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Advances in Medical and Surgical Cornea

From Diagnosis to Procedure

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Essentials in Ophthalmology

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Advances in Medical and Surgical Cornea

From Diagnosis to Procedure

Springer

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Preface

The field of cornea and external diseases has changed dramatically in the last decade. From the new technology that we as ophthalmologists have to help us diagnose ocular surface disease, infectious keratitis, and ocular allergies to the new treatment options for these entities, we have many new tools to help us and to help our patients. Techniques and standards of care in surgery have even changed to the point that the same patient who would have walked into our office 10 years ago and would be offered the then standard penetrating keratoplasty for any corneal disorder could now be offered something different and better: anterior lamellar keratoplasty, endothelial keratoplasty, keratoprosthesis, or even laser-assisted penetrating keratoplasty. Furthermore, we can even better help patients avoid the need for surgery, with advances in contact lens technology and collagen cross-linking. Finally, as our surgical repertoire for corneal procedures has increased, the role of the eye bank in facilitating our procedures and in some cases making it possible at all to do our procedures has increased exponentially.

This book aims to present the latest information in the diagnosis and management of the spectrum of medical and surgical corneal diseases, with special focus on new technology. Each chapter is authored by leading authorities in that area, who share my passion for providing the very best and the most cutting-edge care for our patients.

I would like to express my sincere appreciation to these authors for lending us their expertise and providing their valuable contributions to this book. I would also like to thank Springer Publishing and their staff for making this book possible. Finally, and most importantly, I would like to thank my family for their unconditional love and support: my wonderful wife Linda; our three beautiful children Cassie, Dailen, and Garin; my loving parents Arco and Er-An; and my dear sister Eileen.

Baltimore, MD, USA — Bennie H. Jeng, MD, MS

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1.1 Introduction

Dry eye syndrome is a prevalent disease. Population-based studies in various US cities have utilized questionnaires to evaluate the prevalence of DES and found a prevalence estimate of approximately 15 % (Begley et al. 2001; Schein et al. 1997; Moss et al. 2000; Bandeen-Roche et al. 1997; Munoz et al. 2000). Similar studies conducted in several countries around the world have resulted in similar estimates (Brewitt and Sistani 2001; McCarty et al. 1998; Chia et al. 2003; Hikichi et al. 1995; Uchino et al. 2008a, b; Shimmura et al. 1999; Lekhanont et al. 2006; Sahai and Malik 2005; Lee et al. 2002). Once thought to be a disease predominantly of women, recent studies out of the Veterans Affairs Medical Center have found that approximately 1 in 5 male veterans carry a diagnosis of DES (Galor et al. 2011, 2012). Taken together, these studies suggest that DES is more prevalent than diabetes (~8 % of US population) (NDIC 2011) and heart disease (~7 % of US population) (CDC 2007).

DES is also a disease associated with significant morbidity. The Impact of Dry Eye on Everyday Life (IDEEL) questionnaire was developed to assess DES-specific morbidity. Two studies utilizing this questionnaire found that dry eye symptoms were correlated with difficulties in performing activities of daily living and working and had negative effects on mental functioning (Rajagopalan et al. 2005; Pouyeh et al. 2012). A case-control study assessing the impact of symptoms on everyday activities found that patients with DES had difficulties with reading, carrying out professional work, television watching, and driving (Miljanovic et al. 2007). Utility assessment has demonstrated that patients with severe dry eye symptoms have utility scores in the range of conditions like class III/IV angina (Schiffman et al. 2003). Given its prevalence and morbidity, it is not surprising that DES is a leading cause of visits to eye care clinics and has significant cost implications. The estimated economic burden of DES approaches $3.8 billion annually in the United States, with estimated indirect costs exceeding $55 billion (Yu et al. 2011).

1.2 Diagnosing Dry Eye Syndrome

Despite its prevalence and morbidity, DES is a difficult entity to diagnose, primarily due to a lack of a gold standard definition for disease. Some clinicians and researchers use symptoms to diagnose disease, while others use signs or combination of symptoms and signs. Furthermore,

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few clinicians systematically screen for DES in the same manner as they do for other ophthalmic diseases such as glaucoma and age-related macular degeneration. As symptoms are the main source of DES morbidity, one suggestion is to have patients fill out one of several validated symptom questionnaires at the time of their visit to assess for the presence of significant symptoms. Two validated DES questionnaires which can be easily administered are the Ocular Surface Disease Index (OSDI, 12 questions, score of 0–100) (http://dryeyezone.com/encyclopedia/documents/OSDI.pdf) and the dry eye questionnaire 5 (DEQ5, 5 questions, score of 0–22) (http://www.dryeyesmedical.com/diagnosis/diagnostic-questionnaires/deq-5.html).

Unfortunately, not all patients with severe symptoms on the questionnaire have DES. Therefore, patients with severe symptoms (generally ≥20 on the OSDI or ≥12 on the DEQ5) need to have further evaluation to determine the source of their symptoms. It is important to first assess a patient's environmental exposures. Certain environmental exposures have been associated with DES symptoms including work exposures (toxins, chemicals) (Zuskin et al. 1998; Bulbulia et al. 1995), video display terminal use (Uchino et al. 2008b), and the use of a continuous positive airway pressure (C-PAP) machine (Hayirci et al. 2012). If found, certain exposures may be addressed, such as refitting a C-PAP machine, with subsequent elimination of symptoms. It is also important to elicit a patient's medication history, paying special attention to local and/or systemic therapies that can affect the ocular surface. Locally, glaucoma medication is well known to cause ocular surface disease and thereby dry eye symptoms (Anwar et al. 2013). In a similar manner, many systemic medications including antihistamines, antidepressants, and anxiolytics have been found to associate with DES (Galor et al. 2011).

The examination of a patient with significant DES symptoms starts with an external exam, evaluating for the presence of skin abnormalities such as rosacea or seborrheic dermatitis. If present, treating the skin abnormalities is a vital step in relieving symptoms, and coordination with a dermatologist is often helpful. Second, it is important to carefully examine the ocular anatomy as anatomical abnormalities can lead to DES symptoms. There are a number of conditions that can masquerade as DES and these need to be examined for including malpositioned eyelids (ectropion, entropion), conjunctival abnormalities (pterygium, conjunctivochalasis), superior limbic keratoconjunctivitis, and corneal pathology (anterior basement membrane disease) (Table 1.1). Very frequently, patients with the above conditions present to the eye care professional with a diagnosis of DES which has been unresponsive to therapy. Identifying and addressing these anatomical abnormalities can often times lead to resolution of symptoms.

After external and anatomical considerations, the next step in diagnosing DES is evaluating which part of the tear film is dysfunctional. The tear film is a complex fluid made up of lipids, an aqueous layer, and mucins (Fig. 1.1). Most patients with DES have dysfunction in more than one layer although there is typically one that is most affected. For examples, patients with Sjogren's syndrome or graft-versus-host disease (GVHD) typically have primarily aqueous tear deficiency (ATD), while patients with rosacea typically have mostly evaporative dry eye (LTD). Several tests are used to evaluate tear function as this information has implications for treatment (Table 1.2). Schirmer's

Table 1.1 Conditions that may mimic dry eye syndrome

Eyelid abnormalities
Ectropion
Entropion
Lagophthalmos
Floppy eyelid syndrome
Conjunctival abnormalities
Pinguecula
Pterygium
Trabeculectomy
Superior limbic keratoconjunctivitis
Conjunctivochalasis
Corneal disorders
Anterior basement membrane disease
Recurrent erosion syndrome
Salzmann nodular degeneration

test with or without anesthesia can be used to assess aqueous production (Fig. 1.2), while tear break-up time and evaluation of meibomian gland parameters can evaluate the composition and function of the lipid layer (Fig. 1.3). Other tests, such as measurement of tear osmolarity, can give a global assessment of tear health as hyperosmolarity is believed to be a key player in the pathophysiology of disease (Fig. 1.4) (DEWS 2007b). It is important, however, to understand that none of the tests are a perfect mirror of tear function and that the results can vary substantially both due to testing methodology and to the dynamic biology of the tear film. With regard to the former, tear break-up times vary substantially by the amount of fluorescein placed in the eye. With regard to the latter, tear osmolarity values can vary substantially when measured in the same individual 3 times in a row, a finding that suggests the presence of ocular surface instability. Despite these limitations, a general "gestalt" of tear function can be obtained by measuring some or all of these parameters. Newer tests are currently being evaluated that may better assess the dynamic state of the tear film including func-

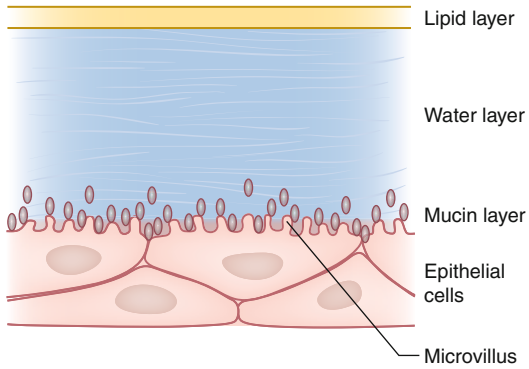

Fig. 1.1 An illustration of the tear film demonstrating its complexity, with a mucin, aqueous, and lipid layer (Used with kind permission from Allergan)

Table 1.2 Common tests used to evaluate tear and ocular surface health

Global assessment of health
Tear osmolarity (TearLab, San Diego, CA)
Corneal staining
Conjunctival staining
Tear film debris
Presence of filaments
Presence of irregular astigmatism by corneal imaging (topography, tomography)
Elevated level of MMP-9 (InflammaDry, Rapid Pathogen Screening, Sarasota, FL)
Aqueous tear function
Schirmer's test
Inferior meniscus volume (inspection at slit lamp or with ocular coherence tomography)
Lipid tear function
Tear break-up time
Meibum quality
Meibomian gland inspissation
Eyelid vascularity
Eyelid "foaminess"
Interferometer (LipiView, Tear Science, Morrisville, NC)

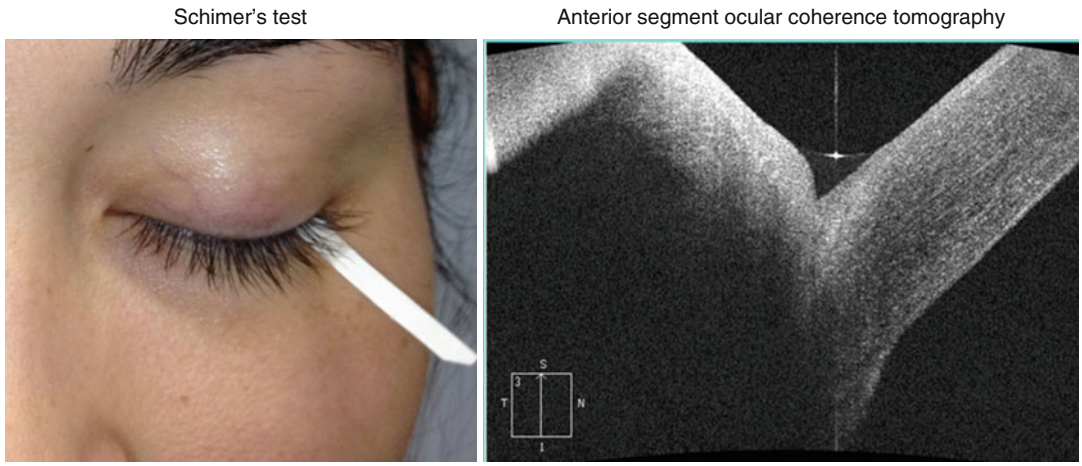

Fig. 1.2 Commonly used tests in dry eye syndrome (DES) to assess the aqueous component of tears

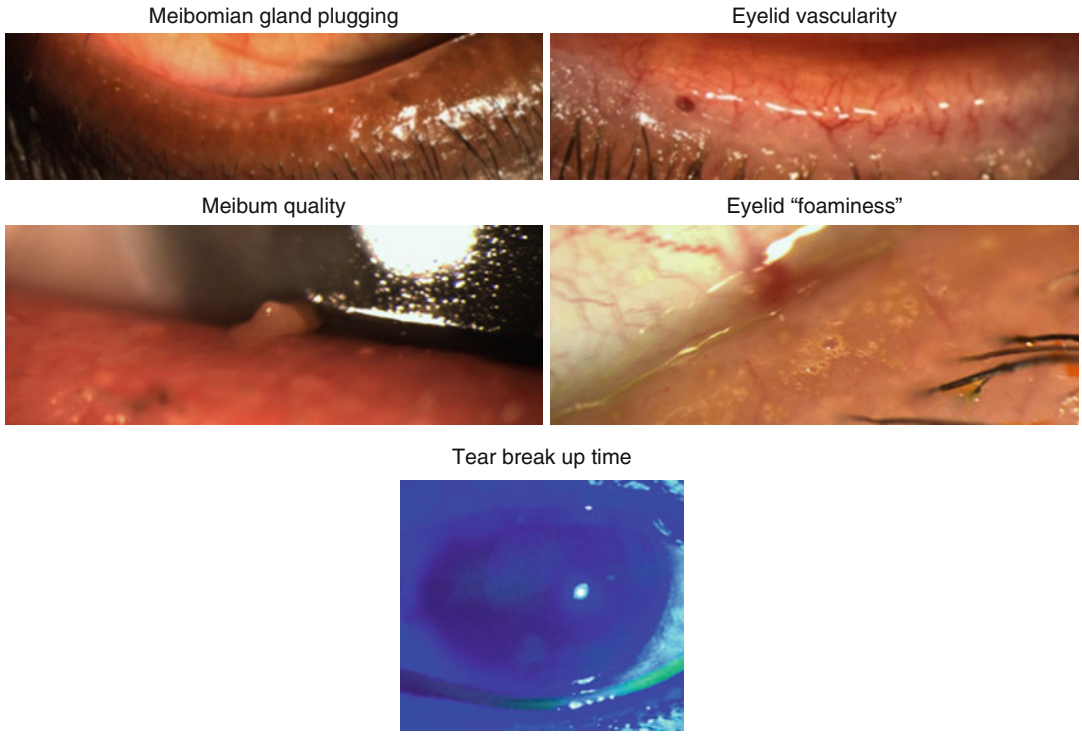

Fig. 1.3 Commonly used tests in dry eye syndrome (DES) to assess the lipid component of tears. For example, morphologic evaluation can include degree of inferior eyelid meibomian orifice plugging (0 none; 1 less than 1/3 lid involvement; 2 between 1/3 and 2/3 involvement; 3 greater than 2/3 lid involvement), degree of eyelid vascularity (0 none; 1 mild engorgement; 2 moderate engorgement; 3 severe engorgement) (Foulks and Bron 2003), and meibum quality (0 = clear; 1 = cloudy; 2 = granular; 3 = toothpaste; 4 = no meibum extracted) (Tomlinson et al. 2011). Expression of meibum can be done with a cotton-tipped applicator or with the Meibomian Gland Evaluator, a device that applies a uniform pressure to the outer skin of the lower eyelid

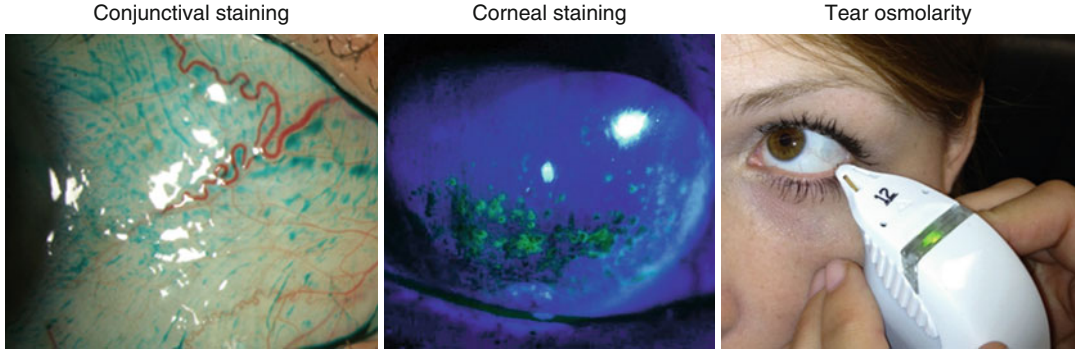

Fig. 1.4 Commonly used tests in dry eye syndrome (DES) to assess global ocular surface health. For example, a score for corneal staining can be generated by assessing staining in different sections of the cornea (superior, inferior, nasal, temporal, center) or by assigning an overall score for severity (DEWS 2007a). A similar can be used for conjunctival staining

tional visual acuity (FVA) testing (Goto et al. 2006; Ishida et al. 2005) and evaluating tear film stability with consecutive topographic images (Tear film Stability Analysis System) (Gumus et al. 2011). However, these newer tests are not in widespread use in the clinical arena.

Interferometry is another test that can be performed to evaluate the health of the lipid layer (Tomlinson and Khanal 2005). In this technique, interference fringes are produced by light reflected at the air-lipid and lipid-aqueous interfaces of the tear film. This specular reflection from the tear surface is imaged and recorded digitally. Several researchers have developed grading patterns to interpret the recorded images, most focusing on the uniformity of the fringe pattern. Overall, research has demonstrated that a thicker lipid layer is associated with greater tear film stability and that loss of uniformity indicates tear film instability (Tomlinson and Khanal 2005). LipiView® (Tear Science, Morrisville, NC) is a commercially available interferometer that comes as part of the Tear Science diagnosis and treatment system (described below).

Another adjuvant study that can be used to evaluate for the presence of ocular surface inflammation is the InflammaDry™ assay (Rapid Pathogen Screening, Sarasota, FL). This test detects elevated levels of matrix metalloproteinase-9 (MMP-9) in the tear film. MMP-9 is a nonspecific marker of inflammation and has been found to be elevated in various ocular surface disorders and corneal ulceration (Kaufman 2013). An advantage of the test is its ease and rapidity; the applicator is placed in the lower conjunctivae to sample tears, and the results are available within 10 min. A limitation, however, is that the test result is reported in binary fashion: two lines indicate an elevated MMP-9 level; one line indicates a normal level.

Newer data suggest that DES may be a manifestation of a corneal neuropathy (Rosenthal et al. 2009; Rosenthal and Borsook 2012) and evaluation of corneal sensation should be considered, especially in patients with extensive corneal staining and minimal disease symptoms. Available technologies include the more qualitative cotton-tip swab which can compare sensation between the eyes and the more quantitative Cochet-Bonnet esthesiometer (Luneau Ophthalmologie, Chartres, France). Belmonte et al. (1999) developed a noncontact gas esthesiometer that can measure corneal threshold to mechanical, thermal, and chemical stimulation. Unfortunately, this esthesiometer is not commercially available and only four modified versions of the instrument are available worldwide.

Another commercially available tool that can be used to study corneal nerves is the confocal microscope (Confoscan 4, Nidek, Fremont, California). In vivo confocal microscopy can be used to image corneal nerves in the sub-basal plexis. Several studies have found abnormal corneal nerve morphology in patients with DES including increased nerve tortuosity, fewer fibers, and higher bead density (Zhang et al. 2011; Villani et al. 2013). This testing, however, is in its infancy, and at this point it is not clear what role nerve imaging will have in the diagnosis and treatment of DES.

1.3 Treating Dry Eye Syndrome

1.3.1 Ocular Surface Protection

The treatment of DES involves a stepladder approach based on the location of the abnormality (Fig. 1.5). The first step in treating ATD is protection of the ocular surface with artificial tears. There are several available products that vary in viscosity, polymer material (methylcellulose, propylene glycol, glycerin, polyvinyl alcohol), and preservative. In addition, some products include additional agents such as lipid replacement (e.g., Soothe (Bausch & Lomb, Rochester NY), Systane balance (Alcon, Fort Worth TX)), while others have properties such as hyposmolarity. A complete list of artificial tear properties and preservatives can be found on the website http://www.dryeyezone.com/encyclopedia/lubricants.html. In general, patients should consider preservative-free options if they require dosing of more than 4 times daily. Patients with more severe symptoms should consider higher-viscosity agents although these tend to cause more visual blurring. Furthermore, gels and ointment are available for nighttime use in those with persistent symptoms.

1.3.2 Treating Inflammation

The next step in ATD treatment is targeting inflammation. Inflammation has been demonstrated to be a key player in DES. T cells, cellular markers

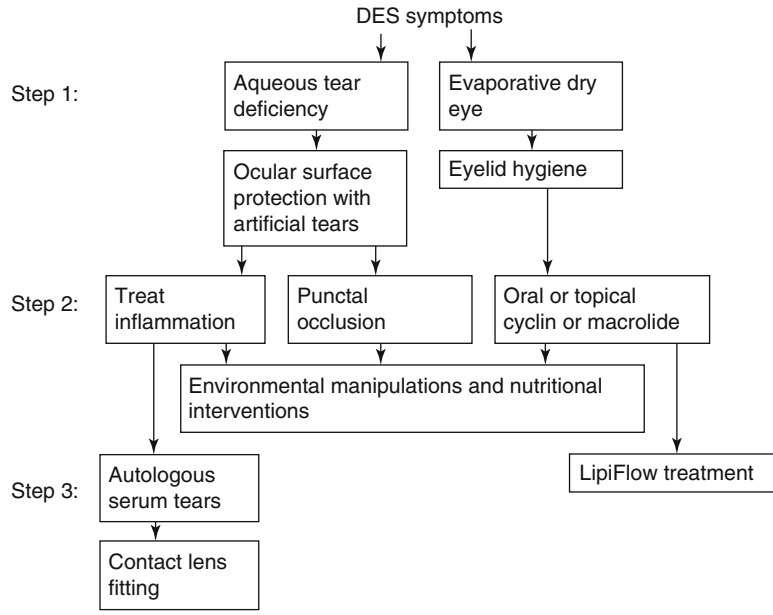

Fig. 1.5 An algorithm for treating dry eye symptoms

of inflammation (human leukocyte antigen (HLA) DR), inflammatory cytokines (interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), and chemokines (IL-8 (CXCL8)) have all been found on the ocular surface of dry eye suffers (Stevenson et al. 2012). Targeting inflammation is therefore one important avenue of treatment. While topical corticosteroids are an effective treatment, their side effects of cataract formation and intraocular pressure elevation limit their use in chronic diseases. Cyclosporine 0.05 % (Restasis, Allergan, Irvine CA) is the only Food and Drug Administration (FDA)-approved product for DES in the USA. Several clinical trials demonstrated improvement in symptoms, signs, and inflammatory markers with the use of topical cyclosporine (Stevenson et al. 2000; Sall et al. 2000; Brignole et al. 2001). In patients with immune-mediated ocular inflammation such as those with graft-versus-host disease, one can consider using cyclosporine compounded at a higher concentration (0.5 %, 2 %). Other anti-inflammatory agents are being evaluated in DES but have not yet received FDA approval. Topical tofacitinib, a Janus kinase inhibitor, is one such agent that has been tested in patients with DES in a phase I/II trial. While the agent did not meet its primary endpoint for efficacy, tofacitinib was superior to cyclosporine emulsion with respect to ocular surface symptoms and side effects. However, neither agent was more effective than vehicle in reducing corneal staining (Liew et al. 2012; Huang et al. 2012).

1.3.3 Punctal Occlusion

Another option for the treatment of ATD is temporary or permanent occlusion of the punctae. While this option should be considered in patients with primary and likely irreversible ATD such as those with GVHD, Sjogren's syndrome, or radiation keratopathy, there is less enthusiasm for the procedure in those with concomitant LTD and/or significant ocular surface inflammation. This is because the punctae are likely one avenue for the elimination of cellular and soluble inflammatory mediators from the ocular surface and their occlusion can exacerbate disease.

1.3.4 Treating Lid Disease

The first-line treatment for LTD is lid hygiene (Fig. 1.5). This process involves heating the

eyelids and massaging the meibomian gland openings. There are many different ways to perform this routine including adding baby shampoo to warm water or applying a heated sock filled with rice to the eyelids. The main barrier to treatment response is patient compliance as many patients enthusiastically follow the instructions for a short time prior to discontinuing therapy. It is therefore important to stress that lid hygiene must be incorporated into a patient's daily routine, with cues such as placing a note on the bathroom mirror as a reminder until the routine has been solidified.

Oral or topical cyclins or macrolides are a second-line therapy for LTD. Doxycycline 20–100 mg once or twice daily or minocycline 50–100 mg once daily can be used for varying lengths of time (typically for at least 1 month). It is important to counsel patients on potential side effects of therapy which include but are not limited to gastrointestinal upset and sensitivity to sunlight. Azithromycin is an alternative medication that can be used topically or orally to treat lipid tear abnormalities (Igami et al. 2011; Luchs 2008; Greene et al. 2014). It is important, however, to remember that a rare but serious side effect of oral azithromycin is heart block (FDA 2013). Topical azithromycin 1 % (Azasite, Merck, Boston MA) can be used twice daily as an off-label treatment for LTD, often for a similar length of time as oral agents (Luchs 2008).

Tetracycline derivatives likely affect lipid deficiency both through their antibacterial and anti-inflammatory properties. Doxycycline has been shown to downregulate the expression of proinflammatory cytokines and chemokines and inhibits the activity of matrix metallopeptidase (MMP) (Stevenson et al. 2012).

A newer option for the treatment of LTD is the LipiFlow® Thermal Pulsation System (Tear Science, Morrisville, NC). This device has two arms, an interferometer (LipiView®) to aid in the diagnosis of concomitant LTD and the treatment arm (LipiFlow). The interferometer illuminates the tear film and measures the interference pattern of the reflected light. This pattern is analyzed by software included with the device and generates a thickness measurement for the lipid layer. The software then advises based on the thickness and pattern of interferometry whether the LipiFlow treatment is advised. LipiFlow uses heat and gentle pulsatile pressure to unblock obstructed meibomian glands during an in-office procedure with the goal of restoring the natural production of lipids. Twenty-one patients with LTD who received one LipiFlow treatment were found to have improved symptoms, meibomian gland secretion scores, and tear break-up times both 1 and 9 months after treatment (Greiner 2012). Its current use, however, is limited mainly by the cost of treatment as patients must usually pay out of pocket for the procedure.

1.3.5 Nutritional Considerations

There is epidemiologic support that nutrition can affect dry eye status with low levels of antioxidants being a risk factor and elevated levels of omega-3 fatty acids (FA) being a protective factor for dry eye (Cejkova et al. 2008; Cermak et al. 2003; Miljanovic et al. 2005). A multicentered, masked, randomized trial of omega-3 and omega-6 FA oral supplementation found a significant decrease in conjunctival inflammation, as measured by the percentage of HLA-DR-positive cells, in the treatment group after 3 months of therapy (Brignole-Baudouin et al. 2011). These findings, taken together, suggest that all patients with symptomatic DES can be counseled on the use of dietary supplementation with antioxidants and omega-3 FA as an adjuvant to their dry eye therapy. Omega-3 FA may improve tear health through several mechanisms including influencing inflammation and modulating meibum quality. With regard to inflammation, omega-3 FAs were found to block the production of proinflammatory eicosanoids and cytokines (IL-1 and TNF) (Stevenson et al. 2012). With regard to meibum quality, one study of women with Sjogren's syndrome found a difference in polar lipid profiles based on intake of omega-3 (Sullivan et al. 2002).

1.3.6 Recalcitrant Dry Eye Syndrome

Dry eye can be a difficult disease to treat, and there are patients who continue to have debilitating symptoms after trying all therapies listed above. In these patients, there is support for the use of autologous serum tears and/or contact lenses to alleviate disease morbidity. Autologous tears are produced by drawing a patient's blood and separating its components via centrifuge. The serum component is removed and mixed with sodium chloride to create serum tears of variable concentration (typically 20–100 %) which are dosed 4 times a day. Serum tears are believed to contain growth factors, anti-inflammatory molecules, and other proteins that help propagate their effect. Several trials have shown improvement in the signs and symptoms of DES with the use of serum tears (Urzua et al. 2012; Kojima et al. 2005). A retrospective review of Kaiser Permanente Northern California patients treated with autologous serum tears revealed that of 30 patients with a follow-up visit within 3 months of initiating therapy, 16 reported fewer DES symptoms and 12 had improvement in corneal staining. Furthermore, the use of topical lubrication and corticosteroids decreased (Dalmon et al. 2012).

Another option for patients with severe DES is the use of the prosthetic replacement of the ocular surface ecosystem (PROSE) lens (Boston Foundation for Sight, Boston MA) (Fig. 1.6). The PROSE lens is custom designed and fitted to vault the cornea and maintain a constant supply of fluid on the ocular surface. This option is typically reserved for those patients with severe ATD such as those with GVHD and radiation keratopathy. This lens improved symptoms and quality of life in 33 consecutive patients with GVHD who were unresponsive to conventional therapy (Jacobs and Rosenthal 2007).

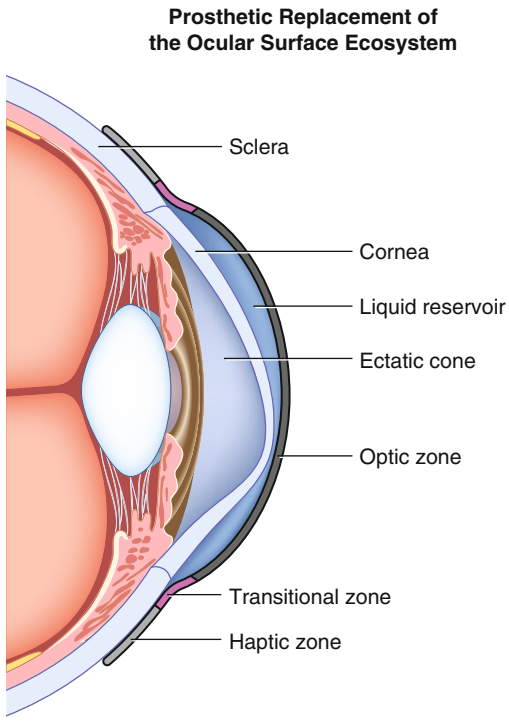

Fig. 1.6 An illustration of the prosthetic replacement of the ocular surface ecosystem (PROSE) lens as it vaults a patient's eye and maintains a constant supply of fluid on the cornea

Conclusions

While much has been learned about the pathophysiology of DES, there are still many unanswered questions regarding tear film physiology and pathophysiology. One knowledge gap is why symptoms and signs of disease often do not correspond to each other. There are many patients with severe DES symptoms and almost normal tear film indices and other with no symptoms and a very unhealthy ocular surface. Understanding the discrepancy between symptoms and signs of disease is important as it will lead to new diagnostic criteria and treatment algorithms. Other areas of active research include meibum properties and its effect on lipid health, the role of mucin in DES, ocular surface inflammatory pathways, and osmolarity in disease. While more needs to be learned about DES pathophysiology and treatment, it is important for eye care providers to acknowledge that DES is a real disease and formulate a screening and treatment algorithm to systematically address and treat patients.

Compliance with Ethical Requirements Anat Galor declares that she has no conflict of interest.

No animal or human studies were carried out by the author for this article.

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2 Advances in the Diagnosis and Management of Infectious Keratitis

Elmer Y. Tu

2.1 Introduction

All forms of infectious keratitis confer a significant personal and economic burden on those afflicted as well as on the society in which they live. While the simple treatment cost for an episode of corneal ulceration varies from less than a US$ 100.00 in India, above the average monthly wage, to over US$ 1,000.00 in Australia, the additive costs of significant visual loss and subsequent attempts for visual rehabilitation drives those costs into the thousands of dollars and beyond (Keay et al. 2008; Prajna et al. 2007). Further, the patients most commonly afflicted are working-age men and women in the third and fourth decades of life (Erie et al. 1993; Jeng et al. 2010) where lost wages and productivity not only impact during their treatment but is compounded for decades if profound visual loss results. Very significant differences exist in the incidence of infectious keratitis primarily dependent on a region's economic development which in turn affects a number of known risk factors including rates of contact lens wear, occupation, and domestic and environmental sanitation, among others. Regional incidence in the USA has been estimated to have risen from .25 to 1.0 per 10,000 person years in Olmsted county Minnesota from 1950 to 1980, although a recent study by Jeng et al. places the incidence at 2.76 per 10,000 person years in Northern California in 1999 (Erie et al. 1993; Jeng et al. 2010). In contrast, the incidence in South India was estimated to be 11.3 per 10,000 in 1993, potentially affecting more than 800,000 individuals yearly (Gonzales et al. 1996). Further, visual outcomes are highly dependent on prompt diagnosis and treatment with relatively dismal rates in regions with limited health-care resources to relatively reasonable outcomes in developed health-care systems where nearly 90 % will maintain a best corrected vision of better than 20/40 and where blindness is uncommon (Burton et al. 2011; Stapleton et al. 2008).

An understanding of associated risk factors is integral to the diagnosis, management, and prevention of infectious keratitis. In developing countries, trauma is the primary risk factor and combined with environmental exposure leads to a predominance of fungal keratitis (Gopinathan et al. 2009). In developed countries, agricultural and work-related trauma is far less common with contact lens-related keratitis comprising approximately 1/3 of all cases (Ibrahim et al. 2009). Consequently, the more favorable prognosis for these cases of bacterial keratitis and, to a lesser extent, *Acanthamoeba* keratitis shifts the predominance of corneal blindness to herpetic

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keratitis in these regions. For nonviral corneal infections, the most important factor in a successful outcome is limitation of corneal scarring through rapid, effective eradication of the offending pathogen and control of inflammation through prompt diagnosis.

2.2 Diagnosis

The most important step in the diagnosis of a potential infectious keratitis is the recognition of the possibility of infection. The history should identify the circumstances of the infection including any specific risk factors that would both suggest an infection as well as a potential etiology primarily for the purpose of identifying the need for special cultures or other diagnostic interventions not routinely performed (Table 2.1). For example, most bacterial infections have a rapid, crescendo clinical course while atypical mycobacterial, fungal, and parasitic infections are usually more slowly progressive but can be more painful in the later stages. Patients with herpes simplex keratitis will often have a history of oral or genital lesions as well as a history of recurrent red eye or keratitis. Failure of prior therapy, especially of antibacterial and antiviral therapy where clinical resistance is uncommon, should direct suspicion to other pathogen classes.

Clinical examination may also be helpful, although acanthamoebal and herpetic infections at various stages may mimic other pathogens as well as noninfectious etiologies of keratitis. Multiple studies have, however, confirmed the pitfalls of basing empiric treatment solely on the history and clinical appearance, but they may offer direction in the absence of positive studies (Dahlgren et al. 2007; Mascarenhas et al. 2012; Dalmon et al. 2012). Prior corticosteroid use will significantly alter the appearance and prognosis of any form of infectious keratitis and should be noted in context to its clinical appearance. Corneal scrapings offer minimal volume for examination and, therefore, need to be apportioned carefully to the studies that offer the highest probability of yield. Standard tests include Gram and Giemsa stains, direct plating of blood agar and chocolate agar for bacterial species, as well as Sabouraud's dextrose agar (Fig. 2.1) without antifungal additives for fungal isolation and a broth or other media for anaerobic organisms (Bhadange et al. 2013). Superficial scrapings may be obtained either with a moistened calcium alginate swab or metallic instrument such as a platinum spatula or scalpel blade with reasonably equal yields (Benson and Lanier 1992).

2.2.1 Bacteria

The most common type of corneal infections in developed countries is caused by bacteria usually presenting as a single, suppurative lesion with significant pain, photophobia, and intraocular inflammation (Fig. 2.2). A history of ocular surface compromise, chronic corticosteroid use, ocular surgery, and/or contact lens wear should suggest first a bacterial etiology. Besides simple detection of bacteria, a Gram stain should be helpful in directing therapy since the activity of most antibacterials act on the bacterial cell wall type identified by a Gram-positive or Gram-negative result. Unfortunately, numerous studies have shown a poor correlation with subsequent culture results making the Gram stain unreliable in this regard (Sharma et al. 2002). In an untreated ulcer, standard testing methods should yield an organism in about 70 % of cases (Bourcier et al. 2003). Acid-fast stains may be more helpful in detecting atypical mycobacteria in the setting of chronic corticosteroid use in ocular surface disease or, more recently, LASIK surgery (Fig. 2.3). These lesions are minimally necrotic with small raised white lesions that are gritty on corneal scraping. Pain is often significant in these patients. Lowenstein-Jensen media and 7H11 agar slants offer an environment conducive to the isolation of these organisms. Nocardia, a filamentous bacterium, is also partially acid fast and is most often detected with Gram or acid-fast stains in about 65 % of cases and grow slowly on charcoal agar with a yeast extract additive (BCYE) (DeCroos et al. 2011). The lesions may have a wreath-like appearance with raised edge

Table 2.1 Diagnostic tests for microbial keratitis

Organism	Stains	Culture media	PCR target	Confocal microscopy
Bacteria				
Aerobic	Gram	Blood	16 s RNA	No, exc. specific patterns, e.g., infectious crystalline keratopathy
	Giemsa	Chocolate		
	Acridine orange	Broth (thioglycollate, eugonic, etc.)		
Anaerobic	Gram	Blood (anaerobic incubation)	16 s RNA	No
	Giemsa Acridine orange	Broth (thioglycollate, eugonic, etc.)		
Mycobacteria	Acid fast	Lowenstein-Jensen	16 s RNA	No
	Ziehl-Neelsen	7H11		
Nocardia	Gram	Buffered charcoal agar with yeast	Hsp65	Yes
	Acid fast	extract (BCYE) Sabouraud's dextrose agar (SDA) slant	16 s rRNA	
Fungi				
Yeasts	Giemsa	SDA with chloramphenicol or gentamicin	18 s rRNA	Yes
	Periodic acid-Schiff	Brain Heart Infusion (BHI)	28 s rRNA	
	Calcofluor white	Blood (25 °C)	ITS	
Filamentous molds	Giemsa	SDA with chloramphenicol or gentamicin	18 s rRNA	Yes
	Calcofluor white	Brain Heart Infusion (BHI)	28 s rRNA	
	Acridine orange Gomori methenamine silver KOH prep	Blood (25 °C)	ITS	
Virus				
Herpes simplex	Direct fluorescence antigen (DFA)	Human cell line (A549, MRC-5, others)	Thymidine kinase	No
	Tzanck	Serotyping	DNA polymerase	
Adenovirus	Indirect immunofluorescence	Human cell line	Hexon	No
		Serotyping	Fiber	
Parasitic				
Acanthamoeba	Giemsa	Non-nutrient agar with bacterial overlay	18 s rDNA	Yes
	Calcofluor white	BCYE		
	Acridine orange KOH Hematoxylin-Eosin	Sabouraud's		
Microsporidia	Giemsa	Cell lines	16 s rRNA	Yes, uncommon
	Calcofluor white	Monkey (Vero)	18 s RNA	
	Modified trichrome	Rabbit (RK-13)	ITS	
	Gram	Human (MRC-5) Canine (Madin-Darby)		

and an irregular base. Antibiotic sensitivity testing should be performed on all isolates so that the information is available if a patient does not respond appropriately to empiric therapy.

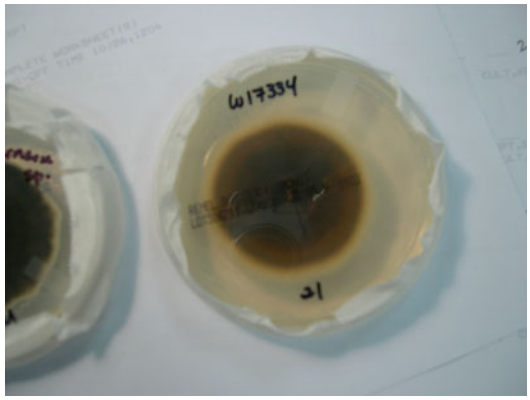

Fig. 2.1 A subcultured colony of an *Alternaria* alternata keratitis isolate on Sabouraud's agar

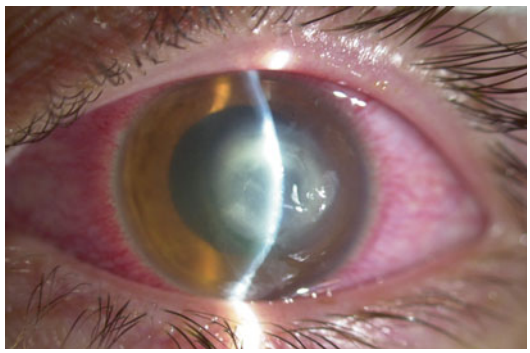

Fig. 2.2 An acutely suppurative contact lens-related *Pseudomonas* corneal ulcer

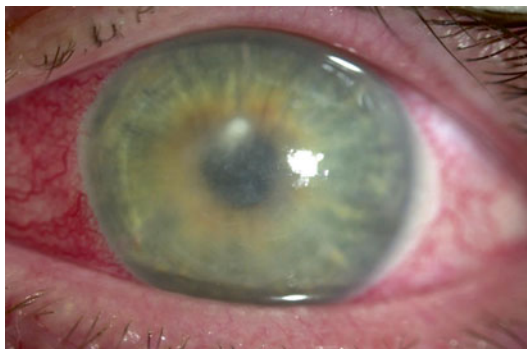

Fig. 2.3 Atypical mycobacteria after LASIK with limited inflammation sequestered in the corneal interface

2.2.2 Fungi

The presentation of fungal keratitis is species dependent with the most common filamentous mold, *Fusarium*, presenting early with significant pain and proportionally less inflammation than a comparable bacterial ulcer but eventually becoming more infiltrative and characterized by a hypopyon, endothelial plaque, satellite lesions, as well as severe pain and injection (Fig. 2.4). Fusarium may rapidly and directly penetrate into the deep stroma and past an intact Descemet's membrane to enter the intracameral space. However, slower-growing species of *Alternaria* or *Beauveria* may be much more indolent with less inflammation, less pain, and a more superficial appearance. *Candida* spp. are the most common overall fungal keratitis pathogen in the more temperate climates of North America and present initially with a creamy-white, superficial infiltrate, but its pseudohyphae may penetrate into deep stroma (Figs. 2.5 and 2.6).

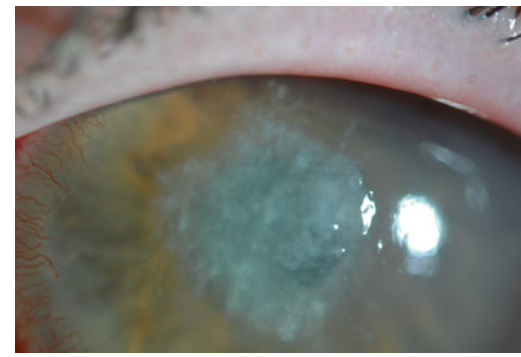

Fig. 2.4 Fusarium keratitis in a contact lens wearer

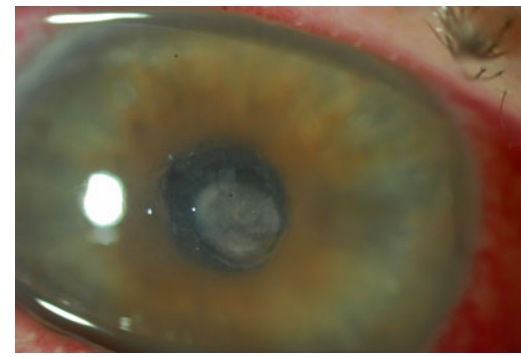

Fig. 2.5 *Candida* ulcer in a patient on chronic topical corticosteroids

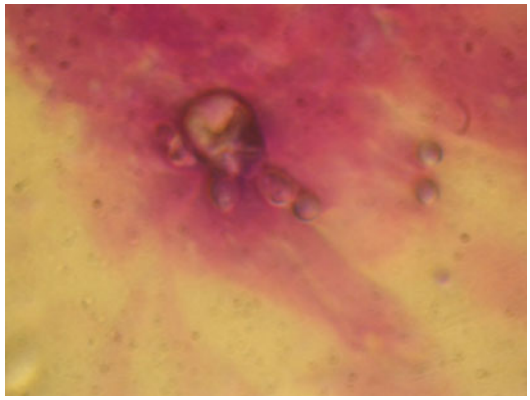

Fig. 2.6 Budding *Candida* sp. on a Diff-Quik smear (original magnification 100×)

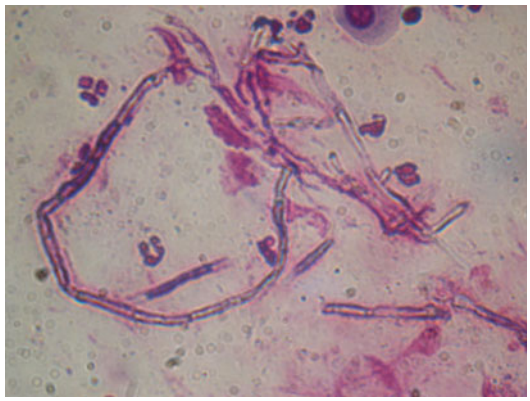

Fig. 2.7 Diff-Quik stain of *Fusarium* sp. hyphae from a corneal scraping (original magnification 100×)

Although yeast and filamentous molds may both be detected on Gram stain, molds are more readily identified on stains that highlight cell walls such as a Giemsa stain and KOH preps where hyphae are easily detected (Fig. 2.7). Similarly, acridine orange and calcofluor white stains have been shown to be more sensitive in detecting larger pathogens like fungi and acanthamoeba but require an epifluorescent microscope to excite the stain (Gomez et al. 1988). The majority of ocular fungal pathogens can be isolated with Sabouraud's dextrose agar or Brain Heart Infusion Agar with non-antifungal additives, e.g., chloramphenicol or gentamicin, since these additives do not affect the saprophytic fungi usually nonpathogenic in other organs (Bhadange et al. 2013). Alternatively, fungal keratitis pathogens will also grow on standard

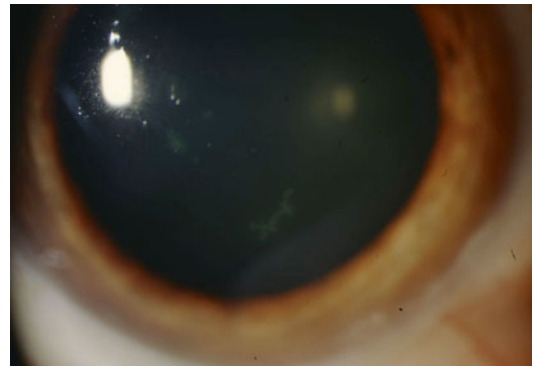

Fig. 2.8 HSV epitheliitis seen in a chronically systemically immunosuppressed chemotherapy patient

blood and chocolate agar plates incubated at 36 °C. Antifungal sensitivities have been poorly reflective, historically, of clinical drug efficacy, but recent refinement of CLSI testing methods and break points have improved correlation of in vitro and in vivo antifungal activity, the knowledge of which can be critical to a successful outcome (Oechsler et al. 2013).

2.2.3 Virus

A diagnosis of herpetic viral disease is most commonly based on the history and clinical appearance. Herpes simplex keratitis is due more commonly HSV 1, associated with above-the-waist disease, but HSV 2 is also commonly isolated (Fig. 2.8). Patients may have a history of oral or genital herpes simplex as well as a past history of vesicular lesions in and around the eye. Although recurrent disease may surface from latency established from a primary infection from any dermatome served by the trigeminal ganglion, recurrences from prior corneal infection is usual. Epithelial HSV keratitis demonstrates a characteristic dendritic pattern with terminal bulbs, leaving an imprint on the anterior stroma after resolution. Geographic lesions may also occur with both stained by Rose Bengal of fluorescein dyes. Primary disease is almost always epithelial, but recurrences may be an epithelial or stromal interstitial keratitis with a conjunctival limbitis, endotheliitis, or

uveitis less common. Patients with atopic keratoconjunctivitis are especially susceptible to severe, bilateral disease. The need for microbiologic confirmation is restricted to neonates and to those patients where the diagnosis is in question. Samples may be obtained through epithelial debridement, swab, or impression cytology of the superficial lesion and submitted for culture, immunofluorescence (IFA), or polymerase chain reaction (PCR) detection. Culture is the least sensitive method while both PCR and IFA have been shown to have similar sensitivities (60–80 %) and high specificities for the detection of HSV-1 in ocular samples (Farhatullah et al. 2004). Serologic testing may be helpful in naïve patients, especially children to rule out HSV as a potential pathogen, but a significant majority of adults have had previous exposure making a positive test unhelpful.

Other herpesviruses including herpes zoster (HZV), Epstein-Barr virus, and cytomegalovirus have been described to cause keratitis. Herpes zoster may manifest as pseudodendritic lesions (poorly branching, absent terminal bulbs), mucoid plaques, stromal keratitis, and/or uveitis characteristically leaving sectoral iris atrophy. Whether some or all of these entities represent immune response or active viral disease is controversial, but virus has been detected in late dendritic disease of HZV which are highly responsive to antiviral therapy (Pavan-Langston et al. 1995). Epstein-Barr virus more commonly causes a nummular keratitis but may also manifest as subepithelial infiltrates or a deep stromal keratitis. Acute and convalescent titers of Epstein-Barr-related IgM and IgG and EBV early antigen may be helpful in this setting. Monoclonal antibodies and PCR of corneal scrapings have been reported but are rarely done (Pflugfelder et al. 1990). Adenoviral epidemic keratoconjunctivitis may similarly be isolated and genotyped from swabs of the ocular surface but is seldom performed except in the setting of tracking large outbreaks of disease. A rapid in office antigen test has been available with a reasonable sensitivity (88 %) and specificity (91 %) to guide treatment and isolation of certain patients (Sambursky et al. 2006).

