic disease.[35] Certainly, these effects were generally accounted for in the various studies of endothelial cell density, which supported the notion of cell redistribution[9-11,13] by employing age-matched control groups and by avoiding subjects who were suffering from any systemic or eye disease or who had previously undergone ocular surgery.

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32 Endothelial Polymegethism

In the 1980s, a series of articles[1-6] alerted contact lens practitioners to a potentially adverse effect of contact lens wear that could be observed in the cornea – namely, endothelial polymegethism (Fig. 32.1). These observations were made soon after Zantos and Holden[7] published their reports of transient changes in the endothelium induced by contact lenses (endothelial blebs; see Chapter 30). A picture of previously unknown acute and chronic lens-induced endothelial changes was emerging at that time. The critical role of the endothelium in maintaining corneal health was well understood, so reports of endothelial compromise were of considerable concern to eye care practitioners.

Since then, extensive clinical and laboratory research has been undertaken in an attempt to gain an appreciation of the nature and magnitude of the endothelial response to contact lens wear and the possible ramifications of these changes. As is often the case with scientific enquiry, differences of opinion have emerged, and some issues still remain unresolved. This chapter will examine the phenomenon of contact lens–induced endothelial polymegethism from a clinical and scientific perspective and will consider the debate on these changes being of any real clinical significance.

Normal corneal morphology

The variation in apparent size of cells in the endothelium (or in any other tissue layer) is expressed as the *coefficient of variation of cell size* (COV); this dimensionless ratio is calculated by dividing the standard deviation of the cell areas in a defined field by the arithmetic mean area of all cells in that field. The COV is a measure of the degree of *endothelial polymegethism*. ('Polymegethism' is derived from the Greek word 'megethos' meaning 'size'; 'poly' means 'many'[8]).

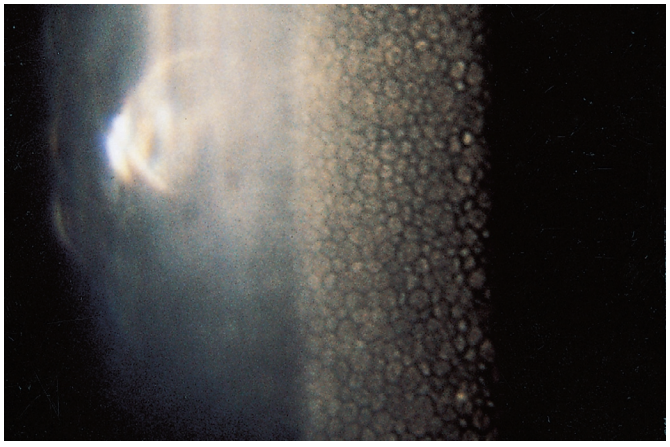


Fig. 32.1 High-magnification slit lamp biomicroscope photograph of a corneal endothelium displaying extensive contact lens–induced polymegethism. (Courtesy Rolf Haberer, Bausch & Lomb Slide Collection.)

Endothelial cells can also vary in shape. The term 'endothelial polymorphism' means 'many shapes', and the term 'pleomorphism' means 'different shapes'. Individual endothelial cells can have anything from three to nine sides, although the majority of cells in a normal endothelium have six sides.

In the normal eye, the COV increases throughout life. Thus, any changes thought to be attributed to contact lens wear should be referenced against these normal age-related changes. Consequently, the term 'endothelial polymegethism', when discussed in this chapter in the context of an induced change, should generally be taken to mean a degree of change in excess of that expected for a given age.

Signs and symptoms

The endothelium of a newborn baby has a very regular and uniform appearance, with all cells being almost exactly the same size and displaying classical hexagonality. In, say, a 25 year old – an age when contact lens wear might begin – the endothelium will typically display a low degree of polymegethism. The ratio of the diameter of the smallest cell to the largest cell that can be seen could be 1:5. In advanced cases of polymegethism, the ratio of smallest to largest cell can be as great as 1:20 (Fig. 32.2). It is possible to make a qualitative assessment of the extent of polymegethism based on observation of the endothelial mosaic; techniques for assessing endothelial polymegethism are described under 'Observation and grading'.

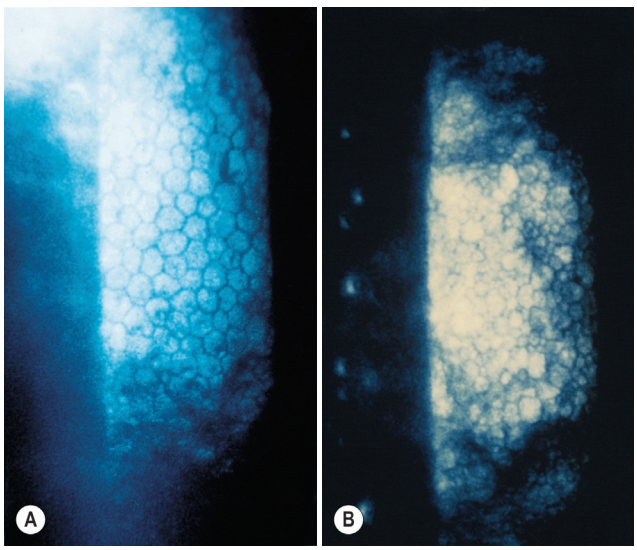


Fig. 32.2 Very-high-magnification slit lamp biomicroscope photographs of **(A)** low-grade and **(B)** high-grade contact lens–induced corneal endothelial polymegethism. (Courtesy Brien Holden, Brien Holden Vision Institute.)

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Reports of contact lens–induced endothelial polymegethism were first published by Schoessler and Woloschak in the early 1980s.[1,2] These authors provided a convincing anecdotal demonstration of endothelial polymegethism in 10 patients who had worn polymethyl methacrylate (PMMA) lenses for at least 5 years. Subsequent researchers have quantitatively demonstrated increases in endothelial polymegethism associated with PMMA,[3,9-15] rigid gas permeable[14,16-19] and conventional hydrogel[6,11,13,15,16,20-26] lenses. Silicone hydrogel[27,28] and silicone elastomer[29] lenses apparently do not induce significant levels of polymegethism.

Figure 32.3 is a compelling illustration of the effect of contact lens wear on the corneal endothelium; illustrated is a pair of endothelial photomicrographs of a patient who wore an extended-wear lens for 5 years in one eye only because of uniocular myopia. The bottom frame is the endothelium of the lens-wearing eye and the top frame is that of the fellow non-lens-wearing eye. A greater variation in endothelial cell size (polymegethism) is evident in the lens-wearing eye.

Hirst et al.[3] also reported a substantially lower percentage of hexagonal cells in patients wearing PMMA contact lenses compared with matched non-lens-wearing control eyes. Such polymorphic changes are generally associated with changes in polymegethism.

To assess corneal endothelial cell morphometry in patients with diabetes who wear contact lenses, O'Donnell and Efron[30] analysed images of the central corneal endothelium in a group of contact lens wearers with diabetes (type 1, $n = 26$; type 2, $n = 4$) and a group of age-matched contact lens–wearing control subjects without diabetes. Endothelial cell characteristics were similar for the two groups ($p > 0.05$), although four of the patients with diabetes (and none of the patients without diabetes) displayed folds in the endothelial mosaic.

As discussed in Chapter 31, a number of authors[9-12,16,21,22] have described an apparent reduction in central endothelial cell density in long-term contact lens wearers. Wiffen et al.[16] explained that there is no actual loss of cells. Rather, there is a redistribution of cells from the centre to the mid-periphery of the cornea, resulting in a decrease in endothelial cell density of the central cornea and an increase in cell density of the mid-peripheral cornea. There is no presumed net change of the endothelial cell density of the entire cornea. As will become evident later in this chapter, the cell redistribution theory is an important consideration in the construction of models of the aetiology and pathology of age-related polymegethism versus contact lens–induced polymegethism.

