PREFERRED PRACTICE PATTERN®

Corneal Edema and Opacification

AMERICAN ACADEMY® OF OPHTHALMOLOGY
The Eye M.D. Association

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CORNEA/EXTERNAL DISEASE PREFERRED PRACTICE PATTERN DEVELOPMENT PROCESS AND PARTICIPANTS

The **Cornea/External Disease Preferred Practice Pattern® Panel** members wrote the Corneal Edema and Opacification Preferred Practice Pattern® guidelines ("PPP"). The PPP Panel members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in March 2013. The document was edited in response to the discussion and comments.

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The Corneal Edema and Opacification PPP was then sent for review to additional internal and external groups and individuals in June 2013. All those returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered. Members of the Cornea/External Disease Preferred Practice Pattern Panel reviewed and discussed these comments and determined revisions to the document.

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FINANCIAL DISCLOSURES

In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at www.cmss.org/codeforinteractions.aspx), relevant relationships with industry are listed. The Academy has Relationship with Industry Procedures to comply with the Code (available at http://one.aao.org/CE/PracticeGuidelines/PPP.aspx). A majority (70%) of the members of the Cornea/External Disease Preferred Practice Pattern Panel 2012–2013 had no related financial relationship to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to August 2013 are available online at www.aao.org/ppp.

TABLE OF CONTENTS

OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern® guidelines that **identify characteristics and components of quality eye care.** Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern® guidelines are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

These documents provide guidance for the pattern of practice, not for the care of a particular individual. While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Pattern® guidelines are not medical standards to be adhered to in all individual situations. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved U.S. Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern® guidelines are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the "approved by" date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at http://one.aao.org/CE/PracticeGuidelines/PPP.aspx) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Corneal Edema and Opacification PPP are ophthalmologists.

METHODS AND KEY TO RATINGS

Preferred Practice Pattern® guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization (WHO), the Agency for Healthcare Research and Policy, and the American College of Physicians.[3]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- The Highlighted Findings and Recommendations for Care section lists points determined by the PPP panel to be of particular importance to vision and quality of life outcomes.
- All recommendations for care in this PPP were rated using the system described above. To locate ratings for specific recommendations, see Appendix 3 for additional information.
- Literature searches for the PPP were undertaken in May 2012 and January 2013 in PubMed and the Cochrane Library. Complete details of the literature search are available at www.aao.org/ppp.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

The impact of corneal edema on activities of daily living—particularly those influenced by ambient light levels at home, work, and during leisure activities—is often underappreciated. Standard measurement of visual acuity does not give a true representation of the patient's functional vision. Confluent guttae in the absence of corneal edema may diminish visual function, which may not be correlated with Snellen acuity.

Reduced vision in cases of corneal opacification is more often related to corneal surface irregularity than to the opacity itself. A refraction over a rigid gas-permeable contact lens can be very helpful in determining if visual loss is due to a corneal surface irregularity. It does not distinguish between a stromal opacity or vision loss from a cause unrelated to the cornea.

Endothelial function is best evaluated by slit-lamp examination and may be supported by changes in corneal thickness noted on serial pachymetric measurements performed at the same time of day. Specular microscopy is not a direct measure of endothelial function or functional reserve. When diffuse endothelial guttae are present on slit-lamp biomicroscopy examination, specular microscopy rarely provides any valuable information because it is difficult to image the endothelial cells.

Corneal pachymetry, measured in the morning, is a helpful indicator of the ability of the endothelium to regulate corneal hydration appropriately. Corneas that are abnormally thick in the morning hours may be less able to tolerate proposed intraocular surgery.

If the cataract surgeon or cornea specialist thinks that decompensation, if not imminent, is likely to occur in the near future, a discussion about modifying the intraocular lens (IOL) power calculation is worthwhile to adjust for changes induced by endothelial keratoplasty (specifically a hyperopic shift due to Descemet's stripping automated endothelial keratoplasty [DSAEK]). A full discussion of the added risks of subsequent corneal decompensation is very important in this group of patients. Engaging the patient in the decision-making process related to the timing of surgery and the choice and sequence of surgical procedures is beneficial, and it helps to shape their expectations with respect to their condition and the surgery.

Endothelial keratoplasty has supplanted penetrating keratoplasty as the procedure of choice in cases of endothelial failure in the absence of corneal scarring because patients achieve more rapid visual astigmatism. The dramatically reduced risk of postkeratoplasty astigmatism, suture-related infections, and traumatic wound rupture are further advantages of endothelial keratoplasty. The preferred technique continues to evolve.

INTRODUCTION

DISEASE DEFINITION

Corneal Edema

Corneal edema is the retention of excess fluid within one or multiple layers of the cornea. See Table 1 for the etiology of corneal edema.

TABLE 1 ETIOLOGY OF CORNEAL EDEMA

	Unilateral	Bilateral
Early Onset		
Congenital glaucoma	•	•
Dystrophies:		
Congenital hereditary endothelial dystrophy – autosomal dominant (CHED – AD)		•
Congenital hereditary endothelial dystrophy – autosomal recessive (CHED – AR)		•
Posterior polymorphous corneal dystrophy (PPCD)		•*
Intraocular inflammation	•	•
Trauma:		
Birth	•	
Intrauterine	•	
Late Onset		
Acute angle-closure glaucoma	•	•
Dystrophies:		
Fuchs dystrophy		•
PPCD		•*
Hypotony	•	
Hypoxia		•*
Intraocular inflammation/uveitis	•	•
Irido-corneal-endothelial (ICE) syndrome	•	
Keratitis:		
Infectious	•	
Keratoconus – hydrops	•	
Toxicity:		
Amantadine		•
Cancer chemotherapy[4]		•
Chlorhexidine	•	•
Silicone oil	•	

* Occasionally unilateral.

Corneal Opacification

Corneal opacification results from the presence of additional material (e.g., fluid, scar tissue, inflammatory debris, metabolic byproducts) within one or multiple layers of the cornea that is associated with loss of corneal clarity. Possible causes are as follows:

- Congenital
  - Axenfeld-Rieger anomaly
  - Peters anomaly
  - Sclerocornea
  - Dermoid
  - Leukoma
- Degenerations
  - Calcific band keratopathy
  - Crocodile shagreen
  - Spheroidal degeneration
  - Salzmann nodular degeneration
  - Pterygium
- Dystrophies
  - Epithelial basement membrane dystrophy
  - Reis-Bücklers dystrophy
  - Thiel-Behnke corneal dystrophy
  - Gelatinous drop-like dystrophy
  - Lattice corneal dystrophy
  - Granular corneal dystrophy
  - Macular corneal dystrophy
  - Schnyder corneal dystrophy
  - Congenital hereditary stromal dystrophy
  - Congenital hereditary endothelial dystrophy
  - Posterior polymorphous corneal dystrophy
  - Posterior amorphous corneal dystrophy
  - Fuchs dystrophy
- Inflammatory and immunologic
  - Infection (bacterial, fungal, parasitic, and viral)
  - Interstitial keratitis (non-sterile and sterile)
- Metabolic
  - Mucopolysaccharidosis
  - Mucolipidoses
  - Lipidosis
  - Hypolipoproteinemias
  - Cystinosis
  - Fabry disease

- Depositional
  - Amyloid
  - Cryoglobulinemia/multiple myeloma
  - Drugs
  - Lipid keratopathy
- Neoplastic
  - Conjunctival/corneal intraepithelial neoplasia
  - Melanosis/melanoma

PATIENT POPULATION

The patient population includes individuals of any age who have corneal edema or opacification.

CLINICAL OBJECTIVES

- Assess the degree of vision loss
- Evaluate the degree of functional impairment and its effect on the patient's activities of daily living
- Identify the underlying ocular condition responsible for the corneal edema or opacification
- Assess the potential for progression of the disorder, development of discomfort, and/or improvement of vision
- Determine which optical, medical, or surgical treatment alternatives are most appropriate

BACKGROUND

NATURAL HISTORY OF CORNEAL EDEMA AND OPACIFICATION

Corneal edema and opacification may or may not progress. Conditions that affect primarily the periphery may be subtle and asymptomatic (Brown-McLean syndrome, Salzmann's nodular degeneration), whereas those that involve the central, pupillary region generally cause symptoms (Fuchs dystrophy, scarring secondary to disciform keratitis).

RATIONALE FOR TREATMENT

The reduction or elimination of corneal edema or opacification is indicated when it is associated with functional visual loss or discomfort. Chronic epithelial breakdown associated with underlying stromal or endothelial dysfunction or disease may necessitate intervention to stabilize the ocular surface to prevent further complications. Less commonly, cosmesis is an indication for treatment.

CARE PROCESS

PATIENT OUTCOME CRITERIA

- Reduce the signs and symptoms of corneal edema or opacification
- Maintain, restore, or improve visual function according to the needs of the patient

DIAGNOSIS

Initial evaluation of the patient with symptoms and signs of corneal edema or opacification should include the relevant aspects of the comprehensive medical eye evaluation.[5] The diagnosis of corneal edema or opacification is usually based on a typical patient history and characteristic findings. Ancillary testing may be helpful.

History

Questions about the following elements of the patient history may elicit helpful information:

- Symptoms and signs: blurred or variable vision, often with a diurnal character (worse upon waking and clearer later in the day); photophobia; redness; tearing; intermittent foreign-body sensation; intense, disabling, or task-disrupting pain
- Age of onset: all ages
- Rapidity of onset: acute symptoms versus gradual or fluctuating presentation

  Most conditions associated with edema present gradually over weeks, months, or longer. At times, it may be so gradual that the patient adjusts surprisingly well and is able to function at a much higher level than the slit-lamp biomicroscopic examination might lead one to expect. Exceptions include edema that is due to the following:

  - Elevated intraocular pressure (IOP), often resulting from topical corticosteroid treatment of the underlying corneal disorder
  - Moderate to severe corneal or intraocular inflammation
  - Corneal hydrops associated with keratoconus, other ectatic disorders, and trauma

  Non-infectious corneal opacification (e.g., depositional or scarring disorders) develops more gradually in most cases. Exceptions include acute medication-related band keratopathy[6,7]

  Infectious corneal opacities frequently present acutely.
- Persistence: transient or permanent
  - Inflammatory and pressure-related corneal edema often clears as the underlying problem resolves. Neonatal forceps injury, in which the break in Descemet's membrane eventually heals and the resulting stromal edema resolves, is another example. If sufficient endothelial damage occurs, corneal edema may recur years later.[8]
  - Transient blurred vision upon waking in the morning, on humid days, or after taking a shower can be seen with edema associated with endothelial dysfunction. Vision is often better later in the day due to evaporation, which reduces this edema.
  - Most non-inflammatory corneal opacities are permanent. Inflammatory infiltrates frequently resolve when the underlying cause disappears. Metabolic deposits due to cysteine crystals[9] and, to a lesser degree, mucopolysaccharidosis,[10] may resolve with treatment.
- Unilateral or bilateral presentation (e.g., herpes simplex virus [HSV] keratitis is usually unilateral, whereas corneal dystrophies are typically bilateral)
- Moderating factors or situations
  - Low humidity and modest air movement may lead to visual improvement with endothelial dysfunction.
  - Visual acuity and visual function may not necessarily correlate with one another. For example, a patient with mild edema associated with Fuchs dystrophy or opacification related to granular dystrophy may have visual acuity of 20/40 or better but may not be able to drive because of disabling glare. Unshielded fluorescent lighting or reflections off surfaces with a high luster and computer screens may cause problems with activities of daily living.[11]
  - Contact lenses (particularly rigid gas-permeable [RGP] lenses) may be able to improve visual function by creating a smoother and more regular refractive surface.
- Ocular history
  - Corneal edema:
    - Acute angle-closure or chronic glaucoma
    - Chemical and traumatic injury
    - Infection