2.2.4 Parasitic

A number of different parasitic organisms can cause corneal disease. Parasites that are primarily spread to the cornea from endogenous sources include *Onchocerca*, *Leishmania*, and *Trypanosoma* are a devastating source of corneal blindness worldwide. They manifest as peripheral stromal interstitial keratitis at their site of entry, although frank corneal ulceration may sometimes occur. *Acanthamoeba* represents the most common ocular parasitic pathogen in Western world. Contact lens wear (>90 %) is the strongest risk factor for *Acanthamoeba* keratitis in that region with nearly 20 cases per million contact lens wearers per year afflicted in the UK with similar numbers now in the USA (Tu and Joslin 2010). Additional risk factors include exposure to contaminated domestic or environmental water while wearing or caring for the lenses and other hygiene related factors (Tu and Joslin 2010). The infection presents in many forms including a diffuse or pseudodendritic epitheliopathy, anterior stromal keratitis, interstitial keratitis, a ring infiltrate, and/or perineural infiltrates leading to confusion with other infectious and noninfectious processes (Fig. 2.9). Pain in the early stages is minimal but increases with the presence of perineural disease or deep stromal keratitis. Corneal scrapings can be subject to Giemsa stain, acridine orange, KOH preps, and calcofluor white for diagnosis with reasonable sensitivity and specificity (Fig. 2.10). Culture on non-nutrient agar with a bacterial overlay

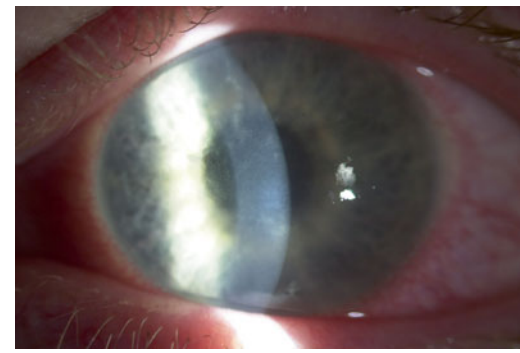

Fig. 2.9 Acanthamoebal epitheliopathy with perineuritis

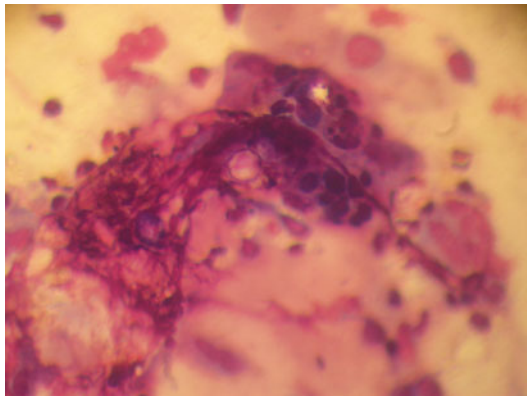

Fig. 2.10 Acanthamoebal cysts on Diff-Quik stain demonstrating classic "pores" in the cyst wall (original magnification 100×)

Fig. 2.11 Confocal microscopy of *Acanthamoeba* exhibiting the classic paired "coffee-bean" appearance on a slit-scanning instrument

(higher yields obtained with *Enterobacter* than *E. coli*) or charcoal agar is relatively simple, but sensitivities are generally low between 35 and 50 %. *Microsporidia* keratitis has been increasingly described in immunocompetent individuals as causing an epithelial/subepithelial keratitis and a stromal interstitial keratitis. These patients usually have some history of exposure to soil or water and have been predominantly described in South Asia. Because it is an obligate intracellular organism, culturing microsporidia is difficult, requiring canine kidney cells for growth. Histologic stains have, therefore, been relied upon to make the diagnosis.

2.2.5 Corneal Imaging and Corneal Biopsy

Confocal microscopy refers to the precise timing of illumination and imaging at a specific focal point or plane to achieve high degrees of magnification, minimizing motion blur and light scatter. The cornea is ideal for this type of imaging because of its relative clarity and lack of reflective elements, to highlight areas of abnormality. Resolution of these instruments are in the 1–2 μm range, making it impossible to image most bacteria and viruses, but specific patterns, e.g., infectious crystalline keratopathy where a biofilm insinuates itself through cornea lamellae, owl eye cells in CMV endotheliitis, and filamentous bacteria (Nocardia) can be recognized (Elmallah et al. 2006; Vaddavalli et al. 2006;. Kobayashi et al. 2012). The greatest utility of the instrument in corneal infectious disorders has been to detect larger pathogens which do not cause dense suppuration such as fungi, acanthamoeba, and, to a lesser extent, *Microsporidia* (Sagoo et al. 2007). Both cysts and trophozoites can be seen, but the cysts are most characteristic observed as a double-walled cyst or a paired "coffee bean" appearance isolated or in chains (Fig. 2.11). The detection of *Acanthamoeba* keratitis has been shown in some centers to have a high sensitivity (>90 %) and high specificity (100 %) when compared to culture and other microbiologic methods (Tu et al. 2008a) but has also been reported to be significantly lower in other facilities (Hau et al. 2010). Similar results have been reported in the detection of the slender, septate branching of corneal fungal pathogens (Vaddavalli et al. 2011; Tu and Park 2007) as well as yeast. Confocal microscopy is invaluable in imaging deeper lesions without easy access for scraping such as *Candida* interface keratitis after endothelial keratoplasty (Lee et al. 2011).

Although confocal microscopy has largely supplanted corneal biopsy in many institutions, it remains a relevant technique for refractory or deep keratitides that otherwise defy identification. A number of techniques have been described,

but all involve dissection of a sample of solid corneal tissue either from the anterior lamellae or from mid- to deep stroma using a flap created manually or via a femtosecond laser (Kim et al. 2008). Specimens are sent for histopathology and microbiologic studies with a success of greater than 40 % in identifying a causative organism in a recent review (Younger et al. 2012). Corneal scarring or perforation can be significant risks to corneal biopsy.

2.2.6 Molecular Diagnosis

Molecular diagnosis refers to identification of pathogens from their molecular signature, primarily DNA or RNA which by definition is unique to each organism. Utilizing primers either specific to an organism, a class of organisms, or universal primers, a single copy of DNA can be multiplied a million times over a period of hours, allowing its easy sequencing. Once its sequence has been determined, it can be matched fully or partially to previously sequenced organisms for identification. Because of its high sensitivity, however, false-positive results can be seen because of contamination at any stage of specimen recovery or with organisms that may be present or nonviable but not pathogenic. Extraneous compounds such as topical anesthetic or fluorescein can decrease the sensitivity of the assays (Goldschmidt et al. 2006). Quantitative and real-time PCR with appropriate validation can reduce the number of false-positive test results. It is most useful in detecting organisms not normally present in the eye and/or is difficult to confirm by other means. For example, PCR of tears or corneal scrapings directed toward the HSV polymerase gene has largely supplanted culture for herpes simplex ocular disease because of culture's low sensitivity for an organism which is not normally found in the eye (Farhatullah et al. 2004; Satpathy et al. 2011). Identification of bacterial pathogens is based on their 16 s ribosomal DNA sequences (Prabhasawat et al. 2010), while a more significant experience with the 18 s ribosomal RNA region for the diagnosis of fungal keratitis has proven its utility (Vengayil et al. 2009; Ferrer and Alio 2011). Recent development of acanthamoebal PCR should lead to its increasing study and validation (Thompson et al. 2008; Goldschmidt et al. 2009).

2.3 Management

Unlike many other organ systems, comparatively small alterations in corneal structure and clarity can profoundly affect lifelong visual function. This combined with the relative inability of the corneal immune response to limit corneal infection makes it imperative to rapidly eliminate pathogens and modulate the corneal immune response to retain as much vision as possible. Empiric therapy is, therefore, directed not only against the most likely responsible pathogens but also against those pathogens most rapidly destructive of the corneal stroma specifically Gram-positive and Gram-negative bacteria. Although other pathogens may be more common in certain regions and mechanisms of injury, atypical bacteria, acanthamoeba, microsporidia, filamentous molds, and yeast are all comparatively slow growing, whereas bacteria may destroy the cornea in a matter of hours.

Since the availability and success of single-drug empiric therapy in the early 1990s, corneal scrapings for culture and smear are no longer routinely employed as part of the initial management of a routine bacterial corneal ulcer. However, microbiologic yields are highest before initiation of any antimicrobial therapy and should be strongly considered in large or deep ulcers, ulcers near the visual axis, ulcers failing prior therapy, and ulcers with either an atypical appearance or history at presentation. Suspicion for a larger, atypical organism at any stage should prompt consideration of confocal microscopy, although corneal biopsy should be reserved for later in the process because of its more invasive nature and higher risk of complication. Ongoing therapy should be directed by initial response or lack of response to initial therapy and directed by microbiologic examination when available.

2.3.1 Bacteria

Since the commercial availability of broad-spectrum fluoroquinolones in the early 1990s, single-drug therapy of presumed bacterial keratitides has been shown to have similar outcomes to multiple, fortified drug therapy (O'Brien et al. 1995; Constantinou et al. 2007). Single-drug therapy has the advantage of availability, easier compliance, and less time off of work, but some studies have pointed to a higher rate of corneal perforation presumably related to its activation of matrix metalloproteinases (Constantinou et al. 2007; Mallari et al. 2001). Although they are considered broad spectrum, having activity against both Gram-positive and Gram-negative bacteria, fluoroquinolones are commonly divided into second (ciprofloxacin, ofloxacin), third (levofloxacin), and fourth (moxifloxacin, gatifloxacin, besifloxacin) generations which predicts their specific antibacterial efficacy. Of these, only besifloxacin has pursued the FDA indication, but more extensive clinical studies of infectious keratitis have sufficiently established the particular spectrums of efficacy of the other fluoroquinolones in bacterial corneal ulceration. In general, the best Gram-negative activity, including *Pseudomonas*, is seen with the second-generation fluoroquinolones, while the fourth-generation fluoroquinolones have added some Gram-positive and atypical mycobacterial coverage. Other antibiotics need to be "fortified" to achieve effective corneal concentrations and combined together to afford the broad-spectrum coverage needed for empiric therapy. This usually consists of topical vancomycin or cephalosporin prescribed with an aminoglycoside like gentamicin or tobramycin.

Inducible antibiotic resistance is increasingly seen in both systemic and ocular infections. For corneal isolates specifically, methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasingly reported in postsurgical corneal ulceration, and the laboratory resistance of *Pseudomonas* sp. to fluoroquinolones is rising secondary to both local and systemic use (Ray et al. 2013; Fintelmann et al. 2011). Despite laboratory resistance, topical ophthalmic antibiotics generally deliver sufficient concentrations of drugs to be clinically effective, but infections may be slower to resolve (Wilhelmus et al. 2003). While MRSA demonstrates high levels of fluoroquinolone resistance, vancomycin still remains almost universally effective against ocular pathogens. Vancomycin-resistant enterococcus is a rare but increasingly reported pathogen for infectious keratitis but may be sensitive to newer antibiotics like linezolid (Tu and Jain 2013). Similarly, 4th-generation fluoroquinolones have some activity against atypical mycobacteria, but primary therapeutic options remain topical fortified amikacin or clarithromycin with recent reports of linezolid sensitivity. *Nocardia* spp. are sensitive to fluoroquinolones but may also respond to amikacin and topical sulfamethoxazole-trimethoprim.

Topical corticosteroids should reduce inflammatory damage by modulating corneal damage in infectious keratitis but theoretically has the potential to worsen infections that require an intact immune response for clearance of the pathogen. Multiple studies have demonstrated a worsening of outcomes in vitro and in vivo when corticosteroid administration precedes effective antibacterial therapy but were less definitive when administered with or after initiation of antibiotics (Wilhelmus 2002). A recent prospective, randomized trial of corticosteroid administration 48 h after antibiotic initiation demonstrated no increase in complications with a trend toward improved visual acuity in those patients presenting with severe visual loss (Srinivasan et al. 2012). Future studies should help define the optimal indications and timing for administration of corticosteroids for bacterial keratitis.

2.3.2 Fungi

The treatment of fungal keratitis is significantly more challenging than bacterial keratitis because of the nature of fungal infections of the cornea and the limited options for topical and systemic therapy. The recognition of fungal keratitis is usually delayed, and fungal pathogens are often more deeply infiltrative which further hampers

sufficient delivery of poorly penetrating antifungals to the deeper cornea (Table 2.2). Natamycin, an ophthalmic suspension of the polyene class drug pimaricin, is the only commercially available antifungal in commercial production. It is most efficacious against filamentous molds and was recently shown to be superior to voriconazole in the treatment of *Fusarium* keratitis, the most common fungal corneal pathogen, and similarly effective for other molds (Prajna et al. 2013). Topical amphotericin B 0.15 %, a compounded polyene antifungal, is effective against most fungi and was considered the drug of choice for yeast pathogens. Both drugs are associated with considerable ocular surface toxicity and irritation with topical use. Systemic use of amphotericin B, 1st- and 2nd-generation triazoles such as ketoconazole, fluconazole, and itraconazole have been described, but penetration into ocular tissues for the azoles is limited and severe side effects from all of the drugs limit their utility in all but the more refractory cases, especially amphotericin B. More recent preparations are much better tolerated. Compounded topical formulations of clotrimazole, itraconazole, and fluconazole have also been described for specific uses (Tu 2009). Because of the long turnaround time from order to result, all suspected fungal ulcers should be isolated, definitive identification pursued and antifungal sensitivities obtained without regard to the initial clinical response so that therapeutic options are available if and when treatment fails.

Table 2.2 Current antifungal drugs utilized for ocular infections

Drug	Topical concentration (common dosage)	Intrastromal concentration	Subconjunctival concentration	Intracameral concentration	Systemic dosing	Spectrum of activity
Polyenes						
Natamycin	5 %	N/A	N/A	N/A	N/A	Filamentous molds Minor activity against yeasts
Amphotericin B	0.1–0.5 % (0.15 %)	5 mcg/0.1 cc	1 mg/0.5 ml	5–10 ug/0.1 cc	0.1–1.5 mg/kg daily dosage slow IV infusion	Broad-spectrum activity against both molds and yeasts
Imidazoles						
Ketoconazole	5 %				2–400 mg po daily	
Clotrimazole	1 %	N/A	N/A	N/A	N/A	Broad spectrum
Miconazole	10 mg/ml	N/A	5 mg/0.5 cc	N/A	N/A	Broad spectrum
Triazoles						
Itraconazole	1 %	N/A	N/A	N/A	200 mg po bid	Broad spectrum
Fluconazole	2 mg/ml	N/A	N/A	N/A	200 mg po QD	Broad spectrum
Voriconazole	1 %	50 mcg/0.1 cc	N/A	50–100 mcg/0.1 cc	200 mg po bid	Broad spectrum
Posaconazole	200 mg/5 ml	N/A	N/A	N/A	400 mg po bid	Broad spectrum
Echinocandins						
Caspofungin	0.5 %	N/A	N/A	N/A	N/A	Yeasts, selected molds
Micafungin	0.1 %	N/A	N/A	N/A	N/A	Yeasts, selected molds

A number of new antifungals from the triazole (voriconazole, posaconazole, ravuconazole) and echinocandin (caspofungin, micafungin, anidulafungin) classes have been recently introduced. The triazoles are better absorbed, achieve higher tissue levels, and have a broader spectrum than previous azoles. Multiple reports of clinical resolution of keratitis and consecutive intracameral fungal endophthalmitis have been reported with systemic administration of these drugs (Tu and Park 2007; Tu et al. 2007). Although topical voriconazole was shown to be inferior to natamycin in *Fusarium solani* keratitis, it has been reported to be successful in a number of atypical fungal keratitides highlighting the utility of antifungal sensitivity testing for individual isolates. Since it is highly aqueous soluble, voriconazole as well as amphotericin B has been delivered intrastromally in recalcitrant fungal ulcers with sometimes dramatic resolution after a single injection (Garcia-Valenzuela and Song 2005; Prakash et al. 2008). Unlike bacterial keratitis, a certain number of fungal corneal infections will not be amenable to medical cure either due to pan-resistance to antifungals or because of the extent of infection. Circumscribable lesions which are responding poorly to medical therapy should be considered for early corneal transplantation. The lack of highly effective antifungals and the potentiation of fungal proliferation makes the use of corticosteroids at any point during routine treatment inadvisable. For this reason, alternative immune suppressants such as topical cyclosporine have been utilized post-keratoplasty.

2.3.3 Virus

In immunocompetent individuals, herpes simplex epithelial keratitis is a self-limited disease. Visual disability from a single episode is uncommon but increases significantly with reactivation of the virus from its latent state in the trigeminal ganglia resulting in repeated episodes epithelial keratitis, stromal or endothelial involvement, and/or uveitis (Young et al. 2010). Therapy is, therefore, directed against primary involvement of the cornea, although infection in any dermatome of CN V may result in corneal recurrence and prevention of recurrent disease. Although topical and systemic therapy is often prescribed to patients with periocular outbreaks, avoidance of direct inoculation is critically important. For corneal epithelial disease, commercially available ophthalmic treatments include topical trifluridine, the most epithelially toxic, and ganciclovir in the USA and topical acyclovir abroad which can reduce the duration of epithelial disease by 1–2 days (Table 2.3). Use of topical drugs should be limited to a 10-day period before reassessment for potential toxicity simulating active disease. The Herpetic Eye Disease Study did not find that a 3-week course of oral acyclovir (400 mg 5×/day) prevented progression of an epithelial HSV keratitis to stromal keratitis or iritis, but did find a suggestion that oral acyclovir may be beneficial in treating HSV iritis. Although topical corticosteroids did not affect final outcome, resolution of HSV keratitis symptoms was significantly more rapid when used in conjunction with an antiviral. Importantly, the study did find that long-term prophylaxis with oral acyclovir

Table 2.3 Current antiviral drugs utilized for ocular infections

Drug	Topical concentration	Systemic dosing HSV	Systemic dosing HZV
Acyclovir	3 % 5×/day	400 mg po 5 ×/day	800 mg po 5×/day
Famciclovir	N/A	250 mg po 3/day	500 mg po 3×/day
Valacyclovir	N/A	500 mg po tid	1 g po tid
Ganciclovir	0.15 % 5×/day	N/A	N/A
Trifluridine	1 % 9×/day	N/A	N/A
Idoxuridine	0.1 (soln)–1.0 (ointment)%	N/A	N/A
Vidarabine	3 % 5×/day	N/A	N/A
Valganciclovir	N/A	CMV – 900 mg po bid	

(400 mg 2×/day) reduced by half the number of recurrences of HSV ocular disease. This benefit has been confirmed in subsequent series (Young et al. 2010). Valacyclovir is a prodrug which is converted to acyclovir in vivo and demonstrates oral absorption ~5 times greater than oral acyclovir. This results in lower-frequency dosing which may be better tolerated and improve compliance with long-term prophylaxis. Long-term prophylaxis, however, may select for acyclovir-resistant strains, already high in patients with HSV keratitis, which would also be resistant to the common systemic alternatives of valacyclovir, famciclovir, or ganciclovir (van Velzen et al. 2013). The development of Herpes simplex vaccines has the potential to reduce both primary infection as well as suppress viral reactivation but has yet to be realized.

Herpes zoster keratitis is also usually self-limited and is not as prone to frequent recurrences, although chronic stromal keratitis can be blinding. Topical antivirals are usually unnecessary except in late pseudodendritic disease or mucoid plaques. Inflammatory stromal keratitis can be treated with topical corticosteroids. Both herpes simplex and herpes zoster keratitis, however, may develop blinding complications related to neurotrophic keratitis and/or chronic stromal inflammation. Persistent epithelial defects may lead to corneal melting and scarring, metaherpetic lesions may mimic persistent infection but require corticosteroids for resolution, and chronic stromal keratitis may lead to vascularization and corneal opacification. Because the prognosis for corneal transplantation is dismal in this setting, every effort should be taken to preserve sufficient clarity of the patient's cornea with adequate immunosuppression, treating the corticosteroid side effects of cataract formation and glaucoma as needed. The effect of the increasing use of herpes zoster vaccines on recurrent ocular disease is yet unknown, but selective application of the vaccine may have unintended consequences in increasing reactivations in patients currently excluded from vaccination windows.

Although adenoviral disease is normally of minimal visual impact, the sheer number of sufferers and the uncommon moderate visual disability caused by EKC attracts attempts at treatment. Several promising antiviral compounds have been found to be of limited benefit and have been abandoned. Topical betadine corticosteroid combinations are currently being studied. Despite the availability of topical ganciclovir, no specific justification for its use in this disorder has yet surfaced.

2.3.4 Parasitic

The management options for *Acanthamoeba* keratitis are limited, and visual outcomes are highly dependent on early recognition and initiation of effective therapy (Tu et al. 2008b). A high index of suspicion should be held in all atypical keratitides especially in contact lens wearers. Once a diagnosis is made, debridement of all involved epithelium to debulk the infection is performed both for therapeutic and diagnostic purposes. The mainstay of therapy are the biguanides, either chlorhexidine 0.02 % or polyhexamethylene biguanide (PHMB) 0.02 % administered hourly for the first several days followed by a slow taper usually over several months based on clinical response (Table 2.4) (Dart et al. 2009). Adjunctive use of diamidines, propamidine or hexamidine, can be helpful in the early stages of treatment to inhibit encystment and kill active trophozoites but exhibit cumulative toxicity over several weeks. A minority of cases may be recalcitrant requiring increased biguanide concentrations, increased frequency of administration, and/or the addition of systemic medications. Topical neomycin and clotrimazole have also been described. Other previous generation azoles have been added systemically with limited evidence of benefit. The successful adjunctive use of topical and the sole use of oral voriconazole have been reported in the cure of *Acanthamoeba* keratitis (Tu et al. 2010; Bang et al. 2010). *Acanthamoeba* keratitis may also cause adnexal disease consisting of limbitis, scleritis, and dacryoadenitis as well as late complications of glaucoma, cataract, and permanent mydriasis. Corneal melting, persistent epithelial defects, and persistent stromal disease can severely complicate treatment. No definitive evi-

Table 2.4 Current antiparasitic drugs utilized for ocular infections

Drug	Topical dosing	Systemic dosing
Aminoglycosides		
Neomycin	15 mg/cc Q1h	N/A
Diamidines		
Propamidine	0.1 % Q1h	N/A
Hexamidine	0.1 % Q1h	N/A
Biguanides		
Chlorhexidine	0.02–0.6 % Q1h	N/A
Polyhexamethylene biguanide	0.02–0.06 % Q1h	N/A
Triazoles		
Itraconazole		200 mg po bid
Voriconazole	1 % Q1h	200 mg po bid
Anti-microsporidial		
Fumagillin	0.3 % qid	N/A
Albendazole	N/A	400 mg po bid × 1 week then 200 mg po bid × 2 weeks then 200 mg po daily × 1 week
Fluoroquinolones	Q1h tapered according to response	N/A
Mechanical debridement	As needed	

dence yet exists for a detrimental effect of corticosteroid therapy on *Acanthamoeba* keratitis, and many of the corneal and extracorneal complications are immune in nature but still should be avoided if not needed. Selected cases may benefit from immune suppression either with corticosteroids or other systemic drugs to preserve ocular function (Dart et al. 2009). Similarly, the prognosis for corneal transplantation in active corneal disease has improved significantly with the use of effective anti-acanthamoebal therapy and should be considered a well-circumscribed, recalcitrant disease (Kitzmann et al. 2009). Microsporidial disease remains rarely described in the USA. Increased incidence of disease in Asia is a considerably different disease entity than previously described in immunosuppressed patients, occurring in immunocompetent individuals and responding to various commercially available topical antibacterials as well as observation only (Tu and Joslin 2012). Some patients will still progress to corneal transplantation, however.

Collagen cross-linking, a therapeutic intervention designed to "harden" the cornea with riboflavin-assisted UV irradiation for cases of corneal ectasia, has been recently described for a number of cases of infectious keratitis of varying etiologies. In vitro studies, however, show no effect on acanthamoebal cysts or fungi and a variable effect on most bacteria with the concentrations of riboflavin and UV exposures utilized for cross-linking. The depth of penetration of standard treatments is also limited to the anterior cornea. Recent studies have demonstrated a reduction in corneal necrosis and overall improvement in bacterial ulcers and some acanthamoebal ulcers as an adjunctive treatment to medical therapy with fungal ulcers being the least responsive (Price et al. 2012; Makdoumi et al. 2010; Alio et al. 2013). There is little agreement on the mechanism, indications, or complications for collagen cross-linking and will be the continued subject of studies for the near future.

Conclusions

Infectious keratitis can lead to significant ocular morbidity and loss of overall function and represents both a diagnostic and management challenge. Prevention and prompt diagnosis relies on an understanding of the prevalent risk factors for corneal infection which vary from contact lens wear in more economically developed areas to trauma in less developed areas. Common pathogens will vary based on

these risk factors as well as climate, local immunosuppression, and mechanism of injury. While almost all initial empiric therapy for infectious keratitis must target common bacterial pathogens because of their propensity for rapid corneal destruction, a high index of suspicion should be held for unresponsive or atypical appearing keratitides. All of these patients should be subject to culture and sensitivity testing. With all forms of infectious keratitis, final visual outcomes are highly dependent on minimizing delay in the administration of effective antimicrobial treatment. Topical ophthalmic administration provides a highly concentrated route of drug delivery. Treatment efficacy should be judged by frequent observation regardless of culture results and changed if found to be ineffective. A flexible approach to utilizing available diagnostic techniques and treatment options alongside innovative drugs, alternative routes of administration, and judicious use of immunosuppressants will improve long-term visual outcomes.

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Allergic Disease of the Eye

3

Neal P. Barney and Scott T. Bauer

3.1 Introduction

Allergic eye disease is typically divided into four distinct types: allergic conjunctivitis subdivided into seasonal and perennial allergic conjunctivitis (SAC and PAC, respectively), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and giant papillary conjunctivitis (GPC). Giant papillary conjunctivitis is considered an iatrogenic form of allergic eye disease. In the discussion that follows, clinical, pathophysiological, and diagnostic aspects of each ocular process will be discussed in detail. These parameters are summarized in Tables 3.1 and 3.2.

3.2 Allergic Conjunctivitis: Seasonal/Perennial

Allergic conjunctivitis (AC) is a bilateral, self-limiting conjunctival inflammatory process. It occurs in sensitized individuals (no gender difference) and is initiated by allergen binding to IgE antibody on resident mast cells. The importance of this process is related more to its frequency rather than its severity of symptoms. The two forms of AC are defined by whether the inflammation and symptoms occur seasonally (spring, fall) or perennially (year-round). While the inflammatory signs and symptoms are similar for both entities, seasonal allergic conjunctivitis ("hay fever conjunctivitis") is more common. It accounts for the majority of cases of AC and is related to pollens (e.g., grass, trees, ragweed) that appear during specific seasons. Perennial allergic conjunctivitis is often related to animal dander, dust mites, or other allergens that are present in the environment year-round. Both SAC and PAC must be differentiated from the sight-threatening allergic diseases of the eye, namely, AKC and VKC.

3.2.1 Historical Perspective

Hypersensitivity reaction description of the ocular surface dates to the earliest descriptions of hay fever or rhinitis. Some of the earliest allergy provocation testing was performed in the conjunctiva.

3.2.2 Epidemiology

Prevalence estimates for allergic conjunctivitis are difficult because allergies in general tend to

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Table 3.1 Allergic diseases of the eye

Disease	Clinical parameters	Signs/symptoms	Differential diagnosis
Seasonal allergic conjunctivitis (SAC)	Sensitized individuals	Ocular itching	Infective conjunctivitis
	Both females and males	Tearing (watery discharge)	Preservative toxicity
	Bilateral involvement	Chemosis, redness	Medicamentosa
	Seasonal allergens	Often associated with rhinitis	Dry eye
	Self-limiting	Not sight threatening	PAC/AKC/VKC
Perennial allergic conjunctivitis (PAC)	Sensitized individuals	Ocular itching	Infective conjunctivitis
	Both females and males	Tearing (watery discharge)	Preservative toxicity
	Bilateral involvement	Chemosis, redness	Medicamentosa
	Year-round allergens	Often associated with rhinitis	Dry eye
	Self-limiting	Not sight threatening	SAC/AKC/VKC
Atopic keratoconjunctivitis (AKC)	Sensitized individuals	Severe ocular itching	Contact dermatitis
	Peak incidence 20–50 years of age	Red flaking periocular skin	Infective conjunctivitis blepharitis
	Both females and males	Mucoid discharge, photophobia	Pemphigoid
	Bilateral involvement	Corneal erosions	VKC/SAC/PAC/GPC
	Seasonal/perennial allergens Atopic dermatitis	Scaring of conjunctiva	
	Chronic symptoms	Cataract (anterior subcapsular)	
		A. *Sight threatening*	
Vernal keratoconjunctivitis (VKC)	Some sensitized individuals	Severe ocular itching	Infective conjunctivitis blepharitis
	Peak incidence 3–20 years of age	Severe photophobia	
	Males predominate 3:1	Thick, ropy discharge	
	Bilateral involvement	Cobblestone papillae	AKC/SAC/PAC/GPC
	Warm, dry climate Seasonal/perennial allergens	*Corneal ulceration and scaring*	
	Chronic symptoms	*Sight threatening*	
Giant papillary conjunctivitis (GPC)	Sensitization not necessary	Mild ocular itching	Infective conjunctivitis
	Both females and males	Mild mucoid discharge	
	Bilateral involvement	Giant papillae	Preservative toxicity
	Prosthetic exposure	Contact lens intolerance Foreign body sensation	
	Occurs anytime	Protein buildup on contact lens	SAC/PAC/AKC/VKC
	Chronic symptoms	Not sight threatening	

be considerably underreported. As high as 40 % of the population may suffer from symptoms of allergic conjunctivitis (Rosario and Bielory 2011). Importantly, 46 % of all allergic conjunctivitis sufferers have associated allergic rhinitis (Palmares et al. 2010). The distribution of SAC depends largely on the climate. For example, in the United States grass pollen-induced SAC generally occurs in the Gulf Coast and southwestern areas of the country from March to October and from May to August, in most of the rest of the country. Conversely, ragweed pollen-induced SAC occurs in most of the country during August through October, but in the southernmost states, it can begin as early as July and stretch out through November. Tree pollens can become a problem as early as January in the south and March in the north. Race and gender predilection follows that of rhinitis sufferers.

3.2.3 Clinical Features

The dominant symptom reported in allergic conjunctivitis is ocular itching (Table 3.1). Itching can range from mild to severe. Other symptoms include tearing (watery discharge), redness, swelling, burning, a sensation of fullness in the eyes or

Table 3.2 Histopathologic and laboratory manifestations of allergic ocular disease

Disease	Histopathology	Laboratory manifestations
Seasonal/perennial allergic conjunctivitis	Mast cell/eosinophil infiltration in conjunctival epithelium and substantia propria	Increased tear
	Mast cell activation	Specific IgE antibody
	Upregulation of ICAM-1 on epithelial cells	Histamine
		Tryptase
		TNFα
Atopic keratoconjunctivitis	Increased mast cells, eosinophils in conjunctival epithelium, and substantia propria	Increased specific IgE antibody in tears
	Epithelial cell/goblet cell hypertrophy	Depressed cell-mediated immunity
	Increased CD4/CD8 ratio in conjunctival epithelium and substantia propria	Increased IgE antibody and eosinophils in blood
	Increased collagen	Eosinophils found in conjunctival scrapings
Vernal keratoconjunctivitis	Increased mast cells, eosinophils in conjunctival epithelium and substantia propria	Increased specific IgE/IgG antibody in tears
	Eosinophil major basic protein deposition in conjunctiva	Elevated histamine and tryptase in tears
	CD4+ clones from conjunctiva found to have helper function for local production of IgE antibody	Reduced serum histaminase activity
	Increased collagen	Increased serum levels of nerve growth factor and substance P
	Increased ICAM-1 on corneal epithelium	
Giant papillary conjunctivitis	Giant papillae	No increased histamine in tears
	Conjunctival thickening	Increased tryptase in tears
	Mast cells in epithelium	

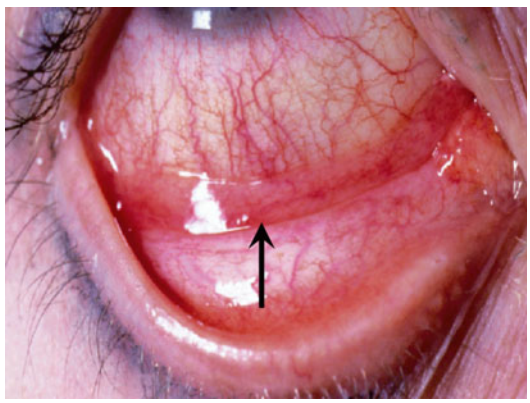

Fig. 3.1 Allergic conjunctivitis. *Arrow* indicates area of chemosis in the conjunctiva

eyelids, an urge to rub the eyes, sensitivity to light, and occasionally blurred vision. As stated previously, allergic conjunctivitis is often associated with symptoms of allergic rhinitis. Conjunctival hyperemia and chemosis with palpebral edema are typical (Fig. 3.1). A rapid test for tear IgE level has correlated the objective sign of giant papillae with the total IgE tear level (Mimura et al. 2012). Hyperemia is the result of vascular dilatation, while edema (chemosis) occurs because of altered permeability of postcapillary venules. "Allergic shiners" (periorbital darkening), due to an increase of periorbital pigmentation resulting from the decreased venous return in the skin and subcutaneous tissue, are also common.

3.2.4 Patient Evaluation, Diagnosis, and Differential Diagnosis

An individual suspected of having allergic conjunctivitis should have a thorough ocular, medical, and medication history. This will help greatly in differentiating AC from other ocular processes (Table 3.1). This history should establish whether the process is acute, subacute, chronic, or recurrent. It should further delineate whether the symptoms/signs are unilateral or bilateral and

whether they are associated with any specific environmental or work-related exposure. Ocular symptoms such as tearing, irritation, stinging, and burning are nonspecific. A history of significant ocular itching and a personal or family history of "hay fever," allergic rhinitis, asthma, or atopic dermatitis are suggestive of ocular allergy. Because AC is secondary to environmental allergens as opposed to transmission by eye-hand contact (infectious etiology), unless occurring in the context of petting an animal then rubbing one's eye, SAC and PAC usually present with bilateral symptoms. This is in contrast to transmissible infections caused by viruses and bacteria that in general initially present in one eye, with the second eye becoming involved a few days later. Itch is an uncommon complaint during infectious conjunctivitis episodes. Furthermore, viral conjunctivitis may cause subepithelial corneal infiltrates not seen in AC. Palpable preauricular nodes would also signify infectious etiology for the ocular symptoms.

The type of ocular discharge (watery, mucoid, or grossly purulent) can also be helpful in determining the underlying cause of conjunctival inflammation. A watery discharge is most commonly associated with viral or allergic ocular conditions. A mucoid or purulent discharge, with morning crusting and difficulty opening the eyelids, would strongly suggest a bacterial infection.

In allergic inflammation, the eye appears red. Vision, pupil shape, ocular movement, light reactivity, and the red retinal reflex remain normal in allergic conjunctivitis. Dry eye (secondary to a decrease of the aqueous portion of the tear film) gives symptoms suggestive of foreign body in the eye and may result in conjunctiva redness. Similar symptoms are possible from anticholinergic side effects of systemic medications. Typically, itch is not reported with dry eye.

Medication history should include questions concerning the patient's use of over-the-counter topical ocular medications, cosmetics, contact lenses, and systemic medications. Any of these can produce acute or chronic conjunctivitis. This inquiry should include direct questions and should not rely on the patient to volunteer information. Many individuals do not appreciate the potential for nonprescription topical ocular medications to cause eye symptoms or partially treat AC. Differentiation of AC from the more chronic and sight-threatening forms of allergic eye disease is discussed below in the context of the specific conditions.

3.2.5 Treatment

Medications approved for use in allergic eye disease are found in Table 3.3. Allergic conjunctivitis can be debilitating and may cause the individuals affected to seek any type of help for relief of symptoms. Itching and tearing may be unbearable and sleepless nights frequent. Allergic conjunctivitis symptoms may be worse than the nasal symptoms in those suffering from rhinoconjunctivitis. Furthermore, treatment of the nasal symptoms with topical nasal steroids may help the rhinitis, but may not be effective for relieving ocular symptoms.

Management of allergic conjunctivitis is, therefore, primarily aimed at alleviating symptoms. The best treatment is avoidance of the specific allergen, which, unfortunately, is usually not possible. Avoidance of scratching or rubbing, application of cool compresses and artificial tears, and refrigeration of topical ocular medications are practical interventions to alleviate discomfort. While oral antihistamines may help to relieve eye itch, first-generation drugs may also decrease tear production, causing more ocular symptoms. Topical medications are generally considered more effective to relieve ocular itching than oral medications and may be additive to relief gained from oral antihistamines.

The treatment of choice for mild to moderate AC is a dual-acting topical ocular medication. The mast cell-stabilizing component of these drugs benefits patients most if treatment is started before the height of symptom onset. Patients usually note rapid onset of relief of itch upon drop instillation, as most dual-action medications have high H_1 receptor affinity. Drug dosing varies from one to four times per day, and efficacy is judged best by symptom relief.

Table 3.3 Topical treatments and activity of compounds

Drug and classification	Inhibition of mediator release from human conjunctival mast cells	Inhibitory effects on other cells	References
Antazoline H1 receptor antagonist	No effect	Inhibits IL-6, IL-8 release from conjunctival epithelial cells in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Pheniramine H1 receptor antagonist	No effect	Inhibits IL-6, IL-8 release from conjunctival epithelial cells in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Emedastine H1 receptor antagonist	No effect	Inhibits IL-6, IL-8 release from conjunctival epithelial cells in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Levocabastine H1 receptor antagonist	No effect	Inhibits IL-6, IL-8 release, ICAM-1 expression on conjunctival epithelial cells in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Olopatadine H1 receptor antagonist Mast cell stabilizer	Histamine, tryptase, PGD_2, TNFα in vitro	Conjunctival mast cell TNFα-mediated upregulation of ICAM-1 on conjunctival epithelial cells in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Ketotifen H1 receptor antagonist Mast cell stabilizer	Histamine in vitro	Chemotaxis and activation of eosinophils in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Azelastine H1 receptor antagonist Mast cell stabilizer	In vitro data not available	Activation of eosinophils in vitro Eosinophils and neutrophils in tears ICAM-1 expression in vivo	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Cromolyn Mast cell stabilizer	Not inhibitory for histamine release in vitro Tryptase in tears	Chemotaxis and activation of eosinophils, neutrophils, monocytes in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Lodoxamide	In vitro data not available	Chemotaxis and activation of eosinophils in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Mast cell stabilizer	histamine and tryptase in tears	Eosinophils, neutrophils, T cells in tears ICAM-1 expression on conjunctival epithelial cells in vitro	
Nedocromil Mast cell stabilizer	Not inhibitory for histamine release in vitro	IgE synthesis from B cells ICAM-1 and HLA-DR expression on conjunctival epithelial cells in vitro Activation and survival of eosinophils in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Pemirolast Mast cell stabilizer	Not inhibitory for histamine release in vitro	Activation of eosinophils and neutrophils in vitro	{Bielory, 2001 #1125;Bielory, 2001 #1126}
Alcaftadine H1 receptor antagonist Mast cell stabilizer	Histamine in vitro	Chemotaxis and activation of eosinophils in vitro	No reference
Bepotastine Mast cell stabilizer	Histamine in vitro	Chemotaxis of eosinophils in vitro	No reference

In severe disease, combination therapy is recommended. This therapy may include topical medications (antihistamines, mast cell stabilizers, NSAIDs, or combinations) and oral antihistamines. Nonsteroidal drugs inhibit cyclooxygenase resulting in decreased formation of prostaglandins and thromboxanes, but not leukotrienes. Therefore, these compounds are useful in controlling itching and some inflammation, but not the infiltration of inflammatory cells. In extreme cases, the use of a topical steroid four times a day should be considered. All patients receiving topical steroids should have their intraocular pressure measured every 3 months if on topical steroids and be evaluated for cataract annually. Specific injection immunotherapy performed by an allergist may be beneficial in decreasing the severity of future ocular allergy symptoms. Sublingual immunotherapy specifically for perennial allergic conjunctivitis has been demonstrated to be effective in relieving symptoms (Potter 2006; Calderon et al. 2011). There is no retrograde passage of nasal steroids up through the lacrimal sac so any ocular effect is considered to be secondary to systemic absorption. Intranasal stimulation is a common method to stimulate reflex tearing, and this is considered a nonspecific reaction. The stimulation may be mechanical, by chemical irritant, or by allergen.

3.3 Atopic Keratoconjunctivitis

3.3.1 Historical Perspective

Atopic keratoconjunctivitis (AKC) is a bilateral, chronic inflammation of the conjunctiva and lids associated with atopic dermatitis. Hogan, in 1953, was the first to describe the findings of chronic conjunctivitis and keratitis in patients with atopic dermatitis (Hogan 1953). Three to 17 % of the population has atopic dermatitis (Garrity and Liesegang 1984; Spergel 2010). From 15 to 76 % of patients with atopic dermatitis have ocular involvement, usually AKC (Garrity and Liesegang 1984; Dogru et al. 1999; Moscovici et al. 2009).

3.3.2 Epidemiology

The onset of disease is usually in the second through fifth decade although the majority of patients with atopic dermatitis are diagnosed by age 5 years. Series report the onset of symptoms between the ages of 7 and 76 (Foster and Calonge 1990; Power et al. 1998; Tuft et al. 1991). The highest male to female ratio is reported as 2.4:1 (Foster and Calonge 1990; Tuft et al. 1991). No racial or geographic predilection is reported.

3.3.3 Clinical Features

Itching is the major symptom of AKC. This may be more pronounced in certain seasons or it may be perennial. Other symptoms, in decreasing order of frequency, include watering, mucous discharge, redness, blurring of vision, photophobia, and pain (Tuft et al. 1991). Exacerbation of symptoms most frequently occurs in the presence of fur-bearing animals and pets (Tuft et al. 1991).

Signs of AKC include skin, lid margin, conjunctival, corneal, and lens changes (Fig. 3.2). The periocular skin often shows a scaling, flaking dermatitis with a reddened base. The skin of the lids may become leatherlike, developing cicatricial ectropion (turning outward of the lid from skin scarring) and lagophthalmos (incomplete closure of eyelids). Lateral canthal ulceration and cracking as well as lash loss (madarosis) may also be present. This may be the principal manifestation in a minority of cases. The lid margins may show meibomitis, keratinization, and punctal ectropion. The conjunctiva of the tarsal surfaces can manifest a papillary reaction and possibly pale white edema. In contrast to VKC, the papillary hypertrophy of AKC is more prominent in the inferior conjunctival fornix. Subepithelial fibrosis is present in many, fornix foreshortening in some, and symblepharon (scar of conjunctival surface of lid to conjunctiva of the globe) in a few. The bulbar conjunctiva may have few findings besides erythema and chemosis. A perilimbal, gelatinous hyperplasia may occur.

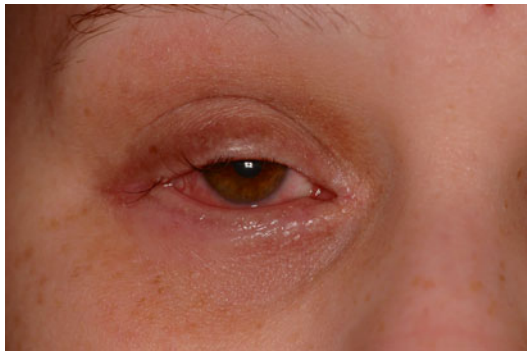

Fig. 3.2 Atopic keratoconjunctivitis. Periocular skin lesions of atopic dermatitis

Horner-Trantas dots (whitish dots that are aggregates of degenerated epithelial and eosinophils that accumulate at the surface of the hyperplastic, gelatinous limbus) have been reported to occur in AKC (Friedlaender 1979).

Significant vision loss in this disease usually results from pathologic conditions of the cornea. Punctate epithelial keratopathy is the most common corneal finding. Persistent epithelial defects, scarring, microbial ulceration, and neovascularization are the main corneal causes for decreased vision (Table 3.1). Penetrating keratoplasty or cornea transplant is at risk of the same surface problems but has been shown to improve vision in some (Ghoraishi et al. 1995). Herpetic keratitis is reported to occur in 14–17.8 % of patients (Foster and Calonge 1990; Tuft et al. 1991). Keratoconus, a noninflammatory progressive thinning of the cornea occurs in 6.7–16.2 % of patients (Foster and Calonge 1990; Tuft et al. 1991).

Anterior uveitis and iris abnormalities are not reported. The prevalence of cataract associated with AKC is probably increased, since steroids are so frequently used in the treatment of the disease. The lens opacity typically associated with AKC, however, is an anterior or subcapsular cataract. This cataract often has the configuration of a multilobed opacity resembling a "milk splash." Retinal detachment with or without previous cataract surgery is the principal posterior manifestation of AKC reported (Hurlbut 1961; Yoneda et al. 1995; Klemens 1966).

3.3.4 Patient Evaluation, Diagnosis, and Differential Diagnosis

Paramount to both diagnosis and treatment in AKC is a careful history. The patient typically describes severe, persistent, periocular itching associated with dermatitis. There is usually a family history of atopic disease in one or both parents and commonly other atopic manifestations in the patient, such as asthma (65 %) or allergic rhinitis (65 %) (Power et al. 1998). A history of seasonal or exposure-related exacerbations is usually present. History and examination reveal features to help differentiate AKC from other atopic ocular conditions. The lack of contact lens wear aids in differentiating AKC from GPC. AKC patients are usually older and have major lid skin involvement compared to patients with VKC. SAC patients have no or markedly diminished symptoms out of their season and show no evidence of chronic inflammation in the conjunctiva. The significant past history or concurrent presence of eczema cannot be emphasized enough as a finding in patients with AKC. The serum level of IgE is often elevated in patients with AKC. A Giemsa stain of a scraping of the upper tarsal conjunctiva may reveal eosinophils. Meibomian gland obstruction is noted to be significant and may be found to exceed that seen in obstructive Meibomian gland disease patients (Ibrahim et al. 2012).

3.3.5 Treatment

The approach to treatment is multifaceted and includes environmental controls as well as topical and systemic medications (Table **3.3**). It is unlikely that the AKC patient will see the ophthalmologist without also being under the care of a primary care physician and allergist. However, the patient must remove environmental irritants in both the home and the employment or school setting. The nature of the irritants may be better defined through allergy testing.

The topical application of a vasoconstrictor-antihistamine combination may bring transient relief of symptoms but is unlikely to alter the

immunopathologic process or its sequelae. There is potential for overuse due to the chronic nature of the disease. The potent topical antihistamines offer much greater H_1 receptor antagonism than over-the-counter antihistamines. The topical administration of steroids such as prednisolone acetate eight times per day for 7–10 days is clearly beneficial in controlling symptoms and signs. These agents, of course, must be used judiciously, since the chronic nature of the disease may encourage overuse. The patient must be instructed that steroid use must be transient only and must be carefully monitored for efficacy; he or she must also be warned of the potential for causing cataract and glaucoma. Nonsteroid medications have been shown to be effective in reducing itching, tearing, and photophobia. Topical mast cell stabilizers one to four times daily are recommended year-round in patients with perennial symptoms. If an exacerbation occurs and the patient is not taking a mast cell-stabilizing agent topically, its use should be initiated one to four times daily concurrent with a short burst of topical steroids (for 7–10 days). Mast cell stabilizers alone such as cromolyn, nedocromil, lodoxamide, or mast cell stabilizer antihistamine combinations such as olopatadine, azelastine, epinastine, and ketotifen may be helpful. Cyclosporine-A and tacrolimus, both orally and topically have been shown effective at treating AKC as well as reducing the amount of topical steroid use (Mohammed Al-Amri 2013; Miyazaki et al. 2009; Rikkers et al. 2003; Hoang-Xuan et al. 1997; Hingorani et al. 1998; Stumpf et al. 2006; Anzaar et al. 2008). Tear levels of eosinophilic cationic protein are reduced following treatment with topical tacrolimus (Wakamatsu et al. 2011). Foster and Calonge recommend maximizing the use of systemic antihistamines (Foster and Calonge 1990). Itch is a major complaint, and newer H_1 receptor antagonists are fairly specific. Only in rare cases of uncontrolled dermatitis with vision-threatening complications are oral steroids indicated. The role of allergen desensitization is similar to that in AC and VKC. Plasmapheresis has been effective in the treatment of AKC (Aswad et al. 1988).

Lid and ocular surface abnormalities may require treatment other than that directed toward the underlying pathologic condition of AKC. Trichiasis or lid position abnormalities, if contributing in any way to corneal compromise, must be corrected. Any staphylococcal blepharitis should receive adequate antibiotic treatment. If, despite adequate control of signs and symptoms of AKC, corneal punctate staining persists, artificial tears should be used to aid in avoiding the development of corneal epithelial defects. It may be extremely difficult to achieve reepithialization in these defects, and surgical approaches have been attempted (Thoft 1984). Lid or ocular surface herpes simplex virus (HSV) infection should be treated with topical antiviral agents. Care should be taken in using these to achieve viral eradication without sustained use and subsequent epithelial toxicity. If frequent recurrent episodes of epithelial HSV keratitis occur, one may consider oral acyclovir (400 mg orally twice daily) as prophylaxis against recurrences.

In summary, courses of topical steroids will control most patients with AKC. The chronic use of steroids must be avoided and early in treatment, steroid-sparing strategies must be considered.

3.4 Vernal Keratoconjunctivitis

3.4.1 Historical Perspective

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral conjunctival inflammatory condition found in individuals predisposed by their atopic background. An excellent review of the history and description of this disease was published by Kumar in 2008 (Kumar 2009). Beigelman's 1950 monograph *Vernal Conjunctivitis* continues to be the most exhaustive compilation on this disease and is unmatched in current times (Beigelman 1950).

3.4.2 Epidemiology

The onset of disease is generally before age 10 and lasts 2–10 years, usually resolving during late puberty. Only 11 % of patients were greater than 20 years of age in the Bonini series (Bonini

et al. 2000). Males predominate in the younger ages, but the male to female ratio is nearly equal in older-age patients. Young males in dry, hot climates are primarily affected. The Mediterranean area and West Africa are areas with the greatest prevalence. Less than 10 % of all patients in a single series had onset of typical signs and symptoms of VKC as adults (Leonardi et al. 2013). VKC is relatively unusual in most of North America and Western Europe. There is a significant history of other atopic manifestations, such as eczema or asthma, in 40–75 % of patients with VKC (Bonini et al. 2004). A family history of atopy is found in 40–60 % of patients (Bonini et al. 2000). Seasonal exacerbation, as the name implies, is common, but patients may have symptoms year-round.

3.4.3 Clinical Features

Severe itching and photophobia are the main symptoms. Associated foreign body sensation, ptosis, thick mucous discharge, and blepharospasm occur. The signs are confined mostly to the conjunctiva and cornea; the skin of the lids and lid margin are relatively uninvolved compared to AKC. The conjunctiva develops a papillary response, principally of the limbus or upper tarsus (Fig. 3.3). The tarsal papillae are discrete, greater than 1 mm in diameter, have flattened tops that may stain with fluorescein, and occur more frequently in European and North American patients (Buckley 1988). Thick, ropy mucus tends to be associated with the tarsal papilla. These are the classic "cobblestone" papillae.