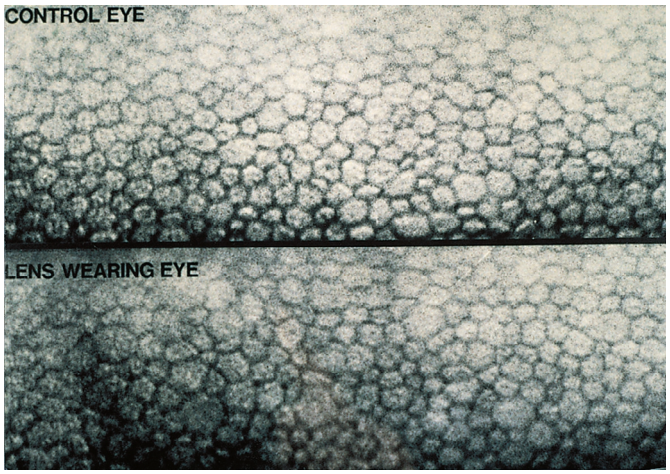


Fig. 32.3 Polymegethous corneal endothelium of the eye of a patient who wore an extended-wear lens in one eye only (bottom frame) for 5 years because of uniocular myopia. The endothelium of the fellow non-lens-wearing control eye is shown in the top frame. (Holden BA, Sweeney DF, Vannas A, Nilsson KT, Efron N. Effects of long-term extended contact lens wear on the human cornea. Invest Ophthalmol Vis Sci 1985;26:1489–501.)

CORNEAL EXHAUSTION SYNDROME

Sweeney[13] drew an anecdotal association between endothelial polymegethism and a condition which was termed 'corneal exhaustion syndrome'. This is a condition in which patients who have worn hydrogel contact lenses for many years suddenly develop a severe intolerance to lens wear characterised by ocular discomfort, reduced vision, photophobia and an excessive oedema response. These patients also display a distorted endothelial mosaic and moderate to severe polymegethism.

Although the link between endothelial polymegethism and corneal exhaustion syndrome is not proven, it is plausible that chronic lens-induced hypoxia induces a number of pathological tissue changes (endothelial polymegethism being one of these), which can result in intolerance to lens wear.

Besides the possibility of corneal exhaustion syndrome, no other symptoms are associated with endothelial polymegethism.

Prevalence

Endothelial polymegethism is a natural age change that occurs in all humans[31,32] (Fig. 32.4). It appears that all lens types that induce some measure of chronic hypoxic stress will induce a commensurate degree of endothelial polymegethism and polymorphism. Thus, the prevalence of endothelial polymegethism in long-term wearers of low-oxygen-transmissibility (Dk/t) contact lenses is likely to be 100%.

Pathology

To understand precisely what happens to endothelial cells when polymegethism develops, it is important to consider how the classic appearance of the endothelium, as viewed under specular reflection, relates to the overall three-dimensional structure of endothelial cells. When the endothelium is viewed under specular reflection, light rays reflect from the tissue plane corresponding to the interface between the apical surface of the endothelium and the aqueous humour. This interface acts as the main reflective surface because it represents a significant change in tissue refractive index; that is, the difference in refractive index between the apical surface of the endothelial cell and the aqueous humour is greater than that between the basal surface of the endothelial cell and posterior limiting lamina of the stroma. The light rays that are reflected from the apical endothelium–aqueous interface give rise to an observed image of the endothelial mosaic. Light rays which strike the junction between endothelial cells are deflected away from the observation path, leaving corresponding dark lines which are observed as cell borders.

Assuming no change in central endothelial cell density, the specular appearance of polymegethism would suggest that some cells are becoming smaller and some are becoming larger. However, according to the theory of Wiffen et al.,[16] endothelial cell

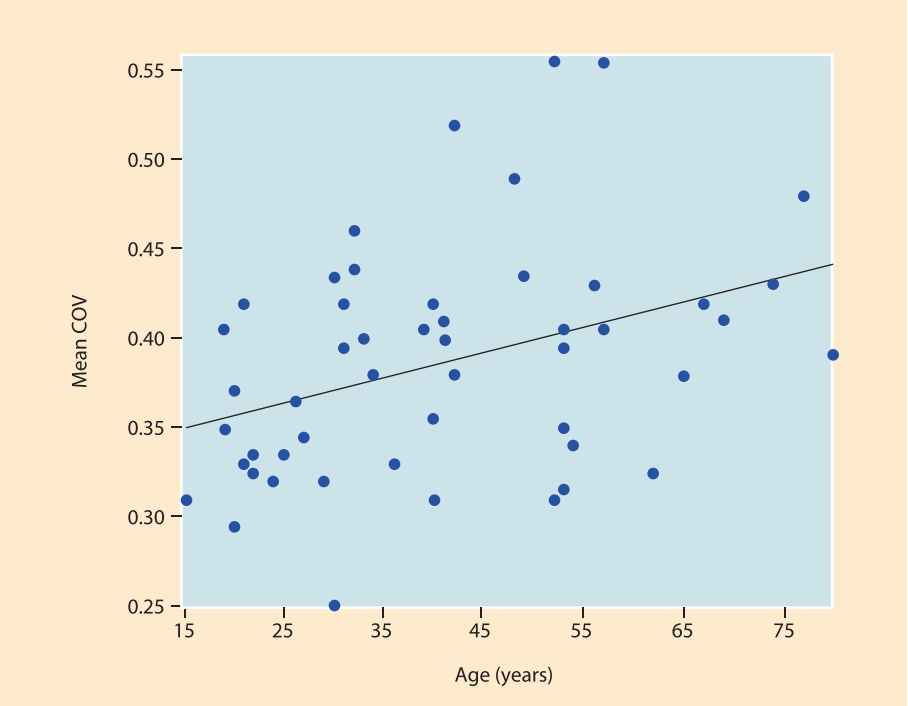


Fig. 32.4 Relationship between percentage increase in coefficient of variation (COV) of endothelial cell size (polymegethism) and age. (Adapted from Hollingsworth J, Perez-Gomez I, Mutalib HA, Efron N. A population study of the normal cornea using an in vivo, slit-scanning confocal microscope. Optom Vis Sci 2001;78: 706–11.)

redistribution away from the centre of the cornea leads to a reduced central endothelial cell density. On the basis of this occurrence, the appearance of polymegethism would suggest that some cells remain the same size and some become larger. Irrespective of the assumption concerning changes in central endothelial cell density, a disparity in cell size is apparent. However, this disparity is evident only at the apical endothelium–aqueous interface and does not necessarily relate to volumetric changes in the cytoplasmic mass of endothelial cells anterior to this interface.

A true appreciation of the morphological changes that constitute polymegethism can be gained by considering the theoretical analysis of Bergmanson,[33] who conducted an ultrastructural study of the corneas of six long-term contact lens wearers. In normal circumstances, the lateral cell walls are extremely interdigitated. Bergmanson[33] noted that the cell walls essentially become re-oriented so that they become normal to the endothelial surface, and they straighten out and align obliquely. The interpretation of this observation in terms of the three-dimensional structure of the endothelium is that endothelial cells have changed shape but that the volume of each cell has remained constant. Thus, by observing only the apical surface of the endothelium under specular reflection, one is presented with the compelling illusion that a disparity in cell size has developed. In reality, the cells have merely become re-oriented in three-dimensional space (Fig. 32.5).

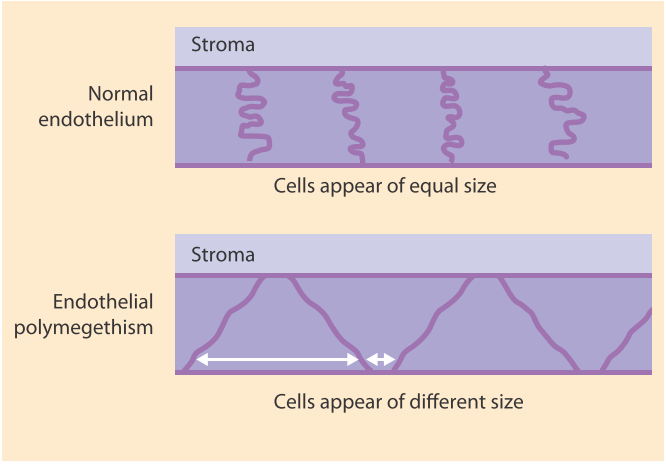


Fig. 32.5 Theory of Bergmanson explaining the pathogenesis and biomicroscopic appearance of corneal endothelial polymegethism. (Adapted from Bergmanson JP. Histopathological analysis of corneal endothelial polymegethism. Cornea 1992;11:133–42.)

A further observation of Bergmanson[33] which is of equal significance is that although the endothelium of contact lens wearers showed some inter- and intra-cellular oedema, the cells were otherwise of a healthy appearance, containing normal, undamaged organelles. This raises the interesting and controversial possibility that rather than representing an adverse effect, endothelial polymegethism is a non-problematic adaptation to chronic metabolic stress.