    - Inflammation
    - Intraocular or keratorefractive surgery
    - Laser iridotomy
    - Keratoconus
    - Ocular or periocular trauma (blunt or penetrating)
  - Corneal opacification:
    - Chemical, thermal, and traumatic injury
    - Infection
    - Inflammation
    - Intraocular and keratorefractive surgery
- Medical history
  - Corneal edema:
    - Inflammatory conditions associated with uveitis (e.g., sarcoidosis, ankylosing spondylitis)
  - Corneal opacification:
    - Metabolic/hereditary (e.g., mucopolysaccharidosis, cystinosis)
    - Immune-mediated diseases (e.g., rheumatoid arthritis, interstitial keratitis, Stevens-Johnson syndrome, ocular mucous membrane pemphigoid [OMMP])
    - Malabsorption syndromes (e.g., following colon resection, bowel surgery, hepatobiliary illness)
- Topical and systemic medications
  - Corneal edema:
    - Amantadine for neurologic disease may produce a reversible endothelial dysfunction if used for a short period or a permanent problem if used long term[12,13]
    - When used in surgical preparation for facial trauma or reconstructive and cosmetic facial surgery, inadvertent exposure of the cornea to topical chlorhexidine preparation may cause toxicity that predisposes to endothelial failure[14-17]
  - Corneal opacification:
    - Amiodarone[18,19]
    - Dietary calcium supplementation[20]
    - Periocular radiation[21-23]
    - Various chemotherapeutic agents[24-26]
- Trauma: blunt or penetrating injury to the eye or periocular region, forceps delivery, chemical injury
- Contact lens wear: rationale, type of lens, wear time, and cleaning routine
- Family history: patients may be aware of a family history or may relate that a relative had a cloudy cornea; required corneal transplantation; or had repeat episodes of pain, tearing, and photophobia (see Table 2).
- Social history
  - Sun exposure at work (e.g., farming, construction) or leisure activity (e.g., boating, golfing) may be related to pterygium development
  - Travel may increase exposure to unusual infectious agents
  - Exposure to domesticated and non-domesticated animals may increase exposure to unusual infectious agents (e.g., *Brucella*, *Borellia burgdorferi*/Lyme disease)

- Diet or dietary deficiencies (e.g., vitamin A deficiency from malabsorption syndromes) may predispose to nutritional problems
- Chemical exposure (longstanding and new)

TABLE 2 SIGNS AND SYMPTOMS ASSOCIATED WITH SPECIFIC HEREDITARY DISEASES

Signs or Symptoms	Corneal Edema	Corneal Opacification
Abnormal or cloudy cornea	• Fuchs dystrophy[27] • Posterior polymorphous corneal dystrophy[28] • Congenital hereditary endothelial dystrophy[29,30] • Keratoconus	• Reis-Bücklers dystrophy • Granular dystrophy • Macular dystrophy • Schnyder corneal dystrophy • Keratoconus • Other dystrophies (e.g., Meesman's, lattice, gelatinous drop-like) • Mucopolysaccharidoses
Pain	• Fuchs dystrophy[27]	• Epithelial basement membrane dystrophy • Lattice dystrophy • Reis-Bückler's dystrophy • Gelatinous drop-like dystrophy
Poor vision	• Fuchs dystrophy[27] • Posterior polymorphous corneal dystrophy[28] • Congenital hereditary endothelial dystrophy[29,30] • Keratoconus	• Epithelial basement membrane dystrophy • Reis-Bücklers dystrophy • Granular dystrophy • Macular dystrophy • Schnyder corneal dystrophy • Keratoconus • Mucopolysaccharidoses

Examination

A comprehensive examination of the eye and adnexa is necessary to determine the etiology of many cases of corneal edema. Particularly relevant aspects of the examination are described below.

- Visual acuity
  - Comparison of visual acuity measurement and functional status
  - Visual acuity tested with the room lights on and off
- External examination
  - Evidence of proptosis, ptosis, lagophthalmos, or floppy eyelid syndrome
  - Lid or facial asymmetry, scarring, and malfunction (e.g., poor blink or lid closure due to facial palsy)
- Slit-lamp biomicroscopy
  - Unilateral or bilateral signs
  - Diffuse or localized edema
  - Primarily epithelial or stromal edema
  - Evidence of epithelial breakdown, stromal infiltration, epithelial ingrowth, striae, focal thickening, thinning, scarring, interface haze, striae or inflammation, or stromal vascularization
  - Evidence of guttae, Descemet's membrane tear or detachment, endothelial vesicles, KP, pigment peripheral anterior synechiae

- Involvement of host tissue (or donor tissue only), if there is a corneal transplant
- Evidence of sectoral corneal edema and a line of keratic precipitates (as with endotheliitis), or an anterior chamber reaction
- Use of various slit-lamp techniques such as sclerotic scatter, specular reflection, or indirect illumination to evaluate all layers of the cornea
- Status, shape, and position of the pupil and iris
  - Sphincter rupture as evidence of past trauma
  - Irido-corneal adhesions, iris transillumination defects, peripheral anterior synechiae, or posterior synechiae as evidence of past trauma, inflammation, or surgery
  - Evidence of intraocular trauma (non-surgical and surgical)
  - Intraocular lens (IOL) capture
- Evidence of vitreous strands or pigment dusting within the anterior chamber or attached to a previous incision or wound
- Status and position of the lens and any other intraocular device

- IOP
  - Goldmann applanation tonometry is somewhat unreliable in abnormal corneas. Therefore, IOP should be measured with alternative electronic devices, such as a pneumatonometer, applanation tonometer, dynamic contour tonometer, ocular response analyzer, or rebound tonometer.
  - Look for old or new corneo-scleral wounds, surgical sites or devices, and signs of intraocular inflammation.
- Fundus examination
  - Chronic serous choroidal detachment or retinal detachment may lead to hypotony and secondary corneal edema.
  - B-scan ultrasonography may be necessary to assess the posterior segment.
- Gonioscopy
  - Look for retained nuclear fragments, foreign bodies

Diagnostic Evaluation

Observations from the comprehensive eye examination are augmented by various tests.

- Potential acuity meter

  The potential acuity meter projects a tiny eye chart directly onto the macula in an effort to bypass anterior segment pathology (specifically corneal opacities and cataracts). A small "window" is necessary for the image to reach the retina. The test can be helpful when the patient can read farther down on the eye chart than they were able to do in a refracting lane or similar testing situation. This indicates that there is a good chance that vision may improve if the pathologic condition is corrected. A poor result, however, does not necessarily indicate poor visual potential, since the anterior segment pathology may be obstructing the optical pathway or potentially correctable cystoid macular edema may be present. Pinhole vision using an illuminated near card in a darkened room can be used in the same way to assess potential acuity.

- Rigid contact lens over-refraction

  Disruption of the central or paracentral ocular surface due to microcystic edema or scarring can have a surprisingly large impact on vision. These changes may actually have a greater impact than an underlying opacity. The easiest way to differentiate between these two problems is to measure the patient's best-corrected vision with eyeglasses and then with an RGP contact lens. This can be quickly done in the office by obtaining a set of keratometry (K) measurements, determining the average K reading, and then fitting the RGP lens slightly flatter than this

measurement. Over-refraction with spherical lenses is then performed. Mire-pattern irregularity should be specifically noted, because this correlates well with the amount of surface irregularity. Improved vision with the RGP lens but not the eyeglasses suggests that the irregular surface is a major factor in a patient's reduced vision.

- Pachymetry

  The measurement of corneal thickness continues to evolve as new approaches and devices become available. Ultrasonic pachymeters (10 to 20 MHz), utilizing a speed of sound of 1636 to 1640 m/second, typically provide information about a single spot on the cornea (i.e., the central cornea). Their range is often limited to between 200 and 1000 µm. Most probes do not have a fixation light, so results can fluctuate from visit to visit because of positioning rather than progression of the disease. With training and careful positioning and probe angulation (kept at 90º), an interobserver standard deviation of 12 µm and variability of less than 2% can be achieved.[31] When consistency, precise serial comparison, and peripheral measurements are important, optical coherence tomography (OCT) and Scheimpflug imaging may provide greater accuracy. Both technologies, however, use light and lose accuracy and resolution as stromal edema or opacification increases. The ultrasound biomicroscope (50 to 70 MHz probes) provides the most accurate measurements when there is significant stromal edema.

  Measurements taken with different types of device are not directly comparable in clinical practice. Comparisons between different instruments have demonstrated varied results, though most large studies report that anterior segment optical coherence tomography (AS-OCT) measurements of central corneal thickness were systematically lower than ultrasound measurements by between 7 and 26 µm.[32-36]

  The greater availability of ultrasonic pachymetry has resulted in a better appreciation of the wide variability of normal corneal thickness. This has made it harder to predict which corneas might decompensate after anterior segment surgery. The risk of corneal failure following cataract surgery is associated with several factors, including 1) a patient history including glare or blurred morning vision that improves during the day, 2) a cornea that demonstrates microcystic edema, stromal thickening, or confluent guttae by slit-lamp biomicroscopic examination, and/or 3) a cornea that demonstrates low central endothelial cell counts by specular microscopy.

  Intraocular pressure and tonicity of the tear film are factors that influence normal corneal thickness. Gradual thinning of the cornea with age (6 to 10 µm per decade) has been demonstrated as well.[37-39]

- Scheimpflug imaging

  Scheimpflug imaging systems are designed to assess the topographic characteristics of the anterior and posterior corneal surfaces and provide measurements of corneal thickness. The tomographic capability can enable assessment of the depth of the corneal opacification, which can aid in surgical planning. Thickness or pachymetric mapping can also be obtained. While there have been attempts to use Scheimpflug imaging to determine the depth of intrastromal lesions or thickness of lamellar flaps, in most cases, these images did not provide any more information than slit-lamp biomicroscopy.[40]

- Specular microscopy

  This provides information about the density of endothelial cells (cells per mm^2), and the shape (% hexagonality) and uniformity of the cell population. The terms *polymegethism* (variability in cell size) and *pleomorphism* (the lack of uniformity of the cell shape) are often used when describing the specular image. While most specular microscopes can image both central and peripheral areas, unless specifically stated, measurements are of the central and pupillary regions. Because this is a fairly large area, from 28 to 50 mm^2, some comment should be made about the number of fields or percent of the endothelial surface examined. A study showed that sampling greater than 20% of the surface was necessary to provide an accurate representation of the full endothelial surface.[41]

Specular microscopy is of greatest value when it is combined with pachymetry and slit-lamp biomicroscopy. It can be very helpful, though, when following a patient over time; progressive loss of cells, as in a patient with vitreous touch syndrome, may be a finding that pushes one towards surgery, where stabilization of the cell count would encourage a conservative approach. When diffuse, confluent guttae are present on slit-lamp biomicroscopic examination, specular microscopy rarely provides any valuable information because of difficulty imaging the endothelial cells.

- Confocal microscopy

  This non-invasive diagnostic technique allows in vivo, microscopic imaging of the layers of the cornea. Endothelial cells are characterized by a relatively regular hexagonal hyper-reflective shape surrounded by hyporeflective borders. Endothelial cell counts with confocal and specular microscopy are comparable.[42] Whereas specular microscopy is often ineffective in visualizing the endothelium in cases of corneal edema, confocal microscopy is capable of imaging the endothelium in cases of moderate corneal edema. This is particularly helpful when assessing unilateral cases of corneal edema. The irido-corneal-endothelial syndrome, epithelial and fibrous ingrowth, and posterior polymorphous corneal dystrophy have distinctive confocal appearances (of the posterior surface) that may be very helpful in identifying an underlying cause for the decompensation preoperatively.

- Anterior segment optical coherence tomography

  Anterior segment OCT provides high-definition, cross-sectional images of the cornea, angle, and anterior chamber. Two types of instruments are presently available: spectral domain and time domain. Spectral domain instruments have higher resolution but less depth of field. Time domain instruments, which use a longer wavelength of light (1310 nm), are capable of imaging the ciliary body as well, though not with the same clarity as ultrasound biomicroscopy (UBM). Measurement tools to document and follow changes in the cornea thickness, angle, and anterior chamber are standard with all models. Pachymetry mapping is available. Anterior segment OCT can be used to follow changes in corneal thickness; however, its greatest value lies in its ability to image deep and retrocorneal structures. Corneal edema or scarring may be hiding a detached Descemet's membrane or a retrocorneal membrane. A large Descemet's break and central stromal cleft may exist in cases of corneal edema associated with keratoconic hydrops or trauma.