Limbal papillae tend to be gelatinous and confluent, and they occur more commonly in African and West Indian patients (Verin et al. 1999). Horner-Trantas dots, which are collections of epithelial cells and eosinophils, may be found at any meridian around the limbus (Trantas 1910). These changes may lead to superficial corneal neovascularization. The forniceal conjunctiva usually does not show foreshortening or symblepharon formation.

The corneal findings may be sight threatening. Buckley describes in detail the sequence of occurrence of corneal findings (Buckley 1988). Mediators from the inflamed tarsal conjunctiva cause a punctate epithelial keratitis. Coalescence of these areas leads to frank epithelial erosion, leaving Bowman's membrane intact. If, at this point, inadequate or no treatment is rendered, a plaque containing fibrin and mucus deposits over the epithelial defect (Rahi 1985). Epithelial healing is then impaired, and new vessel growth is encouraged. This so-called shield ulcer usually has its lower border in the upper half of the visual axis. With resolution, the ulcerated area leaves a subepithelial ringlike scar. The peripheral cornea may show a waxing and waning, superficial stromal, gray-white deposition termed pseudogerontoxon. Iritis does not occur in VKC.

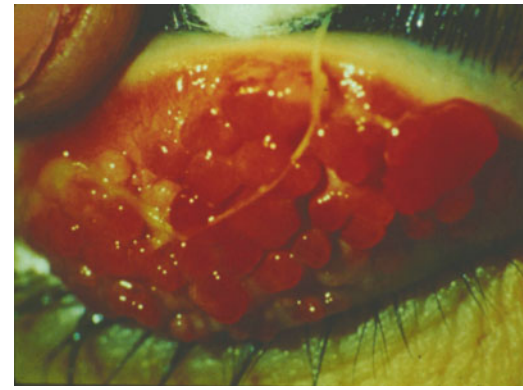

Fig. 3.3 Vernal Keratoconjunctivitis. Cobblestone papillae and ropy discharge on the underside (tarsal conjunctiva) of the upper eyelid

3.4.4 Patient Evaluation, Diagnosis, and Differential Diagnosis

The diagnosis is relatively easily arrived at, based on the history and physical findings. As indicated previously, VKC occurs predominantly in young boys living in warm climates. These patients have intense photophobia, ptosis, and the characteristic finding of giant papillae. The principal differential diagnostic entity is AKC. The two are compared and contrasted in Table 3.1. Tear fluid analysis and cytology and conjunctival scraping for cytology and biopsy are rarely needed to assist in establishing the diagnosis.

3.4.5 Treatment

Table 3.3 reviews the treatment choices for any allergic eye disease. As with any atopic condition, avoidance of allergens is important although many afflicted are skin test negative. Often, this is difficult for VKC patients because of the possible large number of antigens to which they react. Seasonal removal of affected children from their home to a reduced allergen climate is usually not practical for most families. What is practical and should not be overlooked is alternate occlusive therapy, as an allergen avoidance strategy. Allergen immunotherapy in VKC has limitations. It is not feasible to desensitize these children to all of the allergens to which they are responsive. Moreover, some suggest that while skin and lung symptoms are responsive to immunotherapy, the conjunctiva is not (Buckley 1988). Subcutaneous immunotherapy did result in significant reduction in symptoms and serum IgE compared to topically treated patients (Mahdy et al. 2012).

For the patient with a significant seasonal exacerbation, a short-term, high-dose pulse regimen of topical steroids is necessary. Usually, dexamethasone 0.1 % or prednisolone phosphate 1 % eight times daily for 1 week brings excellent relief of symptoms. This should be tapered rapidly to as little as is needed to maintain patient comfort. As in any chronic ocular inflammation, the use of steroids should be limited and steroid alternatives introduced rapidly once symptoms controlled. Cromolyn sodium, a mast cell stabilizer, has repeatedly been shown to be effective in VKC (El Hennawi 1980; Foster and Duncan 1980; Tabbara and al-Kharashi 1999). At the time of an exacerbation, the patient should be given a steroid pulse dose and begin using a mast cell-stabilizing drug topically or a dual-acting drug such as olopatadine, ketotifen, epinastine, or azelastine (Table 3.3) concurrently to provide mast cell stabilization and antihistamine treatment. Oral medications that have a variable role include steroids, antihistamines, and nonsteroidal anti-inflammatory agents (Chaudhary 1990; Abelson et al. 1980). For the care of severe bilateral vision-threatening disease, oral steroids may be used, but using this treatment for VKC alone is unusual. Maximizing the use of nonsedating antihistamines is often helpful.

Topical calcineurin inhibitors of cyclosporine A (CsA) and tacrolimus have been demonstrated to be effective in the treatment of VKC (Takamura et al. 2011; Tomida et al. 2002; Secchi et al. 1990; Pucci et al. 2002; Mendicute et al. 1997; Holland et al. 1993; Gupta and Sahu 2001; Avunduk et al. 2001; BenEzra et al. 1986; Vichyanond et al. 2004). An open pilot study of the use of *Lactobacillus acidophilus* probiotic eye drops in patients with VKC significantly reduced signs and symptoms in patients (Iovieno et al. 2008). The corneal shield ulcer is a vision-threatening complication of VKC. Treatment may include antibiotic-steroid ointment and occlusive therapy. If a plaque forms in the ulcer bed, a superficial keratectomy is sometimes beneficial in promoting epithelial healing (Jones 1961). Phototherapeutic keratectomy and keratectomy with amniotic membrane graft placement have been shown to be effective (Autrata et al. 2002; Sridhar et al. 2001).

Climatotherapy may be beneficial. This may involve simple measures, such as cool compresses over the closed lids. Maintenance of an air-conditioned environment or relocation to a cool, dry climate is most helpful during seasonal exacerbations. However, the economic and geographic restrictions of these measures are obvious.

Cryoablation of upper tarsal cobblestones is reported to render short-term improvement. However, scar formation from this may lead to lid and tear film abnormalities. The risk of these adverse permanent changes is probably not warranted in this usually self-limited disease (Buckley 1988). Surgical removal of the upper tarsal papilla in combination with forniceal conjunctival advancement or buccal mucosal grafting may result in obliteration of the fornix (Beigelman 1950; Nishiwaki-Dantas et al. 2000). Injection of short- or long-acting steroids into the tarsal papilla has been shown to be effective at reducing their size (Saini et al. 1999; Holsclaw et al. 1996). Excision of upper tarsal papillae with or without adjunctive use of mitomycin-C or application of amniotic membrane is reported to

be helpful (Tanaka et al. 2004, 2006; Guo et al. 2013). The therapy of the future will be directed toward diminishing mast cell numbers or function and immunomodulation of the cell-mediated response.

3.5 Giant Papillary Conjunctivitis

3.5.1 Historical Perspective

Giant papillary conjunctivitis (GPC) is a chronic inflammatory process leading to the production of giant papillae on the tarsal conjunctiva lining of the upper eyelids. Most often associated with soft contact lens wear, GPC has been reported in patients wearing soft and rigid gas-permeable contact lenses, as well as in patients with ocular prostheses and exposed sutures in contact with the conjunctiva.

3.5.2 Epidemiology

GPC may affect as many as 20 % of soft contact lens wearers (Allansmith et al. 1977). Rate of development of GPC in gas-permeable contact lens users was found to be 10 % and in soft contact lens users 33 % (Forister et al. 2009). Those patients using daily-wear disposable contact lenses and those wearing rigid contact lenses are about equally affected (Forister et al. 2009). Patients who wear disposable contact lenses during sleep are probably three times more likely to have GPC symptoms than if the lenses are removed daily. GPC represented 15 % of all contact lens-associated complications in a cohort of patients in Singapore (Teo et al. 2011). Patients with asthma, seasonal allergic rhinitis, or animal dander allergies may be at greater risk for GPC (Begley et al. 1990). There are no gender or race predilections reported.

3.5.3 Clinical Features

Symptoms of GPC include ocular itching after lens removal, redness, burning, increased mucus discharge in the morning, photophobia, and decreased contact lens tolerance. Blurred vision can result from deposits on the contact lens or from displacement of the contact lens secondary to the superior eyelid papillary hypertrophy (Fig. 3.4). Initial presentation may occur months or even years after the patient has begun wearing contact lenses.

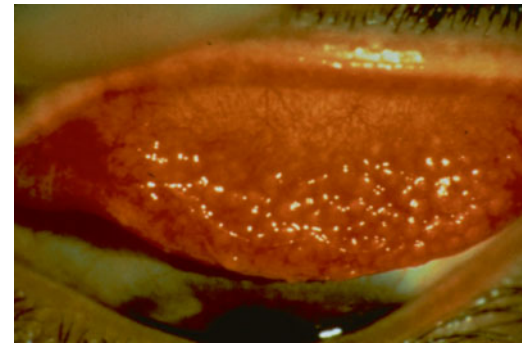

Fig. 3.4 Giant papillary conjunctivitis. Papillae 1 mm or greater in size on the on the underside (tarsal conjunctiva) of the upper eyelid

3.5.4 Patient Evaluation, Diagnosis, and Differential Diagnosis

In mild cases of GPC, small papillae may occur. These papillae are thought to be caused by the contact lens riding high on the surface of the eye with each blink. In very mild cases, this tendency of the contact lens to ride up on the eye may contribute to the diagnosis in the absence of visible papillae. In cases of chronic GPC, tear deficiency may be a contributing factor. Redness of the upper eyelid on ocular examination is one of the earliest signs of GPC, and this observation can facilitate early diagnosis. Abnormal thickening of the conjunctiva may progress to opacification as inflammatory cells enter the tissue. Eventually, the recurrent irritation is so great as to cause the enlarged papillae that will be the source of increased mucous and inflammatory mediators and decrease in wear time. The differential diagnosis includes vernal keratoconjunctivitis that occurs in young boys not wearing contact lenses.

3.5.5 Treatment

Reducing symptoms is the primary aim for management of GPC. A reduction in the wearing time of contacts from a few hours a day to total abstinence may be required. Once a day use contact lenses may be a consideration for persistent cases of GPC. However, in more serious cases, a more aggressive approach may be required to prevent ocular tissue damage. This usually entails a complete holiday from lens wear in conjunction with topically applied anti-inflammatory drug.

Topical mast cell stabilizers have been shown to be effective in the treatment of GPC (Sorkin and Ward 1986; Allansmith 1987; Meisler et al. 1982; Donshik et al. 1984). Combination drugs having mast cell-stabilizing as well as antihistamine activity may relieve the itch and decrease the inflammation. A patient with GPC may require continued use of these drugs once they return to contact lens wear. Steroids have also been approved for the treatment of GPC (Asbell and Howes 1997). Topical steroids may be used four times per day for 2–4 days (Bartlett et al. 1993). A return to contact lens wear can usually be accomplished but may require a change in contact lens style or lens material.

3.6 Conjunctival Provocation Testing

The conjunctival provocation test (CPT) has traditionally been utilized as a means for diagnosing ocular allergy. A discussion of CPT is important in this chapter because it is currently used routinely as a human model system to study allergic conjunctivitis and drug efficacy. Although evaluation of subjects during allergy season is still a valid and important approach to the study of allergic conjunctivitis, variations in exposure to allergens (based on environment and lifestyle) and compliance issues are serious impediments to collecting statistically relevant data.

The currently most widely accepted model protocol for CPT was developed by Abelson and coworkers (Abelson et al. 1990). This protocol allows researchers to examine the ocular response to allergen in a controlled setting. Prior to undertaking a CPT study, subjects must first be skin tested with commercial allergen extracts to determine the appropriate allergen and concentration for each subject. It is very important to conduct CPT out of season for the allergen of interest and to observe published local pollen counts to ensure that no environmental exposure occurs during the course of the study. In the study design, two baseline visits (7 days apart) are utilized to establish the threshold dose of allergen. At the first baseline visit, increasing doses of allergen extract are applied bilaterally into the conjunctival sac of the eye at 10-min intervals followed by observation for hyperemia, itching, chemosis, and lid swelling according to well-established scales as shown in Table 3.4 (43). A threshold of reactivity of 2.0 is considered to reflect the severity of allergic conjunctivitis in season.

A second baseline (7 days later) visit is necessary to establish reproducibility of the ocular allergic reaction to the threshold dose of allergen extract. The CPT protocol consists of a double-blind, randomized design in which the test drug

Table 3.4 Grading scales for symptom scores in conjunctival provocation testing

Score	Itching	Hyperemia	Chemosis	Lid swelling
0.0	None	None	None	None
1.0	Intermittent tickling sensation	Mild – dilated blood vessels	Mild – confirmed with slit-lamp evaluation	Mild – detectable swelling of lower lid
2.0	Mild continuous ocular itching	Moderate – dilation of blood vessels	Moderate – raised conjunctiva	Moderate – definite swelling of lower lid
3.0	Severe ocular itching	Severe – numerous and obvious dilated blood vessels	Severe – ballooning of the conjunctiva	Severe – extremely swollen lower lid
4.0	Incapacitating ocular itching	Extremely severe – large, numerous, dilated blood vessels	Not applicable	Not applicable

is applied to one eye and placebo to the other. After 10 min, the subject is challenged with the previously determined threshold dose of allergen extract. Symptom evaluation is then conducted according to standardized scales and at various time points post-challenge (approximately 20 min for immediate and up to 6 h for late reactions). Subsequent visits may be used to examine other parameters of interest, such as prophylactic potential of the test drug or duration of drug efficacy in response to later time points of allergen challenge. The therapeutic effect of a drug can also be evaluated by performing CPT post-drug exposure.

Application of the guidelines put forth in the Abelson model for CPT has improved the reproducibility and objectivity of topical drug efficacy evaluation in human trials. Important advantages include standardization and confirmation of the threshold dose, utilization of a standardized scale for symptom scores, and comparison of the treated eye to the contralateral untreated eye as an internal control.

In conjunction with the clinical parameters evaluated in the CPT model, many researchers have also been able to analyze tear fluid obtained with the CPT procedure to determine mediators and cell types present (Bonini et al. 1997; Nomura et al. 1997). It has been shown that conjunctival allergen provocation in atopic subjects results in release of mediators in tears known to come from mast cells, such as histamine, tryptase, prostaglandins, and leukotrienes C4 and D4 (Aichane et al. 1993; Butrus et al. 1990; Proud et al. 1990). Additionally, it has been shown that two histamine peaks (20 min and 6 h) follow allergen provocation, not unlike what is seen during the acute and late phase responses in the skin and airways. Since only an early tryptase peak is measured, this may indicate either the involvement of basophils in the late phase or, possibly, refractory mast cells (Lightman 1995). Recent techniques facilitating analysis of cytokines in tears could also be combined with the CPT model to better understand both the mechanisms of action of ocular drugs and the pathophysiology of allergic conjunctivitis (Cook et al. 2001).

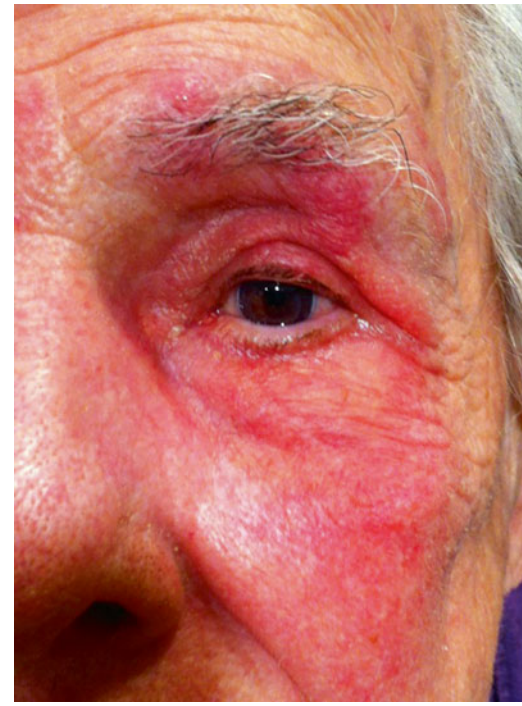

Fig. 3.5 Periocular red skin with distribution consistent with the contact area of a eye drop or ointment

3.7 Contact Dermatitis (Fig. 3.5)

Contact dermatitis is a delayed inflammatory hypersensitivity reaction resulting from contact with a specific antigen or irritant. While not an IgE antibody-mediated process, it deserves discussion in this chapter because contact dermatoconjunctivitis is a commonly observed entity in the ocular adnexa. The eye is affected in this disorder not only via direct application of substances containing irritants (often ophthalmic treatments) and specific antigens but also through eye rubbing following manual contact with an offending irritant or antigen. Since the potential list of substances causing contact dermatitis numbers in the thousands, it is one of the most common skin conditions requiring medical attention.

3.7.1 Epidemiology

It is unclear exactly how many people suffer from the ocular component of this process, but the

recent international workshop estimate for the incidence of contact dermatitis, in general, ranges from 15 to 20 % of the general population in Western industrial nations (Peiser et al. 2012).

3.7.2 Clinical Features

Symptoms and signs of contact dermatoconjunctivitis can include a sudden rash over the eyelids, tearing, redness, itching, stinging and burning sensations, and a sensation of fullness in the eye or eyelid when swelling is involved. The eyelid may appear thickened, red, and sometimes ulcerated. When the conjunctiva is involved, vasodilatation, chemosis, watery discharge, and sometimes formation of papillae can be observed. Chronic inflammation may involve occlusion of lacrimal ducts, conjunctival scarring, corneal neovascularization, and keratinization, but sight loss is uncommon.

A multitude of irritants and antigens has been implicated in ocular contact dermatitis. Some common substances known to sensitize individuals to ocular contact dermatitis include topical drugs and antibiotics (anesthetics, neomycin, antivirals, pilocarpine, timolol), preservatives in ophthalmic solutions (thimerosal, benzalkonium chloride, chlorobutanol, chlorhexidine, EDTA), cosmetics (eye and lip glosses containing waxes, fats, and dyes), perfumes, sunscreens containing para-aminobenzoic acid (PABA), fingernail products (containing formaldehyde resins and sulfonamide derivatives), hair products (dyes, permanent solutions), adhesives (false eyelashes), nickel (eyelash curlers and eyeglass frames), irritant plants (poison ivy, sumac, oak), and latex (gloves). Examples of other irritant substances implicated in contact dermatoconjunctivitis include soaps, detergents, bleach, and solvents.

3.7.3 Patient Evaluation, Diagnosis, and Differential Diagnosis

As with allergic ocular processes, the diagnosis of contact dermatoconjunctivitis is predicated upon physical examination and a thorough history including specific questions concerning daily activities, medications, contact lens products, eye drops, cosmetics, occupation, and hobbies using the above list of culprit irritants and antigens as a guide. The differential diagnosis may include ulcerative blepharoconjunctivitis from staphylococcal infection or AKC. Several tests are utilized for identification of specific antigens or irritants. Patch testing is the most useful diagnostic tool for evidence of contact sensitivity.

3.7.4 Treatment

The best treatment is avoidance of the offending agent(s). Substitution of nonirritating medications (e.g., contact lens solutions, cosmetics) should be attempted when possible. Comfort measures that can be taken include cool compresses 4–6 times/day, avoidance of hot water and soaps, and application of a low-potency steroid cream (rather than ointment which can be irritating to the eye) over the affected area. Topical steroid drops may be indicated.

Conclusions

Allergic eye disease may be divided into self-limiting and vision-threatening disorders. Allergic conjunctivitis is self-limiting and does not threaten vision, and symptoms are often controlled with topical application of antihistamines. Giant papillary conjunctivitis is an iatrogenic disorder associated with contact lens wear, ocular prosthesis, or a retained suture fragment. Removal of the offending agent for a period of time and topical application of an anti-inflammatory medication usually results in reduction of symptoms and findings. Vernal Keratoconjunctivitis and Atopic Keratoconjunctivitis are vision threatening, may result in cornea scar formation and lash misdirection, and can be life altering. Control typically requires the use of topical steroids and subsequently steroid-sparing immunomodulatory drops. Periocular contact dermatitis may occur from the use of multiple classes of therapeutic eye drops. Cessation of the offending agent is paramount in determining resolution of symptoms.

Compliance with Ethical Requirements Neal P. Barney and Scott T. Bauer declare they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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Imaging Techniques for Corneal Disorders

4

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4.1 Introduction

Corneal imaging has developed dramatically since the seventeenth century where Christopher Scheiner reflected images of marbles off the cornea (Naroo and Cervino 2004). Now, technologies such as confocal microscopy, anterior segment optical coherence tomography (OCT), and specular microscopy allow imaging and analysis of both healthy and now diseased eyes which would be previously unable to be evaluated with just the marble. These imaging modalities allow us to evaluate microscopic diseases such as atypical infectious keratitis, Fuchs endothelial corneal dystrophy, and even attachment of endothelial keratoplasty.

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4.2 Confocal Microscopy

The confocal microscope allows in vivo coronal optical sectioning of the cornea. The first confocal scanning laser microscope was described by Petran et al. (1968). This microscope was capable of high-resolution images of cells within tissues. The confocal microscope can capture 2–20 μm optical sections oriented parallel to the tissue surface, without stains or dyes.

4.2.1 Function

The conventional light microscope collects the sum of all light transmitted through a specimen or reflected back from an object, along with light from above and below the focal plane of the microscope's objective lens. This creates optical noise, which results in blurred images with significantly limited resolution. Consequently, to improve the resolution, the specimen needs to be thinly sliced. This need to physically section the specimen, and apply tissue stains, clearly does not allow in vivo imaging and may result in preparation artifacts.

In confocal microscopy, as first described by Minsky in his patent in 1957 (Minsky 1988), the pinhole source of light and its conjugate pinhole detector limit the passage of light from outside of the focal plan. Essentially, the focal point of the light source and the focal point of the microscope's

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optical objective are aligned which allows very high resolution of cells.

Due to the pinhole, the field of view of such a design is very small and a full field of view must be built up by scanning, described by Petran et al. (1986). It can be by rotating a disk with thousands of optically conjugate source-detector pinholes in a spiral pattern, as in tandem scanning. The scanning mirror type of confocal microscope uses an optical slit, which scans the field by mechanically moving a slit beam via a mirror system (Koester 1991). Some of the confocal systems use a laser light source, while other confocal microscopes use a white-light source.

The images captured are oriented parallel to the surface of the tissue. The microscope has the ability to quickly adjust in the z-axis and scan through the tissue. Video and digital imaging capabilities are available on the microscope, which allows the examiner to scan through the full thickness cornea after acquisition. This technique also permits the 3-dimensional reconstruction of the cornea, as well as the study of the images in time (Cavanaugh et al. 1993; Petroll et al. 1993).

Limitations of the technique include the necessity to obtain multiple sections to evaluate larger areas of the cornea and the time of image acquisition and processing. Time to acquire a single image is typically less than 1/30 s, and the observation time in clinical settings is around 5 min.

4.2.2 Normal Anatomy

Sections obtained are oriented parallel to the surface of the tissue being imaged by confocal microscopy. Clinicians generally learn corneal anatomy in sections perpendicular to the surface (coronal sections). Thus, the examiner must learn normal corneal tissue appearance at different depths of the cornea, which are oriented parallel to the surface, in order to evaluate the specimen. All layers of the corneal tissue can be imaged, including the structures that run through the layers and between layers, such as nerves, blood vessels, and keratocytes. It is also important to understand that densities of cells and nerves can differ depending on the depth and central versus eccentric locations within the cornea.

The surface epithelium appears as a cellular mosaic with bright, hyper-reflective central nuclei. The cells of the basal epithelium are smaller and nuclei are not visible. Bowman's layer appears as an amorphous membrane and is best identified by the subbasal nerve plexus that lies beneath the Bowman's layer. This nerve plexus appears as a fine filamentous membrane. The stroma is composed of hyper-reflective, "bean-shaped" keratocyte nuclei, with density greatest just posterior to Bowman's layer and decreasing posteriorly (Prydal et al. 1998). The keratocyte cell bodies become visible when the keratocyte is activated. Nerves are seen running through the stroma and are larger compared to the more superficial nerves. Descemet's membrane is not visible on confocal microscopy unless significant fibrosis is present. The endothelium is composed of hexagonal cells with bright cells bodies with dark borders, similar to specular microscopy (Fig. 4.1) (Dhaliwal et al. 2007; Kitzmann et al. 2005; Cavanaugh et al. 1990).

The depth of each image within the cornea may also be recorded. This can help determine the depth of scars, foreign bodies, or location of infectious agents within the tissue.

Other uses of confocal microscopic imaging of the anterior segment has included imaging of the conjunctiva, lids, and corneoscleral limbus (Pichierri et al. 2008; Patel et al. 2006).

4.2.3 Clinical Uses

One of the major advantages of confocal microscopy is the ability to perform in vivo imaging without the need to mechanically section the cornea or use of stains or dyes (Lemp et al. 1985). The confocal microscopy examination can be performed comfortably on a cooperative patient in the clinical setting. The use of confocal microscopy has been described in many pathological conditions including infection, hereditary disorders (dystrophies), refractive, surgical, and other

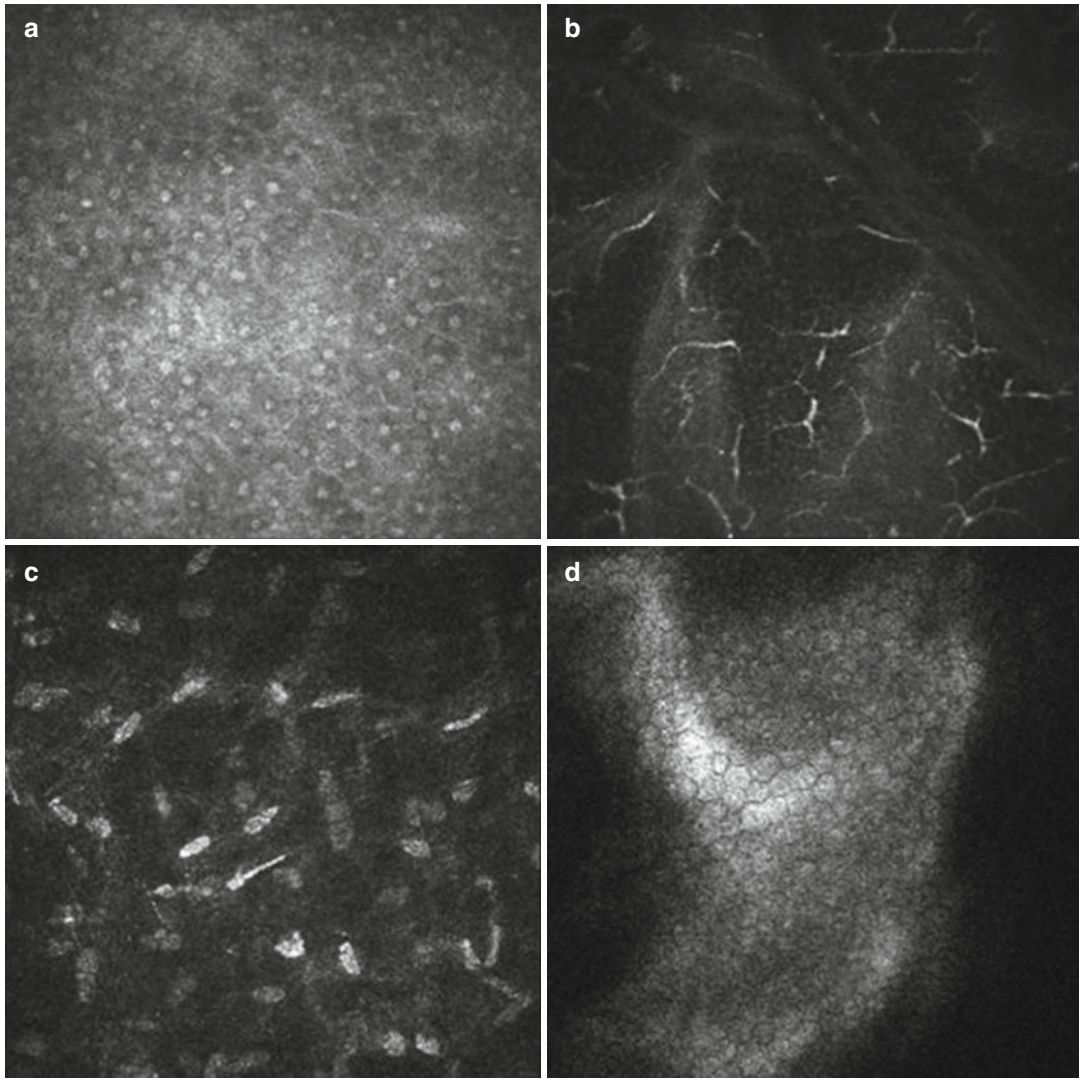

Fig. 4.1 Corneal layers as imaged with the confocal microscope. Corneal epithelium: seen with bright nuclei, (**a**); subbasal nerve plexus, (**b**); corneal stroma with keratocytes, (**c**); corneal endothelium with hexagonal cell borders, (**d**)

miscellaneous uses (Cavanagh et al. 1993). In clinical practice, confocal microscopy has been used to identify *Acanthamoeba* cysts and trophozoites, bacteria, fungi, and other pathogens within the cornea. In clinical research, it can be used for evaluation of responses and complications after refractive procedures, corneal wound healing processes, and a variety of corneal diseases.

Confocal microscopy has been shown to be useful in the diagnosis of *Acanthamoeba* keratitis (Mathers et al. 2000). The appearance of the cystic form of the organism is distinct using this imaging modality. The cyst is a double-walled hexagonal, hyper-reflective structure measuring approximately 10–30 μm in diameter. There may be a surrounding lucent area, representing a microcavitation of the stroma (Fig. 4.2). The trophozoite form can also be seen; however, it is more difficult to discern from surrounding normal keratocyte nuclei. Uniquely, the organism has been shown to be associated with corneal nerves, representing a radial keratoneuritis (Pfister et al. 1997). Confocal microscopy can also help guide

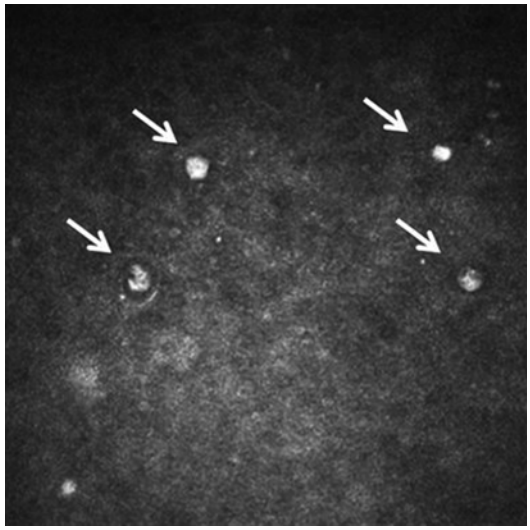

Fig. 4.2 Group of *Acanthamoeba* cysts in the epithelium (*arrows*). Note the hyper-reflective *Amoeba* with a lucent area and a surrounding bright halo

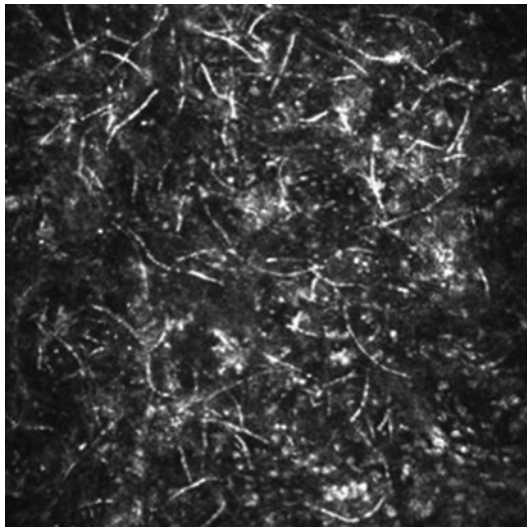

Fig. 4.3 Fungal filaments as imaged by confocal microscopy. Note the hyper-reflective filamentous elements. This fungus was identified as *Alternaria* species, by culture

the clinician in the treatment response in this notoriously difficult to treat condition.

Fungal keratitis has also been explored with the confocal microscope. The organisms are characterized by hyper-reflective filaments or budding forms (Fig. 4.3). The filaments appear to spread parallel to the surface of the cornea, possibly along the lamella of the cornea. There appears to be a role for confocal microscopy for diagnostic purposes (Winchester et al. 1997) especially in cases of deep infection, where a simple culture is not possible.

Due to the small size, most bacteria types cannot be distinguished by confocal microscopy. On exception is the filamentous bacteria, *Nocardia asteroids*, which appears as a hyper-reflective beaded, branching filaments. The branching typically occurs at right angles (Vaddavalli et al. 2006). Aggregates of bacteria have also been seen (Kaufman et al. 1996).

Although viruses cannot be visualized, the inflammatory patterns that accompany many such infections have been described. The subepithelial infiltrates seen after epidemic keratoconjunctivitis can be seen as hyper-reflective Langerhans cells in the basal epithelium and anterior stroma. Hyper-reflective fusiform cells (activated keratocytes) and round cells (inflammatory cells) have been reported in herpes simplex keratitis (Rosenberg et al. 2002).

Confocal microscopy has been used to evaluate postoperative complications in ophthalmic surgery. Examples include epithelial downgrowth after penetrating keratoplasty (Chen et al. 2013) and confirmation of retained Descemet's membrane following penetrating keratoplasty (McVeigh et al. 2013). In epithelial downgrowth, the observer would look for round hyper-reflective nuclei consistent with the epithelium at the level of the endothelium. After penetrating keratoplasty, a decrease in the density of cells at every level of the transplanted cornea has been reported (Niederer et al. 2007).

In the setting of refractive surgery, confocal microscopy has been used to study wound healing as well as surgical complications (Kaufman and Kaufman 2006). Corneal haze after phototherapeutic keratectomy (PRK) has been shown to be correlated with the presence of activated keratocytes (Moller-Pederson et al. 2000). Larger treatments with deeper ablations were noted to have increased numbers of activated keratocytes that remained activated longer. Corneal nerve density has been shown to significantly decrease after PRK but recovered by 24 months to presurgical levels (Erie 2003).

In laser-assisted in situ keratomileusis (LASIK), corneal nerve density has been shown to decrease significantly after 1, 2, and 3 years, not recovering to near preoperative densities until 5 years after surgery (Erie et al. 2005). This may be a significant cause of dry eye experienced after LASIK.

Various corneal dystrophies have been described. Epithelial basement dystrophy, lattice, Schnyder's crystalline, Thiel-Behnke, Reis-Bucklers, granular, and Fuchs' endothelial dystrophies are some of those characterized with confocal microscopy (Rosenberg et al. 2000; Kobayashi et al. 2003, 2009; Werner et al. 1999; Kaufman et al. 1993). The appearance of the Fuchs' endothelial dystrophy on confocal microscopy is similar to the appearance on specular microscopy with polymegathism and pleomorphism. However, one of the advantages of the confocal over specular microscopy in imaging Fuchs' is the ability to image through an edematous, hazy cornea, whereas with specular microscopy, the image cannot be obtained (Chiou et al. 1999a).

The confocal microscopy appearance of iridocorneal endothelial (ICE) syndrome demonstrates corneal endothelial cells consistent with the appearance of epithelial-like cells (Fig. 4.4) (Chiou et al. 1999b).

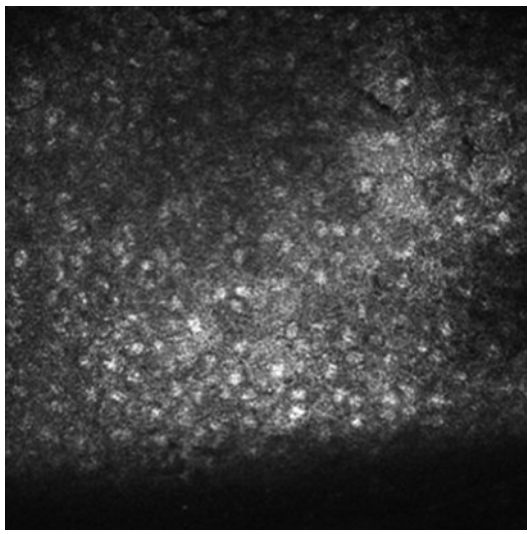

Fig. 4.4 Iridocorneal endothelial syndrome as imaged by confocal microscopy. Note epithelial-like cells with hyper-reflective nuclei at the level of the corneal endothelium

Confocal microscopy use in the cornea has also been described in systemic diseases such as diabetes in the evaluation and diagnosis of diabetic neuropathy (Chang et al. 2006) or in the evaluation of crystalline keratopathy in multiple myeloma (Mazzotta et al. 2014).

4.3 Specular Microscopy

In 1968, David Maurice developed specular microscopy, which then advanced to clinical use in 1975 with Bourne, Kaufman, and Laing (Maurice 1968; Bourne and Kaufman 1976). Specular microscopy is a technique that images tissue using light reflected from the optical interface of the corneal endothelium and the aqueous humor.

4.3.1 Normal Anatomy

Clinical specular microscopy provides quantitative assessment of endothelial cell density (ECD) and morphology as an indirect measure of function. Change in ECD is more important than an absolute value. Morphometric parameters provide information related to whether a cell population is under stress. The coefficient of variation (CV) measures a change in cell size (polymegathism), while % of hexagonal cells (% HEX) measures a change in cell shape (pleomorphism) (Fig. 4.5).

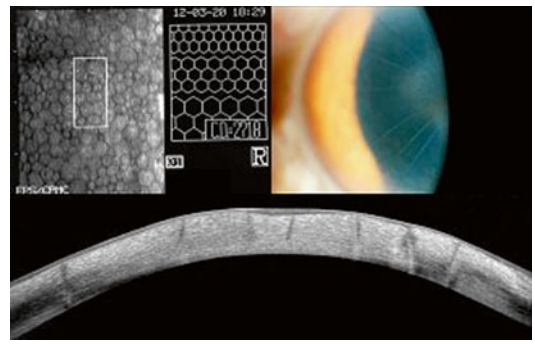

Fig. 4.5 Specular microscopy with anterior segment optical coherence tomography showing the endothelial mosaic after radial keratotomy surgery. Note with OCT the ability to identify the depth of each radial incision with epithelial remodeling

In most individuals, ECD decreases throughout life. Cell loss is most rapid from birth to the first few years of life. After the age of 60 years, ECD decreases significantly in most people, but there is a great degree of variability between individuals. On average, age-related cell loss is approximately 0.5 % per year (Sherrard et al. 1987). Though there is a large variation among age groups, most patients, even those greater than 70 years of age, should have an ECD of at least 2000 cells per mm^2, a coefficient of variation less than 0.40, and greater than 50 % hexagonal cells.

4.3.2 Clinical Uses

Specular microscopy is utilized in evaluating donor corneas, in identifying corneal dystrophies, and in providing valuable information for pre- and postsurgical management. Corneal edema is estimated to occur between 300 and 700 cells per mm^2 (Mishima 1982). Assuming cell loss in the range of 0–30 % for a given intraocular surgery, a patient should have at least 1,000–1,200 cells per mm^2 to safely undergo most anterior segment surgery without an increased risk of permanent postoperative corneal edema. When evaluating early postoperative corneas, imaging both centrally and in the midperiphery will identify regional disparities in ECD and morphology (Glasser et al. 1985). Reports of endothelial cell loss after cataract surgery using a variety of surgical approaches have demonstrated variable cell loss, but following uncomplicated phacoemulsification and posterior chamber intraocular lens implantation using viscoelastic and modern, small-incision techniques is low, ranging from no detectable cell loss to 20 % (Díaz-Valle et al. 1998).

Fuchs' endothelial corneal dystrophy (FECD) is a progressive, bilateral female predominant, endothelial disease that results in progressive corneal stromal edema and eventually epithelial edema and subepithelial fibrosis. The progressive morphologic changes of corneal guttae in FECD, with increased polymegathism and pleomorphism, initially start centrally (Laing et al. 1981). This has led many surgeons to utilize endothelial imaging to help predict postoperative outcomes.

The iridocorneal endothelial (ICE) syndrome, a unilateral female predominant, nonfamilial, progressive group of disorders, shows rounding of cell angles of the endothelium with a loss of cellular definition and a prevalence of pentagonal cells which are smaller than normal while also showing reversal of reflectivity (Sherrard et al. 1991). In contradistinction, posterior polymorphous corneal dystrophy (PPCD), a bilateral, nonprogressive, autosomal dominant disease, clinically appears similar to ICE syndrome, which complicates the diagnosis. However, using specular microscopy, the vesicles of PPCD have a thick dark border in a doughnut-like appearance with the lesion anterior to the endothelium and can be used to differentiate PPCD from ICE syndrome (Brooks et al. 1989).

Many investigators have studied photorefractive keratectomy (PRK) and laser-assisted in situ keratomileusis (LASIK) effects on the corneal endothelium. Most have shown that neither LASIK nor PRK results in a decreased endothelial density; however, ablation of the stroma within 200 μm of the corneal endothelium results in endothelial structural changes and the formation of the amorphous substance deposited onto Descemet's membrane (Edelhauser 2000).

In the Specular Microscopy Ancillary Study (SMAS) of the multicenter Cornea Donor Study (CDS) evaluating penetrating keratoplasty, endothelial cell loss from baseline to 5 years reached a staggering 70 % postoperatively. This does not directly correlate with functional status as in the SMAS; 14 % of the subjects with clear grafts had an ECD below 500 cells/mm^2. The study did note that cell loss continues throughout the life of the graft with highest correlation of long-term graft success using ECD at 6 months (Lass et al. 2010).

Endothelial keratoplasty (EK) has rapidly become the primary procedure for endothelial dysfunction since 2005 nearly surpassing penetrating keratoplasty in 2011 and increasing the gap in 2012. In 2013, the EBAA reported 24,987 cases of endothelial keratoplasty were performed. The procedure has been applied to all endothelial failure conditions, the cause for 40 % of all

corneal transplants in the United States (Eye Bank Association of America 2013). Most authors have reported significantly greater cell loss in the first 6 months after EK compared to PKP. Interestingly, although there is greater loss at 1 year when compared to PKP, the rate of cell loss begins to level off around 6 months, unlike PKP, as observed by several authors. After 1 year, there is minimal loss to the second and third years, 7 % between 6 months and 2 years, and 8 % between 6 months and 3 years, compared with 42 % in the eyes that underwent PKP in the Specular Microscopy Ancillary Study (SMAS) of the Cornea Donor Study (CDS) (Lass et al. 2010; Price and Price 2009).

In type I diabetes the cell density significantly decreases with age. Diabetic corneas also exhibit increased polymegathism and pleomorphism and a decreased percentage of hexagonality (Schultz et al. 1984).

4.4 Anterior Segment Optical Coherence Tomography

Anterior segment optical coherence tomography (OCT) is a high-resolution cross-sectional imaging modality, initially developed for retinal imaging at 830 nm (Huang et al. 1991). Applications for the anterior segment were first described in 1994 by Izatt et al. (1994). Due to limited penetrating through scattering tissue in the anterior segment, a longer wavelength was developed – 1,310 nm.

We have just begun to realize and appreciate the many applications of AS-OCT. Like high-resolution posterior segment OCT, clinicians are now recognizing the significance of AS-OCT for diagnosing, monitoring progression, and clinical decision-making.

4.4.1 Function

The anterior segment OCT is a light-based instrument, based on infrared light that segments ocular structures based on their reflectivity (indexes of refraction) – the ratio between light wave energy reflecting from the surface and light wave energy striking the same interface. Light at 1,310 is strongly absorbed by water. Less than 7 % of light on the cornea reaches the retina resulting in the ability of safely using a much higher power level (15 mW vs. 0.7 mW retina). Using 20× more power for anterior segment scanning equates to 20× faster scanning without sacrificing signal level. The longer wavelength also equals reduced scattering in opaque tissues such as the limbus, sclera, and iris. Also, the longer wavelength allows deeper penetration of the limbus for visualization of the scleral spur and angle recess (Huang et al. 1991).

Concentric or "arc" scanning produces uniformly strong reflections from the anterior and posterior corneal surfaces as well as the stromal collagen lamellae.

This scan maintains nearly perpendicular incidence angle as the OCT beam is scanned in the transverse dimension along collagen lamellae. The strong reflections from these normal structures reduce contrast for corneal scars and LASIK flap interface, making the visualization of these features difficult. Scan width is limited to a fraction of the diameter of the objective lens (Steinert and Huang 2008).

"Rectangular" or "telecentric" scanning produces the least image distortion and provides a range of useful contrast for corneal imaging. At the corneal vertex, the strong specular reflection offers a precise corneal landmark (Fig. 4.6). In the periphery, normal corneal surface and lamellar reflection fade but still remain visible (Steinert and Huang 2008).

Potential limitations include penetration through pigment and imaging the sulcus, zonules, and ciliary body. Image processing, compensation for corneal refraction, and patient fixation are potential causes of artifact. The unprocessed image is distorted by the indexes of refraction at the air-cornea and cornea-aqueous interfaces. Distortion is removed, "dewarping", by the computer software using Fermat's principle.

To achieve precision measurement of very fine anatomic structures, scans must be properly aligned and processed. Wavelength of 1,310 nm provides deeper penetration into tissues, approximately

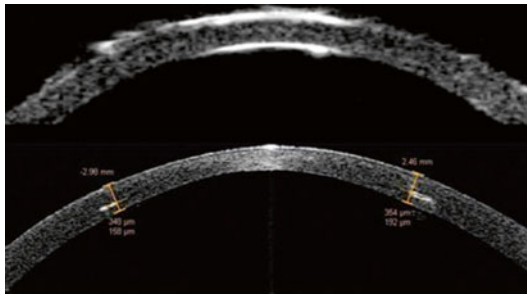

Fig. 4.6 Comparison of ultrasound biomicroscopy above with anterior segment OCT below. Note the resolution of the OCT allowing for identification of a corneal interface with scarring not visualized with ultrasound

18 μm axially. Because of the reduced scattering, AS-OCT can better penetrate turbid tissue of the sclera, angle, and iris. While wavelengths of 830 nm produce a greater axial resolution of approximately 3–5 μm, conversely, the shorter wavelength results in poorer penetration through opaque tissue and a shallow depth of view. Some examiners find the shallower 830 nm best suited for corneal examination (Radhakrishnan et al. 2001).

4.4.2 Clinical Uses

Applications for AS-OCT include corneal measurements, preoperative evaluation for implantation of intracorneal ring segments, angle closure assessment, and review of iris and crystalline lens position. AS-OCT is commonly used as a less invasive form of dynamic gonioscopy, post-iridotomy imaging, post-surgical management of trabeculectomy and/or shunt patency, as well as proving in-depth, high-resolution images of the cornea and anterior chamber. With proper examination and applied metric tools, one can grade the angle as well as the central anterior chamber depth. Most AS-OCT systems also provide pachymetry for central corneal thicknesses, as well (Asrani et al. 2008).

To fully realize the advantages of high-resolution imaging, the Fourier-domain OCT allows improved visualization of pathologic changes in the anterior segment such as corneal guttae, lattice lines, subepithelial changes, and irregular Bowman's layer (Wylegala et al. 2009).

Fig. 4.7 Anterior segment OCT in ICE syndrome showing angle closure and peripheral anterior synechiae with an associated slit lamp photo

4.4.3 AS-OCT Versus UBM

In general, due to its significant advantage of resolution (3–5 μm) versus that of UBM (100 μm), AS-OCT is the better choice for most anterior segment structures (Figs. 4.6 and 4.7).

Besides AS-OCT, ultrasound biomicroscopy (UBM) may also be used for cross-sectional imaging of the anterior segment and the AC angle. When compared to AS-OCT, UBM has the unique advantage of enabling visualization of structures posterior to the iris such as the ciliary body, zonules, and the peripheral lens. However, UBM is relatively more uncomfortable, requires a highly skilled operator in order to obtain good quality images, and has a limited scan width (5 × 5 mm) with the traditional UBM devices. This rarely provides significant advantages except in cases of severe corneal opacification where these other imaging modalities do not penetrate.

Conclusions

No one imaging technique can provide all the information to completely evaluate the cornea. While we strive for imaging that provides anatomical evaluation, we look forward to imaging systems that may also provide the opportunity to evaluate functional status of the cornea as well. Each imaging modality works together with the others to encompass the near complete story of the cornea. AS-OCT imaging provides

the clinician with tools for rapid in vivo cross-sectional imaging of the cornea and anterior segment. In addition to established uses for various corneal and iris diseases and disorders, promising work is being done with iris volume and anterior chamber volume studies. Recently there has been increasing interest in assessing dynamic factors such as iris volume that may identify eyes that are a risk of acute primary angle closure.

AS-OCT imaging provides the clinician in vivo cross-sectional imaging of the cornea and anterior segment. The uses are numerous. Further studies will continue to add to the diagnostic utility of this instrument in the clinic.

Confocal microscopy offers the clinician and researcher in vivo imaging of the cornea at cellular-level resolution. The uses are numerous. Further studies will continue to add to the diagnostic utility of this instrument in the clinic.

Compliance with Ethical Requirements

Conflict of Interest

Alla Kelly, MD; Stephen C. Kaufman, MD, PhD; Jonathan Lass MD; Denice Barsness, CRA, COMT, ROUB, CDOS, FOPS; Beth Ann Benetz, CRA, FOPS; and Pankaj Gupta, MD, MS declare that they have no conflict of interest related to the subject matter in the chapter.

Informed Consent

(2) No human studies were carried out by the authors for this article.

Animal Studies

(2) No animal studies were carried out by the authors for this article.

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5 Advances in Contact Lens for the Treatment of Ocular Surface Disease and the Corneal Ectasias

Deborah S. Jacobs and Joshua S. Agranat

5.1 Contact Lens for the Treatment of Ocular Surface Disease

A properly chosen contact lens can be effective in the treatment of surface breakdown in healthy eyes and in eyes with ocular surface disease. Contact lenses can promote corneal healing through the provision of mechanical support and protection, through reduction of desiccation, and through alleviation of pain. Vision may be improved by a therapeutic contact lens incidental to correction of surface refractive error. Contact lens can also be used on a maintenance basis when there is underlying ocular surface disease. Each of the following lens categories can play a role in the treatment of ocular surface disease:

- Soft lenses
- Mini-scleral (15–17 mm) and scleral (>17.5 mm) rigid gas-permeable lenses
- PROSE treatment

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5.1.1 Soft Lens for Ocular Surface Disease

In the 1960s, the chemist Otto Wichterle developed biologic hydrophilic gels (hydrogels) which laid the foundation for easily fitted and broadly tolerated soft contact lenses (McMahon and Zadnik 2000). Hydrogels with increased water content were introduced in the following decades to increase oxygen transmission through the aqueous component. Various innovations have resulted in lenses labeled for therapeutic use including extended wear, to be used as a "bandage" after trauma, surgery, or in disease.