The suggestion that endothelial polymegethism is a benign tissue change has been challenged by researchers who have demonstrated a link between endothelial polymegethism and corneal hydration control.[12,18] In these studies, the effect of contact lens wear on corneal hydration control was measured by inducing corneal oedema and then recording the exponential rate of corneal de-swelling. Recovery from oedema is significantly slower in the corneas of contact lens wearers (vs. matched controls), and this deficit is dose related (i.e. the effect is more pronounced the longer lenses have been worn).

Figure 32.6, constructed and adapted from data of McMahon et al.,[12] demonstrates that corneal de-swelling occurring after induced oedema in PMMA lens wearers is considerably slower than that in non–lens wearers. Such observations must be considered in the context of a loss of corneal hydration control

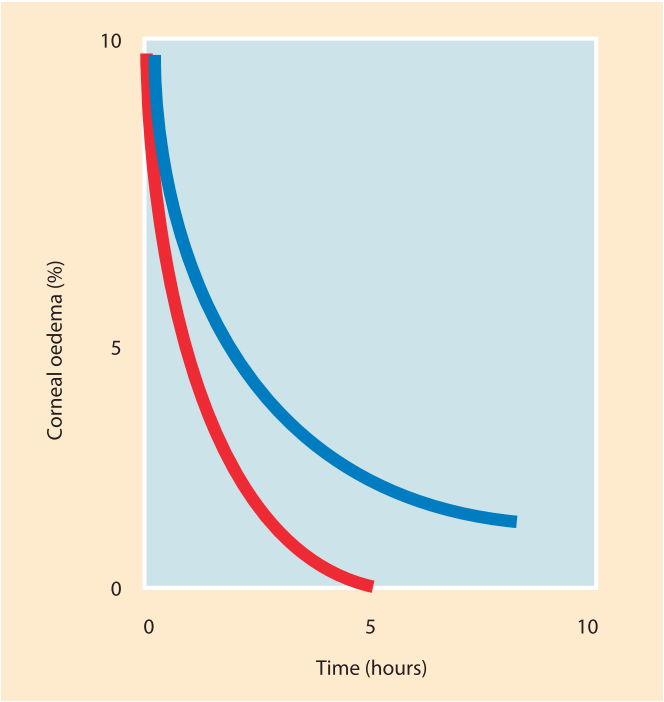


Fig. 32.6 Corneal de-swelling after induced oedema in polymethyl methacrylate (PMMA) lens wearers (blue curve) versus non–lens wearers (red curve). (Adapted from McMahon TT, Polse KA, McNamara N, Viana MA. Recovery from induced corneal oedema and endothelial morphology after long-term PMMA contact lens wear. Optom Vis Sci 1996;73:184–8.)

being a normal age-related change in the human population. Typically, the cornea of a 65-year-old person will take 10% longer to recover from stromal swelling compared with that of a 20-year-old person.[34]

An unfortunate conundrum in science is that correlation does not prove causation. Thus, it cannot be concluded with absolute certainty that the loss of corneal hydration control in contact lens wearers is caused by lens-induced endothelial polymegethism. However, it is not unreasonable to postulate such a causal relationship in view of the critical role of the endothelium in corneal hydration control.

The corneal hydration control process – known as the 'pump leak' mechanism[35] – comprises, as the name suggests, two critical components, both of which are located in the endothelium. The *leak* refers to the constant tendency for water to move from the aqueous humour into the stroma through gaps between endothelial cells, and the *pump* refers to an active mechanism whereby endothelial cells pump bicarbonate ions into the aqueous, creating an osmotic force that draws water out of the stroma (Fig. 32.7).[36] These counteracting forces are metabolically controlled so as to maintain a constant level of stromal hydration, while affording a mechanism of nutrient and waste exchange between the cornea and the aqueous humour.

The suggestion that contact lens–induced endothelial damage results in an increased leak, a reduction in pump efficiency or both is confounded by the fact that Bergmanson could not detect such damage upon ultrastructural examination of the organelles of endothelial cells of long-term contact lens wearers.[33]

Aetiology

It is likely that the aetiology of endothelial polymegethism is precisely the same as the aetiology of endothelial blebs; that is, the former represents a chronic response and the latter represents an acute response to the same stimuli.

The aetiology of endothelial blebs – or acute localised endothelial oedema – has been reviewed in Chapter 30. The key evidence comes from Holden et al.,[37] who attempted to induce blebs by using a variety of stimulus conditions and concluded that one physiological factor common to all successful attempts to form blebs was a local acidic pH change at the endothelium. It is likely that polymegethism in contact lens wearers is also caused by lens-induced endothelial acidosis, for the simple reason that the extent of polymegethism is apparently governed by the same dosed hypoxic response as blebs, albeit on a different time scale.

Two separate factors induce an acidic shift in the cornea during contact lens wear: (a) an increase in carbonic acid resulting from retardation of carbon dioxide efflux (hypercapnia)[38] by a contact lens and (b) increased levels of lactic acid as a result of lens-induced oxygen deprivation (hypoxia)[38] and the consequent increase in anaerobic metabolism (Fig. 32.8). When silicone elastomer contact lenses are worn, such metabolic changes do not take place because of the extremely high oxygen permeability of such lenses. No evidence of endothelial polymegethism could be found by Schoessler et al.[29] in the corneas of patients wearing silicone elastomer lenses.

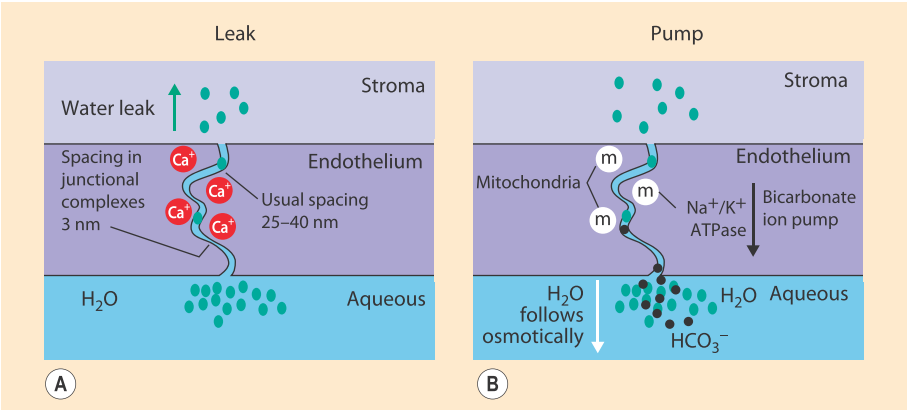


Fig. 32.7 The pump-leak process of corneal hydration control encompasses **(A)** a 'leaky' endothelium and **(B)** an endothelial bicarbonate pump.

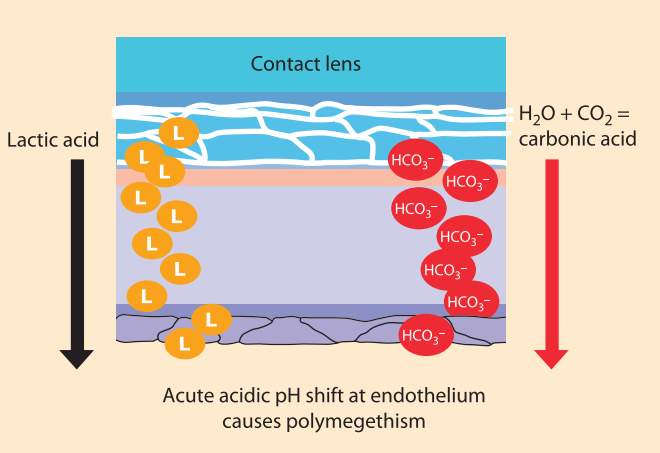


Fig. 32.8 Aetiology of contact lens–induced corneal endothelial polymegethism.

Bonanno and Polse[39] confirmed, with direct measurement, that contact lens–induced hypoxia and hypercapnia result in an acidic shift in the cornea, and these authors noted that the extent of acidosis that they measured is in the range where endothelial function may be affected.

The cornea becomes hypoxic and hypercapnic during sleep, so it would be expected that the consequent acidic changes would induce endothelial polymegethism, which is known to be age related.[31,32] Schoessler and Orsborn[40] published a case report of extreme endothelial polymegethism in the right eye (compared with the left eye) of a 23-year-old female after 4 years of unilateral ptosis in the right eye.

Consideration needs to be given to the mechanism by which acidosis causes changes to the three-dimensional shape of endothelial cells, which, in turn, gives rise to the appearance of polymegethism when viewed under specular reflection. All cells in the human body function optimally when surrounded by extracellular fluid that is maintained within an acceptable range of pH, temperature, tonicity, ion balance and so on. The carbonic acid and lactic acid cause an acidic pH shift in the extracellular fluid surrounding endothelial cells. This may induce changes in membrane permeability and/or membrane pump activity, resulting in water movement that acts to elongate endothelial cell walls.[33] A reconfiguration of cell shape then occurs to preserve cell volume, resulting in the appearance of polymegethism at the apical surface of the endothelium.