- Ultrasound biomicroscopy

  Ultrasound is capable of providing real-time cross-sectional images of the anterior and posterior segment. Its advantage over light-emitting imaging devices is that it is not impeded by opacities of the cornea, anterior segment, or vitreous. Conventional ultrasound uses a frequency of 10 MHz. Ultrasound biomicroscopy uses much higher frequencies (35 to 80 MHz) that result in a significant improvement in resolution. Ultrasound biomicroscopy systems are suitable for imaging of virtually all anterior segment anatomy and pathology, including the cornea, iridocorneal angle, anterior chamber, iris, ciliary body, and lens. The imaging of a ruptured or dislocated Descemet's membrane, retrocorneal membranes, and irido-corneal and lenticulo-corneal adhesions helps in determining the root causes of an edematous or opaque cornea and in surgical planning. It is particularly helpful in congenital and traumatic cases. Additionally, it can locate small anterior segment foreign bodies not seen well by slit-lamp examination or AS-OCT.

MANAGEMENT

General Treatment Goals

The primary therapeutic goal is to control the underlying cause of the corneal edema or opacity (when active or progressive) and enhance the patient's quality of life by improving visual acuity and maximizing comfort. The ophthalmologist should provide the patient with an understanding of available treatment alternatives, balanced expectations of the amount of visual function that can realistically be preserved or recovered, and the risks of potential complications. The requirements for visual function will vary from individual to individual, and these needs must be considered when discussing treatment alternatives. Treatment may be optical, medical, surgical, or a combination, depending on the etiology, nature and severity of the opacity as well as the needs, desires, and health status of the patient.

In most cases, treatment starts with medical management. When these measures are insufficient, surgery may be considered. While improving visual acuity and maximizing comfort are the most frequent reasons to recommend surgery, improving visualization of the posterior segment, reducing the risk of infection, and improving a disfiguring condition may also be reasons that lead to surgery.

Medical Management of Corneal Edema

Chronic corneal edema is most commonly related to elevated IOP, intraocular inflammation, or endothelial dysfunction.[43] A careful ophthalmologic examination will often assist in determining which of these causes is most likely. Lowering of the IOP is helpful when it is elevated or at the upper end of the normal range. Although any hypotensive agent may be beneficial in theory, prostaglandin analogues have a potentially inflammatory character and should be avoided in patients for whom inflammation is a possible contributing factor.[44,45] When endothelial dysfunction is a possible contributing factor, topical carbonic anhydrase inhibitors should not be first line therapy because of their potential to interfere with the endothelial pump.[46,47] When inflammation is present, it should be controlled by adding a topical corticosteroid once possible infection has been ruled out or controlled. The hyperosmotic effect of topical sodium chloride 5% drops or ointment or the use of a hairdryer (for either primary or secondary edema) are commonly suggested treatment routines; however, there are no studies that have determined the optimal routines for use of either of these modalities. Topical antibiotics may be necessary to reduce the risk of secondary infection when bullae rupture.

Microcystic or bullous epithelial disease may produce discomfort or pain, necessitating the placement of a bandage contact lens to alleviate these symptoms. Although many different lenses may be used, thin lenses with high water content and high oxygen diffusion coefficients (i.e., Dk levels) are thought to be most advantageous.[48] Generally, a flat lens that will have some movement on blinking is desirable. If there is a concomitant dry eye, preservative-free artificial tears may be necessary to facilitate sufficient movement of the lens. There is no consensus on the use of a topical antibiotic when a bandage lens is employed or on how frequently such lenses should be changed.

Patients should be informed of the risk of infectious keratitis when wearing a bandage contact lens and the need to contact their treating ophthalmologist if redness, pain, or increased photophobia develops. One study suggested an increased risk of infectious keratitis associated with use of bandage contact lenses, and antibiotics may not protect against the risk of infections.[49] Ideally, bandage contact lenses should be used for a finite treatment period; however, in many cases, longer-term use may be required. In this situation, periodic exchange of the lens is advised. Regular follow-up is necessary under these circumstances to reassess the lens, look for evidence of a change in the patient's ocular status, and re-emphasize the need for vigilance on the part of the patient.[49]

Surgical Management of Corneal Edema

Patients with corneal edema and persistent discomfort, but limited or no visual potential, are generally better candidates for a conjunctival flap, amniotic membrane, or one of a number of scarification procedures. Occasionally, patients with good vision will opt for one of these treatments when extenuating circumstances affecting general health or follow-up care/transportation are an issue.

Patients with longstanding bullous keratopathy often develop a layer of subepithelial scar tissue that is associated with reduced bullae production and reduced pain. Intentional scarification of the corneal surface to recreate this effect has been a longstanding surgical approach when improved vision was not the principal concern. Anterior stromal puncture with an electrocautery[50] or needle[51] has been found to be effective. Intentional scarification requires caution, because overtreatment can lead to necrosis.[52]

Acronyms abound and are often confusing because of their similarities. Good examples are ALK, ALTK, FALK, and FLAK. Table 3 lists many of the more common keratectomy and keratoplasty procedures.

TABLE 3 CONTEMPORARY KERATECTOMY AND KERATOPLASTY PROCEDURES

Acronym	Procedure
ALK (ALTK)	Anterior lamellar keratoplasty (therapeutic)
DALK	Deep anterior lamellar keratoplasty
DLEK	Deep lamellar endothelial keratoplasty
DMEK (DMAEK)	Descemet's membrane endothelial keratoplasty (automated)
DSEK (DSAEK)	Descemet's stripping endothelial keratoplasty (automated)
EK	Endothelial keratoplasty
FALK	Femtosecond anterior lamellar keratoplasty
FLAK	Femtosecond laser assisted keratoplasty
PKP/PK	Penetrating keratoplasty
PRK	Photorefractive keratectomy
PTK	Phototherapeutic keratectomy
SK	Superficial keratectomy

Phototherapeutic Keratectomy

Excimer phototherapeutic keratectomy (PTK) with ablations to a depth of 100 µm or greater has been employed alone[53-56] or in combination with amniotic membrane grafts[57,58] to reduce pain and promote surface stability. Pain relief is purportedly achieved by ablation of the sub-basal nerve plexis.[54] A less involved technique for achieving the same result is an annular keratotomy created by corneal trephination to a mid-stromal depth.[59]

Conjunctival Flap of Gunderson

Rapid corneal healing, ocular comfort, and reduction in ocular inflammation can be achieved with a conjunctival flap.[60,61] Historically, flaps were often used to allow an eye to quiet before more definitive therapy on a non-inflamed eye was performed. An improved understanding of the importance of preserving stem cells has led to the use of amniotic membrane [62-64] in many of these conditions, and conjunctival flaps are used as definitive surgery when additional reconstructive surgery is not anticipated. A number of approaches can be used, the most popular of which is Gunderson's technique of a bi-pedical flap.[60] Amniotic membranes can be performed using an "inlay"[65] or "overlay"[66] technique. In the inlay method, the amniotic membrane acts as a scaffold for epithelial cells that migrate onto the membrane from the surrounding region. It is hoped that some of the membrane will persist after healing to create a barrier effect and prevent new bullae from forming. In the overlay method, the amniotic membrane is applied as a patch and sutured to the conjunctival surface.[66] Here, it functions as a biologic contact lens, and epithelial healing takes place underneath the layer of amniotic membrane, which then resorbs.

Corneal Transplantation

Corneal transplantation, either full-thickness penetrating keratoplasty (PK) or as a lamellar procedure (Descemet's stripping automated endothelial keratoplasty [DSAEK] or Descemet's membrane endothelial keratoplasty [DMEK]), is the most common therapeutic option chosen by patients who have corneal edema and reduced vision or significant pain due to bullous keratopathy. Factors that determine whether full-thickness or lamellar surgery is to be recommended include the presence and extent of subepithelial or stromal scarring, concerns about the impact of ocular surface disease on epithelial healing and stability, and the extent of any reconstructive intraocular surgery that might be necessary at the time of surgery. Prior posterior vitrectomy, aphakia, filtering or shunt surgery for glaucoma, extensive posterior synechiae, and a shallow anterior chamber are findings that impact the success of endothelial keratoplasty (EK) and have to be taken into consideration as well.

Endothelial Keratoplasty

The development of EK has profoundly influenced the surgical management of corneal edema. Prior to 2000, virtually all corneal transplant candidates with decompensated corneas underwent PK. That is in contrast to the 2011 Eye Bank Association of America's.Statistical Report, which indicates that approximately 75% of patients with corneal edema are now being managed with EK.[67] This is a technique that is still undergoing change. It began as deep (posterior) lamellar endothelial keratoplasty (DLEK) and transitioned to DSEK or DSAEK. Now it is being considered whether the added challenges of DMEK (e.g., difficulties preparing and handling the donor tissue, higher detachment rates, and the need for rebubbling or repositioning) will prove to be beneficial in the long term.

The broad acceptance of EK is due to the rapid visual recovery, significantly greater optical (both astigmatic and refractive) predictability, and presence of greater wound strength with DSAEK.[68,69] Outcome parameters that are being carefully studied and compared (PK versus DSAEK versus DMEK) include best-corrected visual acuity (BCVA), postoperative astigmatism and refractive outcome (actual and predicted), endothelial cell count, rate of endothelial cell loss and rejection rate.

The intraoperative and postoperative surgical complications of EK are quite different from those seen with PK. Suture and wound-related complications such as suture erosion and infection, vascularization, and spontaneous or traumatic wound dehiscence encountered in PK patients are rare problems with EK procedures.[70] On the other hand, graft decentration or dislocation with the need to recenter or rebubble in the office or operating room, acute angle-closure glaucoma and lamellar interface infections, and epithelial ingrowth may occur with EK.

Descemet's membrane endothelial keratoplasty is an evolving technique that is increasing in popularity because of reports of better vision and more rapid visual recovery. These benefits are offset by greater difficulty preparing the donor tissue and tissue wastage, difficulties handling and inserting the tissue, and a high detachment rate.

Penetrating Keratoplasty

Graft failures in PK generally occur as a consequence of rejection reactions within the first few years and, as a consequence of endothelial failure, during the later follow-up period. Primary donor failure in DLEK, DSAEK, and DMEK is significantly higher than in PK, presumably due to the greater manipulation of the donor tissue at the time it is processed and during insertion and fixation of the tissue at the time of the surgery itself. The problem of dislocation of the graft is a unique complication of EK surgery and is frequently associated with added tissue trauma due to the efforts of the surgeon to reposition or reattach the tissue.

One might expect to see differences in the rejection rates between procedures because less antigenic tissue is being transplanted (specifically, dendritic cells, which are generally found in the superficial stroma, and donor epithelium),[94] and because loose sutures, a recognized risk factor for rejections, are not an issue with EK.[95] Data from the Swedish Corneal Transplant Registry disclosed a rejection rate of 13% for penetrating keratoplasies in patients with Fuchs dystrophy and pseudophakic bullous keratopathy (PBK).[84,85] This is similar to another study[68] that reported on a group of DSAEK patients who had rejection rates of 6.0%, 14.0%, and 22.0% at 1, 2, and 3 years, respectively. Similar values of 7.6% at 1 year and 12.0% at 2 years were reported in a different study.[69] Two studies that specifically compared the results of PK and DSAEK in Fuchs and PBK showed no statistically significant difference between the two groups with regard to rejection rates.[86,96]

Graft survival for both PK and DSAEK appear similar at 5 years for both Fuchs dystrophy (95%) and PBK (73%).[87,97] Endothelial decompensation, with or without a prior rejection episode, is the leading cause of graft failure for both. Other causes of PK graft failure such as traumatic wound rupture and ocular surface complications are not seen with EK.[77,98] One often under-appreciated advantage of EK is the decreased incidence of delayed surface healing and postoperative surface irregularity in patients with ocular surface disease, specifically dry eye and blepharitis. These factors significantly influence the speed of

visual recovery and visual quality of many patients. Interface opacities and wrinkling of the donor button, with resulting reduction in correctable distance visual acuity, are causes of graft failure that are unique to endothelial keratoplasty and may lead to regrafting (either repeat DSAEK, DMEK, or PK).