There are multiple variables that contribute to the effectiveness of therapeutic lenses. Two critical features are oxygen permeability and mechanical interaction with the ocular surface. Oxygen permeability (Dk) is typically reported as Dk/L or Dk/T for the thickness of a −3.00-power lens. The range of Dk in commercially available lenses may be <10 and as high as 340 in soft lenses made entirely of silicone rubber. Silicone lenses are typically used only in aphakia in infants and very young children because of tendency toward fouling, that is, development of deposits on the lens surface. In these cases, the very high power, ease of fit, high tolerance, and the need for extended wear because of irregular sleep schedule, which necessitates maximal oxygen transmission outweigh any disadvantages of the material.

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In recent decades, the incorporation of silicone into hydrogel polymer, resulting in the silicone hydrogel (SiHy) category of soft lens, has been an attempt to further increase biocompatibility, by increasing oxygen transmission. The goal was lower rates of infection with overnight wear and elimination of the problems associated with care systems and overnight storage. Lenses made of these new SiHy materials were specifically labeled for therapeutic use and resulted in reports of their utility for those purposes (Kanpolat and Ucakhan 2003; Lim et al. 2001). By 2002, 72 % of optometrists and ophthalmologists report having prescribed soft contact lenses for therapeutic purposes, predominantly for corneal wound healing and postoperative management (Karlgard et al. 2004). Clinical experience is that lenses with higher silicone content may be more likely to develop deposits on the lens surfaces reducing tolerance and perhaps negating any advantage of increased oxygen transmission. In general, however, for situations necessitating overnight wear, lenses made of higher Dk materials should be employed. Lenses with higher Dk might be particularly favorable in cases in which corneal neovascularization is present.

Another variable to consider in the choice of a therapeutic soft lens is water content. The water content of a lens is reported as a percentage. If the water content is too low, the lens may cause irritation; if the water content is too high, the lens may act as a sponge and exacerbate symptoms associated with dry eye and aqueous tear deficiency. So, in an apparent paradox, the best lens for a dry eye may not be the one with the highest water content.

Optimizing the fit of a soft lens depends on a number of factors. The most important factor is the topography of the cornea and sclera. The steepness of the lens should increase with increasing corneal steepness. The steepness parameter of a lens is typically recorded in mm of base curvature. Current ophthalmologic practice is for corneal steepness to be reported in diopters; so clinicians must convert higher *K* values to lower base curve and vice versa. Clinicians seeking an adequate fit of a soft lens selected for extended wear should confirm the following clinical findings after 30 min of trial wear:

- Good lens centration.
- The lens should not cross the limbus with extremes of gaze or blink.
- The lens should move slightly with blink or "push-up" test (a nudge delivered through the lower lid by the examiner's fingers while the patient is instructed to look up).
- There should be no report of lens awareness or discomfort.

When a lens is fitted for therapeutic indication, it is worthwhile to evaluate the patient on the next day to confirm retention and absence of tight lens syndrome. Failure to retain the lens may necessitate a steeper base curve or a larger diameter. Soft lenses of very large diameter (>15 mm) can be retained in instances where dryness, exposure, or poor lid function might result in loss of typical-diameter soft lenses.

Large-diameter hydrogel lenses (15–24 mm) can play an important role in the treatment of ocular surface disease. Although currently not available in high-Dk materials, the advantage of retention and mechanical support of the ocular surface might be considered to outweigh any tendency to exacerbate hypoxia. Poor soft lens retention is typically caused by some combination of lid abnormality, aqueous tear deficiency, incomplete blink, and frank exposure. These large-diameter hydrogel lenses are manufactured in various sizes, with the larger diameters having a central steeper zone and a peripheral flatter zone that can be specified in various combinations.

When soft lenses are used on a therapeutic basis, regular follow-up to include lens disinfection or exchange should take place for the duration that extended wear is prescribed (Holland et al. 2013). Daily, as opposed to extended, wear of a therapeutic lens for ocular surface disease with concomitant reduction of risk of microbial keratitis may be appropriate in cases in which the daily insertion and removal can be accomplished without disrupting the ocular surface. There is variation among practitioners in the use of antibiotic prophylaxis against microbial infection with extended wear of therapeutic soft contact lens. The theoretical advantage of prophylaxis must be

weighed against the disadvantages related to expense, inconvenience, and toxic effects of chronic use of drugs and preservatives, as well as potential selection for resistant organisms.

5.1.2 Rigid Lens for Ocular Surface Disease

Rigid gas-permeable (RGP) materials were introduced to the contact lens field in the 1980s. These materials solved the problem of hypoxia that limited previous use of large-diameter glass or PMMA lenses (Ezekiel 1983). Prior to that innovation, rigid lenses by necessity were of diameter substantially less than corneal diameter to allow access to atmospheric oxygen. When a large diameter was required for mechanical stability, typically, holes for air ventilation, called fenestrations, were added to preclude suction and allow oxygen to reach the cornea. Such design results in bubbles and lens and local desiccation, so use for ocular surface disease was not typically undertaken. Gas-permeable polymers eliminated one reason for fenestration, and designs that allowed for fluid ventilation eliminated the other. For this reason, large-diameter rigid gas-permeable contact lenses that are fluid ventilated, using sterile saline or artificial tears in the reservoir, can be used in the treatment of ocular surface disease.

There are numerous designs, available through various manufacturing labs, of large-diameter RGP lenses that can be used in the treatment of OSD. As a group, these large-diameter RGP contact lenses are typically referred to as scleral lenses. The definition of a scleral lens is not entirely standard, but typically it is a lens of 17.5 mm or greater; lenses of smaller diameter but larger than corneal contact lenses are sometimes classified as mini-scleral, semi-scleral, or corneoscleral lenses. These lenses are typically fitted similarly to an RGP corneal lens, are highly oxygen permeable, are of 13–16 mm diameter, and typically touch the cornea apically or peripherally or both. The advantage of these smaller lenses is that they are easier to fit than what is typically defined as scleral lens (17.5 mm or greater), but vigilant clinical observation must follow because the corneal contact can lead to erosion, scarring, and neovascularization (Ye et al. 2007). Conventions as to satisfactory fit of a scleral lens remain to be codified, with some practitioners using patient-subjective tolerance as the only criterion and accepting corneal contact and need for periodic replenishment of reservoir and whereas others demanding lack of corneal contact and specific reservoir depth and alignment of the bearing haptic with the sclera.

Fitting an RGP scleral lens or other larger diameter lens is typically undertaken through the use of a trial set from a specialty lens manufacturing lab for satisfactory fit; subsequent customization is typically required. There is no standard criterion for satisfactory fit, but typically, lenses are dispensed to patients only if there is comfortable wear with little lens movement, minimal corneal touch, and retention of a fluid reservoir. Scleral lenses are typically inserted in the morning and removed at night for overnight disinfection. However, continuous wear with daily removal, disinfection, and reinsertion can be a useful clinical approach in the treatment of some ocular surface diseases (Kalwerisky et al. 2012; Lin et al. 2011).

5.1.3 PROSE Treatment for Ocular Surface Disease

Prosthetic replacement of the ocular surface ecosystem (PROSE) treatment uses custom-fabricated and fitted prosthetic devices, of 17.5–24 mm diameter, to replace and optimize the ocular surface. The treatment was approved by the FDA in 1994 for daily wear for OSD and astigmatism; the devices used have been referred to as the Boston scleral contact lens, the Boston Scleral Lens, the Boston Scleral Lens Device, the Boston Scleral Lens Prosthetic Device, and the Boston Ocular Surface Prosthesis (BOS-P). The devices used in PROSE treatment are made of highly gas-permeable material; fit is typically characterized by fluid ventilation, minimal movement, and no contact with the cornea. Their defining and unique feature is that the curvature

of the device profile is delineated mathematically by spline functions as opposed to the traditional superposition of base curves. The clinician typically works from a diagnostic trial device but then uses CAD/CAM software for design and fabrication to assure fit that is aligned with the sclera and frond and back profiles that are junctionless and comfortable.

PROSE treatment offers replacement of impaired ocular surface function, eliminating desiccation, offering protection from the environment and lids, supporting healing, reducing pain and photophobia, and neutralizing irregular astigmatism. PROSE treatment has been shown to be both cost effective (Shepard et al. 2009) and clinically effective in treating OSD in both the United States (Stason et al. 2010) Gumus et al. 2010) and abroad (Rathi et al. 2011), in children as well as adults (Gungor et al. 2008; Rathi et al. 2012).

5.2 Recent Advances: Ocular Surface Disease

5.2.1 Soft Lens

In the last decade, soft lenses made of SiHy material were introduced with labeling for overnight wear for therapeutic as well as cosmetic indications. It was anticipated that the introduction of the highly gas-permeable SiHy materials would result in lower rates of microbial keratitis. Recent reports for the United Kingdom (Radford et al. 2009) and Australia (Stapleton et al. 2008) failed to find such a reduction, suggesting that higher oxygen transmission is insufficient to protect against microbial keratitis in extended wear. In the populations studied, cosmetic as opposed to therapeutic indication for contact lens wear was predominant, but it can be presumed that failure of these materials to protect against infection would apply to lens wear for therapeutic indications as well. These reports confirmed data from decades earlier that extended wear of soft lenses has a higher risk of infection compared to daily wear of soft lenses which have a higher than daily wear of RGP corneal lenses. Clinicians may consider antibiotic prophylaxis for overnight use of lenses especially in the presence of epithelial defects or with concomitant use of topical steroids.

Daily disposable lenses, also introduced in the last decade, may have the lowest rate of infection of any soft lenses and have the advantage of eliminating potential toxicity from or allergy to care solutions and eliminated potential for infection from contaminated cases. Daily disposable lenses are not labeled for therapeutic use and are not intended for overnight wear. There may be a role for daily disposable lenses in chronic ocular surface disease, when worn on a daily wear basis. In these cases, the ovular surface must be robust enough to withstand trauma from daily insertion and removal. SiHy daily disposable lenses are a very recent introduction, and advantage over daily disposable hydrogel lenses remains to be demonstrated for daily use in ocular surface disease. The benefit–risk ratio for the use of extended wear soft lenses in ocular surface disease might vary with the underlying disease.

Management of ocular surface disease with soft lenses, particularly in eyes with history of persistent epithelial defect, may be complicated by the development of corneal neovascularization. A tight lens or one with low Dk or the thicker edges of a toric design may be contributory. On the other hand, neovascularization might be part of the healing response particularly if there is partial or complete limbal stem cell deficiency. Lens wear should be discontinued if fit, design, or materials are thought to be contributory. If the basis for neovascularization is attributed primarily underlying pathology, then the clinician might consider a lens with greater oxygen permeability and might also prescribe topical steroids or angiogenesis inhibitors. Infections that can occur with any contact lens use are generally due to tear film immobility, hypoxia, and accumulation of toxic metabolites.

Large-diameter soft lenses are useful in the maintenance of hydration and reduction of carrier tissue melt with the Boston KPro. When there is coexisting lid disease or exposure, these lenses may be prone to deposits at the optical axis due to poor blink function, in which case daily disposable or hybrid (rigid center with soft skirt) may be used to advantage (Beyer et al. 2011).

Patients with ocular chronic graft versus host disease had improvement in visual acuity and reduction of OSDI with wear of a SiHy lens that was replaced weekly; no complications in this patient group on this regiment occurred (Russo et al. 2007).

Successful treatment of persistent epithelial defect (PED) with extended wear of SiHy lens combined with other treatments such as autologous serum eye drops has recently been reported (Jeng and Dupps 2009; Choi and Chung 2011). Bandage soft lens therapy for LSCD following penetrating keratoplasty for aniridia has been reported (Ozbek and Raber 2006).

There are recent updates on the use of soft lenses on an extended wear basis in the treatment of recurrent erosion syndrome. Soft contact lenses worn for 3 months (Fraunfelder and Cabezas 2011) and 6 months (Moutray et al. 2011) cause resolution of recurrent erosion syndrome (RES) and should be considered an alternative to procedures such as stromal micropuncture, superficial keratectomy, or phototherapeutic keratectomy. Patient acceptance of this approach is likely to be high when there is coexisting refractive error than can be neutralized. A general guideline as to required duration of wear is that if symptoms recur after ceasing lens wear, then that duration of lens wear should be doubled before another trial period without lens wear is attempted.

5.2.2 Rigid Gas-Permeable Scleral Lenses

The utility of modern RGP scleral lenses for the treatment of OSD has been described (Pullum and Buckley 2007; Severinsky and Millodot 2010). Scleral lenses have recently been shown to be effective in the treatment of LSCD (Schornack 2011) and in the management of ocular cicatricial pemphigoid (Schornack and Baratz 2009), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (Tougeron-Brousseau et al. 2009), ocular chronic GVHD (Schornack et al. 2008) and in patients hospitalized in a burn unit (Lin et al. 2011). Scleral lenses can eliminate the need for tarsorrhaphy in patients with paralytic exposure (Weyns et al. 2013). The utility of mini-scleral RGP lenses for the treatment of moderate to severe dry eye has been reported (Alipour et al. 2012). As mentioned previously, vigilant clinical observation must follow with mini-scleral lenses because corneal contact can lead to erosion, scarring, and neovascularization (Ye et al. 2007).

5.2.3 PROSE Treatment for Ocular Surface Disease

Although first described in 1990 (Schein et al. 1990) and elaborated upon a decade later (Romero-Rangel et al. 2000), the last decade has produced numerous reports on the effectiveness of PROSE treatment for OSD across a broad range of diagnoses including most of the major causes of ocular surface disease. Outcomes as far as improvement in visual function in OSD were found to be equivalent to those in ectasia and astigmatism even though improvement in visual acuity was fewer lines, because of better acuity at baseline in patients with ocular surface disease.

As PROSE treatment has become more widely available, reports on usefulness in OSD subgroups have emerged. A report from India describes (Rathi et al. 2011) SJS patients who were suffering from pain, photophobia, and poor vision and found that following PROSE treatment, there was an improvement in symptoms in all cases (Rathi et al. 2011). Poor cooperation in young children and the presence of symblephara to the limbus limit the use of PROSE treatment in some cases of SJS.

PROSE treatment is useful for patients suffering from the ocular sequelae of chronic graft-versus-host disease (cGVHD) with reports of increase in quality of life, vision, and OSDI scores (Jacobs and Rosenthal 2007; Takahide et al. 2007). PROSE treatment has been proven successful in managing LSCD following treatment of conjunctival melanoma (Grover et al. 2010).

PROSE treatment is reported to be effective in the management of patients in burn units (Kalwerisky et al. 2012; Lin et al. 2008, 2011) and those with exposure from tumor or trauma (Williams and Aquavella 2007).

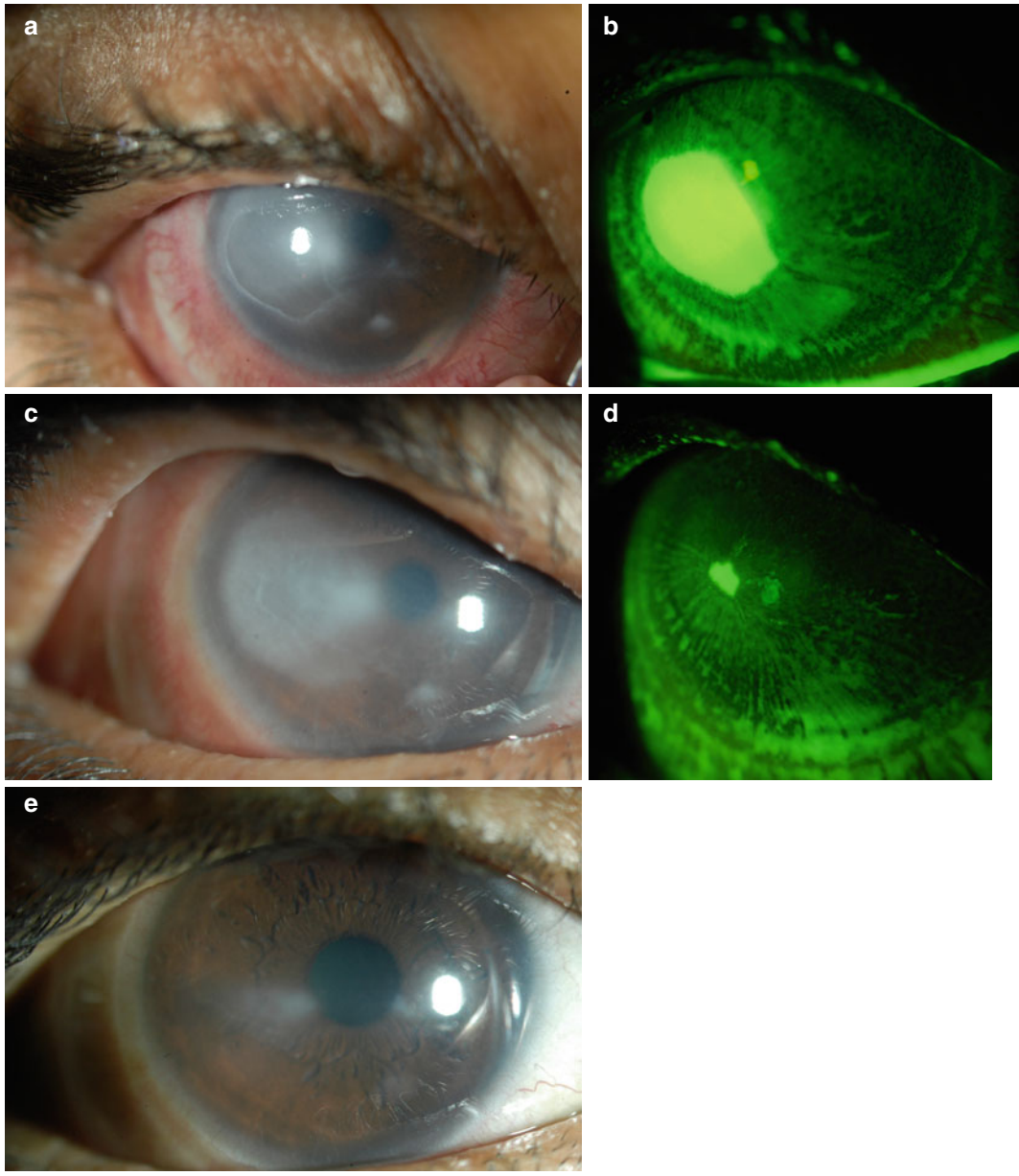

Fig. 5.1 (**a**) Day 1 of PROSE treatment for persistent epithelial defect 8 months after acute Stevens-Johnson syndrome. (**b**) Day 1 of PROSE treatment for persistent epithelial defect 8 months after acute Stevens-Johnson syndrome. Blue light and fluorescein. (**c**) Day 6 of PROSE treatment for persistent epithelial defect 8 months after acute Stevens-Johnson syndrome. (**d**) Day 6 of PROSE treatment for persistent epithelial defect 8 months after acute Stevens-Johnson syndrome. Blue light and fluorescein. (**e**) Week 8 of PROSE treatment

Overnight wear of a PROSE device has also been shown to be effective in treating PED (Gumus et al. 2010; Ling et al. 2013; Lim et al. 2013), with the addition of preservative-free fluoroquinolones in the reservoir apparently reducing rate of infection (Rosenthal et al. 2000) (Fig. 5.1). PROSE treatment can be used as delivery mode for topical administration of VEG-F inhibitors with good effect (Lim et al. 2009; Jacobs et al. 2009).

Patients with both OSD and advanced glaucoma present a particular challenge. Filtering blebs or tube shunts are a relative contraindication to contact lens use because of risk of infection or erosion. The devices used in PROSE treatment can be modified for support of the ocular surface in the presence of advanced glaucoma (Tanhehco and Jacobs 2010).

5.3 Contact Lens for the Treatment of Corneal Ectasia

Corneal ectasia is a progressive thinning and steepening of the cornea that occurs pathologically or after corneal surgery. The corneal ectasias include keratoconus, keratoglobus, pellucid marginal degeneration, Terrien's marginal degeneration, and post-LASIK ectasia. Keratoconus is the most common of the corneal ectasias and is estimated to have an incidence of the single most common corneal dystrophy or degeneration and affects 1 in 2000 Americans (NEI 2013). Typically, the vision deficits due to corneal ectasias can initially be treated with the use of glasses. However, as ectasia progresses, irregular astigmatism may not be corrected adequately with spectacles, requiring soft lenses then hard lenses for satisfactory vision. Some cases are characterized by scarring as well as thinning.

Contact lens failure and intolerance are accepted indications for corneal transplantation (Rabinowitz 1998) even if the cornea is clear. It is worth considering that the rate of postoperative contact lens wear for satisfactory visual rehabilitation after penetrating keratoplasty for keratoconus is 31, 43, and 47% (Silbiger et al. 1996; Brierly et al. 1996; Geerards et al. 2006; Jacobs and Rosenthal 2007; Tomalla and Canolati 2007). A longitudinal study of 1,004 eyes in 518 keratoconus patients over a 30-year period was conducted and found that contact lenses were a successful treatment option and postponed surgery in 99 % of fittings (Bilgin et al. 2009). Once a patient's refractive need extends beyond what soft spherical, soft toric, or convention corneal RGP lenses can offer, "specialty lenses" become an option. Specialty lenses include soft lenses designed specifically for keratoconus and RGP corneal lenses designed specifically for keratoconus, piggyback systems, hybrid lenses, scleral lenses, and PROSE treatment. Specialty spherical or toric soft lenses with steeper base curves are a good option as keratoconus progresses to the point that spectacles or conventional contact lenses are inadequate. Specialty soft lenses provide a number of advantages in treating lower grade ectasia. They typically do not require adaptation on the patient's part, and principles of fitting are similar to those for conventional soft lenses.

RGP corneal lenses are typically the next option for patients with corneal ectasia who cannot be adequately corrected with soft contact lenses or spectacles. RGP corneal lenses offer more complete neutralization of irregular astigmatism due to the fluid tear lake under the lens and rigid interface with the atmosphere. A corneal RGP has tendency to move to the steepest part of the cornea which, in ectasia, is typically inferior; this results in an intrapalpebral fit which is less mechanically stable than the preferred fit characterized by lid attachment (Fig. 5.2).

Piggyback systems are an option to increase mechanical stability and comfort of a corneal RGP lens. A piggyback system involves wearing an RGP corneal lens over a soft lens (Fig. 5.3) and can be useful in cases of RGP lens intolerance in corneal ectasia (O'Donnell and Maldonado-Codina 2004). Eyes wearing hybrid systems should be monitored closely for signs of hypoxia, which is a risk when total lens thickness is high.

Hybrid lenses are lenses of two different materials, assembled concentrically; these lenses have a hard center and soft periphery. The peripheral portion is sometimes referred to as the skirt. Hybrid lenses represent an attempt to combine the optical advantages of a hard lens with the comfort advantages of a soft lens. Hybrid is a lens made of two materials, whereas a piggyback system consists of two lenses, one placed over the other on the yes. Problems with early hybrids included tendency toward hypoxia and neovascularization due to low-Dk materials and tendency to develop suction and adherence under the central optic portion. The lenses tended to suffer

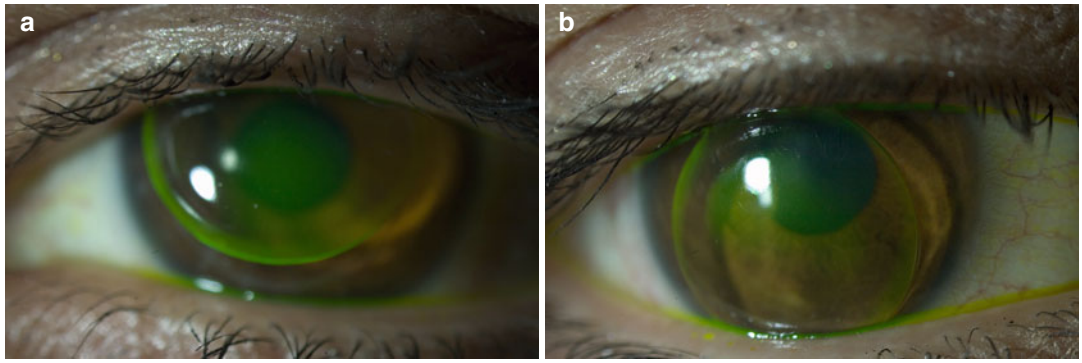

Fig. 5.2 (**a**) RGP corneal lens with optimal fit: "lid attachment". (**b**) RGP corneal lens with adequate fit: "intra-palpebral"

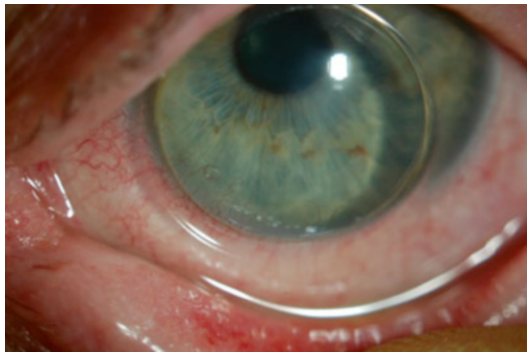

Fig. 5.3 Piggyback lens system in patient with keratoconus and history of Stevens-Johnson syndrome

under handling with disintegration at the junction between materials.

Larger diameter RGP lenses, including corneoscleral, semi-sclera, mini-scleral, and scleral lenses, offer increased stability with equally excellent optics in comparison to corneal RGP lenses. The increased stability related to the larger diameter can increase comfort and reduce lens awareness, as well as reduce likelihood of "popping" lenses, that is, losing lenses during wear.

5.4 Recent Advances: Corneal Ectasia

5.4.1 Soft Lens

In the last several years, specialty soft lenses of SiHy material have been introduced with reports of better comfort and increased tolerance compared to RGP lenses in the early stages of keratoconus (Ozkurt et al. 2012). The newer lenses of higher Dk material would presumably reduce the likelihood of hypoxic complications seen with hydrogel lenses in which a tight fit might have been accepted for mechanical stability and comfort on that basis. Soft specialty lenses are generally available at lower cost than other specialty lenses. Ultimately as ectasia progresses, soft lenses may not be adequate to neutralize irregular astigmatism as they essentially drape over rather than neutralize any local steepening.

5.4.2 Rigid Gas-Permeable Corneal Lenses

Inferior steepening and absolute steepening of >52 D are predictors of less stable fit. Faced with a choice between a tight fit with apical bearing or a loose fit which is unstable and can result in lost lenses, there are many patients who are maintained in tight fit till scarring occurs, at which time keratoplasty is required. In the last decade, many options including introduction of higher Dk RGP materials and increased appreciation of back surface toric designs have allowed for increased mechanical stability without excessive bearing apically on the flatter meridian.

5.4.3 Piggyback Systems

Modern piggyback systems use a high-Dk silicone hydrogel lens underneath the RGP lens in

an attempt to overcome past issues with hypoxia related to the total thickness of the system. The overall Dk of the piggyback system varies with the Dk thickness of both lenses. Recent report suggests that negative-powered soft lenses may be optically for use in piggyback systems because of reduced aberrations related to local flattening (Romero-Jimenez et al. 2013).

5.4.4 Hybrid Lenses

Hybrid lenses technology has advanced to incorporate higher Dk materials in both the rigid center and the hydrogel skirt. There are new specialty designs to accommodate apical cones and corneas with reverse geometry (central flattening) after cornea transplant or refractive surgery. Earlier problems with hybrid lenses have been addressed with the newer designs and materials of the last decade, with two studies finding 79.5 and 86 % success rates in patients with moderate or advanced disease (Nau 2008; Abdalla et al. 2010). A study from the Cornea Service at Wills Eye Institute administered the Contact Lens Impact on Quality of Life Questionnaire (CLIQ) on 71 consecutive patients who wore soft toric, RGP, or hybrid lenses in at least one eye with keratoconus and found that there was no difference in quality of life among the three groups (Erdurmus et al. 2009). There is an argument that the reason for the slow acceptance of modern hybrid lenses is the relatively high cost compared to RGP corneal or soft lenses and the assertion that they do not improve visual acuity or comfort when compared to RGP corneal contact lenses (Romero-Jimenez et al. 2010).

Corneal complications even with the newest designs have been reported (Fernandez-Velazquez 2011), with clinical experience suggesting that these lenses can develop suction and adherence that may not be detected in the initial fitting process.

5.4.5 RGP Mini-scleral and Scleral Lens

Mini-scleral lenses are reported as a good option for visual rehabilitation after placement of intrastromal corneal ring segments (Karlgard et al. 2004). Any of these larger RGP lenses would have the advantage over corneal RGP lenses in that bearing on the thin cornea directly over the segment is less likely. A reported complication of mini-scleral contact lens wear is nonulcerative keratitis perhaps related to compression from peripheral seal or lens hygiene or care product (Bruce and Nguyen 2013). Advances in lens design and manufacture to incorporate back-surface toricity allowing for alignment with toric sclerae increase the likelihood of success with large diameter RGP lenses (Visser et al. 2006; Baran et al. 2012).

Reports from the United States and Israel demonstrate that RGP scleral lenses are a good alternative to surgery for patients with keratoconus, with success in a majority of patients who might otherwise have proceeded to surgery (Schornack and Patel 2010; Severinsky and Millodot 2010).

5.4.6 PROSE Treatment

PROSE treatment is an effective option for the treatment of corneal ectasia and astigmatism. As described previously, the devices used in PROSE treatment are made of highly gas-permeable material; the fit is typically characterized by fluid ventilation, minimal movement, and no contact with the cornea (Fig. 5.4a, b). The latter features account for the excellent optics and comfort achieved in PROSE treatment for patients with corneal ectasia. A study of patients who were referred having failed contact lens rehabilitation found mean change of −0.54 logMAR (approximately 5 lines improvement) in visual acuity compared to habitual correction and mean of 20 points improvement in visual function in the NEI VFQ-25 questionnaire (Stason et al. 2010). A study of a subsequent cohort confirmed this level of impact on both acuity and visual function and reported that 78/89(88 %) eyes that were fitted with devices were still wearing the PROSE devices and had a mean improvement in VFQ-25 scores of 27.6 ($P<0.001$) on a 100-point scale after 6 months. Eyes that had undergone previous penetrating keratoplasty were included in the

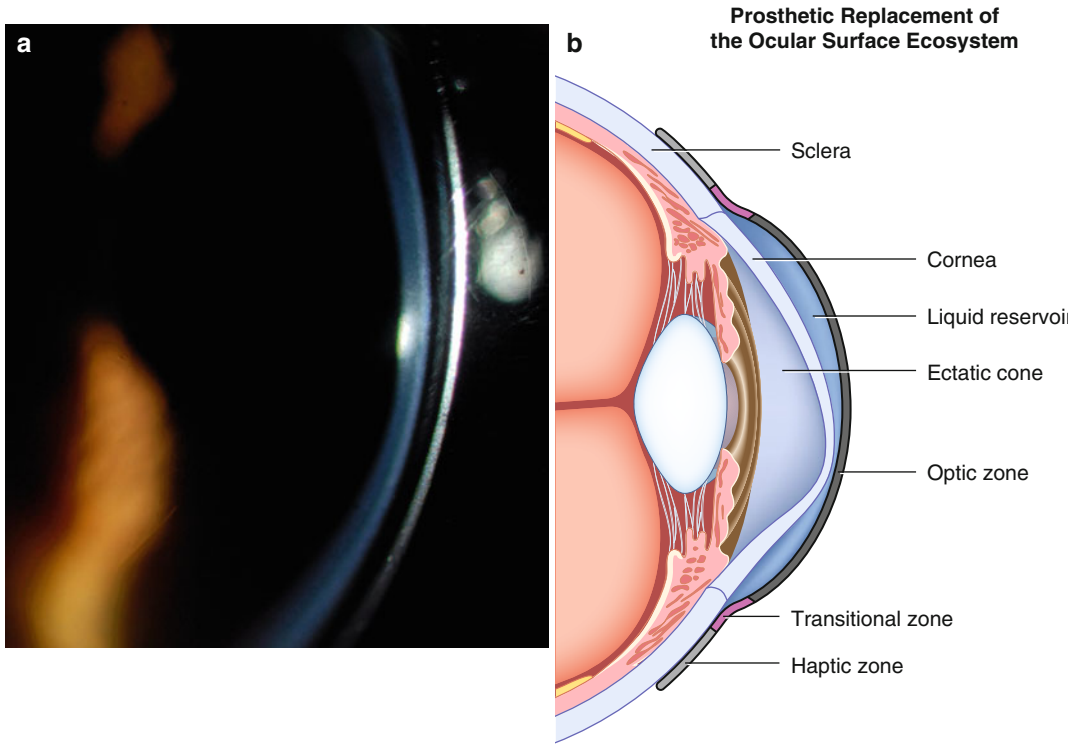

Fig. 5.4 (**a**) Slit lamp image of PROSE treatment. Note fluid-filled space behind back surface of prosthetic device and front surface of cornea. (**b**) Corresponding schematic diagram of PROSE device in cross-section over ectatic cornea

Table 5.1 Contact lens history in patients referred for PROSE treatment

90 % of patients had tried contact lenses
75 % of patients had tried rigid gas-permeable lenses
22 % of patients had tried piggyback lenses
17 % of patients had tried hybrid lenses

Prosthetic devices could be dispensed in all cases

analysis, with similar results. 93.1 % of eyes achieved a visual acuity of 20/40 or better (Baran et al. 2012). There was not one candidate eye that could not be fitted, despite including patients who had failed previous attempts at contact lens treatment using advance technologies such as specialty corneal lenses, hybrid lenses, piggyback systems, and even scleral lenses (Table 5.1) (Baran et al. 2012).

Recent reports reveal that PROSE treatment can serve as platform for the correction of higher order aberrations. There are reports of reduction of HOAs across all diagnosis (Gumus et al. 2010) and of improvement of low-contrast vision in keratoconus with PROSE treatment (Hussoin et al. 2012) using aspheric optics. Because stability of fit and capacity for precise registration on the eye, devices used in PROSE treatment are a suitable platform for custom HOA correction in corneal ectasia (Sabesan et al. 2013).

The advances in PROSE treatment have caused a paradigm shift in the management of corneal ectasia, because a PROSE device can accommodate any corneal shape. PROSE treatment is now widely available across the United States. PROSE treatment is a practical alternative to penetrating keratoplasty for eyes with advanced disease considered to be "contact lens intolerant." Furthermore, "axial opacity" is not sufficient indication for keratoplasty unless vision has been assessed wearing a mechanically stable contact lens or PROSE device.

5.5 Future Innovations

Innovation in contact lens holds promise for treatment of disease in the decade ahead.

Soft hydrogels which can be configured as contact lenses have been investigated as a drug delivery system for antimicrobials in the treatment of ocular surface disease, vision defects, infections, chronic dry eye, and allergies. The advantage of using soft hydrogels over aqueous or oily solutions for drug delivery is that soft hydrogels have been reported to allow for controlled delivery on the ocular surface for 3 days (Kakisu et al. 2013), 2 weeks (Glisoni et al. 2013), and up to 30 days (Lu et al. 2013), whereas topical solutions provide bioavailability over a range of minutes to hours (Glisoni et al. 2013). Contact lenses may be used as a vehicle to deliver and transplant corneal stem cells for ocular surface reconstruction (Di Girolamo et al. 2009).

The field of contact lens fitting is also an area of innovation, particularly for the purpose of fitting large-diameter lenses, in which optical imaging of the cornea may not be sufficient for deriving parameters for fit over the sclera. Three-dimensional imaging of the ocular surface holds promise for image-guided fitting and image-guided lens design. High-resolution image-guided fitting might replace the time and resource consuming trial lens method, especially for scleral lenses and PROSE treatment. The two competing technologies that are working toward this goal are optical coherence tomography (OCT) and laser-guided fitting. Recent reports suggest that OCT technology can be used to guide customization in PROSE treatment (Le et al. 2012) and to increase likelihood of initial lens success in the design of mini-scleral lenses (Gemoules 2008).

Finally, the suitability of devices used in PROSE treatment for the customized correction of HOAs in corneal ectasia (Sabesan et al. 2013) holds promise for other applications specialized optics for presbyopia that might offer increased depth of focus and custom correction of HOAs to achieve "super-vision" for specific applications.

Conclusions

Contact lenses, specialty lenses, and PROSE treatment play a vital role in the treatment of ocular surface disease and corneal ectasia. It is expected that emerging contact lens technology will continue to offer alternatives to current medical and surgical options for complex corneal disease. Clinicians will serve their patients well to be familiar with the full range of therapeutic contact lens options for the treatment of OSD and ectasia.

Compliance with Ethical Requirements Author Deborah S. Jacobs is a full-time salaried employee 501(c)3 of Boston Foundation for Sight. Author Joshua Agranat is a medical student at Boston University School of Medicine. Neither author has proprietary or financial interest in any contact lens or prosthetic device.

Informed consent and animal studies disclosures are not applicable to this review.

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Corneal Collagen Cross-Linking for Keratoconus and Corneal Ectasia

6

Steven A. Greenstein and Peter S. Hersh

6.1 Introduction

Corneal collagen cross-linking (CXL) is a treatment designed to decrease the progression of keratoconus (Wollensak et al. 2003a), in particular, and other corneal thinning processes such as post LASIK and PRK ectasia (Vinciguerra et al. 2009b; Seiler et al. 1998; Salgado et al. 2011; Hafezi et al. 2007). Studies have suggested that cross-linking also can have beneficial visual and optical effects such as decrease in corneal steepness, decrease in refractive error and astigmatism, improvement in best corrected and uncorrected visual acuity, and improvement in topography irregularity indices in some patients.

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6.2 Pathophysiology

An understanding of corneal biomechanics may help to elucidate the cause and natural history of keratoconus and other ectatic processes. The cornea is a viscoelastic structure with both viscous and elastic components (Roberts 2000). In response to stress, there is an immediate elastic response of the cornea followed by a prolonged, time-dependent, viscoelastic recovery. Early studies measured a decrease in elasticity in corneas with keratoconus (Edmund 1988). Currently, while the pathogenesis of keratoconus remains unclear, it appears that a primary event leads to the loss and/or slippage of collagen fibrils and changes to the extracellular matrix in the corneal stroma (Meek et al. 2005). These changes are thought to cause biomechanical instability of the corneal stroma with consequent changes in both the cornea's anatomic and topographic architecture (Gefen et al. 2009).

The progression of keratoconus slows as patients age, secondary to a natural cross-linking of the stromal collagen and consequent stiffening of the cornea with age. In the corneal collagen cross-linking procedure, riboflavin (vitamin B_2) is administered in conjunction with ultraviolet A (UVA 370 nm) irradiation. Riboflavin acts as a

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photosensitizer for the production of reactive oxygen species (singlet oxygen). Both the free radicals produced by this interaction as well as UVA-excited molecules of riboflavin result in the cross-linking effect and cause mechanical stiffening of the cornea (Wollensak et al. 2003b). Whether the actual "cross-links" are between or within collagen molecules, or involve corneal proteoglycans, remains unclear (Sawaguchi et al. 1989, 1991; Wollensak and Buddecke 1990). Wollensak et al. (2003b) reported that immediate in vitro stress measurements increased by 71.9 and 328.9 % in porcine and human corneas, respectively, after CXL. In rabbit corneas, these increases in stress measurements were maintained between 69.7 and 106 % at 8 months postoperatively (Wollensak and Iomdina 2009). Such postoperative increases in Young's modulus have been further demonstrated with collagen hydrogels exposed to UVA/riboflavin therapy (Ahearne et al. 2008).

The biomechanical strength of the cornea resides, predominantly, in the anterior stroma, where the microarchitecture of the collagen fibrils is more interweaved in the anteroposterior axis. The collagen cross-linking procedure, similarly, appears to have its predominant effect in the anterior 300 μm of the cornea (Wollensak et al. 2004b). In studies of the cornea after cross-linking, a number of changes have been reported. These include increased collagen fiber diameter (Wollensak et al. 2004b), keratocyte apoptosis and subsequent keratocyte changes (Wollensak et al. 2004a), resistance to thermal shrinkage (Spoerl et al. 2004a), change in corneal swelling properties (Dohlman et al. 1962), and increased resistance to collagenase degradation (Spoerl et al. 2004b). On clinical examination, corneal haze has been noted after the cross-linking procedure (Greenstein et al. 2010), and a demarcation line is commonly seen in this corneal stroma, delineating the posterior extent of the cross-linking effect (Seiler and Hafezi 2006). Although the exact mechanism of corneal collagen cross-linking has not been elucidated, it is clear from laboratory and clinical studies that the combination of riboflavin with UV light stiffens and strengthens the biomechanically unstable ectatic cornea.

6.2.1 The Cross-Linking Procedure

The general technique of corneal collagen cross-linking is based on the original corneal cross-linking procedure described by Seiler and colleagues (Wollensak et al. 2003a). In brief, a topical anesthetic is administered and the central 9 mm epithelium is removed by mechanical debridement. Riboflavin is then administered topically every 2 min for a total of 30 min. Following riboflavin administration, riboflavin absorption is confirmed on slit lamp examination (Fig. 6.1a). At this time, pachymetry measurements are performed, and if the cornea is <400 μm, hypotonic riboflavin is administered, one drop every 10 s for 2-min sessions, after which pachymetry measurements are performed again, to confirm that the stroma had swelled to ≥400 μm. The goal of this is to provide adequate corneal thickness to absorb the incoming UV light in order to protect the endothelium from damage by the UV-riboflavin interaction. The cornea is aligned and exposed to UVA 365 nm light for 30 min at an irradiance of 3.0 mW/cm^2 (Fig. 6.1b). While the cornea is exposed to UVA light, riboflavin administration is continued every 2 min. Postoperatively, antibiotic and corticosteroid drops are administered, a soft contact lens bandage is placed, and the eye is reexamined by slit lamp examination. The contact lens is removed after the epithelial defect had closed.

6.3 Clinical Outcomes

6.3.1 Visual Acuity and Refractive Outcomes

Generally, CXL appears to stabilize visual acuity and in many cases offers a modest improvement to patient's uncorrected and best correct vision. Previous work has shown that, on average, at 1 year postoperatively, uncorrected vision changed by 0–2.7 Snellen lines (Caporossi et al. 2010; Vinciguerra et al. 2009a; Hersh et al. 2011). In a study of 71 eyes, performed by one of the authors (PSH) as a part of the US multicenter clinical trial of collagen cross-linking, about 25 % of

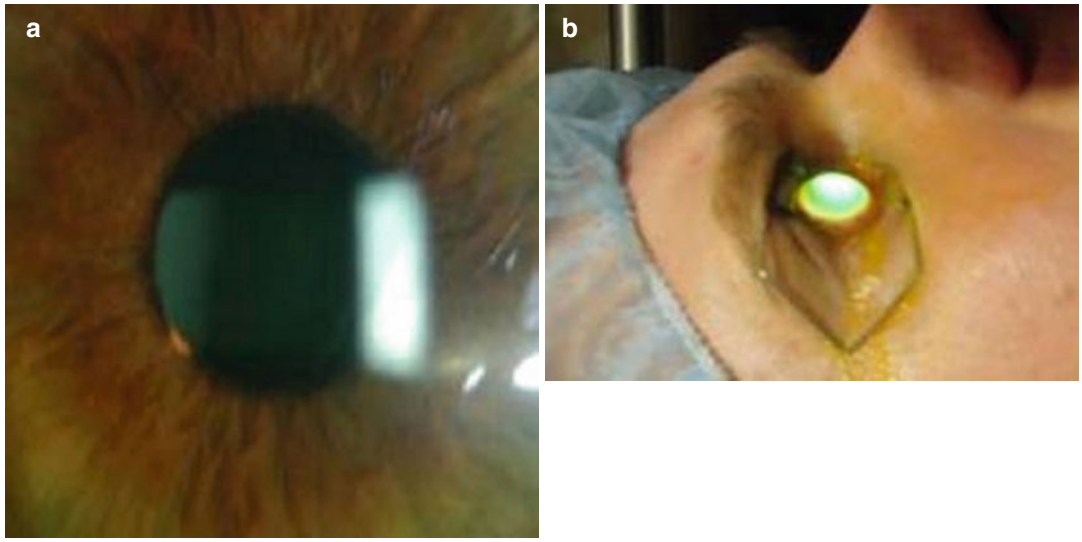


Fig. 6.1 (**a**) Slit lamp image confirming corneal riboflavin uptake and anterior chamber flare. (**b**) Photograph of patient being treated with UVA 365 nm light at an irradiance of 3.0 mW/cm^2

patients gained two or more Snellen lines of uncorrected vision, and about 8.5 % patients lost two or more lines of uncorrected visual acuity at 1 year (Fig. 6.2a) (Hersh et al. 2011).

In our study, while improvement of patient's uncorrected visual acuity after CXL was notable, more clinically significant was the improvement of best corrected visual acuity. Mean 1 year best corrected visual acuity significantly improved by about 1 Snellen line, from logMAR 0.35 ± 0.24 (Snellen acuity = 20/45) to 0.23 ± 0.21 (Snellen acuity = 20/34). Postoperative improvement of best corrected visual acuity has been noted in numerous other CXL studies as well. Vinciguerra et al. (2009a, b) found that in patients with stage III keratoconus, mean best corrected vision (logMAR) improved from 0.28 to 0.14 at 12 months postoperatively. At 1-year follow-up, Raiskup-Wolf et al. (2008) and Caporossi et al. (2010) reported significant improvements in best corrected vision of logMAR 0.08 and 1.34 Snellen lines, respectively, with continued improvement after 1-year follow-up. In our study (Hersh et al. 2011), about 21 % of patients gained two or more Snellen lines of best corrected visual acuity, and only one patient (1.4 %) lost two or more lines of best corrected visual acuity (Fig. 6.2b). More recently, another study reported about 40 % of patients gained two or more lines postoperatively; however, 12 % of patients in this study lost two or more lines of best corrected vision as well (Asri et al. 2011).

Regarding refractive outcomes, significant changes in manifest astigmatism of 0.93 D (Raiskup-Wolf et al. 2008) and 0.26 D (Vinciguerra et al. 2009a) have been reported. However, in other studies, mean manifest astigmatism essentially remained unchanged following CXL (Hersh et al. 2011). A vector and double-angle plot analysis, performed 1 year after CXL, revealed that mean induced astigmatism at 12 months, compared with preoperative values, was 0.75 D × 76°. Mean induced astigmatism was 0.99 × 88.8 and 0.65 × 44.7, in the right and left eyes, respectively. These refractive analyses suggest that there are directional changes in the cones and cylinder of keratoconus patients following CXL; however, the changes are random and unpredictable (Hersh et al. 2011).

6.3.2 Topographic Outcomes

Maximum keratometry is a key topographic indicator of the success of CXL, since it

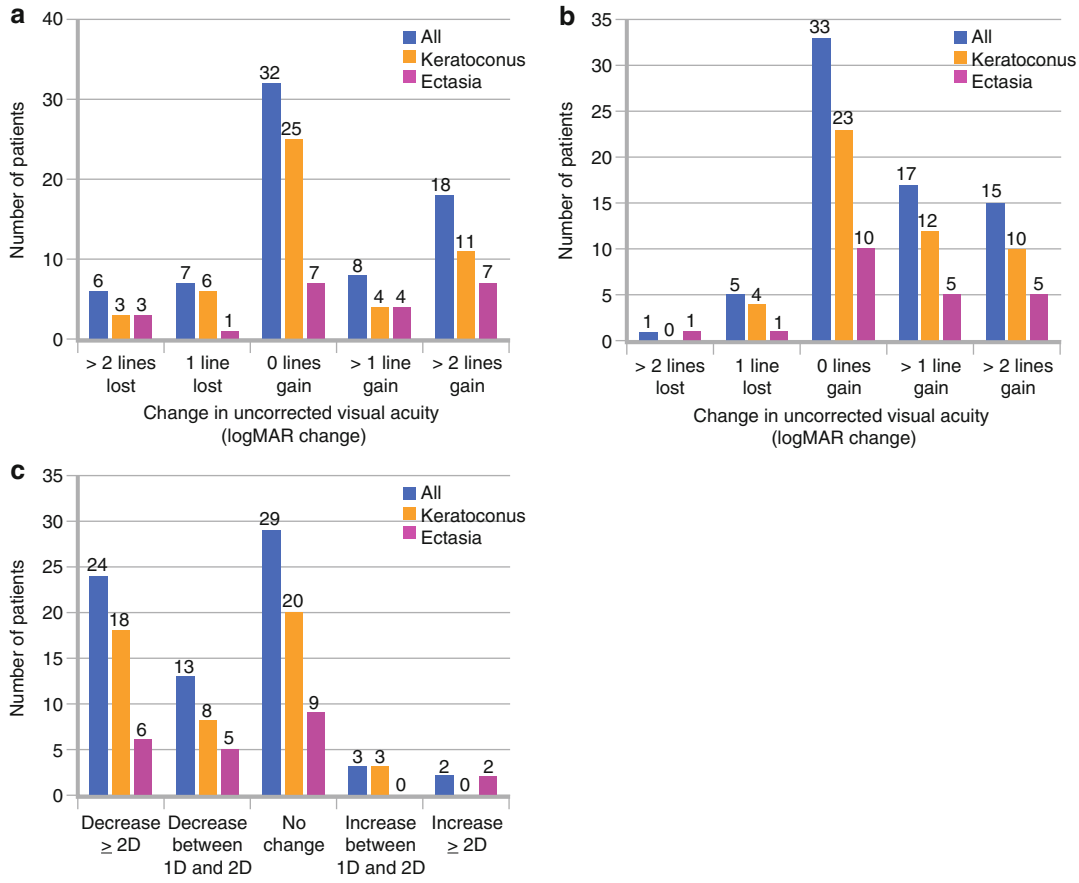


Fig. 6.2 (**a**) Number of individual patients who experienced a change in UCVA Snellen lines between baseline and 12 months after CXL. (**b**) Number of individual patients who experienced a change in BSCVA Snellen lines between baseline and 12 months after CXL. (**c**) Number of individual patients who experienced a change in maximum keratometry (D) between baseline and 12 months after CXL (Hersh et al. 2011)

measures, to some extent, the severity of the keratoconic cone. In the literature, average flattening of maximum keratometry ranges from about 1D to 3D, 1 year after CXL (Wollensak et al. 2003a; Caporossi et al. 2010; Vinciguerra et al. 2009a; Hersh et al. 2011; Caporossi et al. 2006; Koller et al. 2011). Furthermore, Raiskup-Wolf et al. (2008) and Caporossi et al. (2010) reported a continued flattening of maximum keratometry after 1-year follow-up. Individually, maximum keratometry decreased by 2D or more in 21 to 35 % of patients, change between −2D and 2D in 62.0 to 68 % of patients (essentially remaining stable), and steepen by 2D or more in 3 to 6 % of patients (Fig. 6.2c) (Hersh et al. 2011; Asri et al. 2011).