Observation and grading

Techniques that can be used to examine the corneal endothelium include slit lamp biomicroscopy, specular microscopy and confocal microscopy. The clinical application of these techniques was reviewed in Chapter 1. Basically, the slit lamp biomicroscope does not have sufficient magnification or resolution to enable an assessment of the degree of endothelial polymegethism. Such an assessment can only be achieved by capturing an image of the endothelium using one of the instruments described earlier and either (a) subjecting the image to computer-assisted image analysis (whereby the COV and other cell population characteristics can be calculated) or (b) comparing the image with a grading scale for polymegethism, such as that presented in Appendix A.

Figure 32.1 is an enlarged view of the slit lamp biomicroscopic appearance of the endothelium of a young female who had been wearing a soft lens of low Dk/t (38% water content hydroxyethyl methacrylate) for 10 years. Considerable variation in the size of individual endothelial cells (polymegethism) is clearly evident.

Doughty[41-44] has outlined the numerous limitations and caveats with respect to quantification of the degree of polymegethism in terms of the COV. He offered the following advice: (a) The coefficient is valid only for the individual from whom it was obtained, so it cannot be used for inter-subject comparison; (b) the COV can be ambiguous in that it does not indicate whether there is an overall increase or decrease in mean cell area (the COV can be the same in either case); and (c) the error associated with calculation of COV, typically by measuring up to 200 cells, is too great (analysis of 3,000 cells is required for accuracy, which is generally precluded because of time and cost constraints). Doughty and Aakre[45] also highlighted significant discrepancies that can occur when determining COV from the same image with the use of different morphometry techniques. Despite these critical analyses, evaluation of the degree of endothelial polymegethism against grading scales is a valuable technique with which clinically relevant differences can be detected and management decisions made.

Management

Figure 32.9 is a construction of the approximate relationship between COV and Dk/t, which indicates that lenses of lower oxygen performance will induce higher levels of polymegethism. Although this relationship provides a clear indication of ways to minimise or prevent contact lens–induced polymegethism, it is unclear if there is a need to take any measures to reverse or prevent this process because of the uncertainty as to whether endothelial polymegethism is an unwanted pathological change or a harmless physiological adaptation.

Whether or not one would wish to reverse or prevent endothelial polymegethism from the perspective of the health of the endothelium itself is an interesting but secondary consideration.

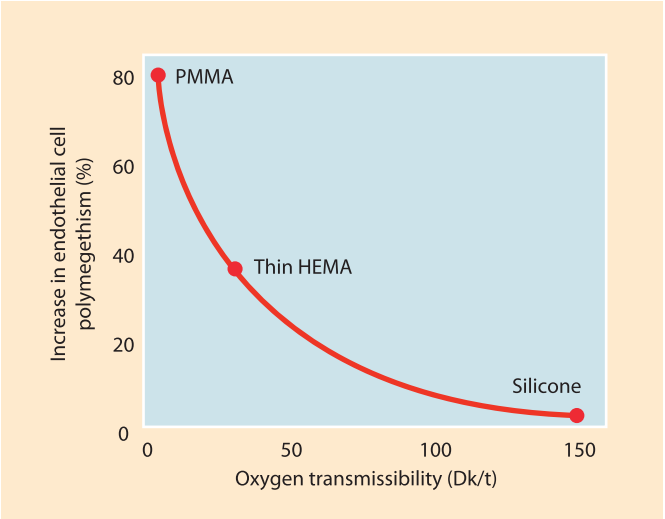


Fig. 32.9 Relationship between percentage increase in coefficient of variation (COV) of endothelial cell size (polymegethism) and lens oxygen transmissibility (Dk/t). Units of Dk/t are ($\times 10^{-9}$ (cm $\times$ mLO_2)/(sec $\times$ mL $\times$ mmHg)).

What is certain is that endothelial polymegethism provides an indication that the cornea has been subjected to prolonged metabolic stress. The source of this stress is probably chronic tissue acidosis, which, in turn, has been caused by chronic contact lens–induced hypoxia and hypercapnia. Clinicians have long recognised the importance of minimizing lens-induced hypoxia and hypercapnia because these changes are known to induce a wide variety of adverse effects to all layers of the cornea and conjunctiva.[4]

Thus, from a clinical perspective, it is essential to take note of the presence of significant endothelial polymegethism and to take action to minimise the metabolic stress to the cornea known to be associated with this change. Strategies for alleviating contact lens–induced hypoxia and hypercapnia include the following:

- fitting soft or rigid lenses made from materials of higher oxygen permeability;
- reducing lens thickness;
- sleeping wearing extended-wear lenses less frequently;
- changing from extended lens wear to daily lens wear;
- reducing lens wearing time; and/or
- fitting rigid lenses with more movement and edge lift (to enhance oxygen-enriching tear exchange).

The real battle against contact lens–induced endothelial polymegethism and, indeed, all chronic lens-induced changes is being fought in the polymer laboratories and lens design studios of the major contact lens manufacturers. Although practitioners will always have a choice to make with regard to the best lens for a given patient, such decisions can only be made within an envelope of available lens designs and materials. This envelope has shifted dramatically since the introduction of silicone hydrogel contact lenses onto the world market in 1999; these lenses now represent three-quarters of all soft lenses prescribed worldwide.[46] The natural outcome of this change has been an overall lowering of the degree of polymegethism and related chronic tissue changes among lens wearers.

Prognosis

The prognosis for recovery from endothelial polymegethism is poor. After removal and cessation of wear of high-water-content contact lenses that had been worn on an extended-wear basis for an average of 5 years, Holden et al.[47] were unable to detect a recovery from endothelial polymegethism during an observation period of 6 months (Fig. 32.10).

MacRae et al.[5] examined the extent of endothelial polymegethism in a group of former users of PMMA contact lenses, who had worn them for an average of 9.6 years but who had discontinued them for an average of 4.3 years. Compared with age-matched controls, these patients demonstrated significant increases in polymegethism and differences in pleomorphism. They concluded that PMMA lens–induced endothelial polymegethism is not completely reversible.

McLaughlin and Schoessler[48] were unable to demonstrate a significant improvement in endothelial morphology 4 months after refitting patients who had been wearing PMMA lenses with rigid lenses of high Dk/t. Thus, all available evidence suggests that contact lens–induced endothelial polymegethism is essentially a permanent change; any recovery back to age-related normality is likely to take many years.

The prognosis for overall corneal health based on action taken as a result of observed endothelial polymegethism may be excellent despite the fact that the endothelium may remain polymegethous for a considerable period or perhaps forever. The reason for this is that many other changes induced by chronic hypoxia and hypercapnia, such as reduced epithelial thickness, reduced oxygen consumption, epithelial microcysts and stromal oedema,[4] will dissipate in a matter of weeks or months after cessation of lens wear.[4,47] These changes can subsequently be minimised by adopting strategies for optimizing corneal oxygen availability during lens wear, such as those outlined earlier.

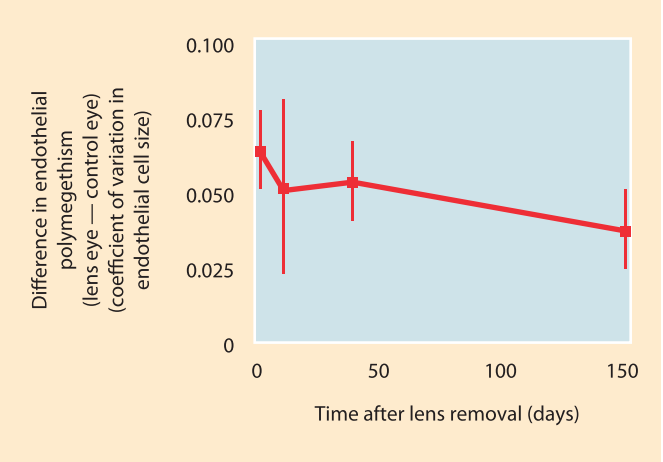


Fig. 32.10 Degree of endothelial polymegethism plotted for 150 days after cessation of lens wear (relative to non-lens-wearing control eyes). The apparent trend towards recovery is not statistically significant. (Adapted from Holden BA, Vannas A, Nilsson KT et al. Epithelial and endothelial effects from the extended wear of contact lenses. Curr Eye Res 1985;4:739–42.)