The most common problems following PK are ametropia and irregular astigmatism. The average postoperative astigmatism following PK was 4 to 6 diopters (D).[99-104] The problem is similar in both phakic and pseudophakic cases. This compares with 1.50 D of total cylinder for DSAEK, where the surgically induced portion ranges from 0.40 to 0.60 D, with a mean of 0.11 D.[70] Induced hyperopia following DSAEK, resulting from the donor lenticule being thicker in the periphery, averages 1.10 D with a range of 0.70 to 1.50 D.[105,106] The more predictable optical result in DSAEK (postoperative spherical equivalent, astigmatism, etc.) is helpful for obtaining accurate IOL calculations for combined transplant/cataract procedures and for restoring or adjusting the target refraction in pseudophakic transplant eyes.

Short-term results for different surgical techniques for corneal edema are included in Table 4.

TABLE 4 COMPARISON OF SHORT-TERM RESULTS FOR DIFFERENT SURGICAL TECHNIQUES FOR CORNEAL EDEMA (FUCHS AND PBK)

	PK	DLEK	DSAEK	DMEK
Dislocation rate	0.0%	6.6%[71,72]	14.5%[70]	5.0–62.0%* [73-76]
Wound dehiscence	1.3–5.8%[77-79]			
Donor failure within 60 days	0.3%[80]	3.3%[71,72]	0–29.0%; mean 5.0%[70]	2.2– 8.0%,[81,82]
Rejection rate at:				
1 yr	17.0%[83]	3.4%[71,72]	6.0–9.0%[83]	0.7–3.0%[81,83]
2 yrs	9.7–13.0%[84,85]	5.5%[71,72]	12.0–14.0%[68,86]	
5 yrs	22.2%[80]		22.0%	
Graft failure rate at 5 yrs	5.0% for Fuchs/ 27.0% for PBK[87]	27.5%[71,72]	5.0% for Fuchs/ 24.0% for PBK[87]	NA
BSCVA:				
% 20/40 or better at 1 yr	65.0–84.0% with selective suture removal[88]	40.0–44.1%[71,72]	38.0–90.0%[70]	94.0% at 6 mos[74] 97.0% 20/30 or better at 1 yr[76]
% 20/20 or better				39.0–47.0%[74,76]
Time to BCVA	6–12 mos with selective suture removal[89]	NA	NA	2/3 stable by 3 mos[74]
Mean keratometric cylinder:				
sutures out	4.40±2.80 D	1.50±1.20 D[71,72]		
at 2 yrs	3.70±3.20 D[90]	0.40–0.60 D induced; mean 0.10 D[71,72,90]	0.40–0.60 D induced; mean 0.10 D[90]	+0.40 D hyperopic shift,[90] no change[81]
with sutures in at 1 yr	2.50 D[88]			
Mean spherical equivalent change	2.80±2.10 D[71]	0.90±0.70 D[71,72]	+1.10 D induced hyperopia[70,83]	+0.24 to +0.32 D [76,91]
Endothelial cell loss:				
1 yr	9.0–19.0% Fuchs† 34.0% Fuchs/PBK[80,92]	43.0–57.9%[71,72]	37.0%[87]	32.0±20.0%, 34.0%[74,81] 36.0%[76,93]
2 yrs	27.0–42.0% Fuchs, 54.0% Fuchs/PBK[80,92]	57.0%[71,72]	44.0%[87]	
5 yrs	69.0–75.0% Fuchs, 61.0% Fuchs/PBK[80,92]	62.0% at 4 yrs[71,72]	53.0%[87]	

BSCVA = best spectacle-corrected visual acuity; BCVA = best-corrected visual acuity; D = diopter; DLEK = deep lamellar endothelial keratoplasty; DMEK = Descemet's membrane endothelial keratoplasty; DSAEK = Descemet's stripping automated endothelial keratoplasty; NA = data not available; PBK = pseudophakic bullous keratopathy

* Only includes dislocations that influenced the result; edge dislocation or tag not counted. If all dislocations are counted = 8.0–24.0%.

† Range – two donor age groups.

Medical Management of Corneal Opacification

Treatment of a corneal opacity can be divided into two phases: the management of the principal, initiating process (i.e., infection, trauma, etc.) and the management of the resulting problems (i.e., surface erosions and irregularity, scarring, thinning, and vascularization). This PPP is focused on this second phase.

Many corneal opacities start as persistent, non-healing epithelial defects that opacify as a result of infection, tissue breakdown, and/or scarring. Conventional treatment involves the use of an antibiotic drop or ointment that will protect against secondary bacterial infection. The choice of antibiotic should take into account the normal skin and conjunctival flora, the patient's immune status, and any underlying medical problems (i.e., diabetes, Parkinsonism).

Adequate blinking during the waking hours and complete lid closure when sleeping are very important for ocular surface healing and need to be assessed in any situation where a defect persists. A temporary glue or suture tarsorraphy or lid splints can be helpful when blinking or lid closure are inadequate. Pressure patching used to be standard treatment for abrasions and erosions; however, recent data suggests that this does not positively impact comfort or the speed of healing.[107,108] A bandage contact lens may be very helpful in cases of delayed healing.

Defects unresponsive to the above measures have spawned a search for alternative agents to promote surface healing. Oral doxycycline,[109] acetylcystine, and ethylenediamine tetra-acetic acid (EDTA) all have been shown to inhibit matrix metaloproteinases and have been investigated, with varying results, to manage persistent epithelial and stromal defects. In vivo benefits are hard to assess, particularly in a structured, double-blind format. Autologous serum,[110] cord blood tears,[111] and platelet-rich plasma[112] have demonstrated beneficial effects for persistent epithelial defects. The need to have these products prepared by a blood bank and/or compounding pharmacy limits their availability. Nerve growth factor,[113,114] substance P and insulin-like growth factor-1,[115] fibronectin,[116] and thymosin beta 4[117] have all shown some benefit in selected cases but remain primarily investigational.

Amniotic membranes, either as an onlay[66] protective flap or as an inlay[65] tissue substitute, are thought to promote healing by their release of various anti-inflammatory, anti-angiogenic, and pro-healing mediators.[118-120] The introduction of these membranes, attached to scleral rings[121] and as wafers that can be placed under a contact lens, has expanded their flexibility and allows for in-office utilization.

Progressive thinning of the cornea or perforation usually require structural support with the application of a tissue adhesive. A small area of marked thinning or an early descemetocele may be coated with a thin layer of adhesive, which if applied to a clean and compact base, may remain in place for 6 weeks or longer. If located peripherally, this may be definitive treatment; if located centrally or paracentrally, the adhesive will facilitate the non-emergent repair of the defect. Leaking descemetoceles may sometimes require the injection of an air bubble into the anterior chamber to halt the leakage temporarily. The base of a defect needs to be dry for the adhesive to adhere properly. Tissue adhesive will work best when the area of impending perforation is small and at the bottom of a crater. Various techniques have been advocated for the application of tissue glue, including the use of a 30-gauge needle, the wooden end of a cotton applicator, or a micropipette.[122] Application of the least amount of glue that will seal or support the defect should be attempted. While tissue glue has not been FDA-approved for use on the eye, it has been widely used internationally for many years. It is advisable to use a sterile product to reduce the risk of a secondary infection.

Topical corticosteroids are often used to reduce intraocular as well as corneal inflammation. Their role in limiting corneal scar tissue development after an acute or subacute process has resolved has not been well established, however.[123,124] A number of studies have looked at their effect on healing and visual acuity when used in the treatment of acute corneal ulcers, and they found no benefit to their use.[125-127] Agents that have been used to reduce the development of scar tissue following glaucoma and refractive surgery (mitomycin-C,[128] 5-fluorouracil,[126] tacrolimus,[123] octreotide,[127] and pirfenidone[129]) have been associated with epithelial surface toxicity at the commonly used doses[130,131] or have not been evaluated as to their anti-scarring effect in corneal disease.

Reduced vision in cases of corneal opacification is often related to surface irregularity (easily demonstrated with the keratometer) in addition to the opacity itself. An RGP lens (hybrid or scleral lens when greater stability is needed) will often improve the vision when surface irregularity is a major factor and may preclude the need for more invasive procedures. A trial fitting with spectacle overcorrection (to demonstrate potential improvement) can be performed easily in the office with a small set of RGP lenses. A formal fitting may be more difficult and time consuming, necessitating the use of bitoric, oversized scleral, or hybrid lenses to clear surface ridges and areas of irregularity and to maintain good lens centration and stability.

Painted contact lenses and scleral shells are also available to hide an opacity when the visual potential is poor. The greater thickness of the scleral shell makes it an ideal choice when there is reduced orbital volume or phthisis bulbi. Painted contact lenses are available with a clear pupillary zone and opaque periphery for patients with peripheral opacities.

Surgical Management of Corneal Opacification

The surgical strategy for managing corneal opacities depends on which tissue layer(s) is involved. In most cases, this is determined at the slit-lamp biomicroscopy examination, however, UBM and AS-OCT can be extremely valuable in some cases. Superficial keratectomy may be indicated for the removal of superficial deposits, lamellar keratoplasty for deeper deposits, and PK for even deeper, multilevel opacities. Table 5 highlights the relationship between depth of disease and surgical alternatives.

Epithelial Debridement

Epithelial debridement is most helpful with lesions anterior to Bowman's layer. Anterior basement membrane dystrophy and Salzmann nodular degeneration are two of the conditions where this is performed most frequently. A lid speculum and a round or curved microblade are the only equipment necessary. An office slit-lamp biomicroscopy examination is often the easiest setting to do this if the patient is cooperative, because the narrow slit beam makes it easier to judge depth. An operating microscope in a minor surgical suite or operating room can also be used if the patient is uncooperative or if other procedures are to be performed at the same time. In epithelial basement membrane dystrophy, the bulk of the epithelium tends to be loose and easily removed. Care needs to be taken to remove multilayered basement membrane, which is often present. In Salzmann's nodular degeneration, once the epithelium is removed, the underlying Salzmann's nodule/subepithelial fibrosis also needs to be excised. Often a plane between the opacity and underlying Bowman's layer can be found, resulting in a relatively smooth corneal surface. When a smooth plane cannot be fashioned, a lamellar keratectomy procedure may be required to achieve the best result.

TABLE 5 LAYER-BASED APPROACH TO THE SURGICAL MANAGEMENT OF CORNEAL OPACITIES

Layer of Pathology	Representative Disease	ED	SK	PTK	ALK	DALK	EK	PK
Epithelium	Redundant, irregular epithelium	•						
Subepithelial	Epithelial basement membrane dystrophy	•						
Subepithelial	Salzmann nodular degeneration	•	•					
Bowman's	Band keratopathy	•	•	•				
Bowman's	Reis-Bücklers dystrophy		•	•	•			
Anterior – mid-stroma	Granular dystrophy		•	•	•			•
Midposterior stroma	Scarring				•	•		•
Endothelium							•	•

ALK = anterior lamellar keratectomy; DALK = deep anterior lamellar keratoplasty; ED = epithelial debridement; EK = endothelial keratoplasty; PK = penetrating keratoplasty; PTK = phototherapeutic keratectomy; SK = superficial keratectomy

Management of Band Keratopathy

Use of disodium EDTA[132,133] to facilitate the removal of a calcific band keratopathy can be very helpful. The goal of treatment is to remove the calcium opacities in the pupil and to restore comfort and vision. When the calcium forms thick flake or plaque-like excrescences, they can be removed with forceps and scrapping, otherwise removal of the overlying epithelium is all that is necessary prior to EDTA treatment.[134] A cellulose sponge or a sterile cotton applicator soaked in a 3% to 4% dilution of disodium EDTA can be rubbed against any residual calcium until dissolution occurs. Alternatively, direct application of EDTA drops to the exposed calcium band, the use of a well filled with EDTA, or the application of an EDTA-soaked cellulose disc directly over the exposed calcium may result in dissolution of the band keratopathy. Treatment time with EDTA may vary depending on the density of the calcium and the approach used. Excess rubbing may be associated with postoperative anterior stromal haze. The mean time to healing may be delayed after EDTA chelation when compared with normal eyes that have a similar-sized corneal abrasion (8 days versus 2 to 3 days), presumably due to alterations in the underlying corneal pathology. Other methods proposed to manage band keratopathy include the use of a diamond burr,[135] Nd:YAG laser,[136] lamellar keratoplasty,[137] and PTK.[138,139]

Use of Mitomycin-C

Mitomycin-C for subepithelial, Bowman's layer, and anterior stromal scarring may be helpful in selected cases where recurrence is a concern.[140,141] Definitive criteria for use of mitomycin-C, as well as the most effective method, dose and period of application, have yet to be established for corneal disorders. The most frequently reported dose used is mitomycin 0.02% (0.2 mg/mL) applied using a wet, but not soaking, cellulose disk. Treatment time roughly divides into two groups: 12 to 20 seconds when used as prophylaxis against the development of postkeratectomy haze or scarring, and 1 to 2 minutes when used to prevent the recurrence of scarring. Care must be taken to ensure that the proper dose of mitomycin is formulated by the pharmacy and that close attention is paid to the exposure time. Copious irrigation of the surface and the surrounding area with saline or a balanced salt solution afterwards is important to reduce the risk of progressive toxicity at the surgical site (specifically endothelial toxicity) or adjacent limbus. The use of mitomycin-C is based on the evaluation by the ophthalmologist and the consideration of potential advantages and disadvantages in each case. Mitomycin-C has not been FDA-approved for use in the eye, and this should be explained to the patient along with the risks and benefits. Its off-label status should be discussed with the patient.