6.3.3 Topographic Keratoconus Indices

In general, topographic keratoconus indices (Table 6.1) are elevated over normal in patients with keratectasia and, therefore, a significant decrease in any of these postoperative measurements after CXL may indicate improvement in the contour of the cornea. Koller et al. (2011) reported a significant improvement in four of seven Pentacam topography indices [central keratoconus index (CKI), keratoconus index (KI), index of height asymmetry (IHA), and minimum radius of curvature (R_{min})] 1 year after CXL. Similarly, we noted an improvement in four of seven indices, including KI and R_{min} as in

Table 6.1 List of the abnormal and pathological values for the Pentacam topographic indices (User manual for the Pentacam Oculus, Wetzlar, Germany)

Index	Description of index	Abnormal	Pathological
ISV	A general measure of corneal surface irregularity	≥37	≥41
IVA	A measure of the difference between superior and inferior curvature in the cornea	≥0.28	≥0.32
KI	As determined by the Pentacam	≥1.07	≥1.07
CKI	As determined by the Pentacam	≥1.03	≥1.03
R_{min}	A measurement of the smallest radius of curvature of the cornea	<6.71	<6.71
IHA	A similar measurement to IVA, but based on corneal elevation	≥19	>21
IHD	A calculation with Fourier analysis of corneal height to quantify the degree of vertical decentration	≥0.014	≥0.016

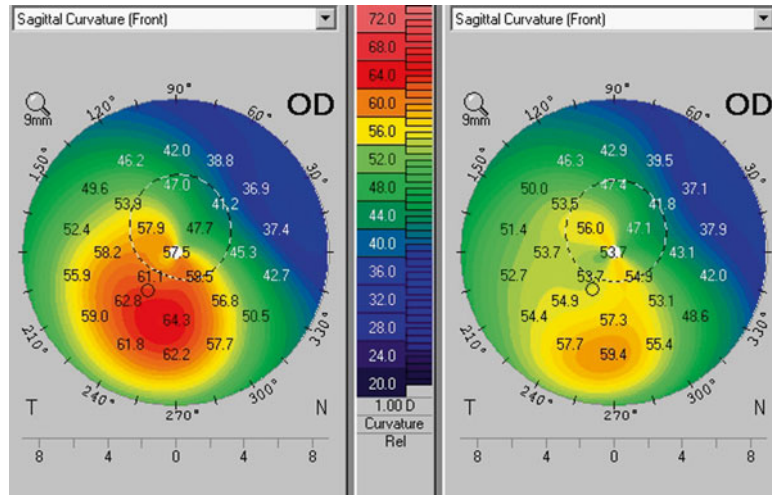


Fig. 6.3 Corneal topography before (*left*) and 1 year after CXL (*right*). Note improvement in corneal contour

the aforementioned study, but additionally, our study revealed improvements of index of surface variance (ISV) and index of vertical asymmetry (IVA) (Greenstein et al. 2011). The improvements observed in ISV indicate a decrease of the curvature variation compared to the mean curvature of the cornea, and IVA, a measurement of the difference between the superior and inferior curvature of the cornea, which may be analogous to an improvement in the more commonly used I-S ratio (Rabinowitz 1995). Furthermore, improvement in KI may indicate that there is a normalization of the keratoconic topographic appearance postoperatively (Fig. 6.3). The overall improvements in the above indices suggest, in general, that the cone is flattening and that the post-CXL cornea is becoming more optically regular and symmetric; however, it is unclear why, in the previous two studies, the improvements were demonstrated, in part, by different Pentacam indices.

6.3.4 Higher-Order Aberrations

Increased anterior corneal, posterior corneal, and total ocular higher-order aberrations are optical sequelae of keratoconus which contribute to the diminished visual function found in these corneal disease processes (Lim et al. 2007; Schlegel et al. 2009). Corneal collagen cross-linking, although developed primarily to mitigate progression of ectatic corneal processes, as discussed previously, has been found to improve visual acuity in many patients as well. Detailed analyses of higher-order aberrations showed significant improvements in ocular and anterior corneal higher-order

aberrations 1 year after CXL (Fig. 6.4a–c) (Vinciguerra et al. 2009a; Hersh et al. 2011; Greenstein et al. 2012a). This finding corroborates the improvement in corneal topography seen. Although improvement both in topography and in aberration profile would be expected to improve vision, interestingly, neither the corneal nor total ocular aberrations were statistically associated with the improvements of postoperative visual acuity in our study. Furthermore, there did not appear to be any clinically relevant associations between improvement of higher-order aberrations and improvement of any subjective visual symptoms (e.g., glare, halos, sunbursts, etc.) after cross-linking as well (Greenstein et al. 2012a). Notwithstanding these statistical analyses, a general decrease in higher-order aberrations and improvement in corneal topographic contour would be expected to have overall beneficial effects to the patients visual function.

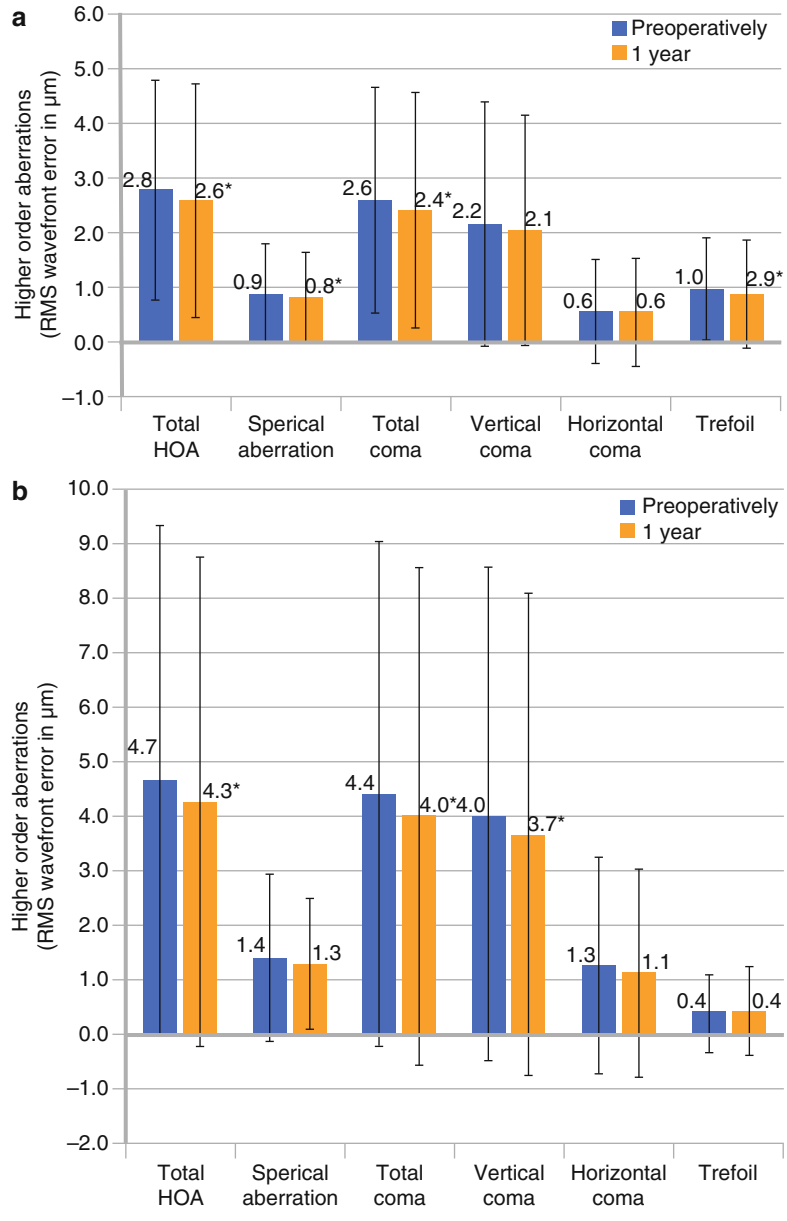
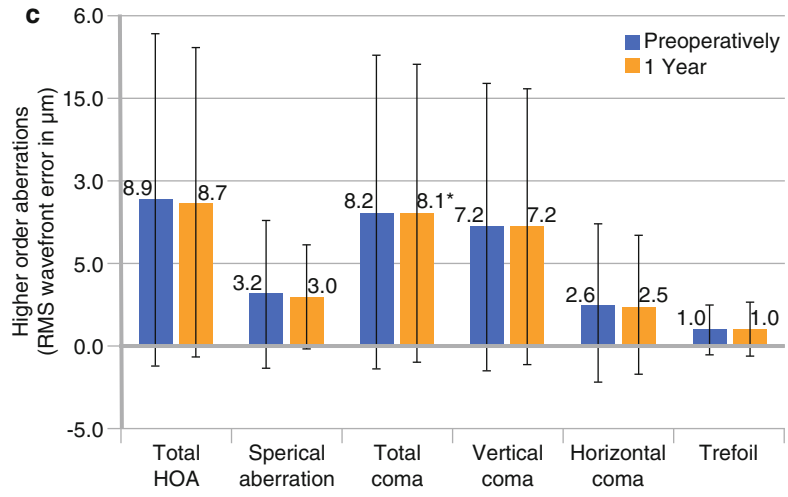


Fig. 6.4 Higher-order aberrations (root mean squared wave front error), measured preoperatively and at 1 year after CXL. *Error bars* represent 2 standard deviations from the mean. *Indicates a significant change compared to preoperative measurements ($P<0.05$). (**a**) Total ocular aberrations. (**b**) Anterior corneal aberrations. (**c**) Posterior corneal aberrations (Greenstein et al. 2012a)

Fig. 6.4 (continued)



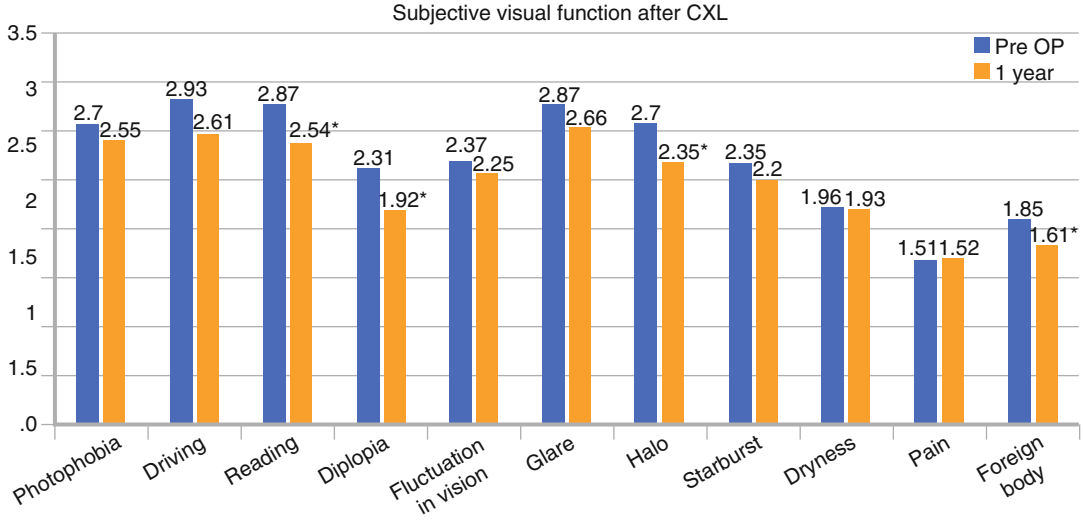


Fig. 6.5 Average rating of subjective visual parameters for keratoconus subgroup preoperatively and at 12 months after CXL. Subjective scale 1–5 (1 = no symptoms, 5 = severe symptoms). *Statistically significant ($p < 0.05$) (Brooks et al. 2012)

6.3.5 Patient Satisfaction

In an effort to expand on the objective postoperative assessment of the cross-linking procedure and to further elucidate the expected clinical response, a self-reported analysis of patients' optical symptoms and visual function was instructive. In our study, we found that patients generally noted subjective improvement in visual symptoms. Specifically, night driving, difficulty reading, diplopia, glare, halo, starbursts, and foreign body sensation were all improved 1 year after CXL (Fig. 6.5) (Brooks et al. 2012). In addition to corroborating the objective postoperative improvements after corneal collagen cross-linking, this speaks to the positive subjective patient satisfaction after the procedure.

6.3.6 Postoperative Timecourse

Looking at the clinical timecourse after cross-linking, there was a significant worsening of vision and steepening of the keratoconic cones at 1 month postoperatively. These changes appear to improve

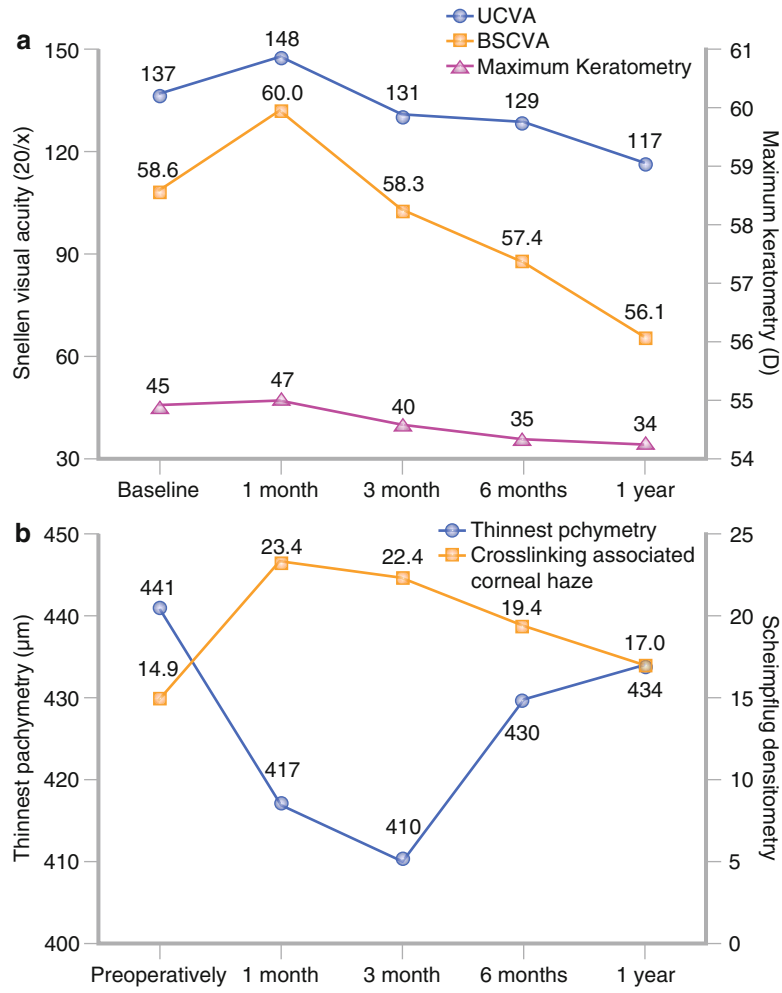


Fig. 6.6 (**a**) Change in UCVA, BSCVA, and maximum keratometry over time. (**b**) Change in thinnest pachymetry and cross-linking-associated corneal haze over time (Hersh et al. 2011)

at about 6 months and plateau thereafter (Fig. 6.6a). Interestingly, these postoperative outcomes appear to be congruous with the postoperative thinning and cross-linking-associated corneal haze changes over time (Fig. 6.6b). It is unclear whether this suggests a remodeling occurring during a "desired" haze and thinning process or if this time course suggests a natural process of corneal would healing irrespective of the changes in cross-linking-associated corneal haze and postoperative thinning (see Sect. 6.5).

6.4 Biomechanical Changes

In vitro, corneal collagen cross-linking has been reported to increase the biomechanical stability of the ecstatic cornea in keratoconus (see Sect. 6.2). Currently, the Ocular Response Analyzer (ORA, Reichert Inc., Buffalo, NY, USA) is one of the few commercially available tools to measure in vivo corneal biomechanics. Two core metrics are used to describe the biomechanical strength of the cornea: corneal hysteresis (CH) and corneal resistance factor (CRF). CH is a measurement of the viscous dampening in corneal tissue, and CRF is a measurement of the entire viscoelastic response of the cornea, in response to both the graded and time-dependent applanation pressures applied by the ORA. To measure CH and CRF, a tube is automatically aligned with the patient's eye, and an air puff is released of a specific time and pressure gradient. Concomitant with the air pulse, the ORA measures two applanation pressures: the first pressure is measured when the cornea is moving inward, and the second pressure is measured

when the cornea returns to its original position. In addition, a waveform of this temporal corneal deformation is captured. Measurements derived from the waveform signal such as peak amplitudes, timing of peaks, width of peaks, and others, have been used to determine the biomechanical properties of individual corneas (Kerautret et al. 2008; Fry et al. 2008; Gatinel and Luce 2009; Lam et al. 2010).

In vivo biomechanical measurements, CH and CRF appear to remain unchanged 1 year after CXL (Fournie et al. 2009; Goldich et al. 2009; Vinciguerra et al. 2010; Greenstein et al. 2012). Interpreting these results is challenging, since postoperative changes to either the viscous or elastic components of the cornea may be too subtle for these ORA metrics to capture and may in part contribute to the lack of significant results (Touboul et al. 2008; Glass et al. 2008). Moreover, the surface optical irregularity of these ectatic corneas may introduce error and variability into the ORA signal that may prevent meaningful quantitative comparison of preoperative and postoperative CH and CRF (Vinciguerra et al. 2009a; Shah et al. 2006). It is also possible that the biomechanical changes after CXL are inherently different than those measured by CH and CRF, and therefore, these metrics may not capture the true biomechanical effect of CXL over time. Development of interpretive models of the waveform itself, similar to those used to grade keratoconus, may better capture the true biomechanical properties of the cornea after CXL (Fry et al. 2008; Gatinel and Luce 2009). Moreover, development of new instrumentation to assess corneal biomechanics will help to better assess the stiffening effects of the cross-linking procedure clinically.

6.5 Complications

6.5.1 Postoperative Haze

On clinical examination, corneal haze has been noted after the cross-linking procedure (Fig. 6.7). Cross-linking-associated corneal haze is different in clinical character from haze after other procedures such as excimer laser photorefractive keratectomy. The former is a dustlike change in the corneal stroma or a mid-stromal demarcation line (Seiler and Hafezi 2006), whereas the latter has a more reticulated subepithelial appearance. Cross-linking-associated corneal haze is most likely a measure of backscattered and reflected light, causing decreased corneal transparency (Caporossi et al. 2010). This haze can be graded at the slit lamp (Wollensak and Iomdina 2009); however, grading slit lamp haze is subject to observer interpretation and is difficult to measure objectively. Moreover, corneal haze has been confirmed using confocal microscopy as well and can be objectively quantified using Scheimpflug densitometry (Fig. 6.8) (Mazzotta et al. 2007).

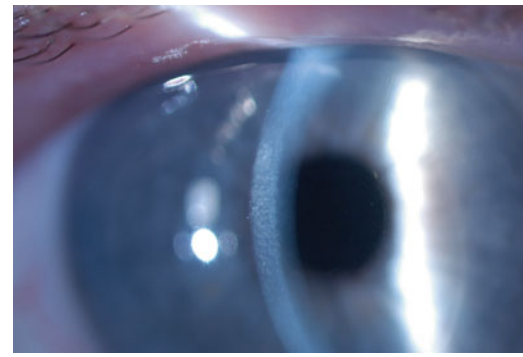


Fig. 6.7 Typical corneal stromal haze after collagen cross-linking

Similar to the timecourse of clinical outcomes after cross-linking, there appears to be an increase in haze, which peaks at 1 month and plateaus between 1 and 3 months. Between 3 and 6 months, the cornea begins to clear and continues to return toward baseline at 1 year (Fig. 6.6b) (Greenstein et al. 2010).

To date, it remains unclear whether this postoperative haze is a true complication or rather a desired wound healing effect demonstrating the efficacy of the cross-linking procedure. Transparency of the cornea is a result of the regular spacing, small uniform diameter of the collagen fibrils (Vinciguerra et al. 2009a), and the cellular structure of stationary keratocytes (Hersh et al. 2011). Increased spacing and changes in fibril diameter could cause increased light scatter and decreased transparency. Furthermore, stationary keratocytes have crystallins in their cytoplasm that have a refractive index similar to that of the extracellular matrix. During wound healing,

Fig. 6.8 Scheimpflug images of cross-linking-associated corneal haze over time

migratory keratocytes have decreased crystallins, leading to an increase in refracted light and a subsequent increase in haze (Hersh et al. 2011). In vitro and ex vivo studies have shown that collagen cross-linking led to an almost immediate loss of keratocytes in the corneal stroma (Gefen et al. 2009; Raiskup-Wolf et al. 2008). Confocal microscopy, in patients with keratoconus, revealed activated keratocytes repopulating the corneal stroma starting at 2 months, and stromal repopulation was almost complete at 6 months (Mazzotta et al. 2007). It is possible that these activated keratocytes contribute to the development of haze, as seen on Scheimpflug imagery. Additionally, a significant increase in collagen fibril diameter, with increased spacing between collagen fibrils, following UVA/riboflavin therapy may play an important role in the decreased corneal transparency as well (Wollensak et al. 2004b; Hersh et al. 2011).

6.5.2 Corneal Pachymetry

Corneal thinning is a general concomitant of the early CXL postoperative course (Fig. 6.6a). Previous studies have noted that intraoperative ultrasound pachymetry decreased after the initial 30 min of riboflavin administration (Wollensak et al. 2004a), and several others have noted corneal thickness changes after CXL (Seiler et al. 1998; Salgado et al. 2011; Hafezi et al. 2007; Roberts 2000; Wollensak and Iomdina 2009; Ahearne et al. 2008; Wollensak et al. 2004a, b). Postoperatively, similar to the timecourse of cross-linking-associated corneal haze, and cross-linking clinical outcomes, the cornea appears to thin at 1 and 3 months and to re-thicken between 3 and 12 months (Greenstein et al. 2011). At 1 year, cornea treated with standard dextran riboflavin alone remained slightly thinner than preoperative measurements.

The physiology of this initial thinning and subsequent re-thickening is, as yet, unclear. Epithelial remodeling is a possible early factor in corneal thickness changes. Although reepithelialization after CXL generally is complete at 4–5 days after surgery (Sawaguchi et al. 1989), continued epithelial remodeling could influence total corneal thickness over time (Fig. 6.9a, b). For instance, the native epithelium may mask underlying stromal contour irregularities, with thicker epithelium over the lower stromal regions and thinner epithelium overlying the cone itself. Thus, removing the epithelium may unmask a greater stromal irregularity, resulting in steeper corneal topography, which then resolves as the epithelium heals and remodels. Aside from epithelial healing, anatomic and structural changes of corneal collagen fibrils such as compression of collagen fibrils (especially the more transverse-oriented anterior fibrils) (Wollensak et al. 2003b; Vinciguerra et al. 2009a), changes in corneal hydration (Hersh et al. 2011) and edema (Raiskup-Wolf et al. 2008; Asri et al. 2011), keratocyte apoptosis (Sawaguchi et al. 1989; Caporossi et al. 2006; Koller et al. 2011), changes in glycosaminoglycans (Rabinowitz 1995), and other processes might be implicated in the distinct clinical timecourse after CXL.

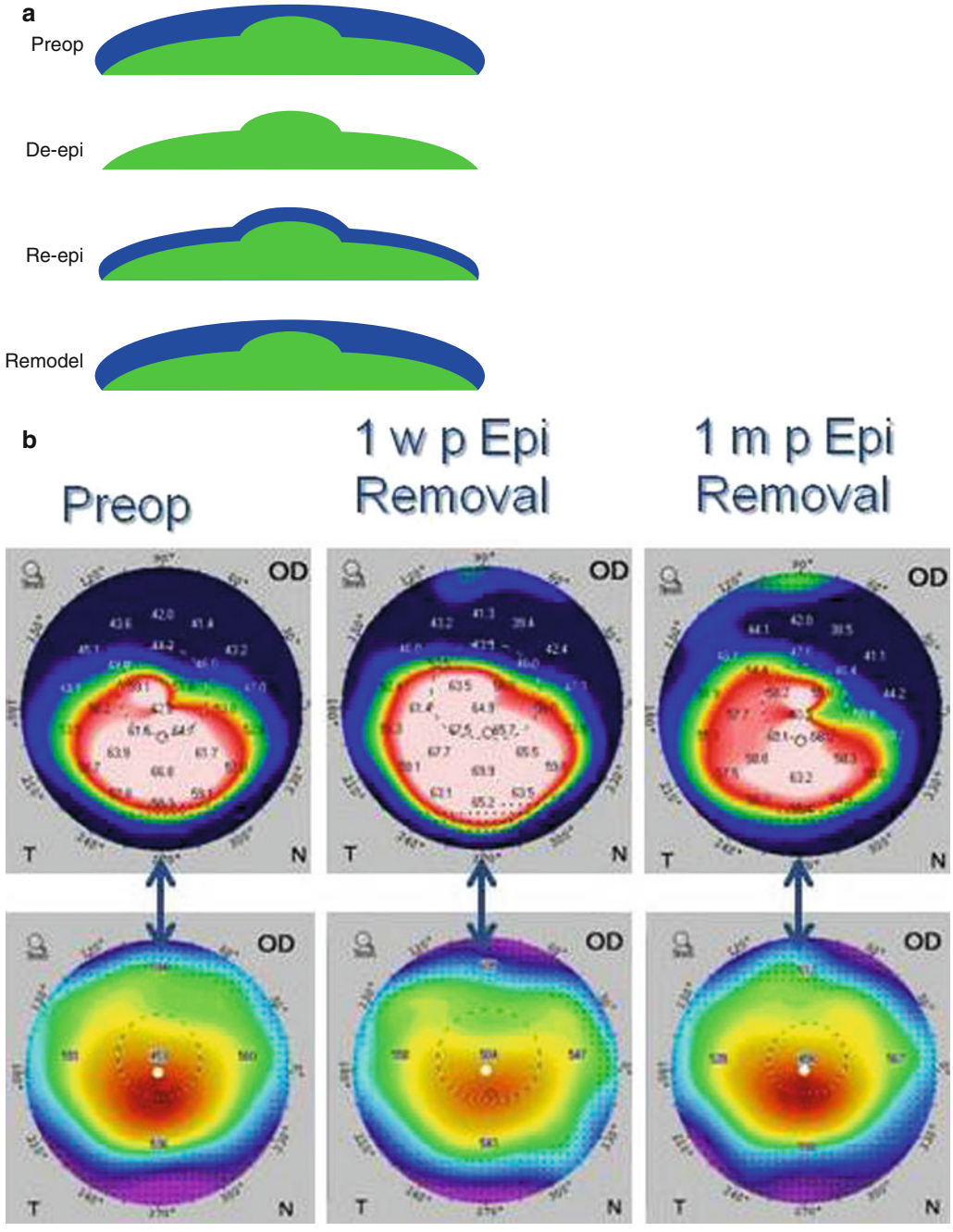


Fig. 6.9 (**a**) Epithelial remodeling as a possible cause of early topography cone steepening after CXL. Note "unmasking" of cone with epithelial removal and subsequent improvement of anterior contour as epithelium remodels, filling in low topographic regions. (**b**) Corneal topography and corresponding thickness preop, at 1 week, and at 1 month. Note the increased cone and thickening over the apex 1 week after de-epithelialization and the improvement in the cone height with thinning of the pachymetry 1 month post-op

6.6 Predictors of Outcomes

The essential goal of collagen cross-linking is to stabilize the progression of the ectatic cornea. With regard to this disease stabilization, cross-linking indeed appears efficacious; 98.1 % of eyes showed <2D and 91.6 % showed <1.0D of topographic progression over 1 year postoperatively. In addition, specific predictors of not only stabilization but rather positive and negative cross-linking outcomes have begun to be elucidated. Two studies from Seiler's group deserve attention (Spoerl et al. 2004b). In the first, of 105 eyes, 3 lost 2 Snellen lines of best corrected vision at 1 year. Two characteristics, age >35 years and best corrected vision better than 20/25, were identified as risk factors for this loss of vision. Eight eyes (7.6 %) showed continued progression of keratoconus 1 year after CXL, defined as an increase in maximum *K* of ≥1.0D. Two preoperative characteristics, maximum *K* >58.0 D and female gender, were identified as risk factors for continued disease progression. In a second study by this group, they found that a preoperative *K* >54.0 D was associated with a greater likelihood of postoperative flattening of >1.0D, a finding corroborated by our study (Greenstein and Hersh 2013). With regard to clinical decision-making, their latter study conflicts somewhat with their earlier conclusion that the *K* >58.0 was associated with greater risk of continued disease progression.

These results may have important implications for patient outcomes after cross-linking. Our multivariate analyses revealed the only independent predictor of a change in postoperative best corrected vision after CXL was preoperative best corrected visual acuity. Those eyes with worse preoperative best corrected visual acuity were more likely to experience an improvement of ≥2 Snellen lines. Specifically, eyes with a preoperative Snellen visual acuity of 20/40 or worse were 5.9 times more likely to improve by two lines or more; 43 % of eyes with best corrected vision 20/40 or worse had an improvement of ≥2 lines compared with only 11 % of eyes who were better than 20/40 (Fig. 6.10a, b). With regard to eyes which lost vision from the procedure, the most salient indicator of an unwanted outcome, there was no independent preoperative indicator.

With regard to postoperative topography, eyes with a maximum *K* ≥55D were 5.4× more likely to have topographic flattening ≥2D after CXL compared with eyes with flatter corneas. However, with regard to eyes in which corneal topography continued to steepen, that is, those in which the cross-linking procedure failed to stabilize the disease, there were no independent predictors of continued topographic steepening even at the more refined ≥1D level (Greenstein and Hersh 2013). All eyes were equivalently likely to be stabilized by the CXL procedure. Specifically, in patients with an initial maximum *K* ≥55D, 40/44 (90 %) eyes showed less than 1.0 D of progression, 1 year after CXL; similarly, in patients with initial maximum *K* <55.0D, 55/60 (92 %) eyes were stable (Fig. 6.11a, b).

From the viewpoint of clinical decision-making, since no independent predictors of failure of cross-linking to stabilize topographic disease progression were identified, it is reasonable that all eyes with progressive keratoconus or corneal

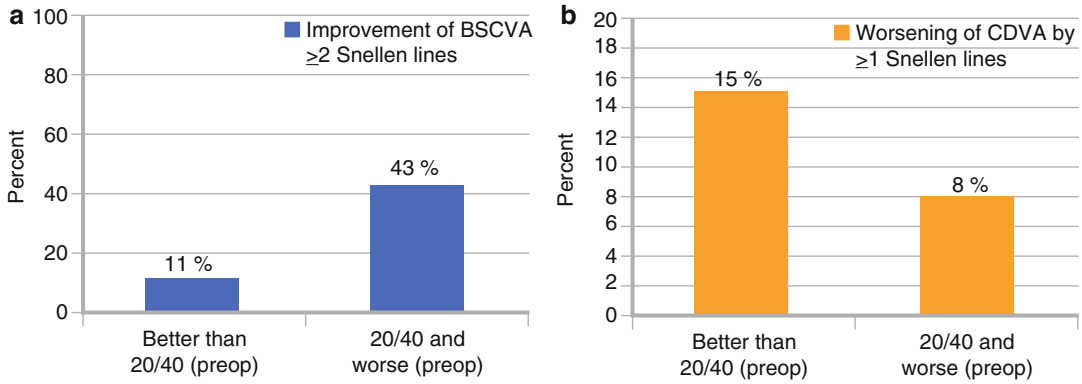


Fig. 6.10 The effect of preoperative BSCVA on CXL outcomes. (**a**) (*Blue*) Percentage of eyes in which BSCVA improved by ≥2 Snellen lines 1 year after CXL. (**b**) (*Orange*) Percentage of eyes in which BSCVA worsened by ≥1 Snellen line 1 year after CXL

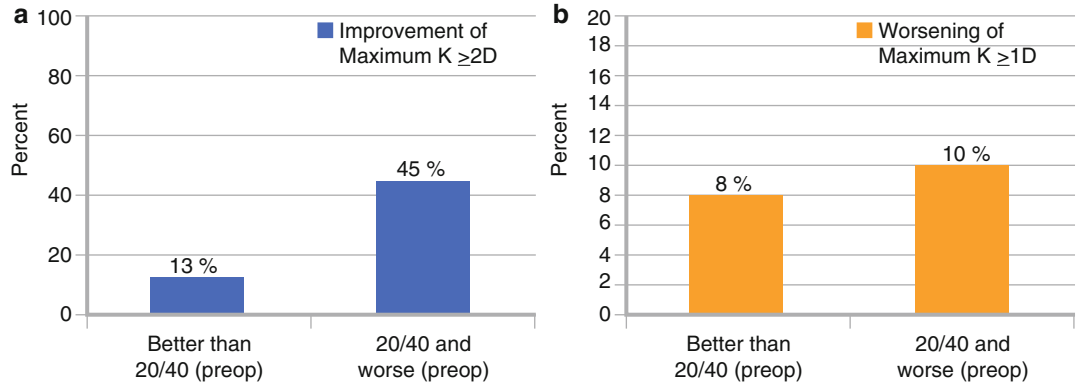


Fig. 6.11 The effect of preoperative maximum keratometry on CXL outcomes. (**a**) (*Blue*) Percentage of eyes in which maximum *K* flattened by ≥2D 1 year after CXL. (**b**) (*Orange*) Percentage of eyes in which maximum *K* steepened by ≥1D 1 year after CXL

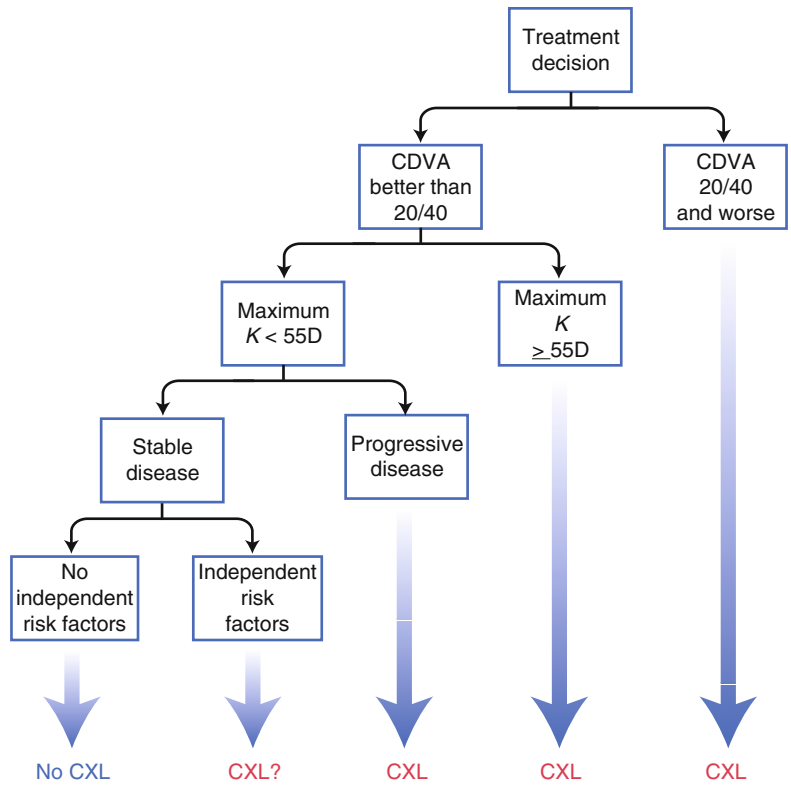


Fig. 6.12 Treatment algorithm for CXL patient selection

ectasia should be considered for cross-linking treatment, with the goal of diminishing disease progression. With regard to postoperative best corrected vision, from our current knowledge, it might be reasonable to conclude that eyes with worse vision initially would expect the greatest chance of actual visual improvement, and all eyes are equally likely to remain stable within 2 lines of best corrected visual acuity, although eyes with initially good vision (better than 20/40) may be somewhat more susceptible to a loss of 1 line (Fig. 6.12). Therefore, eyes with good visual acuity and progressive disease may still benefit from cross-linking treatment but the ophthalmologist should be aware of this possible visual complication and the patient properly counseled.

Finally, preoperative cone location may play an important role in the efficacy of the cross-

linking procedure (Greenstein et al. 2012b). There appears to be more topographic flattening in those eyes with centrally located cones. In our previous work, maximum keratometry flattened by 2.6D in eyes with centrally located cones and by only 1.0D and 0.05D in those eyes with paracentral and peripheral cones, respectively. This difference in topographic outcomes may be explained by a number of mechanisms. The treatment delivered by the current UV technique may not be homogeneous over the entire treatment zone, the "cosine effect" (Hersh et al. 2003) may diminish the relative treatment of the peripheral cornea by cross-linking, and hypothetically, the more symmetric cross-linking effect in centrally located cones may lead to more equal compression of collagen fibrils in all directions, and therefore increased flattening in those patients with centrally located cones. Furthermore, it was noted that patients with post LASIK ectasia (included in the above study) were more likely to have peripheral cones, and therefore, the above study may be elucidating a difference in the disease response to cross-linking rather than the cone location itself.

While the mechanism for the greater improvement of centrally located cones remains uncertain, the effect of preoperative cone location on cross-linking outcomes may be important as cross-linking continues to evolve. With regard to the delivery system, assuring consistent energy over the face of the beam may give more consistent treatment to the corneal periphery. Moreover, topographically guided treatments, either with the beam directed at the cone apex directly or more elegantly delivered as a true topographically guided treatment, could improve cross-linking results independent of cone location. With regard to other procedures to enhance the cross-linking effect, efforts to "centralize" the cone, for instance, by intracorneal ring segments or by conductive keratoplasty (Hersh et al. 2005), could possibly lead to more robust cross-linking results as well.

6.7 Future of Corneal Collagen Cross-Linking

Transepithelial cross-linking, a variation of the standard cross-linking procedure in which the corneal epithelium is not removed, offers several possible advantages. Firstly, it improves patient comfort in the early postoperative reepithelialization phase. Secondly, it reduces the risk for infection, and thirdly, it offers faster visual recovery with an earlier potential return to contact lens wear. The approach to transepithelial cross-linking is evolving. Standard riboflavin in a dextran solution does not penetrate the corneal epithelium well. Therefore, many investigators utilize riboflavin without dextran and also use a solution containing benzalkonium chloride (BAK) to increase the permeability of the corneal epithelium and allow for the penetration of the riboflavin into the corneal stroma before exposure to the UV light (McCarey and Edelhauser 2007). Early results of transepithelial cross-linking have been mixed, as are the long-term results for this procedure (Caporossi et al. 2012, 2013; Zhang and Zhang 2012; Koppen et al. 2012). Further long-term studies are required to determine the efficacy of this procedure and, more importantly, to determine the ideal riboflavin and coupling solutions, as well as the application method and optimum UV power to achieve desired results.

Another variation of the standard cross-linking procedure is accelerated corneal collagen cross-linking. In this procedure, the cornea is exposed to a higher power of UV light over a significantly shorter period of time. In vitro studies have shown that despite delivering a higher power of UV light, the safety and integrity of the corneal endothelium remains intact secondary to the very short exposure time. Clinical studies of accelerated cross-linking are now underway.

Finally, there has been increasing focus on the use of corneal collagen cross-linking as part of a larger treatment algorithm for patients with keratoconus. While there are many patients who may benefit from cross-linking alone, there are other patients who may benefit from cross-linking as an adjunct procedure to stabilize the cornea. Other procedures, such as intracorneal ring segments (Vega-Estrada et al. 2013; Saelens et al. 2011; Alio et al. 2006; Kwitko and Severo 2004), PRK (Spadea 2012), topography-guided photorefractive keratectomy, and microwave thermokeratoplasty (Keraflex) (Barsam et al. 2010), are starting to be preformed and studied for patients with more severe keratoconus. These procedures may induce more initial flattening of steeper cones and improve

the contour of the ectatic cornea; however, corneal collagen cross-linking may be required to better stabilize these changes over time.

Conclusions

Corneal collagen cross-linking is a promising new treatment to stabilize and even improve the visual acuity and topography of patients with keratoconus. In the future, faster and more precisely guided UV light delivery systems, as well as new forms of riboflavin, may continue to improve the safety and efficacy of this new procedure. Further studies being conducted will likely continue to reveal the patients who will most benefit from corneal collagen cross-linking whether it is as a standalone procedure or in conjunction with other procedures designed to improve the contour and optical quality of the ectatic cornea.

Compliance with Ethical Requirements

Conflict of Interest

Dr. Greenstein declares that he has no conflict of interest.

Dr. Hersh is a consultant for Avedro, Inc.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Animal Studies

No animal or human studies were carried out by the authors for this article.

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Advancements in Anterior Lamellar Keratoplasty

7

Marwan Atallah and Guillermo Amescua

7.1 Introduction

Anterior lamellar keratoplasty (ALK) is a corneal transplant procedure where diseased anterior corneal stroma is selectively replaced with donor stromal tissue while preserving the host Descemet's membrane and endothelium. The first reports on lamellar keratoplasty date back to 1830 (Reisinger 1824; Mühlbauer 1840), approximately 75 years prior to the first penetrating keratoplasty (PKP) (Zirm 1906). Several improvements in the procedure followed, namely, in 1866 by Von Hippel who described the first successful anterior lamellar corneal transplant using rabbit stromal tissue as a donor (Von Hippel 1888); then by Durr, De Wecker, Fuchs, and Filatov who developed various surgical techniques of anterior lamellar corneal surgery; and later by Hallerman in the late 1950s who introduced the concept of a deep dissection. Despite ALK's longer history, the most commonly performed procedure for the last 100 years has been PKP, and this has been attributed to the technical difficulties in achieving a successful ALK.

However, over the past two decades, improvements in surgical techniques (e.g., Anwar's big-bubble technique) and surgical instrumentation (including the use of the microkeratome and the femtosecond laser) have caused a resurgence in interest in anterior lamellar corneal surgery. Full-thickness penetrating keratoplasty is no longer the standard of care procedure for corneal transplantation. ALK has become the standard of care for the management of pathology anterior to Descemet's membrane and endothelial keratoplasty for pathology involving Descemet's membrane and corneal endothelium.

ALK can be subcategorized as superficial anterior lamellar keratoplasty (sALK), for the treatment of stromal pathology usually involving the anterior 200–250 μm, and deep anterior lamellar keratoplasty (DALK) for the treatment of deeper stromal pathology. These two procedures offer numerous advantages compared to PKP. ALK wounds for one are less susceptible to dehiscence as the donor-to-host interface is larger and Descemet's membrane remains intact. Furthermore, since the endothelium is the layer with the highest allogenicity, anterior lamellar implants are less likely to be immunologically rejected and the need for immunosuppression is reduced. ALK also allows less stringent requirements for donor tissue, as the need for a healthy endothelium is not needed. Lastly, ALK is considered an extra ocular procedure and, if carried through, does not involve opening the globe. This decreases the risks of suprachoroidal hemorrhage, retinal detachment, infections, and other complications associated with the open sky technique in PKP.

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ALK can have its drawbacks. For one, visual outcome is dependent on the smoothness of the interface, and achieving a smooth dissection is technically challenging. Also, in situations where a deep scar is involved and DALK is required, the margin of error becomes very narrow as a deeper stromal dissection would risk Descemet's membrane perforation. Attempts at DALK can often end with the need to convert to full-thickness keratoplasty if Descemet's membrane integrity is violated. Furthermore, the lamellar interface can be a nidus for vascular ingrowth, epithelial ingrowth, lipid deposition, and leukocyte, blood, or other debris entrapment. All of these can result in visual compromise or graft failure.

7.2 Indications

Broadly, ALK, including DALK, is the transplant procedure of choice for stromal diseases when the endothelium is healthy. The main categories include corneal stromal diseases compromising vision, corneal stromal diseases affecting structural integrity, and both. Other indications include certain tumors, inflammatory or infectious debris, and perforation (Table 7.1).

7.3 Donor Tissue Selection

For DALK and sALK donor tissue can be lamellar/patch grade. It is important that tissue with good endothelial function is available in case the surgical procedure needs to be converted to a full-thickness procedure.

7.4 Anesthesia Planning

Anterior lamellar surgery can typically be performed under local anesthesia (peribulbar or retrobulbar block) using a long-acting drug under monitored care by the anesthesia service. In cases where the surgeon expects a longer surgical time, it is recommended to use a lid block. General anesthesia can be considered for cases not related to the surgical technique such as pediatric age group, deafness, mental retardation, claustrophobia, etc. If general anesthesia is going to be used, it is important that the anesthesiologist is aware that depending on the surgical technique, an intraocular air injection may be used and for this reason nitrous oxide should not be used.

7.5 Surgical Procedures

7.5.1 Superficial Anterior Lamellar Keratoplasty

When superficial anterior lamellar keratoplasty (sALK) is being considered, a complete ophthalmic evaluation is warranted with special attention to the degree of the anterior scar and the amount of regular versus irregular astigmatism. A rigid gas-permeable contact lens over-refraction is recommended. This will provide the surgeon with information that will determine if the vision loss is mostly related from the stromal opacity or is secondary to a high degree of astigmatism. sALK is often associated with postoperative astigmatism, and this should be explained to the patient.

There are many surgical techniques available for the removal of anterior stromal corneal pathology. The three most common are manual dissection, microkeratome-assisted ALK, and sutureless femtosecond laser-assisted anterior lamellar keratoplasty (FALK).

7.5.2 Manual Dissection

For doing a manually dissected sALK, a partial-thickness trephination is performed followed by a manual lamellar dissection with a sharp spatula

Table 7.1 Most common indications for DALK

Stromal scarring	Corneal ectasia	Corneal dystrophy	Iatrogenic
Post-infectious	Keratoconus	Granular	Post-pterygium surgery
Trauma	Post-refractive surgery ectasia	Lattice	Post-ocular surface tumor excisions
		Macular	

or crescent blade. A donor graft is fashioned to fit the excised area and then sutured in placed. Due to the irregular interface obtained when this type of dissection is performed, the rate of interface haze is high, and for this reason this procedure is rarely utilized for optical purposes.

7.5.3 Microkeratome-Assisted Superficial ALK

This surgical technique is a type of ALK that utilizes the principles of LASIK surgery of using a microkeratome to create a smooth flap surface with the goal of minimizing interface haze. For this procedure the microkeratome is set to create a "free cap" that is usually about 130–160 μm in thickness for the treatment of anterior stromal opacities. For this reason, this technique is used for opacities located within the 150–200 μm of the anterior stroma. This technique was described by Busin (2006). The recipient eye is usually prepared using the 130 μm head of the microkeratome and with the ring set at 0 number (Busin 2006). The microkeratome is also used to cut the donor tissue using a whole globe or a donor graft mounted on an artificial anterior chamber. Since the donor tissue will be thin, it is recommended to mark the anterior surface of the cornea before performing the cut, to avoid losing proper orientation.

Once the donor tissue is obtained, this tissue is placed onto the recipient bed. Overlay sutures are recommended to secure the graft in place. The overlay suture technique involves passing the needle only at the host cornea and this way avoiding any distortion of the thin donor graft to minimize postoperative astigmatism. Another alternative is the use of a bandage contact lens. The report of the technique by Busin included a group of 20 patients with a minimum follow-up of a year and showed that all patients improved to a best-corrected visual acuity of at least 20/40. Postoperative astigmatism was less than 4 diopters.

Another advantage of this procedure is that the patients' postoperative refractive outcome can be improved with the use of excimer laser stromal ablation. The flap can be lifted and the patients' corneal stroma can be ablated for the desired correction. One of the drawbacks for this procedure is that just like in LASIK surgery, the epithelium can grow and cause epithelium ingrowth, and patients can have all the other known related LASIK corneal flap complications such as flap striae, interface debri, etc. (Karabela et al. 2014).

This technique has also been evaluated in patients with anterior stromal opacities after a penetrating keratoplasty. A report by Patel et al. demonstrated in 9 eyes of 8 consecutive patients that the procedure was safe and was effective. Eight of the nine patients recovered a vision of 20/40 or better within the first month of surgery. In one patient the vision remained unchanged (Patel et al. 2012).

7.5.4 Sutureless Femtosecond Laser-Assisted Anterior Lamellar Keratoplasty

The unique capability of the femtosecond laser (FS laser) to photo-disrupt tissue with minimal collateral tissue damage has revolutionized the corneal surgical field. Since the FDA approved the FS laser for lamellar use in 2000, its use has widely spread and is now routine for surgical procedures such as LASIK flap creations, penetrating keratoplasty, and endothelial keratoplasty (Shousha and Yoo 2010).

The use of the FS laser for SALK is not an exception. It has been demonstrated that the FS laser can precisely cut the anterior stroma and these cuts are highly reproducible. One of the theoretical benefits of the use of FS laser for a lamellar cut is that this laser can precisely do a vertical cut at the graft-host junction, compared with the horizontal cut of the microkeratome.

In 2008, Yoo et al. introduced a new concept of sutureless superficial anterior lamellar surgery using the FS laser called femtosecond laser-assisted sutureless anterior lamellar keratoplasty (FALK) (Yoo et al. 2008). This technique can be performed under topical anesthesia and can be performed at a refractive surgery suite. For this surgery the patients' anterior corneal opacity depth is imaged and measured using ocular coherence tomogra-

phy (OCT). The donor graft is obtained using a donor whole globe or a donor graft mounted on an artificial chamber maintainer. The corneal epithelium is removed before the flap is cut. The donor graft is cut with the femtosecond laser. The donor thickness is set to 20 % more from the measurement obtained with the OCT (to adjust for tissue edema). A spiral method is used. The diameter is determined by the patient's needs and the surgeon's surgical plan. The recipient cornea is created using similar settings except that it is 0.1 mm smaller in diameter than the donor graft. The host cornea is removed and then replaced by the donor graft. It is recommended to mark the anterior surface of the corneal graft for proper orientation. The graft is observed for 5–10 min to allow donor tissue to dehydrate for a better fit. Then bandage contact lens is placed (Fig. 7.1). The range of energy needed for the side cuts and the spiral cuts is adjusted according to the density of the corneal scar. Higher spiral energy and lower tangent and radial spot separation for denser scars are required. Since the amount of posterior corneal stroma needed to preserve corneal tectonic stability has not been studied, Yoo et al. recommend a LASIK 250 μm residual bed safety margin concept.