Notwithstanding the good prognosis for corneal health described previously, it has been suggested that the existence of endothelial polymegethism, in itself, may represent a continuing liability in view of the finding of Rao et al.[49] that corneal oedema induced by cataract surgery takes a lot longer to recover in patients displaying pre-operative corneal endothelial polymegethism. Although this observation has subsequently been challenged,[50] the possibility that endothelial polymegethism may compromise corneal health if surgical intervention of the eye is required later in life should not be discounted.

Differential diagnosis

A variety of degenerative (acquired) and dystrophic (hereditary) changes in the endothelium have been described, but a detailed account of these is beyond the scope of this book. These conditions are characterised by opacities, lesions or bleb-like formations (as in the case of Fuch's endothelial dystrophy), which generally cannot be confused with endothelial polymegethism.

What is more important in the context of differential diagnosis is the capacity to distinguish between the aetiologies of any observed endothelial changes. As well as being a natural age-related change,[31,32] endothelial polymegethism can occur as a result of, or in association with, both ocular insult (e.g. injury,[51] chronic solar radiation,[52] ptosis,[40] endothelial guttatae,[53] intraocular surgery[54] and keratoconus[55]) and systemic disease (diabetes mellitus[56] and cystic fibrosis[56]). Practitioners should, therefore, be alert to the fact that endothelial polymegethism observed in the eyes of contact lens wearers may have been caused by factors or conditions other than contact lens wear.

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This book is rededicated to
my wife, Suzanne,
my daughter, Zoe,
and my son, Bruce

APPENDIX

A

Grading Scales for Contact Lens Complications

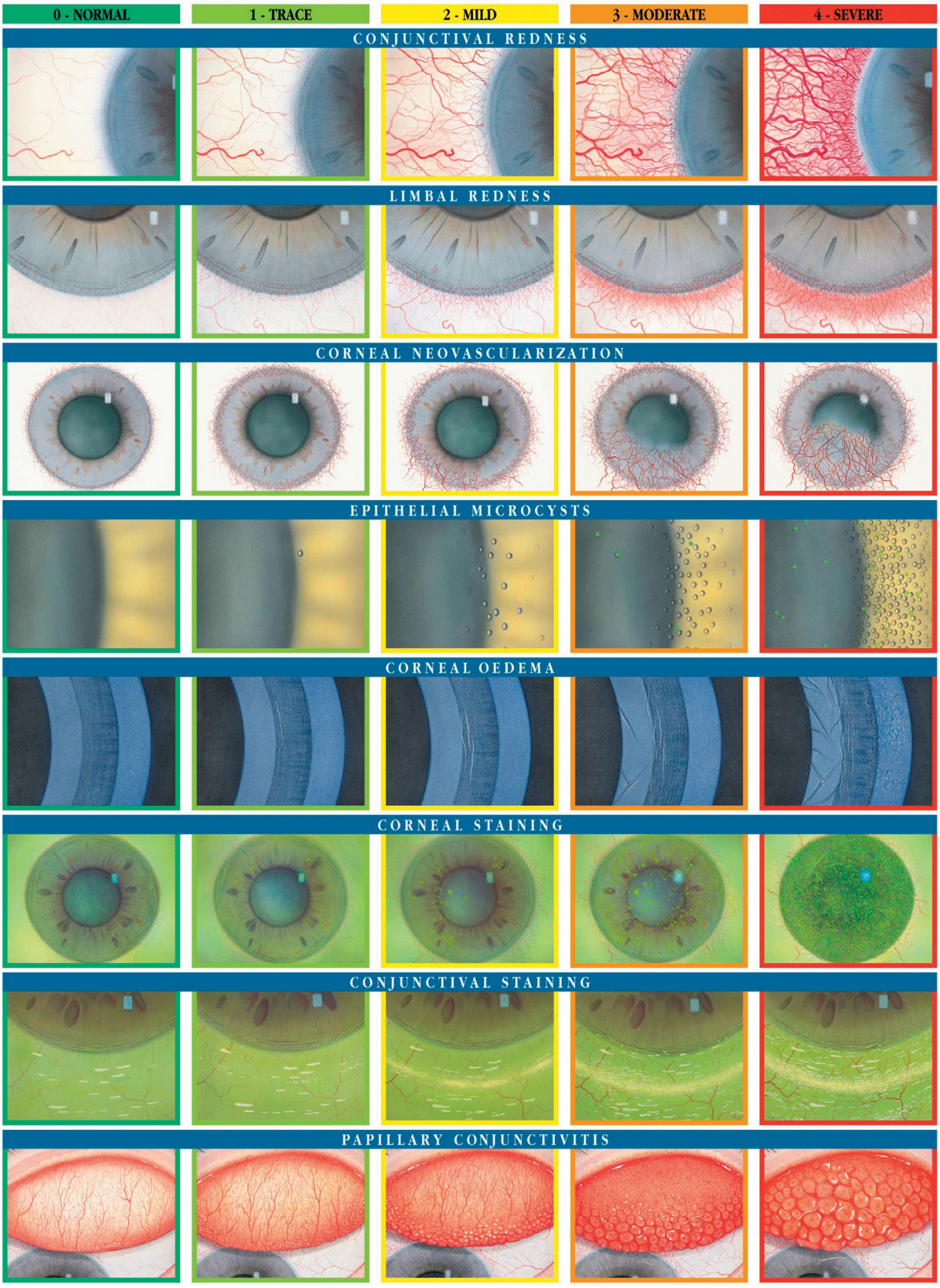
The grading scales presented in this Appendix were devised by Professor Nathan Efron and painted by the ophthalmic artist, Terry R. Tarrant.

These grading scales are presented in two panels and are designed to assist practitioners to quantify the level of severity of a variety of contact lens complications. The eight complications on page 344 are those that are more likely to be encountered in contact lens practice. Many of these complications are graded routinely by some practitioners. The eight complications on page 346 are encountered less commonly in contact lens practice or represent pathology that is rare or unusual. The order of presentation of the complications on each panel, from top to bottom, reflects the likely order in which these complications may be encountered in the course of a systematic examination with use of the slit lamp biomicroscope.

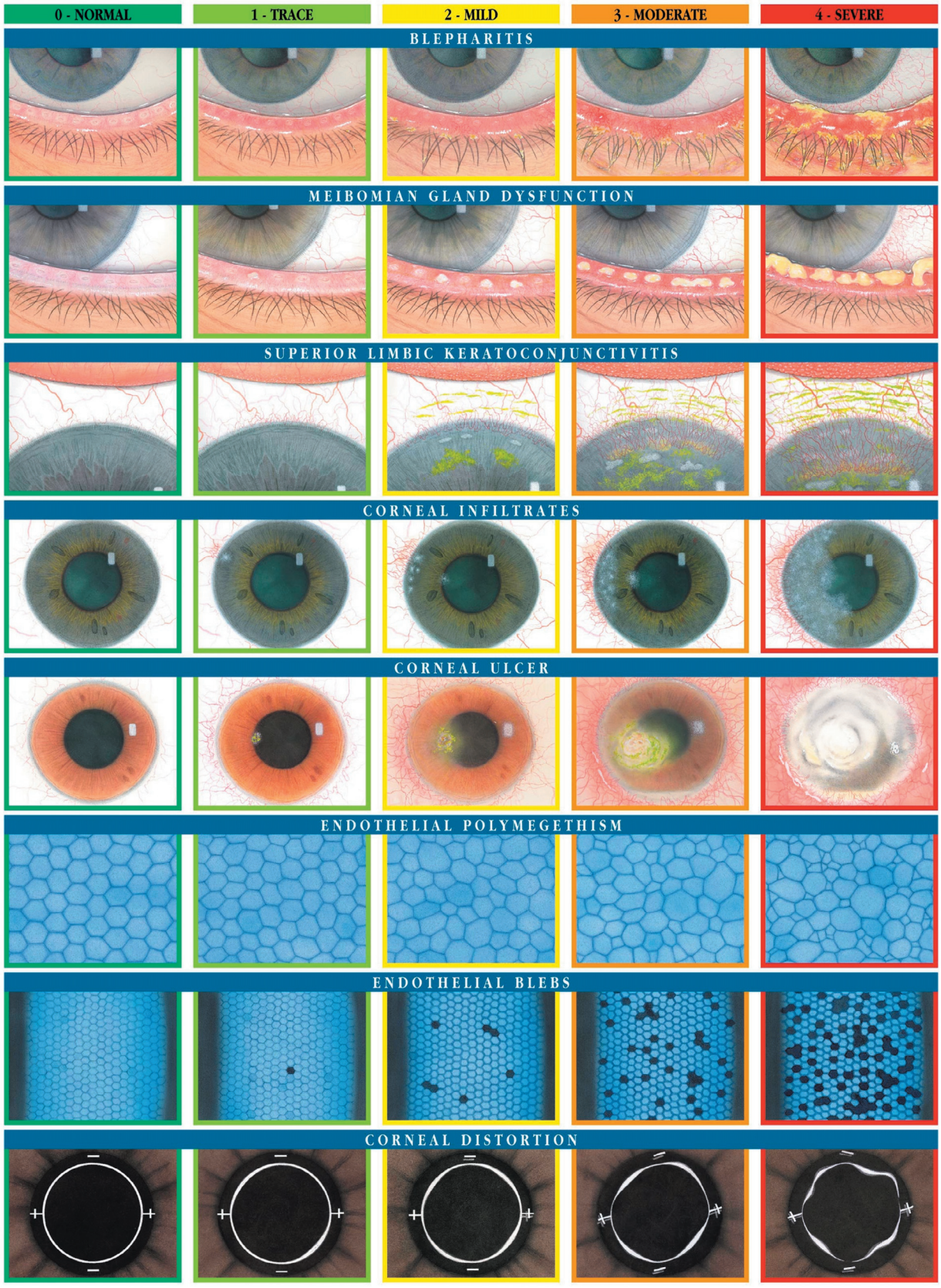
Opposite each of the two grading scale panels is a table (set out in the same format as the corresponding panel of complications) that briefly explains the salient features of each image. An explanation as to how to use these grading scales in clinical practice is given in Chapter 2.