Corneal Tattooing

Corneal tattooing has been used for centuries to treat cosmetically objectionable corneal leukomas. The original technique involved imbedding India ink or carbon particles in the anterior and mid-stroma using a process similar to corneal stromal puncture. Often, the procedure had to be repeated to achieve the desired distribution and density of pigment. Over time, the pigment tended to migrate from the puncture wounds and the procedure needed repeating. The most versatile techniques in use now involve the creation of a lamellar pocket or flap (by hand or femtosecond laser) into/under which pigment is instilled. This technique is easily adapted to corneal opacity of almost any size and shape. The density and color distribution of the pigment can be varied according to the case. Densely pigmented, discretely edged tattoos often appear to be "stuck on" the surface of the cornea. This lack of depth is usually not a major problem when functional issues are the primary concern, but it needs to be kept in mind when cosmetic issues are dominant.

Management of Anterior Stromal Opacities

Anterior corneal lesions that extend beyond Bowman's layer into the anterior and mid-stroma require more extensive treatment than described above. Measurements of the size and depth of the corneal opacity obtained with the AS-OCT, UBM, or confocal microscope may be very helpful in determining which management approach is most suitable.

Superficial Keratectomy

Lamellar keratoplasty and superficial lamellar keratoplasty or ALK are techniques that have been utilized since the early 1900s and until the early 1970s were the prevailing surgical approach to manage diseases that did not affect the endothelium.[142] "Freehand" lamellar keratectomies, regardless of the depth, have the advantage of requiring minimal equipment (a microblade, lamellar dissector, or spatula). However, the difficulty in achieving a uniform or smooth interface and the associated poor visual results has limited its utility.[134,143,144]

An ALK performed using a microkeratome or femtosecond laser has the advantage of achieving a smoother bed than one that is achievable with most freehand dissections. The epithelium can be allowed to cover the stromal bed or an onlay lamellar transplant can be applied.[145,146] The depth of the microkeratome (base plates range from 120 to 350 µm) or femtosecond dissection and the thickness of the resulting bed determine whether tissue replacement is necessary. Superficial corneal flaps, created using either system, combined with excimer laser ablation to the stromal bed, can be performed to remove an anterior-to-midstromal opacity either partially or totally when the overlying stroma is clear.[147-150] Stromal haze (reduced using mitomycin-C) and hyperopia are post-treatment issues that need to be taken into account when planning treatment.

In cases of simple microkeratome/femtosecond laser keratectomy or combined procedures (with PTK), the visual results (i.e., final BCVA and contrast sensitivity) show significant improvement.[151] Both measurements are influenced by the amount of postoperative surface and interface irregularity and residual stromal haze or scar tissue.[138,139] In most cases, uncorrected visual acuity (UCVA) is not significantly improved at 6 months.[140,141] Best-corrected visual acuity, however, is significantly improved at 2-, 6-, and 12-month time points in cases of mechanical/femtosecond flaps combined with PTK.[140,141] The aberrometric data demonstrate that the improvement of visual acuity is correlated with an improvement of corneal transparency, corneal regularity, and optical quality.[141]

Excimer PTK is used in the management of superficial and anterior stromal opacities to improve epithelial stability or visual acuity. Some of the more common diseases treatable using this modality are epithelial basement membrane dystrophy,[152] bullous keratopathy,[54] residual subepithelial haze or scarring following removal of band keratopathy or Salzmann nodular degeneration,[153-155] anterior stromal scarring, Reis-Bücklers,[156] and granular and lattice dystrophies.[157] Multiple treatments are possible with recurrent disease and can be combined with refractive treatment to reduce ametropia or astigmatism.[158] Visual rehabilitation tends to be fairly rapid, and most patients achieve improvement in BCVA when the underlying reason for treatment was corneal opacification. In some cases (e.g., granular and lattice dystrophies), it may be possible to avoid or at least defer lamellar keratoplasty or PK.

Recurrence of the underlying disease process, post-treatment surface irregularity, and hyperopia are the most frequent problems seen with PTK. The application of mitomycin-C at the time of the initial or follow-up PTK treatment has been investigated as a means of diminishing recurrent scar tissue or stromal deposits. Mitomycin-C 0.02% (0.2 mg/mL) was applied using a saturated circular methylcellulose sponge for 2 minutes.[156,159,160] No patient presented with a recurrence in these studies during a 1- to 37-month follow-up period (average follow-up was 8.3 months[53] and 15 months[134]).[54,153] Delayed epithelial healing, keratolysis, and postoperative stromal edema were not observed in these series. Copious irrigation of the surface and the surrounding area with saline or a balanced salt solution afterwards is important to reduce the risk of progressive toxicity at the surgical site (specifically endothelial toxicity) or adjacent limbus.

The excimer laser removes tissue equally from raised and depressed areas. As a result, treatment of an irregular surface etches the surface topography into the underlying layers. To prevent this and facilitate creation of a smooth surface, a masking agent (often methylcellulose or sodium hyaluronate) is used. This fills the valleys so that the peaks can be ablated first. Dense scar tissue and calcium require more energy for ablation than

normal tissue. Masking of normal tissue adjacent to a dense scar or calcium is therefore necessary to prevent the development of a surrounding moat.[161-163]

Greater depth of treatment has been associated with post-PTK haze as well as a hyperopic shift.[164] The flattening effect that causes this can be reduced by treating along the outer edge of the ablation zone with small spot ablations[165] or by using a refractive setting.[151,152]

Table 6 summarizes some of the differences between these keratectomy techniques.

TABLE 6 COMPARISON OF TECHNIQUES USED IN SUPERFICIAL AND ANTERIOR LAMELLAR KERATECTOMY

	Freehand	Microkeratome	PTK	Femtosecond
Depth of dissection	Flexible but less accurate	120–350 μm	Flexible but less accurate due to uneven ablation	90–280 μm
Flap parameters	Flexible	Limited	NA	Flexible
Flap complications	Occasional	Occasional	NA	Rare
Bed smoothness	Worst	Better	Variable	Best

NA = not applicable; PTK = phototherapeutic keratectomy

Keratoplasty

Removal and replacement of diseased layers of the cornea is necessary when managing corneal opacification or edema if significant tissue thickness is involved, or when the endothelium is compromised and unresponsive to conservative measures. Surgical and eye-banking advances have had a significant impact on the availability of donor tissue, the indications for surgery, the frequency with which keratoplasty is performed, and the procedure's rate of success.

Corneal transplantation (keratoplasty) has been the mainstay of treatment for corneal opacities involving the mid and deep stroma. Since the late 1960s, full-thickness PK was the standard approach. Endothelial keratoplasty has supplanted PK as the procedure of choice in cases of endothelial failure in the absence of corneal scarring because patients achieve more rapid visual astigmatism. The dramatically reduced risk of postkeratoplasty astigmatism, suture-related infections, and traumatic wound rupture are further advantages of EK. The preferred technique continues to evolve. Within the realm of lamellar keratoplasty, further advances have enabled surgeons to perform anterior lamellar, deep lamellar, and endothelial lamellar procedures.

Lamellar Keratoplasty

Anterior Lamellar Keratoplasty

Tissue replacement is necessary when ALK removes sufficient tissue to thin the cornea and create conditions that might lead to progressive ectasia (as may be seen for refractive procedures) or surface irregularity. While optical and tectonic rehabilitation can be achieved with ALK, it is more often viewed as a tectonic procedure because of the difficulty of controlling interface scarring and achieving a smooth dissection. Moreover, the optical results are rarely as good as those achieved via PK.

The advantages of ALK over PK include the absence of endothelial rejection, greater wound strength, and improved safety (since it is an extraocular procedure). These advantages have stimulated efforts to produce a smoother recipient base and donor stromal surface, using improved manual microkeratome and femtosecond laser-dissection techniques. Numerous studies have demonstrated improvement in the quality of the interface with these techniques.[166,167] Correspondingly, visual acuity improvements to 20/30 or 20/40 have been reported by numerous investigators using microkeratome-assisted ALK[166] or FALK.[168-171] In some cases, no sutures were used to secure the donor lenticules, resulting in reduced post-keratoplasty astigmatism.[169]

Anterior Lamellar Therapeutic Keratoplasty

Partial-thickness defects related to melting disorders (e.g., central corneal ulcers, peripheral ulcerative keratitis, Terrien marginal degeneration) or peripheral ectasia (e.g., pellucid marginal degeneration, post-PK wound thinning) may need to be managed surgically if excessive thinning or descemetocele formation develops. Central grafts are usually circular in shape, and the size is determined by the size of the defect and whether the graft's edge will impinge on the pupil. In the periphery, the pathology may be annular in nature and require a concentric donut or partial crescentic graft. These are technically more difficult, and although they are often done because of thinning and the secondary astigmatism that results from this, they are frequently associated with modest postoperative astigmatism. In some cases, a full-thickness patch or crescentic graft is needed. Donor tissue for ALTK procedures may be partial-thickness irradiated tissue, glycerin preserved tissue, or preserved tissue provided by an eye bank.[172-174]

Deep Anterior Lamellar Keratoplasty

Lamellar keratoplasty using DALK techniques can be considered for cases of mid to deep stromal scarring. The deep lamellar keratoplasty technique removes all or nearly all of the corneal stroma down to Descemet's membrane. The benefits of DALK are that it preserves the host endothelial layer and reduces the long-term endothelial cell loss characteristic of PK. While stromal rejection reactions can occur in both DALK and PK, this risk is reduced since the host keratocytes replace the donor cells. The risk of endothelial rejection, however, is not an issue in DALK because this layer is preserved.[168,175,176]

A variety of manual techniques exist to aid in the separation of the posterior stroma from Descemet's membrane, including the Melles technique, the big-bubble technique, and variations on the big-bubble technique.[20,177] The femtosecond-assisted big-bubble technique utilizes a femtosecond laser program to trephine the cornea, followed by big-bubble formation in the posterior stroma and placement of a femtosecond laser-trephined cornea to complete the DALK.[178]

Outcomes

Most of the comparative studies looking at DALK and PK relate to keratoconus; however, similar results and issues would be expected to apply to noninflammatory, nonvascularized and non-progressive central corneal opacities as well. The studies comparing visual results of these procedures in keratoconus patients appear conflicting until they are viewed according to how much posterior stroma was left behind. Greater variation in the postoperative visual acuity and contrast sensitivity following DALK has been correlated to increased thickness of the residual recipient posterior stromal bed and donor-host interface reaction. When baring of Descemet's membrane was achieved, visual results are reported to be comparable with PK.[168,179-185] Unfortunately baring of Descemet's membrane is not consistently achieved, as reported in 47% to 82% of eyes, even in experienced hands.[177,182,186,187] A residual bed of less than 20 µm is ideal for achieving similar visual results when compared with PK.[179] Overall, studies have found that the complication rate (including converting to PK) remains higher for DALK when compared with PK. This may be associated with the surgeon's learning curve and may decrease with increased surgeon experience with the technique.[168,186] Endothelial cell loss was significantly lower with DALK performed without Descemet's membrane perforation, when compared with full-thickness keratoplasty.[187-191]

Complications

Complications related to LK include suture-abscess formation, surface erosions, interface opacities, infectious keratitis, neovascularization, and graft rejection and failure. Endothelial rejection, however, is not seen. Complications that are unique to DALK include rupture of Descemet's membrane while attempting to separate it from the overlying stroma (more likely with scarring that involves Descemet's membrane or a history of a Descemet's membrane rupture [spontaneous, as with hydrops, or surgical]). When the rupture is small, the procedure may be completed or, if large, conversion to PK will be needed. If LK is attempted in the presence of a larger perforation, fluid may accumulate in

the space between Descemet's membrane and the graft, resulting in a "double anterior chamber." Studies comparing the visual results of PK with DALK indicate that DALK patients are less likely to achieve 20/20 vision compared with PK recipients if baring of Descemet's membrane is not achieved.[168] Stromal rejection is another complication of DALK, with an incidence reported between 2% and 12%, suggesting that corticosteroid treatment regimens play an important role in postoperative management of DALK.[192]

Penetrating Keratoplasty

Penetrating keratoplasty has been the mainstay of treatment for corneal opacities, particularly those that involve the posterior stroma and endothelium. It may be the procedure of choice if additional anterior segment surgery (i.e., iris reconstruction, cataract removal, IOL exchange, or vitrectomy) is also required..