Yoo et al. reported that with a mean follow-up of 12.7 months, the mean difference between preoperative and postoperative BCVA was a gain of 3.8 lines. No graft rejections, infections, or epithelial ingrowth was reported (Fig. 7.2). Shousha et al. then later reported the long-term results of FALK. The report included 13 consecutive patients with a follow-up range of 12–69 months. The study concluded that FALK improves the BCVA of patients with anterior corneal pathology with rapid visual rehabilitation and no significant induced astigmatism (Shousha et al. 2011).

7.6 Deep Anterior Lamellar Keratoplasty

DALK is used for opacities or stromal diseases located deep in the stroma. Otherwise, indications for this procedure are similar to those described for other ALK. During the preoperative evaluation, Descemet's membrane needs to be carefully evaluated to be sure that this layer has not been violated. Preoperative OCT can help assess the cornea and, for instance, identify the involvement of Descemet's membrane with scar (Fogla 2013). The most recent DALK techniques further improve on the superficial counterpart in that they achieve visual outcomes comparable to PKP in addition to higher survival of the endothelium and the graft (Borderie et al. 2012; Funnell et al. 2006; Shimazaki et al. 2002; Watson et al. 2004). However, because deeper dissection is involved, there is a higher chance to rupture Descemet's membrane. PKP quality donor cornea thereby must be available should it be needed.

The most common techniques for performing DALK are manual dissection (open dissection) (Anwar 1972), Melles technique (closed dissection) (Melles et al. 1999, 2000), Anwar's big-bubble technique (Anwar and Teichmann 2002a), and femtosecond laser-assisted technique (Farid and Steinert 2009; Price et al. 2009; Suwan-Apichon et al. 2006)—in addition to modifications of those techniques (Chamberlain and Cabezas 2011; Ramamurthi and Ramaesh 2011; Sharma et al. 2010).

7.6.1 Manual Dissection

The manual dissection approach is similar to manual dissection described above for sALK. It carries the same drawbacks of unreliable depth and irregular surface causing astigmatism and interface haze, respectively. Also, the depth of the stromal dissection and Descemet's membrane is difficult to visualize, which increases the risk of perforation or incomplete stromal removal. Techniques like hydrodelamination, intrastromal air injection, and viscoelastic dissection (Maurino et al. 2002) have been developed to improve visualization, decrease operative time, and decrease the risk of perforation.

7.6.2 Melles Technique

The Melles technique was first described by Melles et al. in 1999 (Melles et al. 1999). In this

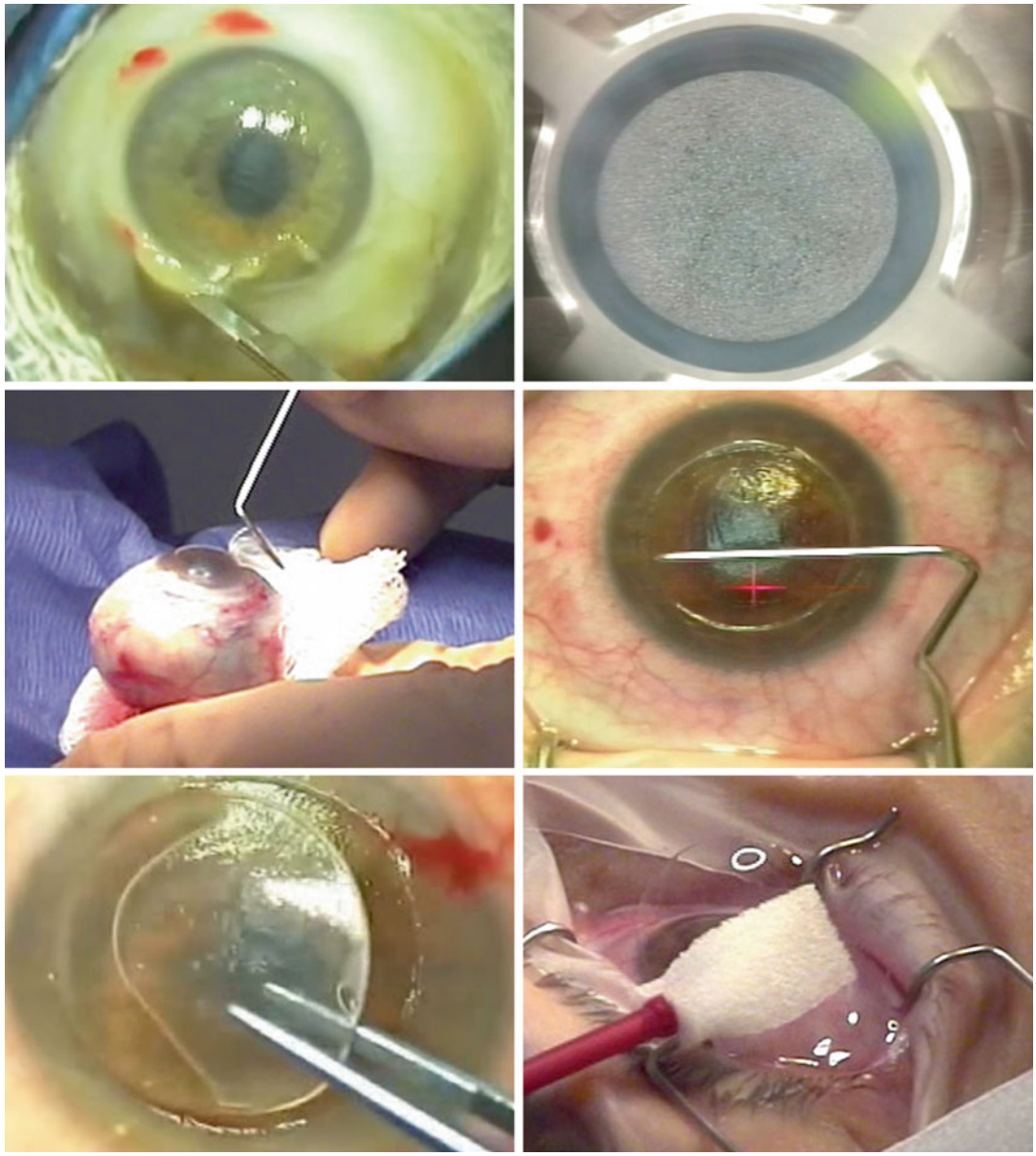

Fig. 7.1 Major steps of the sutureless femtosecond laser-assisted anterior lamellar keratoplasty. (*Top left*) Manual removal of the epithelium from donor whole globe. (*Top right*) Creation of flap with femtosecond laser. (*Middle left*) Manual separation of the flap. (*Middle right*) Flap removal after femtosecond laser cutting on the host cornea. (*Bottom left*) Placement of donor flap over the host cornea. (*Bottom right*) Placement of bandage contact lens after a 5 min wait period and speculum removal (Courtesy of Florence Cabot, Mohammed Abou Shousha, and Sonia H. Yoo, Bascom Palmer Eye Institute)

technique aqueous is exchanged by air through a self-sealing limbal side port using a blunt cannula. This creates a mirrorlike air to the endothelium interface that serves as a reference plane for subsequent dissection. A dissection blade is introduced tip down creating a darker band between the blade tip and interface representing the stroma. Dissection is done vertically through this stroma until the interface is reached. The blade is then positioned parallel to the posterior

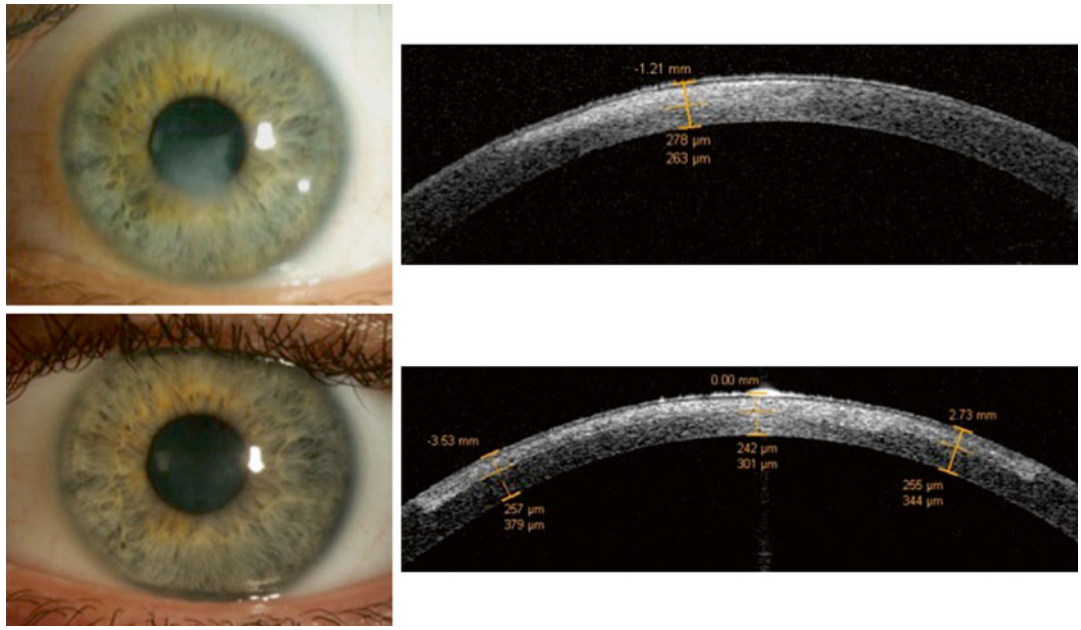

Fig. 7.2 (*Top*) Preoperative sutureless femtosecond laser-assisted anterior lamellar keratoplasty slit lamp photo and anterior segment optical coherence tomography showing superficial corneal scar. (*Bottom left*) Postoperative slit lamp photo showing the scar resolution. (*Bottom right*) Anterior segment optical coherence tomography showing the lamellar bed and overlying graft (Courtesy of Florence Cabot, Mohammed Abou Shousha, and Sonia H. Yoo. Bascom Palmer Eye Institute)

surface, and a deep stromal pocket is created across the cornea. The pocket is then filled with viscoelastic fluid to allow separation of the posterior side, protecting it from perforation during subsequent trephination. Remaining, unincised stromal attachments are cut with curved micro-scissors, and the anterior corneal lamella is removed. Perforation was reported in 1 out of the 7 (14.3 %) cases in the original article. In terms of outcomes, all eyes maintained structural integrity with minimal interface scarring. The best-corrected visual acuity ranged from 0.25 to 1.0, and the astigmatic error ranged from 1 to 3.5 with no evidence of epithelial or stromal edema over a mean +/− SD follow-up period of 4.9 ± 2.9 months.

7.6.3 Anwar's Big-Bubble Technique

The Anwar big-bubble technique is a popular technique where air is injected in a certain way to aid in the separation of Descemet's membrane from the stroma before excising the stroma (Anwar and Teichmann 2002a). In contrast to earlier methods using air to aid dissection where air injection precedes trephination (Archila 1984; Chau et al. 1992), Anwar and Teichmann's technique starts by performing a partial-thickness trephination. A needle is then inserted into the paracentral corneal stroma and air is injected.

In most cases, this forms a large air bubble between Descemet's membrane and the deepest stroma. Resistance in the needle plunger eases as a whitish bubble suddenly appears. This is the desired outcome. Less frequently (9 % of cases), the air can keep infiltrating the central disk without a discernible bubble appearing (Anwar and Teichmann 2002b). In this case, the surgeon should stop injecting air when it approaches the trephine grove as formation of the bubble is unlikely from there. Up to 4 trials can be done before switching to traditional ALK or hydrodelamination. A small opening is then made in the air bubble, and the remaining stromal layers are lifted with an iris spatula, severed with a blade, and excised with scissors. Using this technique on 181 keratoconus patients,

Anwar and Teichmann reported 16 cases of DM perforation (Anwar and Teichmann 2002a). A study comparing the Anwar and the Melles techniques of DALK found no statistically significant difference in visual acuity, refractive outcomes, aberrometric profiles, biomechanical properties, corneal thicknesses, or endothelial cell densities. However, patients who underwent the Anwar technique showed better contrast sensitivity (Baradaran-Rafii et al. 2013). The technique is limited to patients with a healthy Descemet's membrane and no hydrops or previous perforation.

7.6.4 Femtosecond Laser-Assisted Deep Lamellar Anterior Keratoplasty

The advent of femtosecond laser technology has improved various corneal procedures; and DALK is not an exception. This technology helps create a smoother more standardized interface that theoretically will minimize haze. For DALK procedures, FS laser have been used to aid in creating matching donor-host trephinations and smoother lamellar cuts that leave down to 70 μm thickness paving the way for further manual, Melles, or Anwar's dissection (Chan et al. 2010; Farid and Steinert 2009; Price et al. 2009).

7.7 Technique

There are many variations to the femtosecond laser-assited deep lamellar anterior technique. The key steps of this surgical procedure will be summarized in this section. First, the recipient corneal diameter and thickness are carefully measured. Several measurements are recommended to achieve accurate results given the precision required to create a deep posterior cut. Chan et al. use 8 measurements for thickness in the central 7 mm and set the laser parameters so as to leave 100 μm forming the thinnest measurement. After proper centration, the patient interface is placed on the laser, the cornea is applanated, and the laser incision created. Incisions can be of different configurations, and the most common consist of a posterior side cut, an anterior side cut, and a lamellar cut (Fig. 7.3). As the laser starts cutting posteriorly, attention should be given to any bubbles seen in the anterior chamber. These would indicate that the programmed cut is too deep and reaching the anterior chamber. Cutting should be stopped immediately and depth should be reset.

As for the donor tissue, the graft can either be ordered as precut tissue with a specified shape and anterior cut diameter or mounted on an artificial anterior chamber and cut using similar laser settings as the recipient cornea (Chan et al. 2010; Farid and Steinert 2009; Price et al. 2009). The donor tissue needs to be thicker, taking in consideration the edema caused by the eye banking storage time. It is also recommended that the donor tissue diameter is cut 0.1 mm larger than host diameter.

From this point, dissection of the precut lamella can be carried out in different techniques:

1. In cases where manual dissection is performed, a plane is started at the depth of the laser incision. The dissection is carried across the cornea to create the bed. In some cases, a second, deeper dissection can be made if the initial one appears too shallow (Price et al. 2009). Alternatively, an excimer laser can be used for a +4 sph corneal ablation to reduce the peripheral stromal thickness followed by wide phototherapeutic keratectomy smoothing ablation with fluid mask, to reach as much of the Descemet's/endothelium layer as possible (Mosca et al. 2008, 2011).
2. In cases where the Melles technique is planned, a self-sealing paracentesis is created followed by aqueous exchange with air. Viscoelastic fluid is then injected into a dissected lamellar plane. The posterior stromal cut is completed and the lamella excised (Chan et al. 2010) (see Melles technique above).
3. In cases where a big bubble is planned, a needle is inserted through the incision or into the deep stroma in the midportion of the bed. A big bubble is then created and the lamella dissected according to Anwar's big-bubble technique above (Farid and Steinert 2009; Price et al. 2009). After completing lamellar dissection, the donor button can be placed and sutured in the stromal bed.

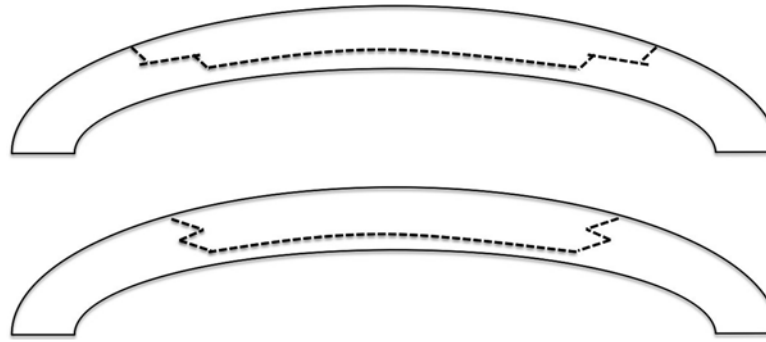

Fig. 7.3 Zigzag (*top*) and mushroom (*bottom*) incision configurations for femtosecond laser-assisted deep lamellar anterior keratoplasty

The Melles or Anwar's techniques are still recommended to complete the lamellar dissection once the femtosecond laser has completed the trephination. With the current FS lasers available in the market, the precision and quality of a deep lamellar cut is not as good as a superficial stromal lamellar cut. The deeper the cut, the more scattering of the laser energy, and this can translate to an irregular lamellar cut. It is also important to understand that the current FS laser technology will cut the lamellar flap only in a predetermined geometrical shape. This geometrical shape takes its reference point from the applanator surface. As a result, cutting a deep lamellar surface of a patient with high degree of ectasia from keratoconus will cause an irregular imprint of the lamellar cut.

7.8 Outcomes

Final outcomes of femtosecond laser-assisted techniques were not statistically different from their manual trephination counterparts in terms of vision, wound stability, graft success, and complication. Using the femtosecond laser however significantly improved visual recovery time up to 3 months and standardized the trephination process (Buzzonetti et al. 2011; Shehadeh-Mashor et al. 2014). The major disadvantage of femtosecond laser application is the necessity of suction and applanation during trephination.

7.9 Surgical Complications and Management

The most common intraoperative complication of DALK is the perforation of Descemet's membrane. This can happen at any stage of the surgery. The size of the perforation is going to determine if it is possible to continue with the procedure or if there is a need to convert to PKP. Descemet's membrane perforation has been reported to occur in about 10–30 % of the cases, depending on the surgeon's experience (Fogla and Padmanabhan 2006).

In order to prevent perforation of Descemet's membrane during trephination, it is important to have a pachymeter available to give the surgeon information on the thinnest point of the host cornea. Commercially available trephines with adjustable cut depth are recommended. Descemet's membrane can be detached or dissected from the stroma before trephination using a Melles technique or approaching Descemet's membrane by constructing a scleral flap.

When perforation of Descemet's membrane happens during stromal dissection, the pressure of the anterior chamber should be decreased in order to decrease the extension of the perforation. If the perforation is peripheral and small, the surgeon can determine whether or not to remove the central stroma and proceed with the surgery. Once the central stroma is removed, the graft is placed and carefully sutured with

interrupted sutures. An intracameral air injection is performed to tamponade the break. It is important to monitor the patient's intraocular pressure and look for early signs of pupillary block (Leccisotti 2007).

When a perforation of Descemet's membrane is suspected, the surgeon must look for a possible double anterior chamber during the slit lamp examination in the early postoperative period. OCT imaging can help to better categorize the degree and location of these common postoperative complications (Lim et al. 2008). A spontaneous reattachment on Descemet's membrane is possible, but an intracameral injection is recommended to expedite the visual recovery.

Conclusion

Anterior lamellar keratoplasty is a technically challenging procedure that offers multiple advantages for patients with corneal stromal opacity. The new surgical instrumentations such as more precise microkeratomes and FS laser now offer the possibility of a surgical approach under topical anesthesia with faster visual recovery for patients with anterior stromal pathology. The Anwar and Melles DALK are by far the most used surgical techniques that offer very good clinical outcomes. As the FS laser technology evolves, the precision and quality of deeper stromal lamellar cuts will improve outcomes and decrease surgical complexity.

Compliance with Ethical Requirements

Conflict of Interest

Marwan Atallah and Guillermo Amescua declare that they have no conflict of interest.

Informed Consent

No human studies were carried out by the authors for this article.

Animal Studies

No animal studies were carried out by the authors for this article.

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Endothelial Keratoplasty

8

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8.1 History, Innovations, and Terminology

The concept of selective replacement of endothelium in diseased eyes was first described by Tillet in 1956, who named it posterior lamellar keratoplasty (Tillett 1956). The success of modern EK is attributed to the pioneering work of Melles, who in 1998, described that a posterior lamellar graft could be successfully attached to the recipient stroma without the use of sutures and could lead to improvement in vision (Melles et al. 1998, 2002a). Terry et al. popularized this technique as deep lamellar endothelial keratoplasty (DLEK) in the United States (Terry and Ousley 2001). As DLEK required a manual stromal lamellar dissection of the host, it was technically challenging and not widely adopted.

In 2003, Melles et al. proposed a simplified technique that only involved removal of the Descemet membrane and placing the endothelial graft onto the back of the posterior stroma (Melles et al. 2004). This technique was modified and popularized by Price et al. and termed Descemet stripping endothelial keratoplasty(DSEK) (Price and Price 2005, 2006b). The lamellar dissection of the donor cornea was simplified with the use of a semiautomated microkeratome and either called Descemet stripping automated endothelial keratoplasty (DSAEK) or DSEK (Gorovoy 2006; Price and Price 2006a; Chen et al. 2008). In 2005, eye banks began performing the lamellar dissection and providing "precut" donor tissue to surgeons. DSEK was rapidly adopted worldwide and is currently the most popular form of endothelial keratoplasty among corneal surgeons, because the procedure is relatively easy to learn and replicate, has good outcomes, and is suitable in eyes with almost any associated complexities in the anterior chamber (Basak 2008; Ólafsdóttir 2011; Price and Price 2006c, 2007; Covert and Koenig 2007a, b; Price et al. 2007; Lee et al. 2009).

DSEK adds posterior stromal tissue and irregularity in the dissected surface, or folds that develop in the donor tissue as it conforms to the back of the recipient cornea can affect vision; therefore, visual recovery is sometimes delayed and visual results do not always reach the full potential. These

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limitations generated interest in transplantation of isolated endothelium and Descemet membrane, and Melles developed a procedure called Descemet membrane endothelial keratoplasty (DMEK) (Melles et al. 2002b, 2006). Despite several advantages over DSEK, the adoption of DMEK has been relatively slow because technically it is more challenging than DSEK.

Several alternatives were developed in an attempt to overcome the surgical challenges with DMEK. One approach involved delivering the Descemet membrane with a small peripheral skirt of posterior stroma. This was termed DMEK with stromal rim (DMEK-S) when performed manually or Descemet membrane automated endothelial keratoplasty (DMAEK) when a microkeratome was used to perform the lamellar dissection step (Studeny et al 2010; McCauley et al. 2009). This procedure combined the visual advantages of DMEK and tissue handling ease of DSEK, but the donor preparation was more challenging with a higher rate of tissue loss. Another approach to improving visual outcomes was to create a thinner donor lenticule with the microkeratome; this was called ultrathin DSAEK (Busin et al. 2013; Taravella et al. 2013). This technique is also associated with increased tissue wastage, but many surgeons now request thinner DSAEK tissue. Concomitantly, refinements in the surgical steps of DMEK along with compelling evidence of its superior visual results and lower rejection rates have made it the preferred approach for endothelial diseases at several centers. The technique is likely to gain popularity on a much wider scale soon. Ultrathin DSAEK approaches the advantages of DMEK but increases the risk of endothelial damage and makes tissue manipulation more challenging relative to regular DSAEK.

The wide range of endothelial disorders can be managed by different techniques of endothelial keratoplasty. Figure 8.1 depicts the varied indications of endothelial keratoplasty, and Fig. 8.2 shows the different types of endothelial keratoplasty.

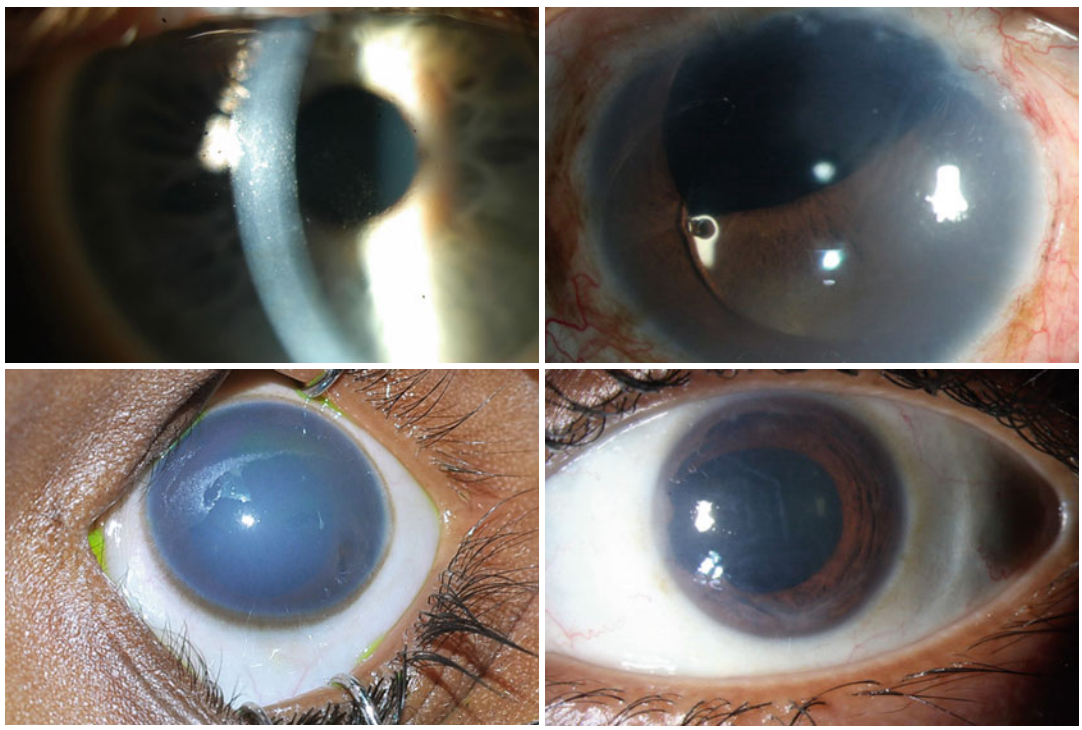

Fig. 8.1 Various indications for endothelial keratoplasty. *Upper row* (*L-R*) – Fuchs endothelial corneal dystrophy; pseudophakic corneal edema (posterior chamber intraocular lens in the anterior chamber). *Lower row* (*L-R*) – Congenital hereditary endothelial dystrophy; iridocorneal endothelial (ICE) syndrome

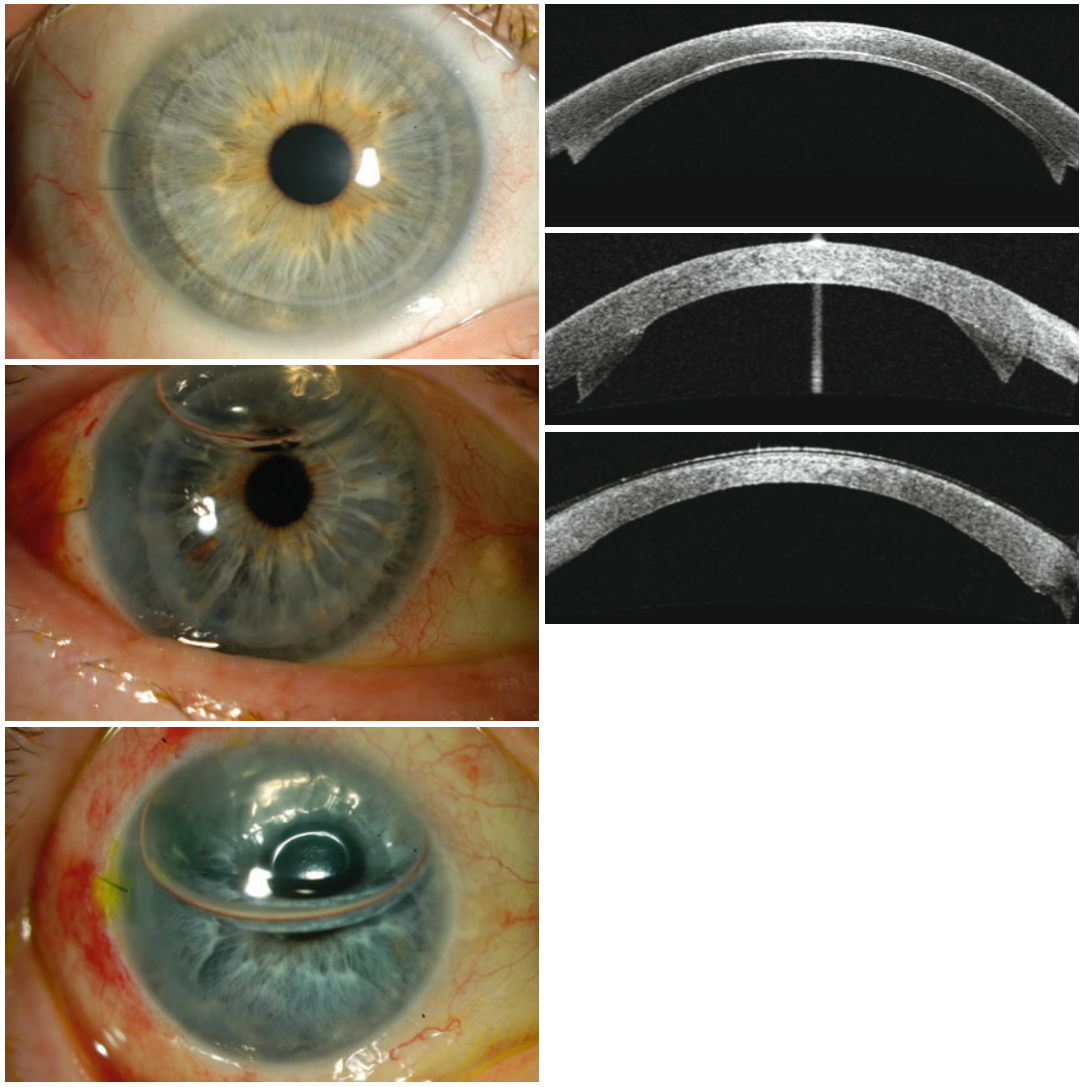

Fig. 8.2 Slit lamp and anterior segment optical coherence tomography images of 3 types of endothelial keratoplasty. *First row*: Descemet stripping automated endothelial keratoplasty (DSAEK). *Second row*: Descemet membrane automated endothelial keratoplasty (DMAEK), with residual air bubble 1 day after surgery. *Third row*: Descemet membrane endothelial keratoplasty (DMEK), with residual air bubble and bandage contact lens in place 1 day after surgery

8.2 Surgical Techniques

8.2.1 DLEK

The DLEK technique initially involved creation of a 9.0 mm scleral wound and a deep corneoscleral lamellar pocket down to about 75–85 % corneal depth along the entire length of the wound. The stromal dissection was completed to the limbus for 360° using semisharp dissectors to create a deep lamellar corneal pocket. The posterior stromal disc was trephined and excised. The donor corneoscleral tissue was mounted onto an artificial anterior chamber, and anterior stromal tissue was resected either manually or using a microkeratome, leaving approximately 150 μ of the posterior stroma. The donor tissue was trephined to the same diameter as the recipient bed,

inserted into the anterior chamber, and attached using an air bubble. The scleral wound was closed with several interrupted sutures. The procedure was later performed through a 5–6 mm incision by folding the graft for insertion.

Although not ideal, DLEK was the first successful EK procedure. It certainly had several advantages over PK because there were no anterior corneal incisions and suturing of the graft. So, the visual recovery was better and the suture-related complications as seen with PK were prevented. The surgical difficulties involved with the procedure led to exploration of alternative approaches.

8.2.2 DSEK

The procedure comprises 3 steps: (a) preparation of a posterior lamellar graft, (b) removal of the host Descemet membrane and dysfunctional endothelium, and (c) insertion of the graft into the anterior chamber and positioning using air tamponade.

(a) Donor preparation: The donor cornea is mounted on an artificial anterior chamber for lamellar dissection; then it is placed on a tissue-cutting block and trephined to the desired diameter (usually 8–9 mm) from the endothelial side. Methods of lamellar dissection include:

Manual dissection (Fig. 8.3, first row)—An initial 4–5 mm curvilinear incision is made at the limbus to a depth of 300–350 μm with a guarded diamond/Bevers's blade. Short and long curved dissecting blades are used to extend the lamellar dissection 360° to reach to the limbus.

Microkeratome dissection (Fig. 8.3, *second row*)—The donor dissection plane is created with a microkeratome. The microkeratome heads can be chosen (usually 300–350 μm) according to the desired plane of lamellar dissection. Microkeratome dissection produces a smoother and more regular dissection plane compared to manual dissection. Numerous eye banks have microkeratomes and provide pre-dissected tissue.

Femtosecond (FS) laser dissection (FS-DSEK)—The feasibility of using a femtosecond laser to create lamellar cuts was assessed, but the regularity of deep lamellar ablations required for posterior lamellar grafts was suboptimal and failed to produce encouraging results (Mehta et al. 2008; Cheng et al. 2008).

(b) Stripping of the host Descemet membrane (Fig. 8.4, *first row—first*): Host DM is removed within an area corresponding to the graft diameter or slightly smaller. DM stripping is necessary in Fuchs endothelial dystrophy to remove the guttae; however, this step may be optional in conditions where the DM is optically clear and devoid of any structural alterations, such as in failed PK and pseudophakic corneal edema (Nottage and Nirankari 2012; Chaurasia et al. 2011a, b; Kobayashi et al. 2008).

(c) Graft insertion and positioning: The graft is inserted through a 3–5 mm incision using devices such as forceps, glides, and inserters. Currently used donor insertion instruments include:

Forceps—The donor tissue is folded into a 60/40 configuration (with the endothelium facing inward and protected with a small amount of viscoelastic) and inserted into the anterior chamber using atraumatic non-coapting forceps (e.g., Charlie II, Goosey, Kelman forceps) (Melles et al. 2002a; Price and Price 2005, 2006b).

Sheets glide—This method can be helpful in eyes with a shallow anterior chamber and predisposed to iris prolapse. The anterior chamber is maintained using an anterior chamber (AC) maintainer. A Sheets intraocular lens (IOL) glide is inserted halfway into the chamber, which serves to keep the iris behind. The donor graft is placed onto the glide with the endothelial side down protected with a generous amount of viscoelastic. An intraocular forceps is inserted through the site opposite to the main incision. The donor edge is grasped with the forceps and pulled inside the anterior chamber (pull-through method) (Mehta et al. 2007). Alternatively, the graft may be

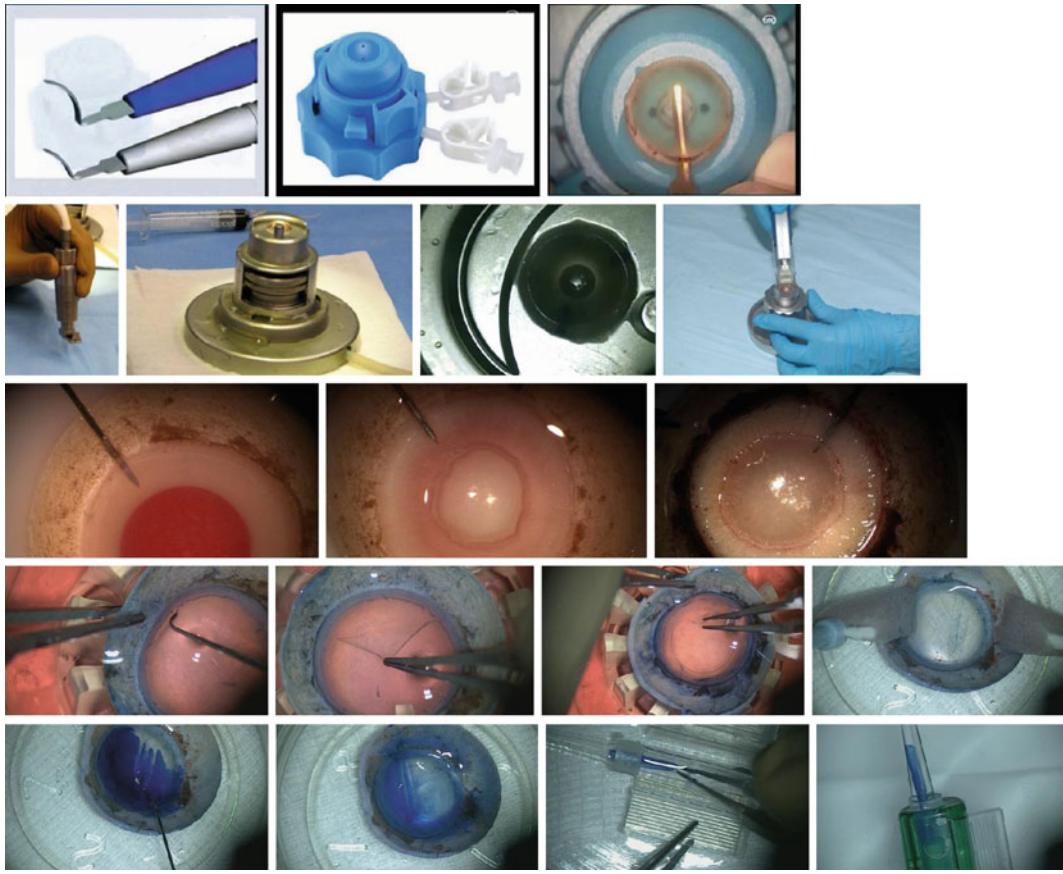

Fig. 8.3 Donor tissue preparation: equipment and methods. *Upper row* (*L-R*): Descemet stripping endothelial keratoplasty (DSEK): manual dissectors (DORC, the Netherlands); Barron disposable artificial anterior chamber (Katena Products); manual dissection with donor cornea mounted on artificial anterior chamber. *Second row* (*L-R*): Descemet stripping automated endothelial keratoplasty (DSAEK): microkeratome (Moria); reusable artificial anterior chamber (Moria); microkeratome-assisted donor dissection; Microkeratome (Gebauer, Germany). *Third row* (*L-R*): Descemet membrane automated endothelial keratoplasty (DMAEK) graft preparation: air is injected via a needle inserted through the peripheral scleral rim; this creates a big bubble; the big bubble is enlarged with more air to separate the Descemet membrane (DM) from the posterior stroma. *Fourth row* (*L-R*): Descemet membrane endothelial keratoplasty (DMEK) graft preparation: peripherally scored DM is separated from underlying stromal tissue circumferentially using a microfinger; DM is peeled in four quadrants leaving it attached at the center; final peel to free the center of the tissue; scrolled donor Descemet membrane and endothelium. *Fifth row* (*L-R*): DMEK graft insertion: trypan blue is being used to stain the DM scroll to improve visualization; the stained DM scroll; the tissue is being loaded into the cartridge of an intraocular lens inserter; the DM scroll within the inserter

inserted through the main incision using a Sinskey IOL dialer (push-in method) without the use of an AC maintainer.

Busin glide (Fig. 8.4, *first row—second*)—This reusable funnel glide (Moria, Inc., Antony, France) curls the graft into a cylindrical shape to minimize endothelial trauma during insertion (Busin et al. 2008). The edge of the graft is grasped and pulled into the anterior chamber with an intraocular forceps introduced through the opposite site incision.

Suture pull-through—In this method (Macsai and Kara-Jose 2007), a10-0 Prolene suture is passed through a 5 mm superior lamellar incision and across the AC to exit

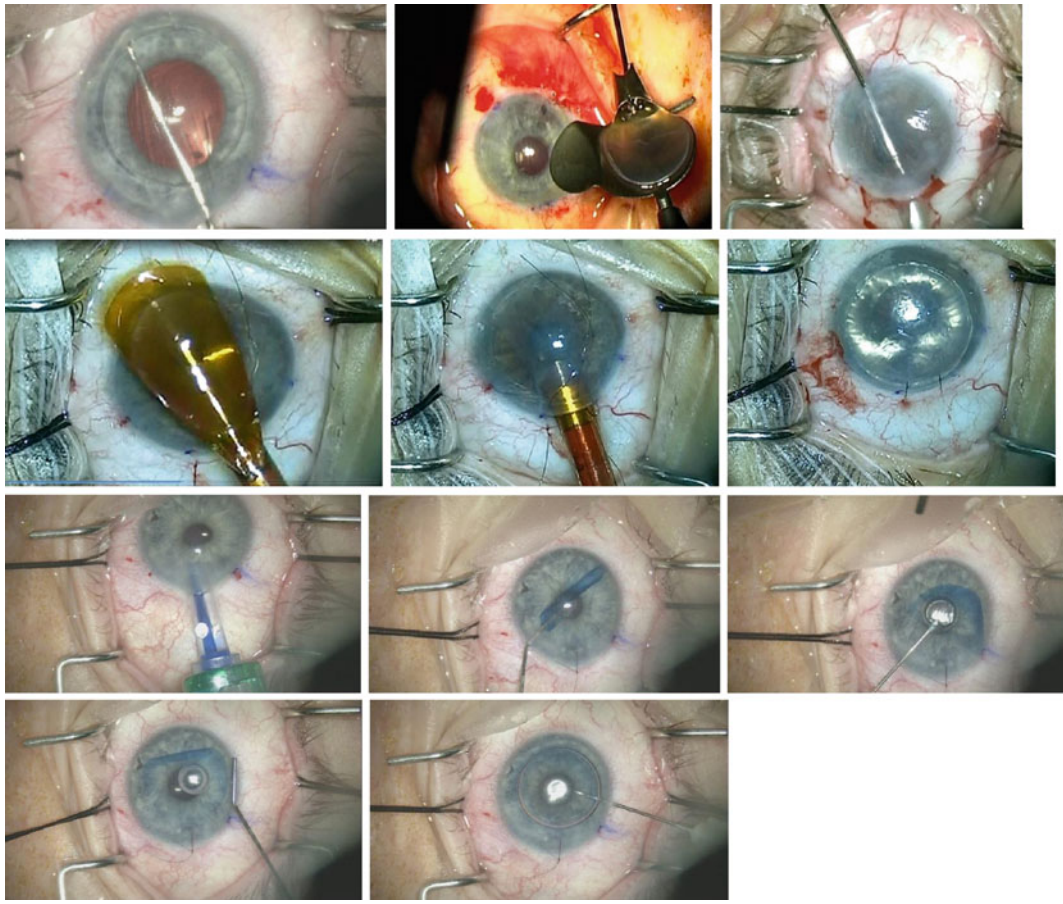

Fig. 8.4 Recipient preparation, graft insertion, and positioning. *First row* (*L-R*): Descemet membrane scoring; loading a DSEK graft into a Busin glide (Moria); pull-through method of graft insertion using a Busin glide and intraocular forceps. *Second row* (*L-R*): loading a DSEK graft into an EndoSerter (Ocular Systems, Winston-Salem, NC); graft insertion with EndoSerter; air tamponade. *Third row* (*L-R*): DMEK graft insertion; short bursts of balanced salt solution unfold the scrolled tissue; partial unfold achieved. *Fourth row* (*L-R*): unwrapping the scrolled DMEK donor tissue over a posterior air bubble (the air bubble helps anchor the graft in the correct position); final air injection to press the donor tissue against the recipient cornea

through the cornea approximately 1 mm beyond the edge of stripped DM. The donor endothelium is coated with viscoelastic, and the second arm of the suture is passed through the periphery of the donor lenticule, entering from the endothelial side and exiting from the stromal side. It is then passed through the incision, across the AC and through the cornea 1 mm central to the edge of stripped DM. The donor lenticule is gently folded in half with the suture at the leading edge, and the anterior edge of the incision is lifted as both ends of the suture are pulled to guide the graft into the eye. The graft unfolds as the AC is filled with air, and it is secured by tying off the suture, which helps minimize the risk of graft dislocation.

Injectors/Inserters (Fig. 8.4, *second row—first*, *second*) – Several single-use devices have been designed to deliver the graft with minimal endothelial trauma (Khor et al. 2011; Kuo et al. 2008). Adoption has been limited by the cost and the good results surgeons have obtained with the other methods described above.

After the graft is inserted, it is positioned and attached to the host posterior stroma using an air bubble (Fig. 8.4, *second row—third*). Complete air fill in the anterior chamber is maintained for 10–12 min, followed by a partial air-fluid exchange to avoid risk of raised intraocular pressure (IOP) secondary to pupillary block. Alternatively, a prophylactic inferior iridectomy may be made prior to graft insertion to prevent pupillary block due to air. Postoperatively, supine positioning is maintained for 15–20 min or longer.

8.2.3 DMEK

The procedure involves isolation of donor DM and endothelium followed by inserting, unwrapping, and positioning in the proper orientation. Just as in DSEK, the central host DM is removed before inserting the donor tissue.

(a) Donor preparation (Fig. 8.3, *fourth row*): Donor DM can be isolated by direct peeling (Lie et al. 2008) or by injection of air to create a big bubble (Venzano et al. 2010). Direct peeling has a higher success rate with less endothelial cell loss (Yoeruek et al. 2012). Giebel and Price described a direct peeling method called submerged cornea using backgrounds away (SCUBA) that has a success rate of almost 99 % (Giebel and Price 2009; Guerra et al. 2011a). The donor corneoscleral rim is submerged with the endothelial side up in a viewing chamber filled with corneal storage solution, or it can be placed on a cutting block. The DM is lightly scored 1–2 mm inside the trabecular meshwork using a Y-hook. Trypan blue staining improves visualization of the scored edge, which is then lifted circumferentially with a microfinger (Moria Inc.). The edge of the DM is grasped with a blunt forceps. DM is partially peeled in four quadrants, leaving the center part attached. The membrane is floated back into position and the donor is trephined lightly into the stroma. The donor is placed back in the viewing chamber for a final peel to detach DM centrally. The detached DM spontaneously forms a scroll with the endothelium on the outside. The DM scroll is placed either in the storage medium or used immediately for transplantation.

The DM thickens with age, and so grafts from older donors generally scroll less tightly which makes graft unwrapping easier during surgery. Therefore, donor tissue over 40 years of age is preferable for DMEK. As with DSEK, DMEK donor tissue can be prepared several days before the surgical procedure (Feng et al. 2013a).

(b) Graft insertion, unfolding, and positioning: The DM scroll can be loaded into a glass pipette or IOL cartridge and injector and inserted through a 2.8-mm-wide corneal incision. Various types of IOL cartridges are suitable for graft delivery including Softec (Lenstec, Inc, St. Petersburg, FL, USA); Carl-Zeiss inserters (Jena, Germany) and Viscoject (Medicel AG, Wolfhalden, Switzerland) (Fig. 8.3, *fifth row*). Graft adhesion is reported to be better with the use of IOL cartridges that form a closed system without any addition of viscoelastic (Chaurasia et al. 2014b).

Several graft unfolding maneuvers are available (Fig. 8.4, *third and fourth row*). Liarakos et al. (2013) described 4 standard and 3 auxiliary techniques for unfolding the graft in the anterior chamber depending upon the orientation and how tightly the DM is curled. Essentially, the DM scroll in the anterior chamber is opened using short quick bursts of BSS. A portable slit beam or slit beam or optical coherence tomography attachment on the operating microscope can be used to confirm the graft orientation (Burkhart et al. 2013). After the scroll is partially unwrapped, a small air bubble is injected under the donor to secure the orientation (Guerra et al. 2011a). The recipient corneal surface is stroked to center and unfold the graft completely, followed by air fill in the anterior chamber. The patients are advised to keep supine position for 60 min to allow for donor adherence.

8.2.4 Hybrid Techniques

Hybrid techniques have been developed to combine the optical outcomes of DMEK with the

easier handling of DSEK. Studeny described transplantation of a posterior corneal lamellae consisting of endothelium and DM centrally with a stromal supporting rim (DMEK-S), and McCauley et al. described a partially automated variation (DMAEK) (Studeny et al. 2010; McCauley et al. 2009). The bare central endothelium and DM provide excellent optical outcomes, comparable with those of successful DMEK patients, while the stromal rim fixes the thin, fragile central part, helping to maintain its shape and prevent scrolling.

The donor tissue is dissected as in DSEK. Then the DM is detached from the posterior stroma using a big bubble technique (Fig. 8.3, *third row*). An incision is made through the stromal bed overlying the big bubble, and the disk of the posterior stroma is excised within the area of the detached DM. The donor tissue is inserted into the eye using the pull-through technique with Busin glide, and air is injected to attach the donor against recipient stroma. Donor insertion and positioning is easier than DMEK, because the tissue unfolds spontaneously, but the donor tissue preparation is more complicated and the rate of tissue loss is higher, which has limited the adoption.

8.2.5 Ultrathin DSAEK

Some surgeons have reported better visual acuity and faster visual recovery with thinner endothelial grafts (Taravella et al. 2013). Busin et al. described a microkeratome-assisted double-pass method for obtaining ultrathin posterior lamellar grafts (<100 μ) (Busin et al. 2013). The first pass is done with a 300 or 350 μm microkeratome head to debulk the cornea. The thickness of the residual bed determines the selection of the microkeratome head for the second pass, which is necessarily made going the opposite direction to help avoid perforation because the blade goes deepest at the beginning of the pass. Nomograms, which take into account donor thickness, corneal storage medium, pressurization of the artificial anterior chamber, and cutting speed, have been devised to help select the appropriate microkeratome head size to obtain thin EK donor tissue with either single- or double-pass techniques (Taravella et al. 2013). The risk of tissue loss from perforation is higher with ultrathin grafts compared with standard DSEK grafts.

8.3 Surgical Considerations with Ocular Comorbidities

EK is most straightforward in an eye with a normal anterior segment and a stable posterior chamber IOL. Because of the well-known advantages of DSEK over PK, the indications for EK have expanded to eyes with anterior segment complexity such as those with pupillary abnormalities, peripheral anterior synechiae, glaucoma-filtering procedures, glaucoma tube shunts, prior PK, or anterior chamber IOL. While DSEK can be attempted successfully in all mentioned conditions, the decision for DMEK is more reserved because the DM graft is delicate and requires more manipulation in comparison to DSEK. When deciding about the type of EK, the advantage of one procedure needs to be balanced with the technical ease of the procedure in an individual case scenario.

8.3.1 Aphakic Eyes with Complete or Partial Aniridia

In eyes with aphakia with complete or partial aniridia, a potential concern is intraoperative or postoperative graft detachment, which may result in graft dislocation into the posterior segment. Several options are available to manage this situation depending upon the extent of iris abnormality (Price et al. 2007). A posterior chamber IOL (sulcus/scleral fixated) with or without iris reconstruction/pupilloplasty can be planned simultaneously or a few weeks before the DSEK procedure. A Sheets IOL glide can be used during graft insertion to direct the graft and avoid posterior migration. A temporary fixation suture through the recipient cornea and the endothelial graft can be placed at the end as a measure to prevent posterior dislocation of the graft (Macsai and

Kara-Jose 2007). In eyes with large iris defects, the host DM stripping should be avoided or performed cautiously to prevent the fragments from falling into the posterior cavity. Prolonged air tamponade and supine positioning may be additional measures to promote graft adhesion.