The development of these grading scales was kindly sponsored by Hydron Ltd. (now CooperVision).

The original paintings of the complications depicted in these grading scales are housed in the archives of the British Optical Association Museum at the College of Optometrists, London, UK (catalogue number C-2014.364).


0 - NORMAL
1 - TRACE
2 - MILD
3 - MODERATE
4 - SEVERE
CONJUNCTIVAL REDNESS
LIMBAL REDNESS
CORNEAL NEOVASCULARIZATION
EPITHELIAL MICROCYSTS
CORNEAL OEDEMA
CORNEAL STAINING
CONJUNCTIVAL STAINING
PAPILLARY CONJUNCTIVITIS

0 - NORMAL	1 - TRACE	2 - MILD	3 - MODERATE	4 - SEVERE
CONJUNCTIVAL REDNESS				
'White' bulbar conjunctiva One major vessel Clear cornea	Small increase in conjunctival redness Major vessel more engorged	Further increase in conjunctival redness Limbal redness Slight ciliary flush	Conjunctiva very red Increased limbal redness Ciliary flush	Conjunctiva extremely red Limbus very red Intense ciliary flush Reflex on major vessel
LIMBAL REDNESS				
'White' limbus White corneal reflex	Slightly increased limbal redness White corneal reflex	Increased limbal redness Increased conjunctival redness White corneal reflex	Limbus very red Increased conjunctival redness Speckled corneal reflex	Limbus extremely red Conjunctival redness Hazy corneal reflex
CORNEAL NEOVASCULARIZATION				
Clear cornea White reflex	Vessels encroach <1 mm from lower left quadrant (LLQ)	Vessels encroach 2–3 mm from LLQ Limbal redness Reflex less crisp Central corneal haze	Vessels encroach 4–5 mm from LLQ Corneal haze around vessels Speckled reflex	Vessels encroach 6 mm from LLQ Lipid at leading edge of vessels Very diffuse reflex
EPITHELIAL MICROCYSTS				
High magnification view of pupil margin Clear cornea	Single microcysts at pupillary margin Microcyst displays reversed illumination	16 microcysts Some appear faint (newly formed)	About 70 microcysts Some microcysts at the surface stain with fluorescein	About 180 microcysts Many at the surface stain with fluorescein
CORNEAL OEDEMA				
Clear cornea and 3 mm wide parallelepiped Left: endothelium Centre: stroma Right: epithelium	Single vertical stria in posterior cornea	Three vertical striae in posterior cornea	Many vertical striae in posterior cornea Folds in endothelium	Many vertical striae in posterior cornea Many folds in endothelium Epithelial bullae
CORNEAL STAINING				
Clear cornea No staining Fluorescein in eye Cobalt blue reflex	Light punctate staining Slight conjunctival redness	More punctate staining Increased redness	Light pan-corneal punctate staining Diffuse reflex	Heavy pan-corneal punctate staining Very diffuse reflex
CONJUNCTIVAL STAINING				
Clear cornea Fluorescein pooling in some folds Cobalt blue reflex	Increased fluorescein pooling in folds Slight staining at position of lens edge	More fluorescein pooling in folds Interrupted lens edge staining Increased conjunctival redness	Widespread fluorescein pooling in folds Continuous lens edge staining Conjunctival redness	Widespread fluorescein pooling in folds Heavy lens edge staining Conjunctival redness Limbal staining
PAPILLARY CONJUNCTIVITIS				
Pale conjunctiva Vessels clearly visible Slight roughness at tarsal fold	Pink conjunctiva Vessels visible Increased roughness at tarsal fold	Red conjunctiva Vessels less visible Papillae at tarsal fold Reflexes on some papillae	Very red conjunctiva Vessels barely visible Large papillae Bright papillary reflexes Single mucus strand	Extremely red conjunctiva Vessels not visible Very large papillae Bright papillary reflexes More mucus strands


0 - NORMAL
1 - TRACE
2 - MILD
3 - MODERATE
4 - SEVERE
BLEPHARITIS
MEIBOMIAN GLAND DYSFUNCTION
SUPERIOR LIMBIC KERATOCONJUNCTIVITIS
CORNEAL INFILTRATES
CORNEAL ULCER
ENDOTHELIAL POLYMEGETHISM
ENDOTHELIAL BLEBS
CORNEAL DISTORTION

0 - NORMAL	1 - TRACE	2 - MILD	3 - MODERATE	4 - SEVERE
BLEPHARITIS				
Pale lid margin Openings of meibomian glands visible Clean lashes	Pink lid margin Openings of meibomian glands less visible Clean lashes	Red lid margin Openings of meibomian glands barely visible Yellow crust at base of lashes Some lashes stuck together	Telangiectasis of lid margin Increased crusting More lashes stuck together Bulbar conjunctival redness	Severe telangiectasis of lid margin Excess yellow crusting Lashes stuck together Increased bulbar conjunctival redness Skin irritation
MEIBOMIAN GLAND DYSFUNCTION				
Pale lid margin Openings of meibomian glands visible Clean lashes	Pink lid margin Cloudy expression at some gland orifices	Red lid margin Milky expression at most gland orifices Increased tearing	Red lid margin Yellow expression at all gland orifices Expressions becoming continuous	Thick creamy yellow expression at all gland orifices Expressions continuous Bulbar conjunctival redness
SUPERIOR LIMBIC KERATOCONJUNCTIVITIS				
Clear conjunctiva Clear superior limbus Clear cornea Clear reflex	Increased conjunctival redness Slight limbal redness Clear cornea	Conjunctival redness and staining Increased limbal redness Corneal staining and infiltrates	Greater conjunctival redness and staining Increased limbal redness 2–3 mm fibrovascular pannus Greater corneal staining and infiltrates	Severe conjunctival redness and staining Severe limbal redness 5 mm fibrovascular pannus Severe corneal staining and infiltrates
CORNEAL INFILTRATES				
Clear cornea Clear conjunctiva and limbus Clear reflex	Single small grey infiltrate at 10 o'clock near limbus Adjacent limbal redness	Five small grey infiltrates at 9–10 o'clock near limbus Adjacent limbus more red	Numerous small hazy grey infiltrates at 8–10 o'clock in peripheral cornea Adjacent limbus very red	Hazy grey confluent infiltrates that cover left half of cornea Adjacent limbal redness from 5 to 11 o'clock Mild conjunctival redness
CORNEAL ULCER				
Clear cornea Clear conjunctiva and limbus Clear reflex	<1 mm corneal ulcer at left pupil margin Stains with fluorescein Mild limbal redness at 7–11 o'clock	2–3 mm corneal ulcer Haze around ulcer Intense limbal redness at 7–11 o'clock Ciliary flush	6 mm corneal ulcer Haze around ulcer General corneal haze Intense circumlimbal redness Conjunctival redness Increased ciliary flush	White pan-corneal ulcer Cornea opaque Intense circumlimbal and conjunctival redness Intense ciliary flush
ENDOTHELIAL POLYMEGETHISM				
Cells same size Hexagonal shape Coefficient of variation (COV) = 0.15	Small variance in cell size COV = 0.25	Increased variance in cell size COV = 0.35 Some five-, six- and seven-sided cells	Considerable variance in cell size COV = 0.45 Some three-, four-, five-, six- and seven-sided cells	Substantial variance in cell size COV = 0.55 Some three-, four-, five-, six-, seven-, eight- and nine-sided cells
ENDOTHELIAL BLEBS				
Cells same size Hexagonal shape No blebs	One bleb	Three single blebs Two double-cell blebs	Large number of blebs 'Thickened' cell borders	Very large number of blebs Increased spacing between cells
CORNEAL DISTORTION				
Bright, sharp, circular keratometer mire	Slightly distorted keratometer mire Variation in thickness of circle	Distorted keratometer mire Variation in thickness of circle Loss of focus of right and top +/– signs	Very distorted keratometer mire Greater variation in thickness of circle Loss of focus and distortion of all +/– signs	Extremely distorted keratometer mire Greater variation in thickness of circle with some gaps Loss of focus and distortion of all +/– signs