Indications

The objectives of a PK depend on the corneal pathology and related problems. Visual improvement is the most common reason for a full-thickness cornea transplant. When a cornea is thin or perforated, tectonic restoration is often required. A therapeutic transplant for an unresponsive microbial infection is an additional indication. Further, cosmetic transplants are performed in some cases where there is an opacification but where other factors are expected to prevent improvement in vision.

Special Indications and Approaches

Crescentic patch grafts and rotational autografts are special forms of PK. Peripheral opacities that are associated with significant tissue loss and increased astigmatism (e.g., Terrien marginal degeneration, post-infectious keratitis) but with a clear central cornea may require either partial or full-thickness grafting. These may take the form of oval or crescentic grafts.[193,194]

In some situations, a central corneal scar may be managed by an ipsilateral rotational autograft. The graft position is offset (rather than in the more typical central position) so that, on rotation, the scar is shifted into the far periphery.[195] Care should be taken that the graft-host junction is not too close to the pupil, causing postoperative distortion. Because of the eccentricity of the graft, irregular astigmatism is a common postoperative problem that has limited the application of this approach.[196]

Oversized or tectonic grafts are typically used in conditions of significant peripheral thinning (e.g., decentered keratoconus, pellucid marginal degeneration or keratoglobus) or infection (e.g., sclero-keratitis) when the peripheral edge of the pathologic process extends beyond the central 7.5 to 9.0 mm. In some cases, the treatment should be staged. The first stage is an LK that thickens the stromal bed. The second stage is a conventional PK, done many months later, through the thickened bed. Many of these cases are accompanied by other anterior segment reconstructive procedures (e.g., angle reconstruction, pupilloplasty, lensectomy, or lens repositioning).

Opacified corneas may at times be associated with serious vitreo-retinal pathology (e.g., following accidental or surgical trauma). The opacified cornea will preclude the safe repair of the retina. A temporary plastic corneal insert—typically referred to as a temporary keratoprosthesis—may be placed at the time of the retinal surgery, left in place for the duration of the retinal procedure, and then removed and replaced with a full-thickness penetrating graft. The view through the temporary keratoprosthesis is excellent and, in most cases, is superior to that which might be obtained through a recently performed corneal transplant, the only other alternative in many of these cases.

Femtosecond laser-assisted keratoplasty is a relatively new technique that utilizes the femtosecond laser for trephining both the donor and recipient corneas. Trephine patterns designated as top-hat, mushroom, or zigzag have been studied and have the theoretical advantage of being able to create additional wound surface area that might result in a stronger wound, when compared with standard trephination techniques. This allows for earlier suture removal and quicker visual rehabilitation.[197-199] With better control of wound healing, management of wound shape and postoperative astigmatism should be improved.[198,199]

Outcomes

Outcomes, defined as graft clarity and visual improvement, can be quite varied in this diverse group of conditions. In the case of a non-vascularized central scar with no other related ocular damage, the percent achieving graft clarity is well over 90%.[200] This is in contrast to scarring related to a chemical injury where there is also extensive corneal vascularization and limbal stem cell damage, where the success rate is quite poor. Visual acuity will often depend on the presence of other, non-corneal factors such as a cataract, glaucomatous damage, or retinal pathology. Variable and unpredictable postkeratoplasty astigmatism remains an issue. It is common practice for surgeons to leave sutures in place long term when selective suture removal has achieved a low level of astigmatism and good vision. The disadvantage of this practice is the risk of late suture breakage, irritation, and infection or rejection.[201,202] Studies have shown that FLAK results in greater improvement in astigmatism in the early postoperative period compared with conventional PK techniques, but this advantage disappears after 6 months.[198] Earlier suture removal is possible with FLAK due to greater mechanical stability and wound healing.[199]

Contraindications

Corneal transplant success is improved by addressing as many active or concomitant problems as possible in advance of the surgery. Good control of IOP, resolution of adnexal and intraocular inflammation and infection (e.g., chronic dacryocystitis, blepharitis, conjunctivitis, keratitis), and repair of any lid abnormality (e.g., trichiasis, entropion, ectropion, lagophthalmos, and exposure) are crucial. Identification of thinned areas in which graft-host thickness mismatch may occur, deep stromal vascularization that may jeopardize the new graft, and ocular surface disease (e.g., dry eye, past chemical or radiation injury, OMMP, or Stevens-Johnson syndrome) are important factors in reduced long-term graft survival..

Complications

Complications can be divided into those that occur during surgery and those that occur afterwards:

Intraoperative

- Technical complications:
  - Scleral perforation with fixation suture
  - Improper trephination
  - Damaged donor button
  - Retained Descemet's membrane
  - Iris-lens damage
  - Torn posterior lens capsule with or without vitreous loss
  - Anterior chamber or vitreous hemorrhage
- Non-technical complications
  - Expulsive suprachoroidal hemorrhage

Postoperative

- Wound leak or misalignment
- Persistent epithelial defect
- Filamentary keratitis
- Suture-related immune infiltrate
- Suture infection/abscess
- Endophthalmitis
- Elevated IOP

- Anterior synechia formation
- Hyphema
- Choroidal detachment
- Retinal detachment
- IOL dislocation

Primary donor failure occurs when the donor tissue fails to clear itself during the first 4 weeks postoperatively in the absence of other problems that may be causing stromal edema (e.g., a persistent epithelial defect, elevated IOP). It is thought to be due to inadequate endothelial cell function because of poor health of the donor endothelium or an inadequate number of cells. It is generally viewed as a problem related to corneal selection, preservation, or storage. Fortunately, it is a rare occurrence. Excess trauma or manipulation of the donor tissue at the time of surgery that leads to persistent postoperative stromal edema is not usually defined as primary donor failure. Regrafting is usually performed as soon as the diagnosis is established.

Late donor failure is the term that refers to failure of the donor tissue when it occurs years after the transplant. This is thought to be related to gradual endothelial cell loss,[80,92,203] but it may be accelerated if prior rejection reactions, infections, or elevated IOPs have occurred. Excess manipulation of the donor tissue at the time of surgery, shallowing of the anterior chamber due to wound dehiscence, or repositioning of the donor tissue following DSAEK may also contribute to premature donor failure.

Corneal transplant rejection reactions are the most frequent cause of corneal graft failure. Allograft rejections complicate from 2.3% to 68% of cases of PK.[204] Early, aggressive treatment with topical and systemic corticosteroids may be able to reverse a rejection reaction. Identification of high-risk cases or those with a history of recurrent inflammation (e.g., herpes simplex virus keratitis, zoster, uveitis) is important because standard treatment protocols following PK may need to be augmented with higher daily doses of corticosteroid or oral antiviral agents. Two studies that specifically compared the results of PK and DSAEK in Fuchs dystrophy and PBK showed no statistically significant difference between the two groups with regard to rejection rates.[86,96]

Keratoprosthesis

Ophthalmologists have pursued the ideal artificial cornea for well over 100 years, with glass as the first material.[205] Innovative designs, materials, and surgical procedures have characterized this endeavor. Cardona,[206] osteoodonto-keratoprosthesis,[207] AlphaCor,[208] and the Boston keratoprosthesis[209,210] are designs that have attracted the most interest over the past decades. Significant improvements in the design and postoperative management of the Boston type 1 keratoprosthesis has resulted in a steady rise in the number of these procedures performed both in the United States and abroad.[211,212] Reduced incidence of postoperative stromal necrosis and bacterial endophthalmitis due to the chronic use of protective soft contact lenses and topical antibiotics has resulted in improved retention and visual outcomes and has had a positive impact on surgeons' perceptions of when to recommend keratoprosthesis.[211-214] Once considered a procedure of last resort in patients with severe bilateral visual impairment, it is now being used for a variety of unilateral and bilateral indications, such as ocular trauma,[215,216] herpetic keratitis,[217,218] aniridia,[219] Stevens-Johnson syndrome,[220] and congenital corneal opacification.[221] More recently, as corneal surgeons have gained a greater appreciation of the failure rate of repeat corneal transplantation,[222] a role for a keratoprosthetic in cases of multiple graft failure has become clearer.[212-214]

The retention rate of the Boston type 1 keratoprosthesis at 1 year has been reported to be 90% to 92%[211,223] of patients, with a 2-year retention rate of 80% to 87%.[211,214,224] Persistent epithelial defects, especially in patients with limbal stem cell deficiency, infectious keratitis, and stromal necrosis play a significant negative role in keratoprosthetic retention.

Visual acuity improved to 20/200 or better in 56% to 89%[211,213,214] and 20/50 or better in 32% to 43%[211,213] of patients at 1 year. Rapid stabilization of vision in patients with a healthy retina and optic nerve is facilitated by the smooth, spherical front surface of the Boston type 1 keratoprosthesis. Glaucoma is the most challenging postoperative problem following keratoprosthetic surgery. Unfortunately, the majority of patients currently undergoing keratoprosthesis surgery (as high as 72% to 85%) already have some glaucomatous optic nerve damage prior to receiving the device. (See Table 7 for complications of keratoprosthesis.) The vision loss from glaucoma is potentially preventable, although there is no reliable method to measure IOP after implantation of a keratoprosthesis. When tube-shunt surgery is performed prior to the keratoprosthesis implantation, the rate of worsening of glaucoma in eyes with poorly controlled IOP that requires surgery during a follow-up of an average of 17 months has been reported to be as low as 2%. Others, however, report rates as high as 38%, particularly when patients with other co-morbidities such as autoimmune ocular surface diseases were included. Frequent reassessment of the optic nerve and visual field studies are necessary to monitor these patients optimally and preserve their vision.[225-227]

Patients with severe dry eye and autoimmune ocular surface diseases (particularly Stevens-Johnson syndrome and OMMP) remain a difficult management group despite the other successes of the Boston type 1 keratoprosthetic. Epithelial defects, scleral necrosis, extrusion, and endophthalmitis are the principal concerns. This group of patients has had some success with a Boston type 2 keratoprosthetic[210] designed to be used through the lid and the osteo-odonto-keratoprosthesis.[207]

TABLE 7 COMPLICATIONS OF KERATOPROSTHESIS*

Complication	Incidence
Glaucoma[214]	pre-existing in 72.0–86.0%
Retroprosthetic membrane formation[80,211,213,228]	25.0–55.0%
Persistent epithelial defects[211]	38.0%
Stromal necrosis[211]	16.0%
Endophthalmitis[214]	12.5%
Cystoid macular edema[211]	8.7%
Infectious keratitis[211,229]	8.0%
Extrusion of implant	0–12.5%

* Changes in prosthetic design, the use of therapeutic hydrophilic contact lenses, and the chronic use of topical antibiotics have reduced the frequency of many of these complications.