In aniridic eyes with an artificial iris implant, the graft can slide between the edge of the implant and the wall of the eye and fall into the posterior segment. To prevent this from happening, air should be injected under the graft before it is released from the insertion forceps, and a temporary fixation suture should be used to hold the graft in place (Price et al. 2007). Alternatively, the graft can be inserted with a suture pull-through technique and the pulling sutures can be used to affix the graft until adherence is confirmed in the postoperative period (Macsai and Kara-Jose 2007).

8.3.2 Phakic Eyes

In eyes with significant cataract, a triple procedure (cataract surgery with DSEK or DMEK) is the preferred approach. It is also advantageous with DSEK because cataract extraction deepens the anterior chamber and facilitates unfolding the graft. In patients with endothelial disease and clear crystalline lens, one may contemplate endothelial keratoplasty alone (Tsui et al. 2011). It is prudent to avoid iatrogenic damage to the clear lens and the endothelial graft by avoiding anterior chamber fluctuations.

As with PK, following EK, the rate of cataractogenesis is accelerated as a result of intraocular manipulations during surgery and the postoperative use of steroids. The probability of cataract progression requiring extraction is significantly associated with the age of the patient (Price et al. 2010).

8.3.3 Prior Glaucoma Filtering/Tube Surgery

Here, there may be difficulties in achieving an air fill in the anterior chamber as the injected air finds its way into the subconjunctival space through the ostium and so may require several attempts. Also, after obtaining adequate air tamponade, IOP needs be strictly monitored to avoid extremes of high pressure for prolonged periods which can be detrimental to the already compromised optic nerve. Rarely in cases where the air just escapes easily and the pressure cannot be increased enough to firm the eye, a few drops of viscoelastic can be placed over the end of the tube or ostium of the filter to block the flow. Viscoelastic should not be used until the graft is in place to prevent it from coating the graft interface. Once the patient sits up, the viscoelastic will fall away from superior tubes and ostia; so postoperative IOP spikes should not be an issue.

In the eyes with glaucoma drainage devices, it is important to ensure that mechanical contact between the graft and tube is avoided by proper trimming and repositioning of the tube, if required.

8.3.4 Vitrectomized Eyes

Eyes with prior vitrectomy and associated iris/zonular defects may have difficulties in graft adhesion as air may escape into the vitreous cavity increasing the risk of appositional angle closure/graft detachments. Similar to other situations, prolonged tamponade may facilitate in avoiding these problems.

8.3.5 Failed Prior PK

DSEK under a failed graft can successfully restore the graft clarity and avoid repeat PK. However, in situations where the refractive result of the prior PK was unsatisfactory, it would be better to consider a repeat PK rather than EK.

As mentioned earlier, the DM may be left intact in a failed graft if it does not show any abnormalities (Price and Price 2006c; Nottage and Nirankari 2012). This prevents the weakening of the graft–host junction that may occur inadvertently during the stripping maneuver. In eyes with prior therapeutic PK, the DM may be

hazy and require removal for optimal results (Chaurasia et al. 2014a). If stripping of DM is planned, it should be made internal to the graft–host junction or even in a small area overlying the pupil to avoid disrupting the incision.

The graft can be oversized, undersized, or same sized. Oversizing provides the advantage of a larger endothelial cell reserve, while undersizing avoids the need for the EK graft to conform to the irregularity at the graft-host junction that may interfere with the graft attachment process.

One of the most remarkable findings in a series of 60 eyes with DSEK after failed PK was that neither neovascularization nor the number of previous graft failures increased the risk of graft failure. The only preoperative characteristic associated with increased risk of graft failure was previous filtration surgery, either trabeculectomy or tube shunt (Anshu et al. 2011).

8.3.6 Iridocorneal Endothelial (ICE) Syndrome

These eyes may have a very shallow anterior chamber because of broad peripheral synechiae (Price and Price 2007). In addition, they may have undergone a prior glaucoma filtering surgery/drainage surgery for IOP control. Extensive synechiolysis may be required for deepening the anterior chamber. Postoperatively, frequent follow-up and aggressive control of IOP are needed for graft survival (Chaurasia et al. 2013).

8.3.7 Pediatric Endothelial Keratoplasty

DSEK can be more challenging in pediatric eyes as compared with adults. The main reasons for performing EK in pediatric eyes are for failed graft, congenital hereditary endothelial dystrophy, and pseudophakic corneal edema. Surgical challenges involve insertion and unfolding of the donor tissue in the small anterior chamber of a child, avoiding trauma to the crystalline lens, postoperative positioning, and anesthesia issues (Ramappa et al. 2012). Pediatric eyes can have a positive vitreous pressure which can make the surgical maneuvers difficult. Discussing with the anesthetist the need for hypotensive anesthesia during graft insertion and use of an anterior chamber maintainer during the surgery helps in maintaining the anterior chamber during the surgery.

8.4 Surgical Outcomes

8.4.1 Visual Acuity

When compared with PK, the visual recovery is remarkably rapid, occurring within a few weeks of EK, and mean visual outcomes continue to further improve for up to several years afterward. The average Snellen corrected distance visual acuity (CDVA) reported after DSEK has ranged from 20/30 to 20/60 in different studies, with variable follow-up periods (Lee et al. 2009; Li et al. 2012b). Several factors may interfere with complete visual recovery: graft folds, thickness irregularity, centration, interface haze, and residual anterior abnormalities in the host cornea.

DMEK eliminates any thickness variation or stromal interface and thereby results in better and faster visual recovery with fewer higher order aberrations from the posterior surface of the cornea (Rudolph et al. 2012). Most patients achieve 20/25 or better vision within several months with DMEK (Giebel and Price 2009; Guerra et al. 2011a). Like DMEK, DMAEK also provides superior visual recovery with high rates of 20/25 or better vision (Taravella et al. 2013). The relationship between DSEK graft thicknesses and visual acuity has been debated (Shinton et al. 2012; Seery et al. 2011). While some believe that thinner grafts are associated with better vision, others have failed to establish this association. Thinner, well-centered, and planar grafts may induce fewer higher order optical aberrations and contribute to superior visual results. Busin et al. have reported excellent visual outcomes with ultrathin DSAEK (Busin et al. 2013).

8.4.2 Refractive Results

DSEK does not significantly alter anterior corneal topography, but tends to cause a mean hyperopic shift of 0.75 to 1.5 D through changes in the posterior corneal curvature (Holz et al. 2008). Due to the nonplanar configuration of the DSEK donor lenticule, a minus lens is introduced on the posterior corneal surface. Also, increase in the thickness of the cornea by implanting additional stroma leads to a decrease in the radius of curvature of the posterior surface. The hyperopic shift should be taken into consideration when planning a triple procedure to achieve the target refraction. Although DMEK does not increase the corneal thickness or introduce a minus lens effect, it also results in a mean hyperopic shift of 0.25–0.50 D that is attributed to the resolution of the corneal edema after restoration of the endothelial function (Laaser et al. 2012; Price et al. 2009).

8.4.3 Endothelial Cell Loss

The endothelial cell loss reported at 6 months after DSEK is 18–35 %, followed by 31–36 % at 1 year, 31–41 % at 2 years, 44 % at 3 years, and 54 % at 5 years (Khor et al. 2011; Phillips et al. 2012; Chen et al. 2010; Price and Price 2008; Price et al. 2011, 2013; Talajic et al. 2013). Compared with the 5-year cell loss experienced with PK procedures performed in the Cornea Donor Study for similar indications, the cell loss at 5 years seems to be lower with DSEK (Price et al. 2013). Hence, despite the high initial endothelial cell loss in DSEK compared to PK, the rate of subsequent cell loss appears to be less with DSEK for reasons that have not been fully elucidated.

There are few reports so far on long-term endothelial cell loss after DMEK because the technique is relatively new. In a report by Tourtas et al., the mean endothelial cell loss at 6 months after DMEK and DSAEK was comparable (Tourtas et al. 2012). In another comparative study between DMEK and DSAEK, there was no difference in the endothelial cell loss at 1 year (Guerra et al. 2011b).

8.4.4 Graft Survival

The reported graft survival rates through 1 year with DSEK range from 55 to 100 % in various studies (Lee et al. 2009; Price et al. 2013; Anshu et al. 2012b). This wide range reflects differences in sample size, indications for endothelial keratoplasty, associated comorbid conditions, and varying rates of iatrogenic graft failure due to the surgeon's initial learning curve. Price et al. reported a 5-year survival rate of 93 % for Fuchs endothelial dystrophy and 76 % for pseudophakic and aphakic corneal edema (Price et al. 2011). Prior glaucoma surgery was the most significant risk factor for early graft failure (Price et al. 2013). With this risk factor taken into account, the 5-year DSEK survival rate was comparable to 5-year PK survival rates at the same center (Price et al. 2011). The reports on 1-year survival rates after DMEK are encouraging, and longer term follow-up is awaited.

8.5 Complications

8.5.1 Early Postoperative Raised IOP

Raised IOP can occur as a result of pupillary block due to air, and it may be relieved with pupillary dilation or partial anterior chamber decompression. Air may migrate to the posterior chamber in eyes with a floppy/abnormal iris tone leading to an appositional angle closure and raised IOP. This may be managed by removing the air from the anterior segment and allowing the iris to drop back into place.

8.5.2 Graft Detachment (Fig. 8.5, First Row)

The reported graft detachment rates after DSEK vary from 0 to 82 % (Lee et al. 2009; Anshu et al. 2012b; Chaurasia et al. 2011a, b). Although the precise mechanism of graft adhesion is unknown, it is probably an interplay of three factors—mechanical, biochemical, and physiological. Achieving a

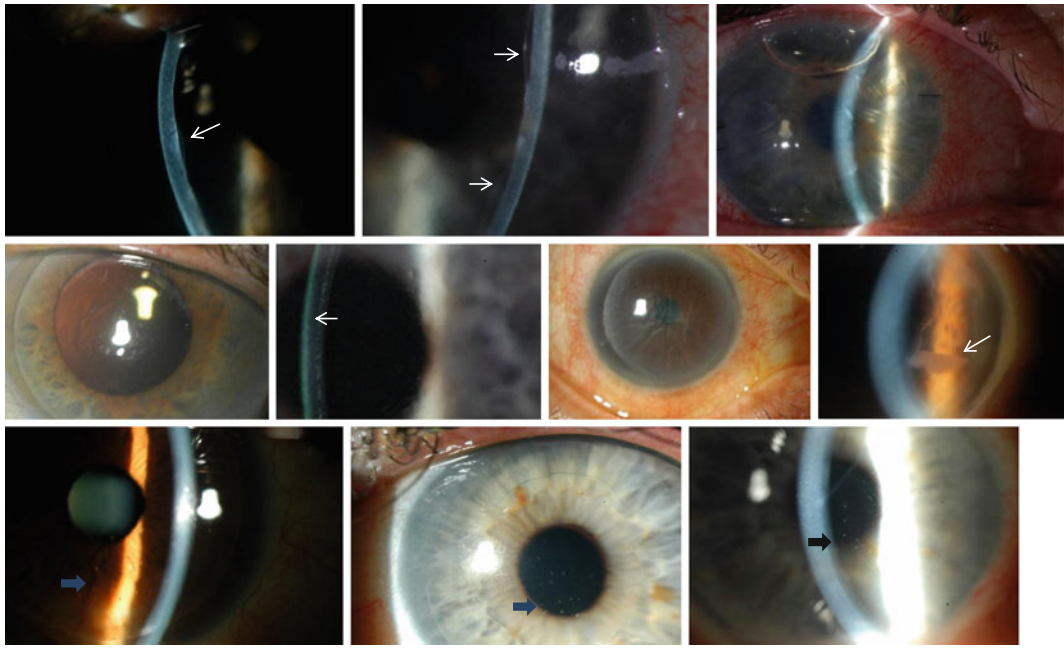

Fig. 8.5 Postoperative complications. *First row* (*L-R*): First and second panels: DMEK partial detachments; third panel: complete detachment (DM scroll shown in the anterior chamber). *Second row* (*L-R*): Folds in DSEK graft; interface haze with DSEK; late DSEK graft failure; epithelial downgrowth at the interface originating from the edge of the DSEK graft. *Third row* (*L-R*): Rejection episodes in DSEK, DMAEK, and DMEK; each showing fresh keratic precipitates without noticeable corneal edema

complete air fill in the anterior chamber helps in the initial mechanical apposition of the graft to the stroma, followed by the physiologic effect of the endothelial pump (Chaurasia et al. 2011b). Graft detachments are more common in situations where it is either difficult to achieve an air fill for a required time interval or to maintain a firm eye such as eyes with vitrectomy, aphakia, glaucoma filtering surgery, or repeated squeezing or eye rubbing on the part of the patient. Strategies described to reduce the risk of graft detachments include: scraping of the peripheral host stromal bed, midperipheral venting incisions, good wound integrity, prolonged air tamponade, and supine positioning, especially in high-risk situations. Graft detachments can be managed by reinjecting air (called rebubbling); however, these grafts may have a higher risk of endothelial cell damage. Spontaneous reattachments have been reported but are unpredictable and may be decentered.

As with DSEK, graft detachment remains a primary complication with DMEK. The risk of graft detachment is higher with DMEK than DSEK. In contrast to DSEK, where residual DM may not affect graft adhesion, remnants of host DM in the stripped bed can definitely interfere with the adhesion of the DMEK graft. Also, the elastic forces of the DM scroll need to be overcome for a firm adhesion of the DMEK graft as compared with DSEK, in which the donor posterior stromal tissue helps in countering this force. In an early report by Guerra et al., the rebubbling rate was 62 % in a prospective series of eyes undergoing DMEK (Guerra et al. 2011a). In this study, the graft insertions were done with an injector that required a viscoelastic plug. With the modifications in the insertion techniques that avoided the viscoelastic use, the rebubbling rates dropped to 15 % (Feng et al. 2013b).

8.5.3 Primary Graft Failure

Primary graft failure is a potential complication following any keratoplasty. The incidence of

primary graft failure after PK ranges from 0.3 to 2 % (Wilhelmus et al. 1995). The reported rates of primary graft failure after DSEK have ranged from 0 to 29 %, suggesting that iatrogenic endothelial trauma may be a factor (Lee et al. 2009; Wilhelmus et al. 1995; Terry et al. 2008a, b; Li et al. 2012a, b). The rate of primary graft failure after DMEK was 8–9 % in early studies that included the initial cases (Guerra et al. 2011a, b). With modifications and refinements in some of the surgical steps, both DSEK and DMEK have become more predictable with consistent results.

8.5.4 Immunologic Rejection (Fig. 8.5, Third Row)

The rate of rejection after DSEK has varied widely in small series from 0 to 46 % with the mean rate of approximately 10 % (Lee et al. 2009; Li et al. 2012a, b; Anshu et al. 2012b). Rejection rates are lower in EK compared with PK because the use of corticosteroids can be continued without much concern about wound healing. Additionally, less donor tissue is implanted in EK vs. PK, and the reduced antigenic load could be another favorable factor. A study by Anshu et al. reported that the DMEK eyes had 15 times lower risk of having an immunologic rejection episode than DSEK eyes and 20 times lower risk than PK eyes (Anshu et al. 2012a).

8.5.5 Glaucoma

The reported rates of glaucoma after DSEK range from 0 to 54 % (Anshu et al. 2012b; Vajaranant et al. 2009). A previous history of glaucoma or ocular hypertension was found to be a significant risk factor for development of raised IOP after DSEK.

8.5.6 Epithelial Downgrowth (Fig. 8.5, *Second Row, Fourth*)

Decentration during trephination can lead to incorporation of donor epithelium with a DSEK donor lenticule, which may lead to epithelial downgrowth. Also, recipient epithelium can be introduced during the donor insertion or introduced through surface venting incisions if proper technique is not employed. Epithelial ingrowth can be associated with graft failure.

8.5.7 Interface Abnormalities

Donor graft interface or thickness irregularities can occur with manual dissection or irregular microkeratome cuts. No attempt is made to match donor and recipient curvature, and a significant mismatch can result in folds and wrinkles in an EK graft that may be visually significant (Fig. 8.5, *second row—first*).

Another cause of interface abnormalities is incomplete removal of viscoelastic after stripping DM (Fig. 8.5, *second row—second*). This haze or reticulated-looking interface may take months to clear if the viscoelastic is not removed. Removing it leads to immediate resolution of the interface haze.

8.5.8 Infections

DSEK techniques create an interface between the donor tissue and the recipient's stroma, in which infectious agents can be introduced and get trapped during the surgical intervention. There have been reports of both bacterial and fungal infection deep in the interface after DSEK (Kitzmann et al. 2009; Sharma et al. 2011). Bacterial infections usually develop within a few days of the procedure. In contrast, fungal contamination may present more insidious course over weeks to months. If both the endothelial lenticle and the recipient cornea show infiltration, a PK is required to ensure complete eradication of the infection. If the infection is limited to the endothelial graft alone, replacement of the EK graft may be attempted.

8.6 Future Prospects

Current research on endothelial diseases is directed towards culturing endothelial cells, pharmacological agents to stimulate endothelial

stem cell proliferation, and inhibition of apoptosis of the endothelial cells (Koizumi et al. 2013; Okumura et al. 2011). The results of these investigations have been promising. It is possible that many new medical modalities may emerge for the management of some of the endothelial diseases.

Conclusions

DMEK is the ideal selective transplant procedure for endothelial disorders providing perfect anatomic replacement of the diseased endothelium. However, DSEK continues to remain the surgery of choice for endothelial diseases associated with more complex anterior segment pathologies. Pharmacological modalities of treating endothelial diseases are an exciting breakthrough, but at this point, it is uncertain whether these have potential to completely replace endothelial keratoplasty or serve as an adjunctive treatment modality in the management of endothelial dysfunctions.

Compliance with Ethical Requirements Author SC declares that she has no conflicts of interest. Author FWP is a consultant for Lenstec, Ophtec, Allergan, and Alcon and has received lecture fees from Bausch & Lomb and Oculus. Authors FWP and MOP own stock in TearLab, ReVital Vision and Calhoun Vision Inc.

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Boston Keratoprosthesis

9

Lauren R. Schneider and Jose de la Cruz

9.1 Introduction

Penetrating keratoplasty has long been the treatment of choice for corneal blindness. In certain clinical scenarios, the ocular environment does not lend itself to successful, long-term graft survival. The Boston type I keratoprosthesis, a type of artificial cornea, has hugely impacted the approach to corneal transplantation in these challenging situations, primarily because it eliminates the threat of recurrent blindness due to graft rejection or failure.

9.2 Indications

In order to be considered for a keratoprosthesis, a patient should have an appreciably high risk of graft failure after a penetrating keratoplasty. The most common indications for a Boston type I keratoprosthesis include previous graft rejection (often repeated rejection), severe ocular surface disease (chemical injury, limbal stem cell deficiency), and significant corneal vascularization, while the less common but emerging indications include bullous keratopathy, herpes simplex keratitis, severe mechanical or thermal ocular injury, corneal dystrophies, aniridia, iridocorneal endothelial syndrome, and congenital corneal opacifications (Zerbe et al 2006; Aldave et al. 2009; Colby and Koo 2011; Akpek et al. 2007) (Fig. 9.1). Perpetual evolutions in the design of the keratoprosthesis and in the approach to postoperative management have expanded the relevance and viability of this procedure as a primary surgery in selected patients (Traish and Chodosh 2010).

According to the WHO criteria, the patient should be either monocular or blind in both eyes. Although, more and more surgeons support the legitimacy of keratoprosthesis surgery despite intact vision in the contralateral eye, due to the potential for improved visual function, possible restoration of binocularity, and enhanced cosmesis in patients postoperatively (Aldave et al. 2009; Pineles et al. 2010). It has been previously believed that a candidate should have a minimum vision of light perception with projection in all four quadrants; yet, this notion has also been refuted by surgeons achieving excellent visual outcomes in patients with preoperative vision as good as 20/50 (Aldave et al. 2009). The patient should have no appreciable evidence of retinal or optic nerve dysfunction and no known history of dense amblyopia. To optimize outcomes, patients must have adequate lid anatomy and good blink function with no evidence of severe keratoconjunctivitis sicca.

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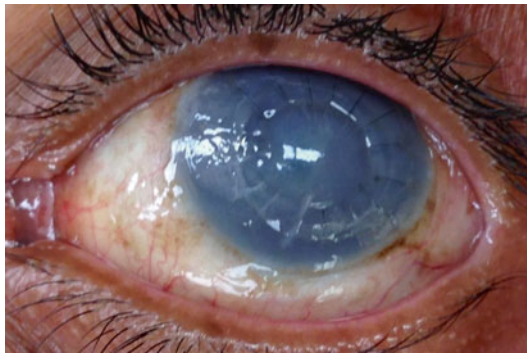

Fig. 9.1 This is a slit lamp photograph of a failed graft after several repeat corneal transplants, which would be high risk for another standard penetrating keratoplasty

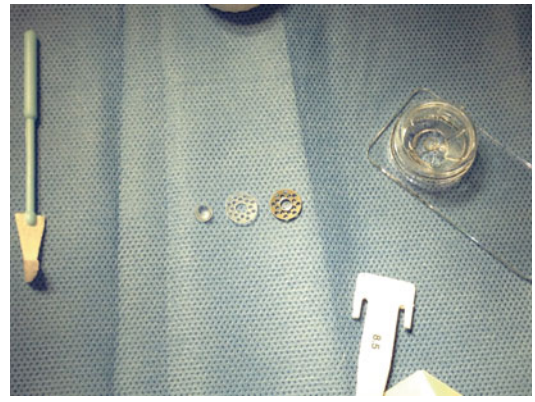

Fig. 9.2 This photo displays the front plate, the PMMA and titanium 8.5 mm back plate options, and the locking ring of a Boston type I keratoprosthesis

Autoimmune disease (such as Stevens-Johnson syndrome (SJS) or ocular cicatricial pemphigoid (OCP)) had once been deemed a relative contraindication, due to their propensity for corneal melts (Colby and Koo 2011). More recently, advancements in postoperative management have expanded the realm of keratoprosthesis surgery to include these complicated patient populations (Colby and Koo 2011; Sayegh et al. 2008).

Prior to surgery, the patient must understand the need for indefinite postoperative prophylactic topical medications and must be committed to frequent follow-up visits. The procedure should be performed by a surgeon well experienced in penetrating keratoplasties, who has direct access to an eye bank, and a multidisciplinary ophthalmology team (glaucoma, retina, and oculoplastics specialists) (Aldave et al. 2009; Ament et al. 2009).

9.3 Design

The Boston type I keratoprosthesis is available for order from the Massachusetts Eye and Ear Infirmary (Boston). The threadless Boston type I keratoprosthesis consists of a central clear front plate and stem (manufactured from medical-grade polymethyl methacrylate, or PMMA), a corneal allograft button with the center trephinated and discarded, a large back plate, and a titanium locking ring (Fig. 9.2). The front plate is either 5 mm or 6 mm in diameter, with a smaller attached posterior stem that is segmented into three parts. The first segment of the stem, which accommodates the corneal graft, is 0.62 mm in height and 3.35 mm in diameter. The second segment, which accommodates the back plate, is 0.84 mm in height and 3 mm in diameter. There is a single-groove anterior to the innermost segment. The locking ring will eventually snap tightly into this furrow, and its dimensions are 0.33 mm in height and 2.74 mm in diameter.

The back plate is available in either PMMA or titanium. There are two size options for the diameter of the back plate: 7 mm or 8.5 mm. The smaller back plate has 8 holes, each 1.3 mm in diameter, and the larger back plate has 16 holes, each 1.17 mm in diameter. These holes allow the aqueous to deliver nutrition and hydration to the corneal graft to lessen the possibility of corneal melts (Harissi-Dagher et al. 2007). The back plate thickness is 0.8 mm centrally and 0.6 mm peripherally. Both types of back plates have a central 3 mm hole. The titanium locking ring has an outer diameter of 3.6 mm and an inner diameter of 2.8 mm with a uniform thickness of 0.23 mm (Harissi-Dagher and Dohlman 2007).

9.4 Surgical Procedure

The appropriate technique for the assembly and implantation of the Boston type I keratoprosthesis has been described (Dohlman et al. 2002).

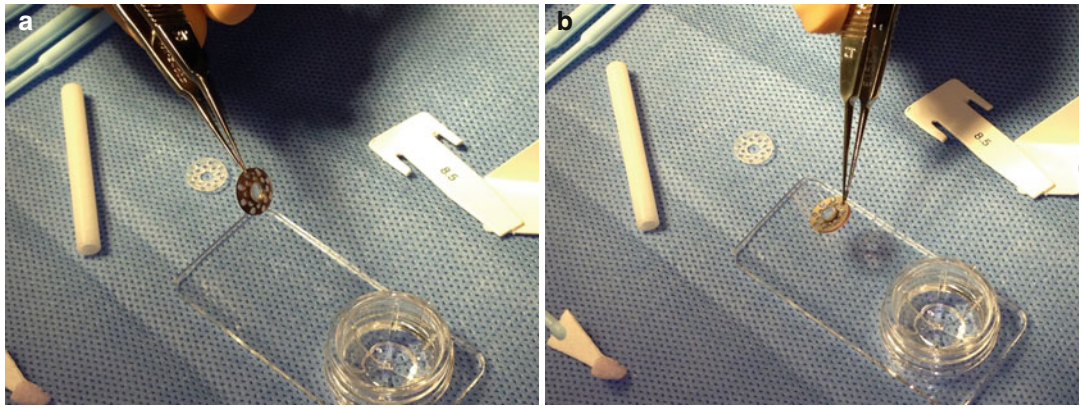

Fig. 9.3 This photograph demonstrates an anterior (*left*) and posterior (*right*) view of the final composition of the Boston type I keratoprosthesis, fastened into the donor cornea

The host cornea should be examined carefully and calipers should be utilized to determine the size of the host trephination which will encompass the diseased cornea, without encroaching upon the anterior chamber angle. The donor cornea is trephinated in the usual fashion to be 8.0–9.0 mm in diameter, on average, so as to oversize the recipient bed by 0.25–0.5 mm. A 3 mm handheld dermatological punch is carefully centered over the endothelial side-up graft and twisted carefully with constant downward pressure, so as to leave behind a central hole. The 3 mm corneal button can be set aside and later discarded. The donor corneal donut is placed over the stem of the front plate, which is anterior side down on a sterile table, and gently pushed down into place. Viscoelastic may be applied to the endothelial surface of the donor cornea. The selection of the appropriate back plate is largely determined by the size of the host trephination created. For example, a smaller sized trephination would necessitate the 7 mm back plate, as it would be difficult to securely insert the 8.5 mm back plate with an 8 mm donor cornea into a host trephination of 7.5 or 7.75 mm. The selected back plate is then centered over the stem of the front plate and placed on top of the endothelial side of the donor cornea. No rotational movements are needed. Finally, the titanium locking ring is the last and most posterior component of the Boston type I keratoprosthesis. The locking ring, which clicks into place with downward pressure and the use of a hollowed pin that accompanies the set, should be placed so as to exactly fit the central stem of the front plate within the opening of the ring. The final composition should be examined to ensure the security of all components (Fig. 9.3).

The approach to the preparation of the recipient bed is not unlike that of a standard penetrating keratoplasty. The patient's eye should be prepped in the usual sterile fashion for intraocular surgery. The recipient trephination should be 0.25–0.5 mm smaller than the selected diameter of the donor corneal button size. If the patient is phakic, a lensectomy must be performed. The posterior capsule should be preserved; yet, if the vitreous presents, then an anterior core vitrectomy should also be executed. Alternatively, if the patient is already pseudophakic with a posterior chamber intraocular lens, the lens implant may remain in place. It is imperative that the status of the lens be determined preoperatively, as the Boston type I keratoprosthesis must be ordered with the appropriate refractive power. If the patient is (or will be) aphakic at the time of transplantation, the axial length of the eye is needed in order to calculate the refractive power of the Boston type I keratoprosthesis. Multiple (12–16) interrupted 9-0 or 10-0 nylon sutures are passed through the corneal donor button portion of the apparatus to secure the Boston type I keratoprosthesis into the recipient bed with all knots buried, as would be done when performing a traditional penetrating keratoplasty. The graft–host

junction should be inspected to be watertight. At the completion of the surgery, a plano soft contact lens (Kontur Kontact Lens Co., Hercules, CA) 16 mm diameter with 9.8 mm base curve is placed on the eye (Fig. 9.4).

9.5 Intraoperative Complications

Intraoperative complications, although rare, may happen. These events include vitreous loss, disassembly of the Boston type I keratoprosthesis components, anterior chamber bleeding, suprachoroidal hemorrhage, and perforation of thin host corneas (Zerbe et al. 2006; Aldave et al. 2009). It is imperative to remain cognizant of these possible occurrences and to always be prepared with a surgical approach to these intraoperative events should they spontaneously arise.

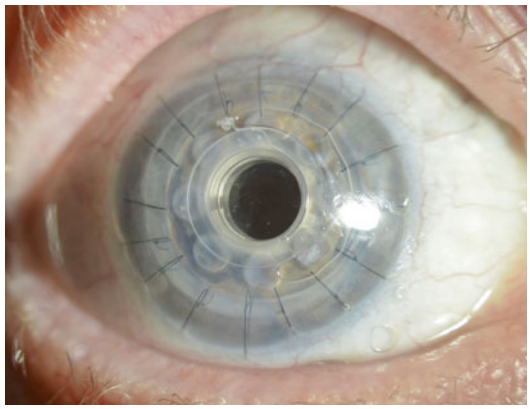

Fig. 9.4 This slit lamp photograph shows the keratoprosthesis after implantation, along with the Kontur soft contact lens

9.6 Postoperative Management

In the immediate postoperative period, the preferred antibiotic regimen recommendation includes a combination of topical fortified vancomycin (typically in a concentration of 15 or 25 mg/cc) and a fourth-generation fluoroquinolone, both one drop four times daily (Zerbe et al. 2006; Durand and Dohlman 2009). According to the International Boston Keratoprosthesis Protocol, an alternative acceptable course of therapy consists of a drop of chloramphenicol 1 % four times daily along with ciprofloxacin 0.3 % (or ofloxacin 0.3 %, levofloxacin 0.5 %, or moxifloxacin 0.5 % if available) four times daily (Ament et al. 2009). The topical antibiotics may be decreased to a maintenance dose of twice daily at postoperative month one, as patients with keratoprostheses must indefinitely administer prophylactic antibiotic drops (Ament et al. 2009). It is also recommended to instill one drop of povidone iodine 5 % once monthly at follow-up visits (Ament et al. 2009).

Perioperative or postoperative systemic steroids or immediate postoperative periocular steroids are utilized as preventive measure for intraocular inflammation and the development of retroprosthetic membranes (Zerbe et al. 2006; Ament et al. 2009) (Fig. 9.5a, b). After

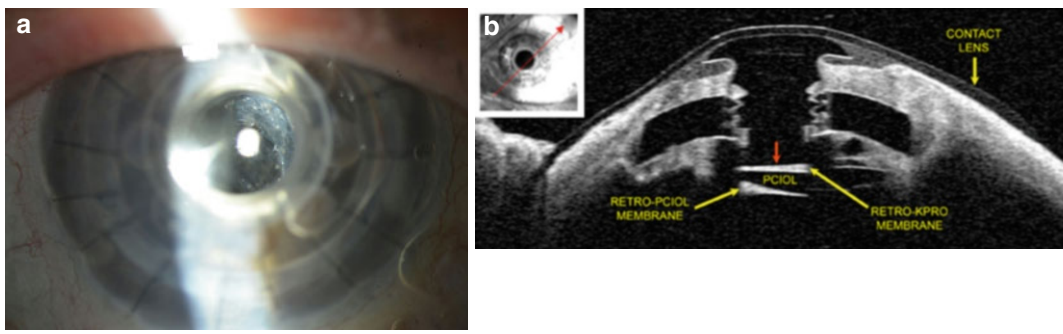

Fig. 9.5 (**a**) This is a slit lamp photo demonstrating a visually significant retroprosthetic membrane (RPM). (**b**) This anterior segment OCT of a different eye demonstrates another view of an RPM

surgery, topical prednisolone 1 % should be dosed at one drop every two hours for 1 week, then four times daily for the remainder of the first month after surgery, and then slowly tapered over the next 1–3 months (Ament et al. 2009). Patients should remain on a maintenance dose of prednisolone one drop daily (Ament et al. 2009).

Patients must keep a Kontur soft contact lens in the eye after surgery at all times. The primary purpose of this contact lens is to prevent drying of the ocular surface, which had led to dellen formation. Other functions served by this contact lens include increased patient comfort, general protection of the ocular surface, cosmesis and glare reduction (colored contact lenses), and correction of any residual refractive error (Harissi-Dagher et al. 2008). This contact lens should be exchanged for a new contact lens every 3–4 months, and the old lens should be cultured (Ament et al. 2009).

9.7 Visual Acuity Outcomes

Most patients evaluated to be candidates for a Boston type I keratoprosthesis have poor preoperative visual acuities. Visual potential is often difficult to assess, because of the inability to perform an adequate posterior exam due to the presence of severe corneal opacification.

As reported in the Multicenter Boston Type I Keratoprosthesis Study, which analyzed data from 136 eyes undergoing surgery to receive a Boston type I keratoprosthesis, only 3.6 % of patients had best-corrected visual acuity (BCVA) ≥20/200 before transplantation, with no eyes having BCVA >20/100. After an average follow-up of 8.5 months postoperatively, 57 % of eyes had BCVA ≥20/200, with 19 % achieving BCVA ≥20/40 (Zerbe et al. 2006). In another large series reported by Aldave et al., 100 % of eyes attained and maintained a visual acuity of ≥20/100 by 36 months of follow-up time. Even more encouraging, of patients who had a preoperative vision ≥20/50 in the contralateral eye, 47 % of eyes achieved a postoperative vision of ≥20/50 (Aldave et al. 2009).

The capability of the keratoprosthesis to provide an avenue towards rapid visual recovery is largely attributable to its design composed of a synthetic, rigid central optical zone. One of the most significant obstacles in patients post-penetrating keratoplasty is the residual refractive error (mean spherical equivalent −2.50 to −4.00 diopters) and the average time interval of 1–2 years after surgery prior to accomplishing BCVA (Dunlap et al. 2010; Silbiger et al. 1996). In a study evaluating the short-term visual outcomes after Boston type I keratoprosthesis surgery consisting of 126 eyes total, as of the last follow-up which ranged from 3 months to 3 years postoperatively, the mean spherical refractive error was −0.57 diopters and the mean astigmatism was 0.10 diopters in a total of 104 eyes. At 1 month after surgery, over half of the total eyes reached their BCVA, with a quarter of the total eyes achieving BCVA within 1 week after the date of operation (Dunlap et al. 2010). Unfortunately, one must appreciate these encouraging results with caution. In a study that followed an initial cohort of 40 eyes undergoing keratoprosthesis implantation, 59 % of eyes reached and retained BCVA ≥20/200 for the first and second postoperative years, followed by a discouraging decline in the percentage of patients maintaining this BCVA in postimplantation years 3 and 4 to 50 and 29 %, respectively (Greiner et al. 2011). The vision loss observed as the time from surgery increased was primarily due to end-stage glaucomatous optic neuropathy (Greiner et al. 2011).

It has been reported that the patients with the best prognosis for reaching BCVA ≥20/200 include those with a history of noncicatricial prior graft failure and those with chemical burns, while the patients with the poorest visual prognosis are those with Stevens-Johnson syndrome or other cicatrizing ocular immune conditions (Zerbe et al. 2006; Yaghouti et al. 2001). Other patients who never benefit from an improvement in baseline visual acuity often have other detrimental comorbidities, such as advanced glaucoma, macular degeneration, or other retinal pathologies (Zerbe et al. 2006).

9.8 Postoperative Complications

Mild to severe postoperative complications can occur in patients with keratoprostheses at any time after implantation. The most common nonsurgical postoperative complication is a retroprosthetic membrane (RPM) (27–77 % of eyes), which can either be observed or, if visually significant, can be treated with yttrium-aluminum-garnet (YAG) laser membranotomy or surgical membranectomy (Zerbe et al. 2006; Aldave et al. 2009; Sayegh et al. 2008; Greiner et al. 2011; Yaghouti et al. 2001; Chew et al. 2009; Kamyar et al. 2012). Concomitant intraoperative procedures at the time of keratoprosthesis implantation have been shown to significantly increase a patient's risk for developing an RPM (Aldave et al. 2009).

Another common and troublesome postoperative issue is elevated intraocular pressure (IOP), which occurs in approximately 40–50 % of patients (Chew et al. 2009; Kamyar et al. 2012). As many as two thirds to three quarters of patients already have a diagnosis of glaucoma prior to keratoprosthesis surgery (Zerbe et al. 2006; Aldave et al. 2009; Sayegh et al. 2008; Chew et al. 2009; Kamyar et al. 2012). Over 90 % of those having elevated IOP postoperatively have no history of prior glaucoma surgery, and about half of these patients will have glaucoma development or progression (Kamyar et al. 2012). Of the patients who are fortunate enough not to experience elevated IOP after keratoprosthesis implantation, almost half of them already have a history of prior glaucoma surgery (Kamyar et al. 2012). Elevated IOP is managed with topical and oral medications, followed by tube shunt surgery if IOP remains suboptimal. Alternatively, most patients with preexisting glaucoma will undergo tube shunt implantation or endocyclophotocoagulation at the time of keratoprosthesis surgery (Aldave et al. 2009; Kamyar et al. 2012). Digital palpation through closed eyelids while the patient is looking downward is the only available method for IOP evaluation in patients with keratoprostheses. As a result, uncontrolled high IOP may go undetected for prolonged periods of time leading to devastating visual loss despite an otherwise uncomplicated postoperative course. In patients whose vision permits them to be capable of participating in formal visual field evaluation, periodic testing should be performed along with frequent optic nerve head evaluation.

Another feared complication after keratoprosthesis implantation is endophthalmitis. The overall prevalence of endophthalmitis after keratoprosthesis surgery was 5.4 % between 2001 and 2011 in a single study (Robert et al. 2012). Other studies report endophthalmitis rates of 11–12.5 % (Chew et al. 2009; Greiner et al. 2011). In a sizable series, the rate of endophthalmitis among the cohort of patients not placed on topical fortified vancomycin was 4.13 % per patient-year, as compared to 0.35 % per patient-year, a statistically significantly lower incidence, in patients on vancomycin maintenance treatment (Durand and Dohlman 2009). Over 80 % of cases of endophthalmitis in keratoprosthesis patients, and 100 % prior to the ubiquitous use of prophylactic vancomycin, are due to Gram-positive cocci (Durand and Dohlman 2009; Nouri et al. 2001). It is important to be mindful of the emerging concern for other, less common etiologies of infectious endophthalmitis in patients who are using prophylactic vancomycin, such as Gram-negative organisms and fungal pathogens (Greiner et al. 2011; Chan and Holland 2012).

Other complications following surgery may include vitreous hemorrhage, retinal detachment, sterile vitritis, choroidal hemorrhage or effusion, chronic nonanatomical hypotony, cystoid macular edema, corneal melting, persistent epithelial defects, wound leaks, infectious keratitis, and traumatic wound dehiscence with possible Boston type I keratoprosthesis extrusion (Zerbe et al. 2006; Dokey et al. 2012). Despite all of the aforementioned possible complications, overall retention rates of the keratoprosthesis of 84–95 % have been reported in multiple large series (Zerbe et al. 2006; Aldave et al. 2009; Greiner et al. 2011).

9.9 Future of Keratoprosthesis

There is an expanding acceptance of the utility of the Boston type I keratoprosthesis as a reliable option in patients who may have otherwise had dismal prognoses for visual rehabilitation. The Boston type I keratoprosthesis is used by some

surgeons as a first-line treatment for corneal blindness in eyes that historically have very poor prognoses with penetrating keratoplasties.

There are a myriad of variables that may potentially affect the overall cost-effectiveness of any medical intervention. In a study that retrospectively reviewed patient data of 82 patients after keratoprosthesis surgery over a 2-year period, the cost-effectiveness of the keratoprosthesis by cost-utility analysis (CUA) was determined to be $16,140 per quality-adjusted life years (QALY). Despite the initial cost for the keratoprosthesis, surgical procedure, and hospitalization, as well as the cost of commonly encountered future complications and additional procedures needed, this treatment modality was deemed to be a highly cost-effective option resulting in a 20.3 % improvement in QALY over no therapy for patients with severe corneal disease (Ament et al. 2010a).

Overseas, economic infrastructures are unable to support a readily available supply of donor corneas suitable for transplantation. The keratoprosthesis may present a new option for the treatment of corneal blindness, although inadequate financial resources for the necessary medical care and medications continue to pose impediments to the widespread use of keratoprostheses in developing nations. Other valid concerns regarding the use of keratoprostheses in nonindustrialized countries include extreme weather, high likelihood of corneal infections, unfavorable geography leading to the impracticality of consistent postsurgical follow-up, unclean water supplies, and cultural barriers to care (Ament et al. 2010b).

The Boston keratoprosthesis has been used with appreciable success in pediatric patients. Penetrating keratoplasties in pediatric patients are notorious for high rates of allograft rejection (40–50 %), low rates of achieving and maintaining clear grafts due to exuberant inflammatory reactions typical in the postoperative period, and significant irregular astigmatism (Nallasamy and Colby 2010). Only approximately 30 % of pediatric patients attain visual outcomes ≥20/200 after corneal transplantation. These inevitable complications augment the already substantial concern for refractive and deprivational amblyopia in pediatric patients with ocular disease. The keratoprosthesis offers many advantages over traditional corneal transplants in the pediatric population largely due to the eliminated possibility of graft rejection, as well as the minimally induced surgical astigmatism. Both benefits provide a prompt avenue to a clear and stable visual axis, which provides for more immediate visual rehabilitation in patients who are of amblyogenic age (Colby and Koo 2011).

Conclusions

There is a multitude of new and innovative approaches to care, with the hope of optimizing the long-term keratoprosthesis postoperative course in complex patient populations. Systemic immunomodulatory agents may become pivotal in improving the outcomes in keratoprosthesis patients with autoimmune diseases (Colby and Koo 2011). Investigational work with drug-eluting contact lenses may eventually help to combat postoperative infection resulting from lack of patient compliance with the maintenance medication regimen (Ciolino et al. 2009). The challenge of obtaining precise IOP assessments in patients with keratoprostheses is the impetus behind active research for new intraocular censor devices (Colby and Koo 2011). Data continues to be collected on patients with keratoprostheses in attempts to further the understanding of the etiology behind common and troublesome postoperative complications, in hopes of someday being able to take preventive measures towards these undesirable obstacles and promote improved long-term sustainability of visual improvements.

Compliance with Ethical Requirements Lauren R Schneider, MD, and Jose de la Cruz, MD, declare that they have no conflict of interest.

No animal or human studies were carried out by the authors for this article.

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Laser-Assisted Keratoplasty and Post-keratoplasty Management

10

Sumit Garg, Julio Echegoyen, Marjan Farid, Matthew Wade, and Roger F. Steinert

10.1 Introduction

The use of the femtosecond (FS) lasers into corneal surgery has catapulted a new era for keratoplasty. First introduced for creation of the corneal flap in laser in situ keratomileusis (LASIK) in the 1990s, the femtosecond laser is an infrared laser that utilizes ultrashort pulses in the range of several hundred femtoseconds, the SI unit of time equal to 10^{-15} of a second. In other words, a femtoseond is to a second what a second is to 31.7 million years! Femtosecond laser pulses create cuts by photodisruption of tissue, a process were bubbles create microcavitation (Fig. 10.1). Contiguous pulses are placed at a precise depth within the cornea; collateral thermal damage to adjacent tissue has been measured to be in the order of 1 μm. The laser may be programmed to fire in multiple patterns that, by translating from deep to superficial and by varying the diameter as the laser translates, can create a wide range of complex incisions that are identical in donor and host corneas.

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10.2 Femtosecond Lasers in Ophthalmology

In the early 1990s, Ronald Kurtz, MD, in collaboration with Tibor Juhasz, PhD, and their associates designed and constructed the prototype of the ophthalmic femtosecond laser system that later became the IntraLase system (Abbott Medical Optics (AMO), Santa Ana, CA). In 2005 the US Food and Drug Administration cleared the use of the femtosecond laser (AMO, Santa Ana, California) for laser-enabled full- and partial-thickness corneal incisions, which was rapidly followed by patient treatments at UC Irvine and elsewhere (Ignacio et al. 2006; Steinert et al. 2007). Currently, the new 6th-generation IntraLase iFS system is in use and allows for significantly faster laser cutting time with lower pulse energies. Several other FS laser platforms have also been modified for laser-enabled keratoplasty including the VisuMax (Carl Zeiss Meditec AG, Jena, Germany) and FEMTO LDV (Ziemer Ophthalmic Systems AG, Port, Switzerland) and the FEMTEC (Bausch & Lomb and 20/10 Perfect Vision, Heidelberg, Germany). The author's experience has been with the IntraLase platform; therefore, this platform will serve as the basis for this manuscript. The fundamental aspects, however, are similar among the available platforms.

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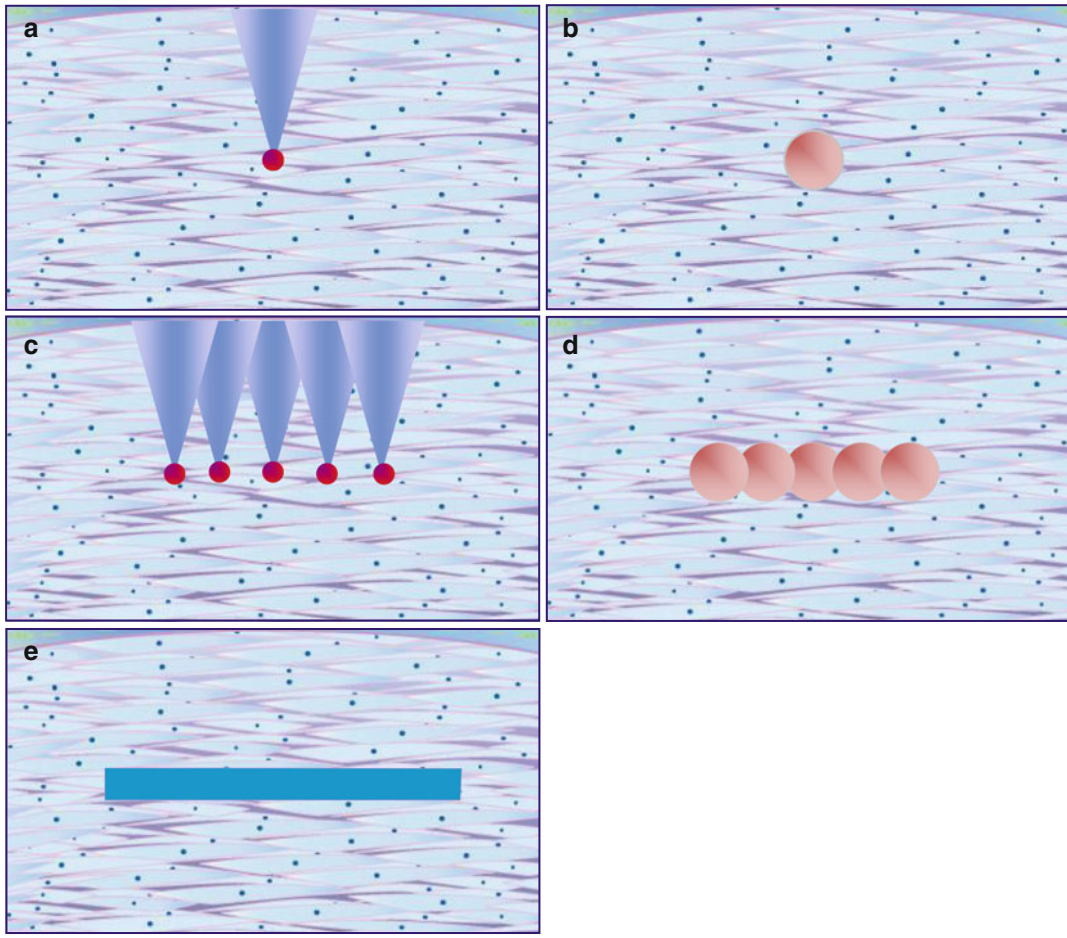

Fig. 10.1 (**a**) The femtosecond laser is focused to the target area within the corneal stroma. Microplasma is created, vaporizing approximately 1 μm of corneal tissue. (**b**) A bubble of gas and water forms around each pulse. (**c**–**e**) Repeated applications allow gas bubbles to coalescence along a single plane, creating a "cut"

10.3 The Femtosecond Laser-Enabled Keratoplasty (FLEK)

The femtosecond laser allows for exact, reproducible and customized trephination patterns on both the donor and host tissues. The "top-hat" button configuration was the first customized trephination pattern using the FS laser (Fig. 10.2a). We have previously demonstrated that the "top-hat" shape leads to increased wound stability, increase in resistance to leakage, and possibly less astigmatism than traditional trephination PKP wounds (Steinert et al. 2007; Farid et al. 2007). Since then, a variety of other complex patterns of laser trephination cuts have been described, including "mushroom," "zigzag," and "Christmas tree" patterns (Fig. 10.2a–d). The "top-hat"–shaped cut replaces greater endothelial cells and may be beneficial in endothelial diseases such as Fuchs' dystrophy as well as creating an internal flange to help seal the wound. In diseases involving primarily the anterior and stromal cornea such as keratoconus or stromal pathologies, the "mushroom" cut may be more advantageous by providing a greater anterior stromal replacement. The "zigzag" cut pattern, however, works well in virtually all settings with an angled anterior side cut that facilitates donor-host interface alignment, potentially decreasing tissue misalignment, and results in less optical

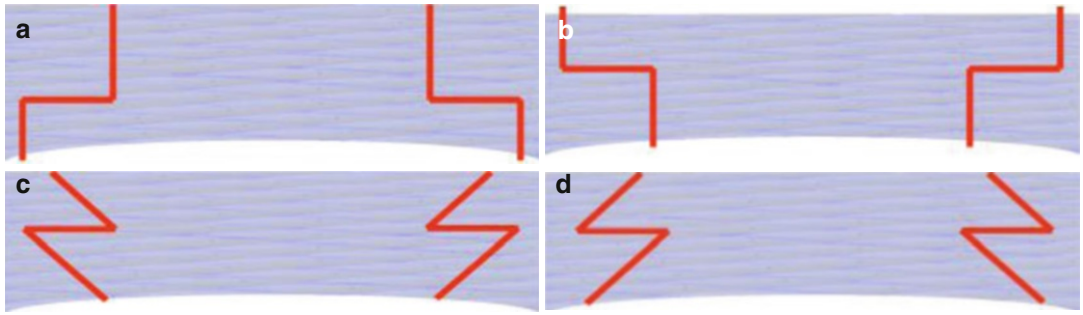

Fig. 10.2 (**a**) "Top-hat" configuration. (**b**) "Mushroom" configuration. (**c**) "Zigzag" configuration. (**d**) "Christmas tree" configuration

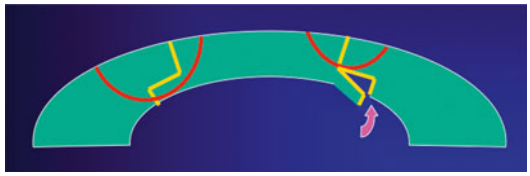

Fig. 10.3 Incorrect placement of suture in "top-hat" incision can lead to posterior wound gape

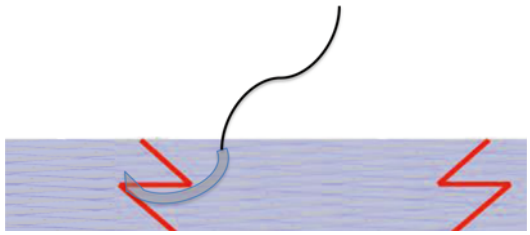

Fig. 10.4 Correct placement of needle at apex of "zigzag" incision

distortion. Furthermore, the "zigzag" configuration has the simplest learning curve for suturing. Where precise care has to be taken to place the suture through the posterior wing of the top-hat cut to prevent posterior tissue separation postoperatively (Fig. 10.3), in the "zigzag" incision pattern, the needle needs to be passed at the easily visualized lamellar tissue apex and then inserted into the corresponding host lamellar space in order to achieve excellent wound apposition (Fig. 10.4). Improved sealing of the incision site permits the surgeon to use less suture tension than traditional keratoplasty, reducing distortion from tight or multiple sutures. In addition, the increased surface area of these incisions leads to improved tensile strength of the wound, allowing for earlier suture removal when indicated (Farid et al. 2009; Buratto and Böhm 2007; Price and Price 2008; Cheng et al. 2008b; Bahar et al. 2009). Lastly, FLEK has been shown to have rapid visual recovery and astigmatism comparable to or often better than traditional blade trephination (Farid et al. 2009; Buratto and Böhm 2007; Price and Price 2008; Cheng et al. 2008b; Bahar et al. 2009).