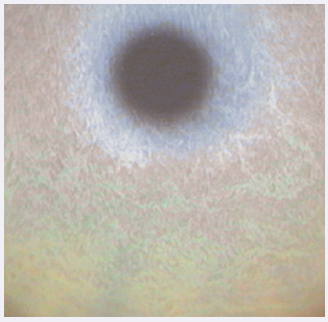
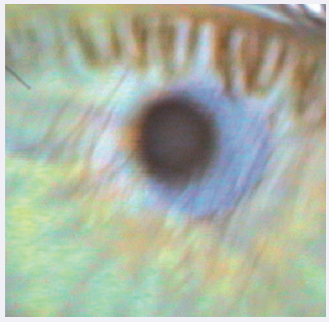
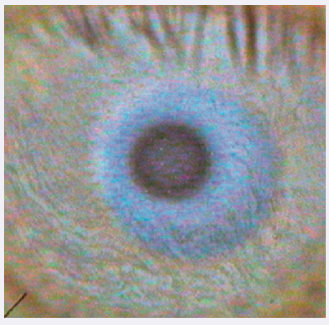
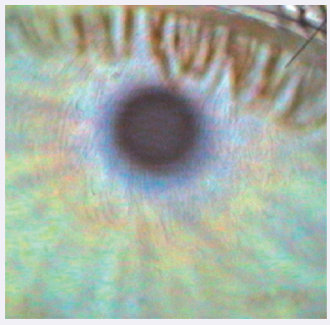
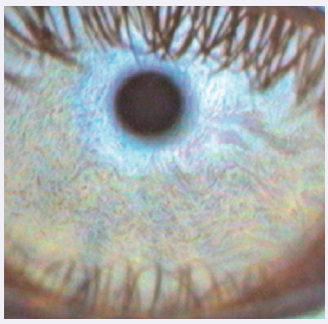
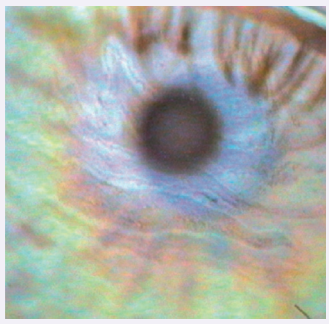
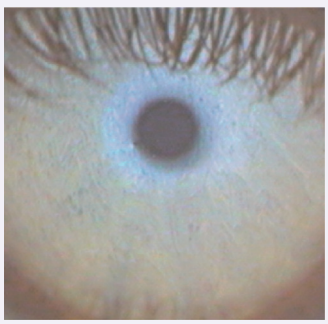
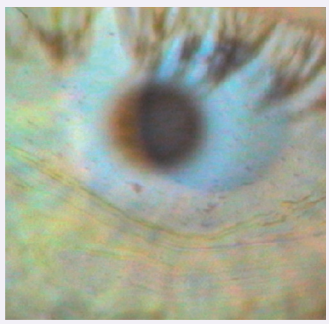
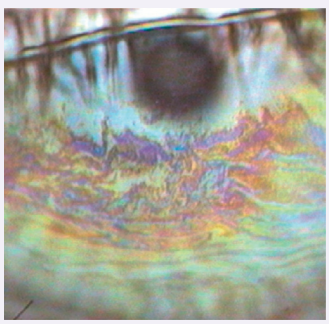
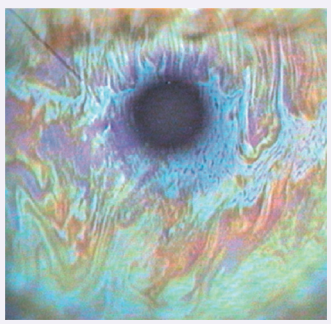
APPENDIX

B

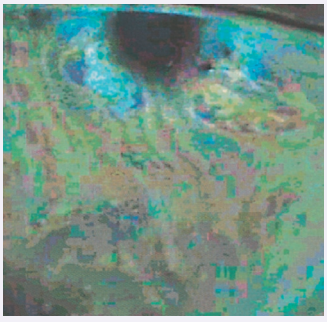
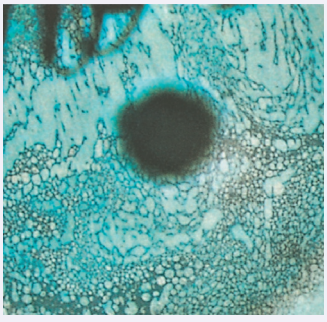
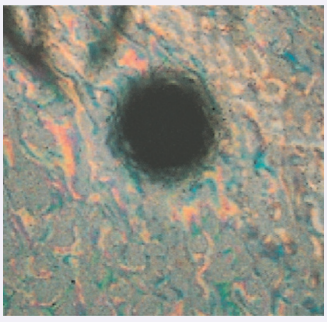
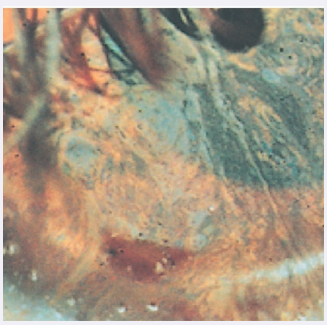
Guillon Tear Film Classification System

All the pre-ocular and pre-lens tear film patterns depicted in this Appendix were imaged and captured photographically by using a tearscope. All tear film lipid patterns should be assessed before any other examination and should be judged 2 seconds after the blink when the upward motion of the tear film (a viscosity characteristic) has stopped.

Pre-ocular tear film lipid patterns

	Dark eye	Light eye	
Open meshwork (marmorial)			Observed in 21% of the population 13–50 nm thickness Grey appearance of low reflectivity Sparse, open meshwork pattern faintly visible after the blink In the lower thickness range, it may not be visible at low magnification Thought to represent a deficient lipid layer
Closed meshwork (marmorial)			Observed in 10% of the population 30–50 nm thickness Grey appearance of average reflectivity More compact meshwork pattern Thought to represent a normal lipid layer
Wave(flow)			Observed in 23% of the population 50–80 nm thickness Pattern of vertical or horizontal grey waves of good visibility between blinks Most common lipid layer
Amorphous			Observed in 24% of the population 80–90 nm thickness Even pattern with whitish highly reflective surface Thought to represent an ideal, well-mixed lipid layer
First-order colour fringes			Observed in 10% of the population 90–140 nm thickness Discrete brown and blue well-spread lipid layer interference fringes superimposed on a whitish background Thought to represent a regular, very full lipid layer

Excessive and contaminated lipids

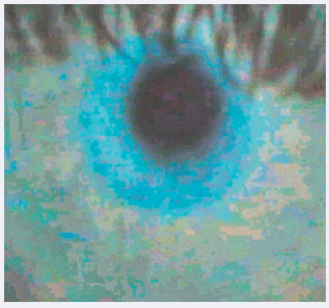
Second-order colour fringes		Observed in 5% of the population 140–180 nm thickness Discrete green and red tightly packed lipid layer interference fringes superimposed on a whitish background Thought to represent an abnormal lipid layer of increased thickness in the coloured areas
Globular lipid with multiple colours		Observed in 7% of the population >180 nm thickness Highly variable colours, but typically combinations of brown, blue, green and red, irregularly spread Sometimes globules of intense colour appear Thought to represent an extremely heavy and irregular lipid layer, often associated with over-secretion, blepharitis or lipid contamination
Lipid break-up and cosmetics		Abnormal lipid pattern Seen when cosmetic products invade the tear film and break the lipid layer Area devoid of lipid coverage appears dark grey as the light is reflected specularly from the bare aqueous phase Area covered by lipid is highly reflective and can be confined to form isolated circular islands
Eye ointments		Abnormal appearance Ointments destroy the normal tear film structure Heavy striated fringes of yellow, brown, blue, green and purple, which are often irregularly distributed, indicating the variable thickness of the ointment
Face cream		Lipid break-up observed when moisturisers or face creams invade and break the lipid layer Coloured fringes on grey background

Pre-soft lens tear film

The following sequence of images can be taken to represent an ideal pre-lens tear film going through the process of thinning caused by drainage and evaporation. Initially, the presence of a superficial lipid layer reduces evaporation and the thick aqueous phase ensures the separation of the lipid and mucus phases. After thinning of the aqueous phase, some lipid components migrate posteriorly and come into contact with the mucus phase and lens surface, which produces non-wetting patches.