Follow-up Evaluation

Frequent follow-up is necessary in many of these cases to reassess the underlying disease process and make adjustments to the medical or surgical treatment. For the management of corneal edema, the goal of follow-up is to monitor endothelial dysfunction. For the management of corneal opacification, follow-up is required to monitor corneal clarity and the degree of surface irregularity. Coexisting problems, particularly intraocular inflammation and IOP (which may be caused by underlying problems or by treatment), need to be reassessed regularly. (See Appendix 4 for additional information on determination of IOP in diseased or post-surgical corneas.)

PROVIDER AND SETTING

The ophthalmologist in the outpatient setting is best equipped to diagnose many of the conditions that result in corneal opacification and corneal edema. The medical management may also be within the experience and expertise of the comprehensive ophthalmologist. It should be noted that infants and young children may require evaluations under anesthesia to obtain all the information necessary to determine a course of treatment. Superficial keratectomies and excimer laser PTKs can often be performed in the office setting or in minor-procedure suites. However, most other procedures require the facilities and sterile conditions found most frequently in an operating room.

COUNSELING AND REFERRAL

Once a definitive diagnosis is made and the related work-up has been completed, a detailed discussion of the causes of the edema or opacity, and of various treatment options, becomes important. When more sophisticated diagnostic or medical management approaches (i.e., those exceeding the training or the level of comfort of the treating physician) are required, or if complex surgical treatments may be needed, the corneal subspecialist may be more equipped to handle the situation. At this point, referral for consultation is recommended. Referrals to retina, glaucoma, or pediatric ophthalmic subspecialists may be needed in some situations. Once the condition has been resolved or has stabilized, referral back to the comprehensive ophthalmologist is appropriate. A team approach is often of great advantage, particularly when geography makes subspecialist visits challenging. The primary care physician should be included in the discussion, especially when surgery is being considered.

When the disease process or its management is complex, every effort should be made to counsel the patient appropriately. This will enable the patient to understand the challenges involved in care more clearly, to have appropriate expectations, and to make informed decisions.

SOCIOECONOMIC CONSIDERATIONS

Globally, corneal opacity is the third leading cause of bilateral blindness after cataract and glaucoma. Of the 7 to 9 million people with bilateral corneal blindness, 90% live in the developing world.[230] Major investments in public health infrastructure and primary eye care services have built a strong foundation for preventing future corneal blindness, as nearly 80% of all corneal blindness is avoidable.[231]

Corneal diseases are associated with poverty and lead to a marked reduction in life expectancy, especially among children with corneal blindness. Efforts aimed at reducing corneal blindness in the developing world are being managed through primary health interventions to combat trachoma, onchocerciasis, vitamin A deficiency, and ophthalmia neonatorum.[232]

The socioeconomic impact of corneal blindness relative to cataract blindness is not reflected just by its prevalence but is magnified by the younger age of those with corneal blindness, with a very high disability-adjusted life years (DALYs). Corneal blindness impacts many in their most productive, child-rearing years compared with the more geriatric population blinded by cataracts.[232]

APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

Providing quality care
is the physician's foremost ethical obligation, and is
the basis of public trust in physicians.
AMA Board of Trustees, 1986

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual, and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients, and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual, and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced, and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
  - The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
  - The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
  - When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
  - The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.
  - The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn they respond in an adequate and timely manner.

  - The ophthalmologist maintains complete and accurate medical records.
  - On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
  - The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
  - The ophthalmologist and those who assist in providing care identify themselves and their profession.
  - For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.
- Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices, or procedures.
- The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

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APPENDIX 2. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES

Corneal edema, which includes entities with the following ICD-9 and ICD-10 classifications:

	ICD-9 CM	ICD-10 CM
Idiopathic corneal edema	371.21	H18.22-
Secondary corneal edema	371.22	H18.23-
Bullous keratopathy	371.23	H18.11-
Corneal edema due to wearing contact lenses	371.24	H18.21- (corneal edema secondary to contact lenses)

CM = Clinical Modification used in the United States; (–) = 1, right eye; 2, left eye; 3, bilateral

Corneal opacification, which includes entities with the following ICD-9 and ICD-10 classifications:

	ICD-9 CM	ICD-10 CM
Minor corneal opacity	371.01	H17.81-
Peripheral corneal opacity	371.02	H17.82-
Central corneal opacity	371.03	H17.1-
Adherent leukoma	371.04	H17.0-
Phthisical cornea.	017.3, 371.05*	A18.59, H44.52-

CM = Clinical Modification used in the United States; (–) = 1, right eye; 2, left eye; 3, bilateral

* Code first underlying tuberculosis (017.3).

Additional Information for ICD-10 Codes:

- Certain ICD-10 CM categories have applicable 7th characters. The applicable 7th character is required for all codes within the category, or as the notes in the Tabular List instruct. The 7th character must always be the 7th character in the data field. If a code that requires a 7th character is not 6 characters, a placeholder X must be used to fill in the empty characters.
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, assign separate codes for both the left and right side. Unspecified codes should only be used when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4th digit, 5th digit, or 6th digit):
  - Right is always 1
  - Left is always 2
  - Bilateral is always 3

APPENDIX 3. PREFERRED PRACTICE PATTERN RECOMMENDATION GRADING

The grades herein report the SIGN grade associated with the included studies supporting each recommendation (I++; I+; I-; II++; II+; II-; III), the GRADE evaluation of the body of evidence (Good, Moderate, Insufficient), and the GRADE assessment of the strength of the recommendation (Strong, Discretionary). Details of these grading systems are reported in the Methods and Key to Ratings section at the beginning of this document.

Highlighted Findings and Recommendations for Care

Page 4: A refraction using a rigid gas permeable contact lens can be very helpful in differentiating visual loss from corneal surface irregularity and surface scarring from non-corneal pathology: III; Good; Strong

Page 4: Endothelial function is best evaluated by slit-lamp examination and may be supported by changes in corneal thickness noted on serial pachymetric measurements performed at the same time of day: III; Insufficient; Discretionary

Page 4: Engaging the patient in the decision-making process related to the timing of surgery and the choice of surgical procedures is beneficial and helps to shape their expectations with respect to their condition and the surgery: III; Good; Strong

Care Process – Diagnosis

Page 7: Initial evaluation of the patient with symptoms and signs of corneal edema or opacification should include the relevant aspects of the comprehensive medical eye evaluation: II++; Good; Strong

Page 11: Intraocular pressure should be measured with alternative electronic devices, such as a pneumanotometer, applanation tonometer, dynamic contour tonometer, ocular response analyzer, or rebound tonometer: III; Insufficient; Discretionary

Care Process – Management

Page 13: The ophthalmologist should provide the patient with an understanding of available treatment alternatives, balanced expectations of the amount of visual function that can realistically be preserved or recovered, and the risks of potential complications: III; Good; Strong

Page 14: If inflammation is a possible contributing factor, prostaglandin analogues have a potentially inflammatory character: III; Insufficient; Discretionary

Page 14: When endothelial dysfunction is a possible contributing factor, topical carbonic anhydrase inhibitors should not be first line therapy because of their potential to interfere with the endothelial pump: II-; Moderate; Strong

Page 14: When inflammation is present, this should be controlled with the addition of a topical corticosteroid once possible infection has been ruled out or controlled: III; Good; Strong

Page 14: Topical sodium chloride 5% drops or ointment or the use of a hairdryer (for either primary or secondary edema) are commonly suggested treatment routines: III; Insufficient; Discretionary

Page 14: Topical antibiotics may be necessary to reduce the risk of secondary infection when bullae rupture: III; Good; Strong

Page 14: Although many different lenses may be used, thin lenses with high water content and high oxygen diffusion coefficients (i.e., Dk levels) are thought to be most advantageous: III; Insufficient; Discretionary

Page 14: Generally, a flat lens that will have some movement on blinking is desirable: III; Good; Strong

Page 14: If there is a concomitant dry eye, artificial tears may be necessary to facilitate sufficient movement of the lens: III; Good; Strong

Page 14: Patients should be informed of the risk of infectious keratitis when wearing a bandage contact lens and the need to contact their treating ophthalmologist if redness, pain, or increased photophobia develops: III; Good; Strong

Page 14: Bandage contact lenses should be used for a finite treatment period: III; Good; Strong

Page 14: If longer-term use is required, periodic exchange of the lens is advised: III; Insufficient; Discretionary

Page 14: Regular follow-up is necessary under these circumstances to reassess the lens, look for evidence of a change in the patient's ocular status, and re-emphasize the need for vigilance on the part of the patient: III; Insufficient; Discretionary

Page 14: Patients with corneal edema and persistent discomfort, but limited or no visual potential, are generally better candidates for a conjunctival flap, amniotic membrane, or one of a number of scarification procedures: III; Insufficient; Discretionary

Page 14: Anterior stromal puncture with an electrocautery has been found to be effective: III; Insufficient; Discretionary

Page 14: Anterior stromal puncture with a needle has been found to be effective: II-; Moderate; Discretionary

Page 15: Excimer phototherapeutic keratectomy with ablations to a depth of 100 µm or greater has been employed alone to reduce pain and promote surface stability: III; Insufficient; Discretionary

Page 15: Excimer phototherapeutic keratectomy with ablations to a depth of 100µm or greater has been employed in combination with amniotic membrane grafts to reduce pain and promote surface stability: I-; Moderate; Discretionary

Page 15: A less involved technique for achieving the same result is an annular keratectomy created by corneal trephination to a mid-stromal depth: III; Insufficient; Discretionary

Page 15: Rapid corneal healing, ocular comfort, and reduction in ocular inflammation can be achieved with a conjunctival flap: III; Insufficient; Discretionary

Page 15: An improved understanding of the importance of preserving stem cells has led to the use of amniotic membrane in many of these conditions, with conjunctival flaps being used as definitive surgery when additional reconstructive surgery is not anticipated: III; Insufficient; Discretionary

Page 15: Factors that determine whether full-thickness or lamellar surgery is to be recommended include the presence and extent of subepithelial or stromal scarring, concerns about the impact of ocular surface disease on epithelial healing and stability, and the extent of any reconstructive intraocular surgery that might be necessary at the time of surgery: III; Good; Strong

Page 15: Prior posterior vitrectomy, aphakia, filtering, or shunt surgery for glaucoma, extensive posterior synechiae, and a shallow anterior chamber are findings that impact the success of endothelial keratoplasty (EK) and have to be taken into consideration as well: III; Good; Strong

Page 18: Conventional treatment involves the use of an antibiotic drop or ointment that will protect against secondary bacterial infection: III; Insufficient; Discretionary

Page 18: The choice of antibiotic should take into account the normal skin and conjunctival flora, the patient's immune status, and any underlying medical problems: III; Good; Strong

Page 18: Adequate blinking during the waking hours and complete lid closure when sleeping are very important for ocular surface healing and need to be assessed in any situation where a defect persists: III; Good; Strong

Page 18: A temporary glue or suture tarsorraphy or lid splints can be helpful when blinking or lid closure are inadequate: III; Insufficient; Discretionary

Page 18: Pressure patching used to be standard treatment for abrasions and erosions; however, recent data suggests that this does not positively impact comfort or the speed of healing: I++; Good; Discretionary

Page 18: A bandage contact lens may be very helpful in cases of delayed healing: III; Good; Strong

Page 18: Autologous serum has demonstrated beneficial effects with persistent epithelial defects: III; Insufficient; Discretionary

Page 18: Cord blood tears have demonstrated beneficial effects with persistent epithelial defects: III; Insufficient; Discretionary

Page 18: Platelet-rich plasma has demonstrated beneficial effects with persistent epithelial defects: III; Insufficient; Discretionary

Page 18: Nerve growth factor has shown some benefit in selected cases, but it remains primarily investigational: III; Insufficient; Discretionary.

Page 18: Substance P and insulin-like growth factor-1 have shown some benefit in selected cases but remain primarily investigational: III; Insufficient; Discretionary

Page 18: Fibronectin has shown some benefit in selected cases but remains primarily investigational: III; Insufficient; Discretionary

Page 18: Thymosin beta 4 has shown some benefit in selected cases but remains primarily investigational: III; Insufficient; Discretionary

Page 18: Progressive thinning of the cornea or perforation usually require structural support with the application of a tissue adhesive: III; Insufficient; Discretionary.