10.4 Patient Selection and Evaluation

Successful postsurgical FLEK outcome is crucially dependent on proper patient selection. Initially, contraindications to the procedure should carefully be excluded: any condition preventing proper laser docking such as severe ocular surface irregularity, elevated glaucoma filtering bleb or glaucoma shunt implant, small orbits, extremely narrow palpebral fissures, and recent corneal perforations. Extreme caution should be utilized if the decision is made to perform FLEK on patients with prior penetrating keratoplasty or globe trauma because of the risk of corneal/globe rupture. Interestingly, a small retrospective case series by Rush et al. did not show any rupture of old corneal wounds with the significant rise in intraocular pressure associated with laser applanation in patients with previous corneal grafts or globe trauma using the IntraLase platform (Rush et al. 2011). Although the FS laser is known to have excellent cut penetration

through even dense scars, severe peripheral corneal neovascularization and/or opacity may be a relative contraindication.

10.5 Tissue Preparation and Surgical Procedure

Several donor configurations are available for the zigzag button arrangement, each with a specific diameter [8.0 mm ("zigzag" A), 8.5 mm ("zigzag" B), and 9.0 mm ("zigzag" C)]. It is our customary practice to have the donor tissue supplied pre-cut from the eye bank. The eye bank uses the surgeon-specified laser parameters to compliment the planned surgery (i.e., "zigzag" C donor into a "zigzag" C host). Alternatively, laser cutting of donor tissue can be accomplished using an artificial anterior chamber with the same laser where the host tissue is cut. For the majority of patients, we use a same-size donor and host trephination; however, if the preoperative keratometry readings are very steep, the surgeon can consider undersizing the graft by one (i.e., "zigzag" B donor into "zigzag" C). Host cutting can be done under topical or retrobulbar anesthesia. Centration of the suction ring on the patient's eye is crucial to achieving centration of the graft. Complex cutting patterns and alignment marks can increase the amount of time the suction ring remains on the eye, thereby favoring preoperative retrobulbar block for patient comfort; however, this has become less significant with the newer, faster generation of femtosecond lasers. Conditions that may complicate host laser cutting such as nystagmus, dementia, excessive anxiety, and children should be offered general anesthesia to ensure safety and success of the procedure; however, this requires coordinated care with anesthesia to provide portable monitoring and anesthesia. Additionally, having the femtosecond laser either in the operating suite or in close proximity to the operating suite allows for FLEK in these unique situations.

The "zigzag" cut results in three distinct cuts that can be readily visualized on postoperative slit lamp biomicroscopy and anterior segment OCT imaging (Figs. 10.5a, b). The femtosecond laser also allows for the placement of radial alignment marks on the host and donor, which facilitate precise suture placement and improved tissue distribution.

It is our customary procedure to leave a 70 µm posterior layer of uncut tissue to maintain a closed eye and formed anterior chamber between laser cut and cap removal. Preoperative pachymetry mapping, obtained either by anterior segment optical coherence tomography (Visante OCT, Carl Zeiss Meditec, Inc., Dublin, California), Scheimpflug photography (Pentacam, Oculus USA, Lynwood, Washington), or ultrasound is necessary to determine the posterior incision depth limit. Studies have demonstrated that side-cut bridges are stronger than lamellar bridges; however, both types of tissue bridges are stronger than full-thickness cuts (Price et al. 2008; Heur et al. 2011). For easier detection and potential graft-host alignment

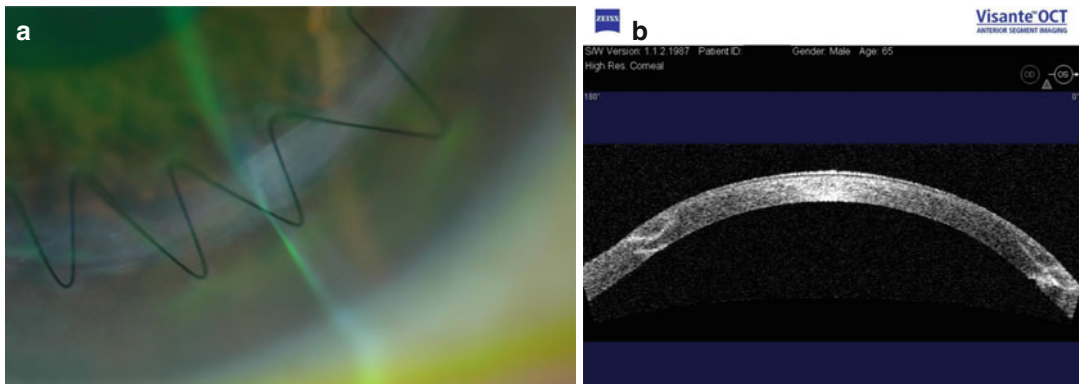

Fig. 10.5 (**a**) Slit lamp photo of "zigzag" incision. (**b**) Anterior segment OCT of "zigzag" incision

issues, a posterior side-cut bridge is preferred over an anterior side-cut bridge.

After the femtosecond laser incision is complete, antibiotic drops are placed in the eye, and the eye is shielded; if the laser is located another surgical room, the patient transported to the operating suite. The host corneal button can be bluntly dissected (i.e., with a Sinskey hook) to reveal the lamellar and side-cut laser incisions. These incisions usually separate cleanly, although limited sharp dissection with a surgical blade or scissors may be needed. Next, the anterior chamber is then entered with a blade and the posterior corneal bridging tissue is cut with corneal scissors. Care should be taken to create a posterior lip of host tissue to aid in a hermetic seal. The donor cornea is sutured into place using the surgeon's suturing pattern of choice. The depth of the suture in the donor and host tissue should be carefully aligned in order to minimize misalignment and tissue distortion (Heur et al. 2011) (Fig. 10.4).

10.6 Literature Review of Femtosecond Keratoplasty

10.6.1 FLEK

FLEK has been shown to have equal or better best spectacle corrected visual acuity (BSCVA) and postoperative astigmatism, when compared to conventional PK. Farid et al., in their preliminary study of 13 patients with femtosecond laser-generated "zigzag" incision configuration, showed over a 9-month period the mean astigmatism to be less than 3.0 diopters at all intervals beginning as early as the first postoperative month (Farid et al. 2007). A larger follow-up study showed that the femtosecond laser generated "zigzag"–shaped incision results in a more rapid recovery of BSCVA and induces less astigmatism as compared to conventional blade trephination PKP with 81 % of the "zigzag" group versus 45 % of the conventional Barron suction trephination group achieved BSCVA of ≥20/40 by postoperative month 3 in patients with good visual potential (Farid et al. 2009). In addition, Chamberlain et al. compared 50 patients with "zigzag" FLEK to 50 patients with conventional PKP and reported statistically significant improvement in astigmatism in the FLEK group in the first 6 postoperative months and earlier suture removal in the FLEK group, however, without significantly improved BCSVA (Chamberlain et al. 2011). The low levels of astigmatism is proving to be stable even after all sutures are removed up to 5 years after the procedure (Wade et al. unpublished data, ASCRS annual meeting abstract 2013). In patients with keratoconus, Gaster et al. found that patients treated with "zigzag" FLEK achieved better BCSVA, lower topographic astigmatism, and earlier suture removal at all time points than patients treated with conventional PKP, but this was only statistically significant at 3 and not at the 6 month end point of the study (Gaster et al. 2012).

In a non-randomized study comparing "top-hat" configuration FLEK with manual trephinated top-hat PKP, Bahar et al. showed that femtosecond "top-hat" PKPs had higher endothelial cell counts and underwent faster suture removal times compared to manual "top-hat" trephination PKPs. Further, the "top-hat" FLEK group had less astigmatism and better BSCVA in comparison to the manual "top-hat" PKPs after 12 months of follow-up (Bahar et al. 2009).

Of note, Chamberlain et al. reported statistically greater posterior surface HOAs in DSAEK than FLEK or PKP, although the differences in anterior surface higher-order aberrations among the full-thickness grafts were not statistically significant but showed a trend of lower HOAs in the FLEK group (Chamberlain et al. 2012).

Traditional penetrating keratoplasty has certainly shown its great efficacy over the last decades. Nonetheless, FLEK continues to prove to be as effective or perhaps advantageous procedure. Studies continue to show that FLEK results in excellent visual acuity and reduced astigmatism which are comparable or improve on conventional trephination PK (Steinert et al. 2007; Farid et al. 2007, 2009; Buratto and Böhm 2007; Price and Price 2008; Cheng et al. 2008b; Bahar et al. 2009; Tan and Heng 2013; Birnbaum et al. 2013; Mootha et al. 2011).

10.6.2 Femtosecond Laser-Enabled Lamellar Keratoplasty

Just as the FS laser has revolutionized penetrating keratoplasty, the FS laser is being used to facilitate lamellar keratoplasty including deep anterior lamellar keratoplasty (DALK), anterior lamellar keratoplasty (ALK), and Descemet's stripping automated endothelial keratoplasty (DSAEK). As the laser platforms improve, the complexity and reliability of stromal cuts continue to improve. Interestingly, when donor tissue is processed for DSAEK, manual trephination may currently be superior to using the femtosecond laser alone or when utilizing a combination of both manual and laser technique (Rosa et al. 2013; Vetter et al. 2013; Murta et al. 2013; Mootha et al. 2011; Farid and Steinert 2009). Nonetheless, as femtosecond technology adapts to endothelial keratoplasties, the femtosecond platform continues to hold great promise with these types of transplants.

10.6.3 Deep Anterior Lamellar Keratoplasty

DALK is the ideal procedure for ectatic diseases of the cornea in which the endothelium is normal, such as keratoconus. Farid and Price independently first described the "zigzag" DALK (Farid and Steinert 2009; Price et al. 2009). The "zigzag" FS laser incision is combined with the big-bubble technique to aid in baring of Descemet's membrane from the rest of the corneal stroma and perform a deep anterior lamellar transplant, combined with the FS laser incision benefits. The posterior cut begins at a depth of 50–100 μm anterior to the endothelium and defines a starting point for needle insertion and big-bubble dissection. In the event of Descemet's rupture during dissection, conversion to a full-thickness transplant can be done while maintaining the benefits of the femtosecond laser incision (Price et al. 2009; Buzzonetti et al. 2010a). An alternate application using the femtosecond laser was described by Buzzonetti et al. (2012). In this technique, a channel to the posterior stroma, 50 μm above the endothelium, can be created using the FS laser. A blunt cannula can then be passed through the channel, minimizing risk of Descemet's perforation, to facilitate big-bubble dissection at the proper corneal plane (Buzzonetti et al. 2012). FS DALK, although a novel technique, is beginning to prove to be an efficacious for treating stromal pathologies providing promising visual acuity and astigmatic postoperative outcomes (Price et al. 2009; Buzzonetti et al. 2010a, 2012; Cheng et al. 2008b; Shehadeh-Mashor et al. 2013; Yoo et al. 2008).

10.6.4 Anterior Lamellar Keratoplasty

ALK is useful for anterior pathologies of the cornea, such as corneal scars. Sutureless techniques for femtosecond laser-assisted anterior lamellar keratoplasty to create smooth lamellar dissections show a mean gain of 3.8 lines of CDVA postoperatively, as reported by Yoo et al. (2008). In their follow-up study of 13 patients ranging in time from 12 to 69 months, Shousha et al. reported no significant difference in astigmatism or spherical equivalent following sutureless FS-assisted ALK compared to preoperative values at the 1 year follow-up period (Shousha et al. 2011). In these studies, ALK depth was determined via anterior segment OCT and allowing for a 10–20 % additional thickness depending on donor tissue quality and edema. The utility of the femtosecond laser in ALK depends on the ability of the laser to focus precisely and create smooth cuts in the deeper stroma. The laser parameters for lamellar cuts in the anterior stroma (e.g., LASIK) are certainly different than those needed for cuts in deeper stroma. As laser-assisted ALK techniques improve, more studies will help determine parameters that will allow reproducible and smooth cuts.

10.6.5 Endothelial Keratoplasty

Endothelial keratoplasties have allowed the selective replacement of unhealthy endothelial

tissue, while preserving healthy stromal layers, thereby decreasing rejection rates and rapidly improving visual function in some diseases (i.e., Fuch's dystrophy). The use of FS laser for endothelial keratoplasty has been more problematic as high rates of graft dislocation and loss of endothelial cells when the femtosecond laser was used to prepare the endothelial graft tissue (Cheng et al. 2008a, 2009). Cheng et al. randomized a group of 80 eyes with endothelial disease to FS laser endothelial keratoplasty versus conventional PKP. The femtosecond laser endothelial keratoplasty group had significantly less postoperative astigmatism. However, the postoperative BSCVA was significantly lower in the femtosecond laser group (Cheng et al. 2008a). Currently, however, the femtosecond laser is utilized only on the donor tissue, while the host endothelium is manually removed.

Several potential problems may arise from current techniques utilizing FS technology for endothelial keratoplasty. First, keratoplasty using the femtosecond laser usually starts cuts from deep to superficial layers. This allows for sharp focusing of the laser energy without interference of the resulting cavitation bubbles. Endothelial graft harvesting requires deep cuts in a single plane; cavitation bubbles have little room to escape and may interfere with laser precision. Further, the manual stripping of the host endothelium does not provide a "laser cut" match that mirrors the donor graft. This mismatch may have poor good host-graft interface apposition, resulting in easier slipping of the graft. Future protocols may provide better donor harvesting and host tissue preparation which may indeed help increase the success rate of femtosecond endothelial keratoplasty.

10.6.6 Pediatric Keratoplasty

Pediatric corneal transplantation has proven difficult secondary to factors such as a more robust host immune response and difficulty with cooperation for suture removal. Further, the fact that astigmatism or corneal edema may result in amblyopia has prevented the wide spread use of conventional keratoplasty techniques. FLEK applications in the treatment of a variety of pediatric corneal pathologies is expanding and potentially holds great promise for children otherwise visually impaired from corneal disease. Several case reports exist with the very first application described by Agarwal and his group. Agarwal describes a case of a 6-year old who successfully underwent femtosecond-assisted anterior lamellar keratoplasty (FS-ALK) for atypical Avellino corneal dystrophy in 2009 (Agarwal et al. 2009). Buzzonetti et al. (2010b) reported a case of a 14-year-old boy who underwent FS-ALK for the management of keratoconus. At our institution, the Gavin Herbert Eye Institute, University of California, Irvine, a 4-year-old child with a traumatic central stromal corneal scar due to a preceding Aspergillus corneal infection and visual acuity limited to counting fingers underwent an uneventful FS-assisted DALK in mid-2011. No intra or post-operative complications were noted in any of the cases to date. FS-assisted DALK holds numerous potential advantages over full-thickness PK in children. Since the eye is never penetrated during the surgery, intraoperative risks of positive pressure, vitreous loss, and suprachoroidal hemorrhage are greatly reduced. Elimination of the risk of endothelial (but not stromal) rejection allows earlier reduction of topical steroids. Furthermore, the shaped trephination pattern allows better wound integrity and apposition, less astigmatic induction, and earlier recovery of potential vision – all of which are essential to preventing postoperative amblyopia.

10.6.7 Post-keratoplasty Management

In general, the post-keratoplasty course is similar in both conventional and femtosecond laser keratoplasty. There are, however, a few differences. Healing post-femtosecond laser keratoplasty can be different that conventional keratoplasty. Given the multifaceted interface, healing is generally quicker and more vigorous. This rapid healing allows for early suture adjustment when a running suture is utilized.

Additionally, as shown in Fig. 10.5, the tissue alignment in FLEK is excellent – translating into a smoother anterior curvature, allowing for lower levels of regular astigmatism. The combination of a stronger wound and lower levels of astigmatism allows for suture removal at an earlier stage (Steinert et al. 2007; Farid et al. 2007, 2009; Buratto and Böhm 2007; Chamberlain et al. 2011).

10.7 Femtosecond Incisions for Correction of Post-keratoplastic Astigmatism

A more recent application of femtosecond lasers in keratoplasty is to treat post-keratoplasty and preexisting or post-cataract surgery astigmatism with either intrastromal or penetrating relaxing incisions. The femtosecond platform offers great reproducibility and accuracy for intrastromal incisions and has been comparable to manual techniques (Wetterstrand et al. 2013; Buzzonetti et al. 2009; Nubile et al. 2009; Kumar et al. 2010; Harissi-Dagher and Azar 2008). One excellent advantage of the femtosecond laser is that incisions may be made without penetrating the epithelium, Bowman's/Descemet's membranes, or endothelium, allowing for quick recovery with low complication rates. A recent series by Wetterstrand et al. (2013) found excellent correction of post-PK astigmatism via intrastromal relaxing incisions. Other studies have also found excellent reduction of post-PK astigmatism, although with incisions that violate the epithelium or Bowman's layer (Harissi-Dagher and Azar 2008; Rückl et al. 2013). Rückl et al. compares arcuate keratectomies (AK) preformed by either femtosecond laser or Hanna keratome. Although there was no statistical significance in reduction of astigmatism or improvement of visual acuity, there is the potential for lower complication rate and better precision with femtosecond AK (Rückl et al. 2013). Future studies will certainly improve on femtosecond astigmatic incision nomograms and surely improve both their efficacy and safety.

Conclusions

Over the last century, corneal transplant surgery has evolved to become the most successful transplantation technique. Corneal surgeons continue to innovate and impressively advance their field. The advent and adaptation of the femtosecond laser into corneal surgery is surely to continue this tradition. As the laser platforms continue to adapt and improve, femtosecond laser-enabled keratoplasty techniques will surely have a seminal role in corneal transplantation. Nonetheless, the corneal surgeon, enabled by many tools and a relentless drive for innovation and excellence, remains the cornerstone of successful keratoplasty.

Compliance with Ethical Requirements Informed consent and animal studies disclosures are not applicable to this review.

Conflict of Interest

Drs. Farid, Garg, and Steinert are consultants to Abbott Medical Optics.

Drs. Echegoyen and Wade declare that they have no conflict of interest.

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Eye Banking: What the Eye Bank Can Do for You Now

11

Marian S. Macsai, Ashiyana Nariani, and Cynthia Reed

Corneal surgeons and their local eye banks have a symbiotic relationship (Lee et al. 2013). Corneal surgeons cannot operate without their local eye banks, and eye banks would not exist without corneal surgeons. They both have the same purpose: to provide safe and effective tissue for patients in order to restore vision and eliminate corneal blindness. Over the past two decades, eye banks in the United States have been able to meet the needs of both surgeons and their patients allowing for scheduled surgery. As cornea transplant surgery has evolved, surgeons have come to expect the availability of corneal tissue when their patient needs a transplant. Transplanting only specific layers of the cornea requires surgeons to either prepare their own tissue in the operating room, risking tissue wastage/cancelled surgery, or order precut tissue from the eye bank. The availability of corneal tissue, particularly tissue that is prepared according to surgeon instructions, has created the perception that corneal tissue is a commodity. However, the fact that corneal tissue availability depends on the generosity of a person or family places it in the category of a precious gift, not a manufactured item, like the intraocular lens that is ordered off the shelf. In fact, with the evolution of corneal surgery to partial-thickness corneal transplantation, corneal surgery now begins in the eye bank with pre-cutting or preparation of the donor cornea for a specific procedure. In Descemet's stripping automated endothelial keratoplasty (DSAEK) or Descemet's membrane automated endothelial keratoplasty (DMAEK), the eye bank technician not only harvests the tissue, he or she cuts the tissue to a predetermined thickness, and may even load the tissue into a delivery system prior to shipping. As a result of these revolutionary changes to cornea surgery and tissue preparation in the eye bank, surgeon involvement, guidance, and partnership with the eye bank are more important than ever to achieve successful sight restoration for patients.

Physicians in the United States began performing corneal transplants in the 1930s, 25 years after Viennese ophthalmologist Dr. Eduard Zirm performed the first corneal transplant. In 1905, Dr Zirm saw a day laborer from a small town in the Czech Republic who had been blinded in both eyes a year earlier while slaking lime. Around the same time, an 11-year-old boy was brought to Zirm's clinic due to an accident that embedded metal in one eye. When attempts to save the boy's eye were unsuccessful, Zirm

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enucleated the eye and transplanted two 5 mm punches from the young boy's cornea into the day laborer, who was later able to return to work after restoration of his vision (Bock 1958).

When physicians in the United States began performing corneal transplants, each physician procured eye tissue for their own patients. For example, New York City ophthalmologist Dr. R. Townley Paton was able to obtain eye tissue from nearby Sing-Sing prison. At the time, Dr. Paton would harvest the donor tissue from prisoners immediately after their execution (Paton 1970). Dr. Paton saw the need for organized community-based eye banks to supply safe, quality corneas for transplantation, and the first eye bank in New York was established in 1944. As more surgeons were trained in other areas of the country, surgeons developed eye banks to provide eye tissue for corneal surgery. In the 1950s, a partnership between ophthalmologists and ham radio operators created the first cornea recovery and distribution system, called Eye Net. To transport tissue beyond the local donation area, a ham radio operator designed a container to keep donated eyes preserved (Paton 1970). Physicians partnering with others to create innovations has dramatically impacted the progression of corneal transplantation and continues to drive inovation today.

By 1961 a team of ophthalmologists and ten eye banks established the Eye Bank Association of America (EBAA) to promote medical standards, exchange information, and undertake legislative action. The Eye Bank for Sight Restoration (New York), the Iowa Lions Eye Bank, Buffalo Eye Bank (New York), Eye Foundation of Delaware Valley (Pennsylvania, New Jersey and Delaware), Lions of District 22-C of Washington, DC, North Carolina Eye Bank, Hawaii Eye Bank, Southern Eye Bank (Louisiana), and the Rochester Eye Bank (New York) were the founding members (Fanko-Gazzari 1991). Today, there are 78 eye banks in the United States (including Puerto Rico) accredited by the Eye Bank Association of America (EBAA) as well as a handful of unaccredited or for-profit organizations who perform one or more of the functions of an eye bank. The EBAA accredits not-for-profit eye banks that meet the EBAA medical standards (EBAA 2013), which cover governance, personnel training/competency, facilities, donor eligibility, recovery, processing, evaluation, quality assurance, and distribution. This structure and process is designed to ensure that corneal tissue provided for surgery is both safe and effective with the best chance of restoring sight. The EBAA is the nationally recognized accrediting body for eye banks and provides a team of professionals with extensive experience in eye banking and/or corneal transplantation to conduct site inspections of eye banks to evaluate adherence to EBAA Medical Standards at least every 3 years. EBAA accreditation meets or exceeds most state and national regulations and encourages public confidence in eye banking.

Table 11.1 Eye Bank Association of American Medical Standards (EBAA) Eye Donor Testing Requirements

Anti-HIV-1, anti-HIV-2 (or combination test)
Hepatitis B surface antigen (HBsAG)
Anti-HCV

The results of the following EBAA required testing be negative or nonreactive for the tissue to be acceptable

Donated eye tissue is unique from other donated body parts due to the limited time frame of tissue viability from death of a potential donor to transplantation. Eye banks have only a few days to get tissue into the hands of a surgeon when a cold preservation method is used. Once an eye bank is notified of a death, they have around 18–24 hours to screen the potential donor, interview the donor family, obtain consent, get a blood sample, and place the donated tissue in preservation media. The eye bank then proceeds to test the donor blood for HIV I/II, hepatitis B and C as well as syphilis (Table 11.1), evaluate the corneal tissue for defects, perform an endothelial cell count, and offer the tissue to surgeons. The eye bank reviews the medical history and cause of death to ensure the donor cornea meets the criteria for donation of the EBAA (Table 11.2) and to determine which procedure the donor tissue is appropriate for (Table 11.3). Surgeons accept the tissue for a specific patient and define the parameters for any additional processing of the tissue for the surgery, such as endothelial

Table 11.2 Eye Bank Association of American Medical Standards (EBAA) contraindications for all ocular donors

All ocular donors[a]
1. Death of unknown cause and there is likelihood of other exclusionary criteria
2. Congenital rubella
3. Reyes syndrome within the past 3 months
4. Active viral encephalitis of unknown origin or progressive encephalopathy (e.g., subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, etc.)
5. Active bacterial or viral meningitis
6. Active bacterial or fungal endocarditis
7. Suspected rabies and persons who, within the past 6 months, were bitten by an animal suspected to be infected with rabies
8. Down syndrome—exclusive for penetrating keratoplasty or anterior lamellar keratoplasty
9. Intrinsic eye disease: retinoblastoma, malignant tumors of the anterior ocular segment or known adenocarcinoma in the eye of primary or metastatic origin, active ocular or intraocular inflammation,[b] or congenital or acquired disorders of the eye that would preclude a successful outcome for intended use[c]
10. Leukemias
11. Active disseminated lymphomas

[a]Tissues from persons with the following are potentially health threatening for the recipient(s) or pose a risk to the success of the surgery and shall not be offered for surgical purposes
[b]Conjunctivitis, keratosis, scleritis, iritis, uveitis, choroiditis, and retinitis
[c]Examples include a central donor corneal scar for an intended penetrating keratoplasty, keratoconus, and keratoglobus

Table 11.3 Eye Bank Association of American Medical Standards (EBAA) contraindications and criteria for specific procedures

Donors for penetrating keratoplasty (PK)
1. Prior intraocular anterior segment surgery Refractive corneal procedures, e.g., radial keratotomy, lamellar inserts, etc. Laser photoablation surgery (these corneas may be used for tectonic grafting and posterior lamellar procedures) Corneas from patients with anterior segment (e.g., cataract, intraocular lens, glaucoma filtration surgery) may be used if screened by specular microscopy and meet the eye bank's endothelial standards
2. Pterygia or other superficial disorders of the conjunctiva or corneal surface involving the central optical area of the corneal button
Donors for anterior lamellar keratoplasty procedures or tectonic grafts
Criteria same as for PK, except that tissue with local eye disease affecting the corneal endothelium or previous ocular surgery that does not compromise the corneal stroma (e.g., donors with a history of endothelial dystrophy or iritis are acceptable)
Donors for epikeratoplasty procedures
Criteria same as for PK, except that tissue with local eye disease affecting the corneal endothelium (e.g., donors with a history of endothelial dystrophy or iritis are acceptable). Death to preservation time may be extended
Donors for endothelial keratoplasty procedures
Criteria same as for PK, except that tissue with noninfectious anterior pathology that does not affect the posterior stroma and endothelium is acceptable. Surgeons must be notified of any prior pathology prior to placing the tissue for transplant
Scleral tissue donors
Criteria same as for PK, except that tissue with local eye disease affecting the cornea is acceptable for use. Death to preservation time may be extended

keratoplasty. If additional processing is needed, then another day or two is required to accomplish those tasks and ship the tissue to the surgeon. Most of the transplants in the United States utilize tissue within 4–6 days from the date of the donors' death, even though corneas in current preservation media are stable for 14 days. The Corneal Preservation Time Study is a

multi-centered randomized prospective trial funded by the National Eye Institute, the EBAA, and the Cornea Society to determine the safety and efficacy of tissue stored for 1 week versus 2 weeks prior to DSAEK. For any eye bank, international placement of tissue results in decreased reimbursement, and this inevitably does not cover the cost of tissue recovery and processing. With ten million corneal blind worldwide, there is a great need for corneas (Whitcher et al. 2001); however, the need would be greater both at home and abroad if eye banks could not economically meet their mission.

Corneal tissue for use of keratolimbal allograft transplantation (KLAL) for severe ocular surface disease (OSD) was described by Holland (1996), who worked with the Minnesota Lions Eye Bank to develop tissue recovery and preparation techniques. These recommendations for tissue procurement and preparation by eye banks were published in 1999, making this advanced surgical technique widely available to surgeons and patients alike (Croasdale et al. 1999).

Full-thickness corneal transplants have been restoring sight for over 100 years (Barraquer 1966). Issues with full-thickness transplants include astigmatism, hyperopic shifts, myopia, suture-induced infection, and loss of the eye from late suture-induced endophthalmitis (Thomas and Purnell 1965). Full thickness cornea transplant wounds can be weak and subject to rupture, even years after the original surgery (Steinberg et al. 2012). The hope of better visual outcomes and a more stable cornea wound led surgeons to investigate replacing only the diseased endothelium of the cornea. Melles, then Terry, showed improved patient outcomes through endothelial keratoplasty (EK) transplants using only the internal 80–200 μm of the cornea, typically prepared by the surgeon during surgery (Melles et al. 1998; Terry 2003). Motivated by the stability of the eye and superior outcomes, surgeons found through endothelial keratoplasty that they could restore and improve more stable vision to patients within 3 months. Surgeons initially prepared their own deep lamellar grafts and evolved to prepare the grafts with a microkeratome (Price and Price 2006). The steep learning curve of graft preparation resulted in perforated and discarded corneas (Glasser 2010). While visual improvement was good news for patients, eye banks could not keep up with the increasing demand and were under more pressure to increase donors to increase available tissue. In 2005, surgeons across the country began to consider the possibility of eye banks preparing their EK grafts, and there was debate for or against non-surgeons doing this technical procedure. However, due to the steep learning curve in preparing the graft, the cost to patients/surgical centers of wasted tissue and the lack of availability of multiple corneas for single surgeries, surgeons were open to the idea of a trained technician taking a cornea that might be 450–550 μm thick and preparing a graft bed of 80–200 μm utilizing a microkeratome. That year, the North Carolina Eye Bank conducted a study demonstrating that eye bank preparation of these grafts did not cause damage to the endothelium (North Carolina Eye Bank 2005).

Although controversial, the advantages of eye bank–prepared tissue began to outweigh the disadvantages. In a retrospective study done at the University of Iowa, eye bank preparation of the tissue saved approximately 25 min of operating room time for the surgeon, the patient, and the surgical facility, as well as reduced the rate of primary graft failure, and improved visual acuity. The study concluded that "Pre-cut donor lenticules are safe and improve OR efficiency" (Silvera et al. 2006). One major advantage was that the surgeon and patient received a graft that was ready to transplant—and the risk of perforation of the cornea was transferred to the eye bank instead of the surgeon. A survey of surgeon satisfaction with precut cornea tissue, conducted by the Iowa Lions Eye Bank in 2006–2007, documented 98 % surgeon satisfaction with eye bank precut tissue. Today, there are some graft preparation eye bank technicians who have prepared thousands of EK grafts, far more than any surgeon could hope to achieve in the same time frame (Kitzmann et al. 2008).

As EK surgery and the request for eye bank–prepared cornea grafts continued to grow, the shortage of corneas also increased, and eye banks began telling surgeons they had no tissue.

Not wanting to return to the days of a surgery waiting list, in 2007 about 40 % of US eye banks joined forces through the EBAA's Cornea Collaborative, a 3-year effort to improve eye banking and, hopefully, improve the cornea supply. Parallel to this effort, a group called "Donate Life America" was working hard to increase organ donation by establishing state registries where people could legally designate their donation wishes before they died. Both the Cornea Collaborative and the Donate Life America efforts have been successful. By 2009 there was no shortage of corneal tissue, and by 2013, with more than 104 million registered donors, Donate Life America continues to promote donation to difficult-to-reach segments of the population (Donate Life America 2013).

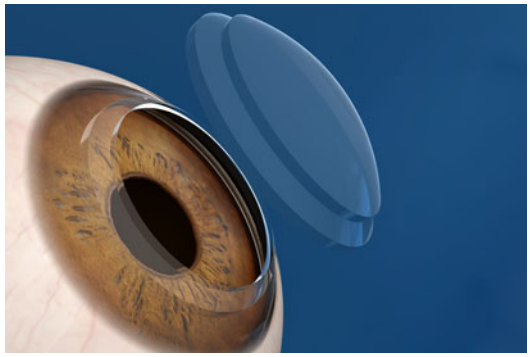

Fig. 11.1 Top hat configuration for femtosecond laser-assisted keratoplasty (Reprinted with permission from Abbot Medical Optics)

With the growth in endothelial keratoplasty, surgeons continued to look for ways to bring improved sight to a greater proportion of their patients. The femtosecond laser had been reliably used in LASIK surgery for years and was adapted to reshape corneal edges in full-thickness transplant surgery. Traditionally, corneal incisions are made with round metal trephines, creating a perpendicular wound. With the femtosecond laser, special-shaped overlapping edges could be created in the patient and the corneal graft. The advantage is a tighter fit of the graft in the eye with fewer sutures required. There are three primary shapes being used: the top hat (Fig. 11.1), mushroom (Fig. 11.2), and the zigzag (Fig. 11.3).

This procedure, termed femtosecond laser assisted keratoplasty (FLAK), interlase-assisted keratoplasty (IEK), or femtosecond assisted keratoplasty (FAK) may improve wound integrity and requires that the surgeon and the eye bank use exactly the same cutting parameters on both the donor and recipient tissue (Ignacio et al. 2006; Baradaran-Rafii and Eslani 2013). Use of this technique requires both the surgeon and the eye bank to have access to a femtosecond laser that has been adapted for this type of surgical procedure. Typically, femtosecond lasers used for LASIK must be modified to cut tissue as deep as is required to prepare the patient and the graft for this type of surgery. Today, there are less than a half dozen eye banks that have the equipment required to prepare this graft, and research has

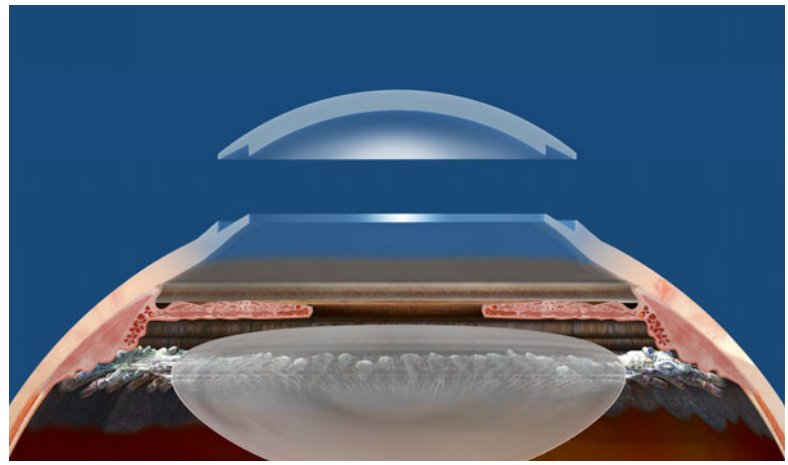

Fig. 11.2 Mushroom configuration for femtosecond laser-assisted keratoplasty (Reprinted with permission from Abbot Medical Optics)

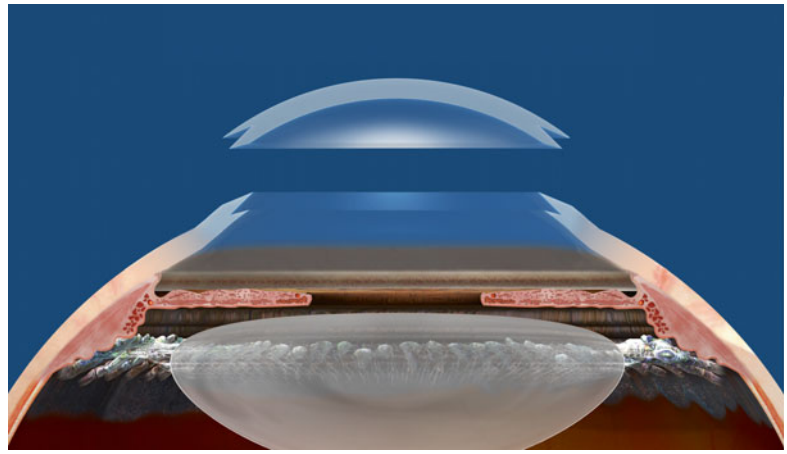

Fig. 11.3 Zigzag configuration for femtosecond laser-assisted keratoplasty (Reprinted with permission from Abbot Medical Optics)

not yet verified the superiority of this graft over a traditional PK (Bahar et al. 2009).

The most recent advancement in the evolution of corneal transplant surgery has been Descemet's membrane endothelial keratoplasty (DMEK). This procedure, including graft preparation, was developed in the Netherlands (Melles et al. 2006), but promptly adopted in the United States due to patients achieving superior visual outcomes in shorter periods of time. Initial graft preparation required that the Descemet's membrane be separated from the cornea, which is very difficult, and if the tissue tears, the graft is unusable. However, initial outcomes research showing that 75 % of patients attained 20/40 vision or better within a few weeks of surgery was very encouraging (McCAuley et al. 2009; Price et al. 2009). Surgeons all over the world have been working to replicate and improve these results, and eye banks are developing reliable, consistent graft preparation techniques for these very thin grafts. So far, the Submerged Cornea Using Backgrounds Away or SCUBA (Geibel 2010), big bubble technique, a double pass technique (Busin et al. 2012), and a femtosecond laser technique (Iowa Lions Eye Bank) are being developed and studied. Lie et al. described Descemet's grafts that could be surgically prepared from organ-cultured donor corneas and stored for an additional 3 weeks with acceptable endothelial cell loss (Lie et al. 2008). Studeny described a novel technique for the preparation and transplantation of posterior corneal lamellae consisting of endothelium and bare Descemet's membrane with a stromal supporting rim (DMEK-S) (Studeny et al. 2010). Recently both Murain et al. and Schlötzer-Schrehardt et al. have described reproducible techniques for DMEK tissue preparations that can be utilized by eye bank technicians (Schlötzer-Schrehardt et al. 2013; Muraine et al. 2013). Eye bank preparation of DMEK grafts saves surgeon time and eliminates the risk of tissue wastage in the operating room.

All U.S. eye banks today are registered with and regulated by the Food and Drug Administration (FDA 2007). Regulation of eye tissue in the United States was not a focus for the FDA prior to the 1990s, when two transplantation events not involving eye tissue commanded the FDA's attention: First, AIDS-infected transplanted body parts resulted in disease transmission and ultimately death of three patients in 1991. Around the same time, the FDA received reports of tainted foreign tissue being imported into the United States without adequate testing and screening. In response to these serious problems, the FDA promulgated its 1993 interim rule on human tissue intended for transplantation to prevent the introduction, transmission, or spread of communicable diseases through transplantation. They required serological testing (FDA 2007) for HIV and hepatitis, banned imports from other countries unless all FDA requirements were met, and outlined criteria for donor selection. They also included provisions to inspect any establishment at any time and ways

to prosecute those that might not allow FDA inspection. Even though ocular tissues were not the problem, they were included as a conventional banked tissue, along with skin and bone.

The goal of the FDA is zero risk of disease transmission. In reality, due to limitations on the specificity and sensitivity of testing currently available for transmissible diseases, such as HIV I/II, hepatitis B, hepatitis C, prion disease, etc., there is no transplant that is risk free. Despite extensive precautions in donor screening, the theoretical risk of disease transmission will always exist. The criteria for donor exclusion (Tables 11.2 and 11.3) are reviewed on a biannual basis by the EBAA's Medical Advisory Board. When an eye bank encounters a situation that is not clearly delineated by the EBAA Medical Standards or the FDA, the eye bank medical director will often contact the Medical Advisory Board for guidance. These uncommon cases are discussed at the Medical Advisory Board to determine if the criteria for exclusion of donors in the Medical Standards require revision. As new information becomes available, criteria are evaluated and incorporated into existing practice to meet these requirements.

Despite all precautions, adverse reactions occur in all fields of transplantation. In corneal transplantation disease transmission, local or systemic, as well as graft failure, are considered serious adverse reactions. In May 2010, the WHO passed resolution WHA 63.22 The Guiding Principles on Human Organ Transplantation: "(7) to collaborate in collecting data including adverse events and reactions on the practices, safety, quality, efficacy, epidemiology and ethics of donation and transplantation" (Dubord et al. 2013). This has resulted in the development of a free public online library: www.notifylibrary.org. Through this online library, surgeons and patients can sort the currently published literature on adverse events and reactions, and it is intended as a communication hub for institutions and organizations worldwide collaborating in the facilitation of access to vigilance and surveillance information.

Regardless of the etiology, an adverse reaction creates concern for the surgeon and eye bank alike. As a transplanting surgeon, when a patient presents with an adverse reaction, the initial focus is on the patient. This may involve culturing an infection to identify the offending organism, determining the source of graft failure, or evaluating the recipient for possible systemic disease. In each of these situations, the eye bank can play a pivotal role in aiding the surgeon. In the case of a localized infectious process, the eye bank may have data of the mated tissue that will influence the treatment course. For example, if a patient presents in the early postoperative period with an interface infiltrate, and the surgeon discovers from the eye bank that the mated tissue post-transplantation culture was positive for a candida organism, the surgeon may choose to use an antifungal agent prior to receiving the culture results which may take several days to weeks, thereby increasing the chances of recovery by early intervention (Rauen et al. 2012). In any adverse reaction, the eye bank is a resource for the transplanting surgeon. While the surgeon may have never encountered an adverse event due to the rarity of their occurrence, the eye bank and the medical director will likely have more experience in handling the specific adverse reaction. If necessary, the eye bank can contact the EBAA, which will help both the surgeon as well as the eye bank in managing the adverse reaction. In rare situations, this may involve utilizing the services of the CDC and the FDA. The surgeon must report all adverse reactions to their local eye bank. The eye bank will then undertake an investigation and report the findings to the Medical Advisory Board through the Online Adverse Reaction Reporting System (OARRS). Often the eye bank investigation will involve the transplanting surgeon, providing information and support for both the surgeon and the patient involved.

Eye bank corneas are used for a variety of surgeries beyond cornea transplantation. Corneas that do not meet the cell count requirements or have other imperfections are used for glaucoma shunt patch grafts, Boston Keratoprosthesis device placement, and tectonic grafts. The eye bank can also assist a surgeon with difficult cases either with special preparation of tissue or by

providing practice tissue to learn new techniques. It is important for surgeons to stay in communication with their local eye bank as they develop new skills and surgical techniques. The eye bank can help in the advancement of surgical skills, and some eye banks have facilities that can be used for practice, training and research. As technology advances, the eye bank can assist a surgeon not only through practice tissue and space but also by sharing their insights as to the qualities and behavior of the tissue. Eye banks work with tissue every day and have become skilled in offering perspectives that can assist surgeons in best utilizing the tissue.

Eye banks can also offer resources that surgeons may be unable to get elsewhere, and through cooperation, difficult patient care issues may be addressed. One example of a surgeon partnering with an eye bank is in the provision of autologous serum eye drops, or ASED. After exhausting other options, the surgeon felt that ASED was the only hope for saving sight in a handful of patients since serum harbors nerve growth factors, neurotransmitters, and neurotrophic and epithelium-maintaining factors. ASED drops can provide nourishment for the eye in a way that is otherwise unavailable from the body. Due to anticipated low volume, the surgeon was unable to convince either the local blood bank or pharmacy to manufacture ASED. After learning of the situation, the eye bank offered to investigate options to see if they could assist. A thorough investigation of regulations (including interstate commerce laws) revealed that the eye bank could make ASED for patients within their own state, but serum could not be shipped beyond state lines. The cost for this service was set at a point where the eye bank could cover their costs and patients could afford the drops. Today, that eye bank makes drops for more than 75 patients per year. Since that time, half a dozen eye banks have also begun preparing these eye drops at surgeons' request for patients with persistent epithelial defect, keratoconjunctivitis sicca, Sjogren's syndrome, Stevens-Johnson syndrome, ocular surface squamous metaplasia, and neurotrophic keratitis (Poon et al. 2001; Tsubota et al. 1999a, b).

Although eye tissue is donated and the federal Uniform Anatomical Gift Act prohibits reimbursement to the family of the donor, there is a cost to making sure tissue is safe for transplant. The cost to procure, evaluate, and distribute corneal tissue, to meet the regulatory requirements and surgeon specifications, is borne by the eye bank. Today, eye bank costs are reimbursed through a combination of tissue reimbursement fees and philanthropy. Tissue fees are paid to the eye bank from the hospital or ambulatory surgery center, who in turn receives their reimbursement for the tissue from third parties (government and private insurance). Approximately one third of U.S. eye banks are sponsored by other organizations such as Lions Clubs and university departments of ophthalmology, receiving "in-kind" services that help defray costs. Most eye banks utilize local philanthropy to fund their community based non-profit organizations.

As part of their mission, a handful of eye banks in the United States request tissue donations for research, education, and training. When a death is called into the eye bank, the decedents are evaluated for transplant and research potential. Some eye banks get consent for research on all donors, while others only if no transplant potential exists. Eye banks then recover whole globes or corneas, depending on the current need. Most research tissue comes from donors outside the eye banks age range for transplant; some research donors are within the transplantable range but for other reasons are considered not suitable for transplant.

Not all eye banks recover tissue for research due to the economics of the reimbursement system. Typically, university-based or larger eye banks will recover tissue for research as their budgets allow and their missions dictate. Researchers may be grant funded and restricted in reimbursing the eye bank for the recovery costs of research tissue. Additionally, eye banks may provide tissue for training, such as when a surgeon needs to practice a new technique, with little or no reimbursement to the eye bank for the expenditures related to the recovery of that tissue. Eye banks are flexible in how research arrangements are structured, with some providing tissue,

some providing space, and one providing a state-of-the-art research facility that physicians or other researchers can utilize to actually conduct short- or long-term studies at the eye bank. This research facility also provides housing for guest researchers and is attached to the eye bank providing easy access to available research tissue. This facility hosts universities, pharmaceutical companies, and other enterprises that need donated eye tissue as a part of their projects.

With the advent of eye bank processing for FLAK, DSAEK or DMAEK, questions have been raised and research conducted jointly by surgeons and eye banks. Three landmark studies regarding the cost savings of precut eye bank tissue (Silvera et al. 2006), physician satisfaction with eye bank precut tissue (Kitzmann et al. 2008), and the safety of eye bank precut tissue (Rauen et al. 2012) were all joint studies between physicians and eye banks. Eye banks are continuing to improve their precut tissue preparations, sharing research and other information regularly with physicians and eye bankers through the EBAA's bi-annual Scientific Session. As new techniques are developed requiring transplantation of thinner and thinner layers of the cornea, eye banks continue to develop and perfect their techniques, learn more about which donors work best for which surgeries, and partner with physicians in the provision of pre-cut tissues.

Despite all evidence to the contrary, some surgeons remain extremely precise about donor parameters prior to accepting tissue from their eye bank. Some surgeons will request tissue from donors under the age of 40 with a cell count of greater than 3,000, with little scientific outcome-based data for this request. Numerous studies from the Cornea Donor Study have failed to substantiate the rationale of these "picky" requests by surgeons (Cornea Donor Study Investigator Group 2008, 2009a). In fact, the Cornea Donor Study has shown us that donor age and preoperative endothelial cell count do not correlate with better graft survival at 5 years. Corneas that met the criteria of the EBAA had excellent graft survival, and the recipient cause for transplantation played a significant role in graft survival with Fuchs corneal dystrophy having a better outcome than pseudophakic or aphakic corneal edema (Cornea Donor Study Investigator Group 2009b). In addition, the impact of such select pre-transplant donor criteria is not only unwarranted, but leads to higher overall costs for corneal transplant tissue (Woodward et al. 2013).

Conclusions

Since 2005, there have been more advances in corneal transplantation and sight restoration than in the last 50 years. Improvements in donor registration, eligibility and suitability determination, preparation of a variety of graft types for transplant, as well as new procedures such as glycerin-preserved corneas for glaucoma shunt grafts and autologous serum eye drops have resulted in more sight restoration procedures than ever before. Surgeons are partners with eye banks to restore sight, and today, eye banks are a critical part of a surgeon's ability to serve patients. As artificial corneas, stem cell growth and genetic tissue engineering advance, eye banking too will continue to morph and change in the future. The unique symbiotic relationship between corneal surgeons and eye banks has in the past and will in the future advance our collective ability to restore vision and eliminate corneal blindness.

Compliance with Ethical Requirements Marian Macsai, Cynthia Reed, and Ashiyana Nariani declare that they have no conflict of interest.
No animal or human studies were carried out by the authors for this article.

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