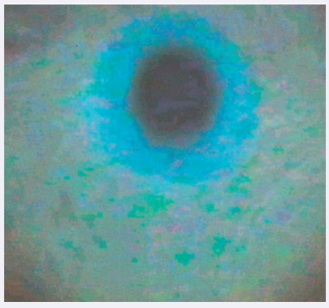
An alternative interpretation of this sequence of images is that they represent different tear film structures that appear immediately after eye opening. In this case, the images are arranged from 'best' to 'worst' and can be used to grade the quality of the pre-lens tear film.

Meshwork lipid coverage



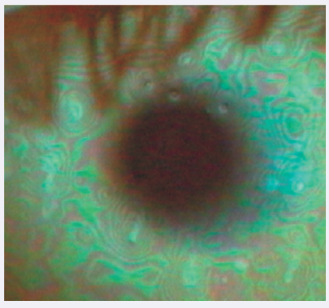
Appearance of a good tear film on the surface of a soft contact lens immediately after eye opening
Thin lipid layer present
Aqueous layer fringes not visible denote an aqueous phase >3.5 μm thick

Lipid with aqueous fringes



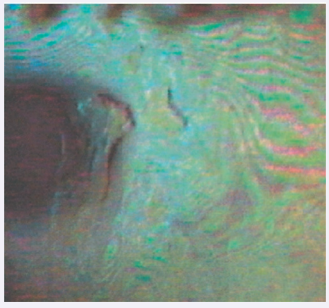
Appearance of tear film on the surface of a soft contact lens 4 seconds after eye opening
Very thin lipid layer of low visibility
Blue, green, yellow and red aqueous interference fringes faintly visible under the lipid layer
Aqueous layer 2–3.5 μm thick

Aqueous fringes



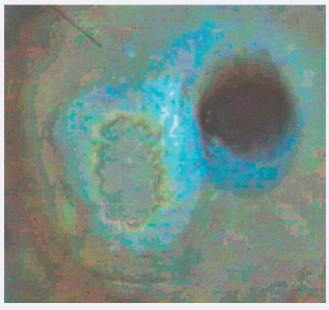
Appearance of tear film on the surface of a soft contact lens 8 seconds after eye opening
Lipid layer virtually absent
Narrow green and red aqueous interference fringes are easily visible
Aqueous layer 2 μm thick

Dry area



Appearance of tear film on the surface of a soft contact lens 12 seconds after eye opening
Lipid layer absent
Widely spaced, bright green and red aqueous interference fringes visible
Aqueous layer <1 μm thick
Edge of the mucus layer visible
Lens surface visible at the centre of the dry spot

Lipid contamination



Appearance of tear film on the surface of a soft contact lens contaminated with lipid
Oval non-wetting patch occurs immediately after eye opening
Contaminating lipids highly visible
Blue, green, yellow and red interference fringes visible in a thin aqueous phase

Pre-rigid lens tear film

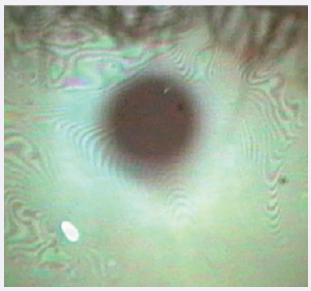
As for the pre-soft lens tear film, the following sequence of images of the pre-rigid lens tear film can be taken to represent either (a) an ideal pre-lens tear film going through the process of thinning, or (b) different tear film structures immediately after eye opening ranked from 'best' to 'worst'.

Complete lipid cover



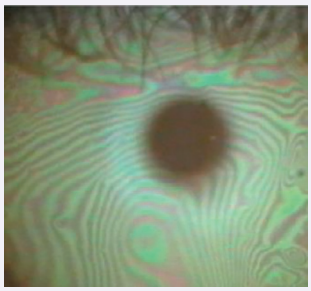
Appearance of an ideal tear film on the surface of a rigid lens immediately after eye opening
Seen in only 5% of cases
Thin and complete lipid cover
Blue, green, yellow and red aqueous layer interference fringes faintly visible

Thick aqueous layer



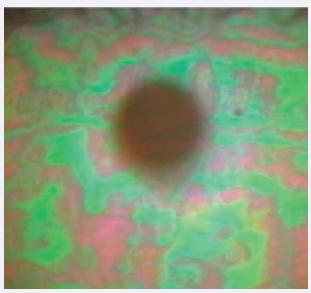
Appearance of tear film on the surface of a rigid lens 4 seconds after eye opening
Very thin lipid layer
Narrow aqueous layer interference fringes denote a thick aqueous phase
Aqueous layer >2 μm thick

Medium aqueous layer



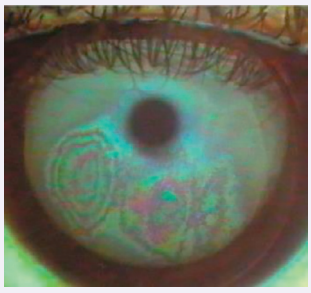
Appearance of tear film on the surface of a rigid lens 8 seconds after eye opening
Lipid layer absent
Well-defined aqueous layer interference fringes
Thinning of aqueous phases superiorly may be induced by the upper tear meniscus
Aqueous layer 1–2 μm thick

Thin aqueous layer



Appearance of tear film on the surface of a rigid lens 12 seconds after eye opening
Lipid layer absent
Broad, bright red and green aqueous layer interference fringes
Aqueous layer <1 μm thick

Drying



Appearance of tear film on the surface of a rigid lens 16 seconds after eye opening
Lipid layer absent
Irregular broad, bright red and green aqueous layer interference fringes visible, some in a circular pattern, formed by the evaporating tear film
Aqueous layer <0.5 μm thick inferiorly and absent superiorly

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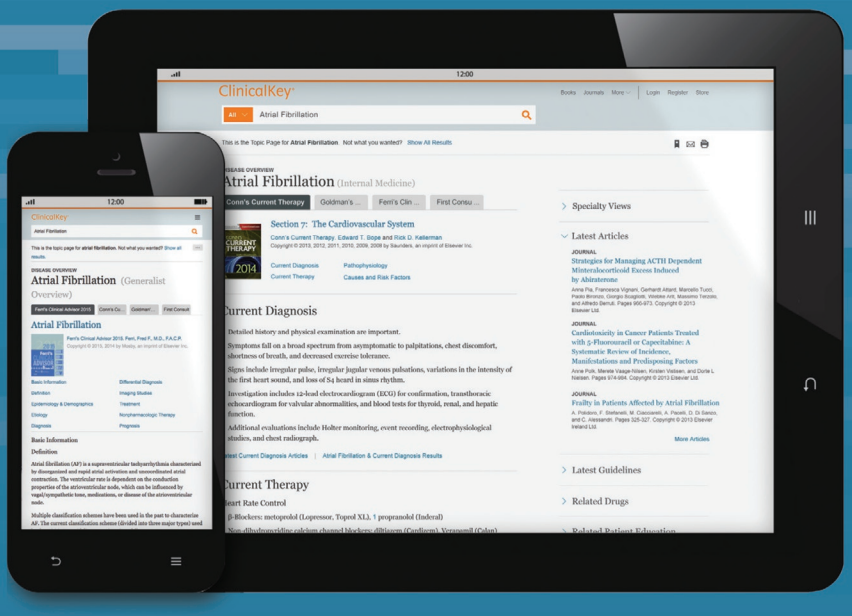
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