Page 18: A small area of marked thinning or an early descemetocele may be coated with a thin layer of adhesive, which if applied to a clean and compact base, may remain in place for 6 weeks or longer: III; Insufficient; Discretionary

Page 18: If located peripherally, this may be definitive treatment; if located centrally or paracentrally, the adhesive will facilitate the non-emergent repair of the defect: III; Insufficient; Discretionary.

Page 18: Leaking descemetoceles may sometimes require the injection of an air bubble into the anterior chamber to halt the leakage temporarily: III; Insufficient; Discretionary

Page 18: Various techniques have been advocated for the application of tissue glue, including the use of a 30-gauge needle, the tip of a cotton applicator, or a micropipette: III; Insufficient; Discretionary.

Page 18: Application of the least amount of glue that will seal or support the defect should be attempted: III; Insufficient; Discretionary

Page 18: Topical corticosteroids are often used to reduce intraocular as well as corneal inflammation: I++; Good; Discretionary

Page 18: Agents that have been used to reduce scar tissue development in glaucoma and refractive surgery have been associated with epithelial surface toxicity at the commonly used doses[130,131] or have not been evaluated as to their anti-scarring effect in corneal disease: III; Insufficient; Discretionary

Page 19: An RGP lens will often improve the vision when surface irregularity is a major factor and may preclude the need for more invasive procedures: III; Insufficient; Discretionary

Page 19: A formal fitting may be more difficult and time consuming, necessitating the use of bitoric, oversized scleral, or hybrid lenses to clear surface ridges and areas of irregularity and to maintain good lens centration and stability: III; Insufficient; Discretionary

Page 19: Painted contact lenses and scleral shells are also available to hide an opacity when the visual potential is poor: III; Insufficient; Discretionary

Page 19: In most cases the surgical strategy is determined at the slit-lamp biomicroscopy examination; however, UBM and anterior segment OCT can be extremely valuable in some cases: III; Insufficient; Discretionary.

Page 19: Superficial keratectomy may be indicated for the removal of superficial deposits, lamellar keratoplasty for deeper deposits, and PK for even deeper, multilevel opacities: III; Insufficient; Discretionary

Page 19: Epithelial debridement is most helpful with lesions anterior to Bowman's layer: III; Insufficient; Discretionary

Page 19: An office slit-lamp biomicroscopy examination is often the easiest place to do this if a patient is cooperative, since the narrow slit beam makes it easier to judge depth: III; Insufficient; Discretionary.

Page 19: An operating microscope in a minor surgical suite or operating room can also be used if the patient is uncooperative or if other procedures are to be performed at the same time: III; Insufficient; Discretionary

Page 20: Use of disodium ethylenediamine tetra-acetic acid (EDTA) to facilitate the removal of a calcific band keratopathy can be very helpful: III; Insufficient; Discretionary

Page 20: When the calcium forms thick flake or plaque-like excrescences, they can be removed with forceps and scrapping, otherwise removal of the overlying epithelium is all that is necessary prior to EDTA treatment: III; Insufficient; Discretionary

Page 20: Alternatively, direct application of EDTA drops to the exposed calcium band, the use of a well filled with EDTA or the application of an EDTA-soaked cellulose disc directly over the exposed calcium may result in dissolution of the band keratopathy: III; Insufficient; Discretionary

Page 20: Treatment time with EDTA may vary depending on the density of the calcium and the approach used: III; Insufficient; Discretionary

Page 20: Another method proposed in the management of band keratopathy is the use of a diamond burr: III; Insufficient; Discretionary.

Page 20: Another method proposed in the management of band keratopathy is a Nd:YAG laser: III; Insufficient; Discretionary.

Page 20: Another method proposed in the management of band keratopathy is lamellar keratoplasty: III; Insufficient; Discretionary.

Page 20: Another method proposed in the management of band keratopathy is phototherapeutic keratectomy: III; Insufficient; Discretionary

Page 20: Mitomycin-C for subepithelial, Bowman's layer, and anterior stromal scarring may be helpful in selected cases where recurrence is a concern: III; Insufficient; Discretionary.

Page 20: Definitive criteria for the use of mitomycin-C, as well as the most effective method, dose, and period of application, have yet to be established for corneal disorders: III; Insufficient; Discretionary

Page 20: Treatment time roughly divides into two groups: 12 to 20 seconds when used as prophylaxis against the development of postkeratectomy haze or scarring, and 1 to 2 minutes when used to prevent the recurrence of scarring: III; Insufficient; Discretionary.

Page 20: Care must be taken to ensure that the proper dose of mitomycin is formulated by the pharmacy and that close attention is paid to the exposure time: III; Good; Strong

Page 20: Copious irrigation of the surface and the surrounding area with saline or a balanced salt solution afterwards is important to reduce the risk of progressive toxicity at the surgical site (specifically endothelial toxicity) or adjacent limbus: III; Good; Strong.

Page 20: The decision to use (or not use) mitomycin-C is based on the evaluation by the ophthalmologist and the potential advantages and disadvantages (i.e., side effects and complications) as they apply in each case: III; Good; Strong

Page 20: The most versatile techniques in use now involve the creation of a lamellar pocket or flap into/under which pigment is instilled: III; Insufficient; Discretionary

Page 20: This lack of depth is usually not a major problem when functional issues are the primary concern but needs to be kept in mind when cosmetic issues are dominant: III; Insufficient; Discretionary

Page 20: Anterior corneal lesions that extend beyond Bowman's layer into the anterior and mid-stroma require more extensive treatment than described above: III; Good; Strong.

Page 20: Measurements of the size and depth of the corneal opacity obtained with the anterior segment OCT, UBM, or confocal microscope may be very helpful in determining which approach is most suitable: III; Insufficient; Discretionary

Page 21: The epithelium can be allowed to cover the stromal bed or an onlay lamellar transplant can be applied: III; Insufficient; Discretionary

Page 21: The depth of the microkeratome or femtosecond dissection and the thickness of the resulting bed determine whether tissue replacement is necessary: III; Insufficient; Discretionary

Page 21: Superficial corneal flaps, created with either system, combined with excimer laser ablation to the stromal bed can be performed to remove an anterior to mid-stromal opacity either partially or totally when the overlying stroma is clear: III; Insufficient; Discretionary

Page 21: Stromal haze (reduced with mitomycin-C) and hyperopia are post-treatment issues that need to be taken into account when planning treatment: III; Good; Strong

Page 21: A common disease treatable with PTK is anterior basement membrane dystrophy: III; Insufficient; Discretionary.

Page 21: A common disease treatable with PTK is bullous keratopathy: III; Insufficient; Discretionary.

Page 21: Common diseases treatable with PTK include residual subepithelial haze or scarring following removal of band keratopathy: II-; Moderate; Discretionary

Page 21: Common diseases treatable with PTK include residual subepithelial haze or scarring following Salzmann nodular degeneration: III; Insufficient; Discretionary.

Page 21: A common disease treatable with PTK is anterior stromal scarring: III; Insufficient; Discretionary.

Page 21: A common disease treatable with PTK is Reis-Bücklers: III; Insufficient; Discretionary.

Page 21: Common diseases treatable with PTK include granular and lattice dystrophies: II-; Moderate; Discretionary

Page 21: Multiple treatments are possible with recurrent disease and can be combined with refractive treatment to reduce ametropia or astigmatism: II-; Insufficient; Discretionary

Page 21: In some cases, it may be possible to avoid or at least defer lamellar keratoplasty or PK: III; Insufficient; Discretionary

Page 21: Copious irrigation of the surface and the surrounding area with saline or a balanced salt solution afterwards is important to reduce the risk of progressive toxicity at the surgical site (specifically endothelial toxicity) or adjacent limbus: III; Good; Strong

Page 21: To prevent this and facilitate creation of a smooth surface, a masking agent (often methylcellulose or sodium hyaluronate) is used: III; Insufficient; Discretionary

Page 22: The flattening effect that causes post-PTK haze and a hyperopic shift can be reduced by treating along the outer edge of the ablation zone with small spot ablations: II-; Moderate; Discretionary

Page 22: The flattening effect that causes post-PTK haze and a hyperopic shift can be reduced by using a refractive setting: III; Insufficient; Discretionary

Page 22: Removal and replacement of diseased layers of the cornea is necessary when managing corneal opacification or edema if significant tissue thickness is involved, or when the endothelium is compromised and unresponsive to conservative measures: III; Good; Strong

Page 22: Tissue replacement is necessary when ALK removes sufficient tissue to thin the cornea and create conditions that might lead to progressive ectasia or surface irregularity: III; Insufficient; Discretionary

Page 22: While optical and tectonic rehabilitation can be achieved with ALK, it is more often viewed as a tectonic procedure because of the difficulty of controlling interface scarring and achieving a smooth dissection: III; Insufficient; Discretionary

Page 23: Partial-thickness defects related to melting disorders or peripheral ectasia may need to be managed surgically if excessive thinning or descemetocele formation develops: III; Good; Strong

Page 23: Central grafts are usually circular in shape with the size being determined by the size of the defect and whether the graft's edge will impinge on the pupil: III; Good; Strong.

Page 23: In the periphery, the pathology may be annular in nature and require a concentric donut or partial crescentic graft: III; Good; Strong

Page 23: In some cases a full-thickness patch or crescentic graft is needed: III; Good; Strong

Page 23: Lamellar keratoplasty using DALK techniques can be considered for cases of mid to deep stromal scarring: III; Insufficient; Discretionary

Page 23: When the rupture is small, the procedure may be completed or, if large, conversion to PK will be needed: III; Insufficient; Discretionary

Page 24: Penetrating keratoplasty is the procedure of choice if additional anterior segment surgery is also required: III; Good; Strong

Page 24: Peripheral opacities that are associated with significant tissue loss and increased astigmatism, but with a clear central cornea, may require either partial or full-thickness grafting: III; Good; Strong

Page 24: In some situations, a central corneal scar may be managed by an ipsilateral rotational autograft: III; Insufficient; Discretionary

Page 24: Oversized or tectonic grafts are typically used in conditions of significant peripheral thinning or infection when the peripheral edge of the pathologic process extends beyond the central 7.5 to 9.0 mm: III; Insufficient; Discretionary.

Page 24: In some cases, the treatment should be staged. The first stage is a lamellar keratoplasty that thickens the stromal bed. The second stage is a conventional PK, done many months later, through the thickened bed: III; Insufficient; Discretionary

Page 24: A temporary plastic corneal insert may be placed at the time of the retinal surgery, left in place for the duration of the retinal procedure, and then removed and replaced with a full-thickness penetrating graft: III; Insufficient; Discretionary.

Page 24: The view through the temporary keratoprosthesis is excellent and, in most cases, is superior to that which might be obtained through a recently performed corneal transplant, the only other alternative in many of these cases: III; Insufficient; Discretionary

Page 25: It is common practice for surgeons to leave sutures in place long term when selective suture removal has achieved a low level of astigmatism and good vision: III; Insufficient; Discretionary

Page 25: Earlier suture removal is possible with FLAK due to greater mechanical stability and wound healing: III; Insufficient; Discretionary

Page 25: Good control of IOP, resolution of adnexal and intraocular inflammation and infection, and repair of any lid abnormality are crucial in corneal transplant: III; Good; Strong

Page 25: Identification of thinned areas in which graft-host thickness mismatch may occur, deep stromal vascularization that may jeopardize the new graft, and ocular surface disease are important indicators of long-term graft survival: III; Good; Strong

Page 26: Regrafting is usually performed as soon as the diagnosis is established: III; Insufficient; Discretionary

Page 26: Identification of high-risk cases or those with a history of recurrent inflammation is important in that standard treatment protocols following PK may need to be augmented with higher daily doses of corticosteroid or oral antiviral agents: III; Insufficient; Discretionary

Page 26: Keratoprosthesis is now being used for unilateral or bilateral ocular trauma: III; Insufficient; Discretionary.

Page 26: Keratoprosthesis is now being used for unilateral or bilateral herpetic keratitis: III; Insufficient; Discretionary.

Page 26: Keratoprosthesis is now being used for unilateral or bilateral aniridia: III; Insufficient; Discretionary.

Page 26: Keratoprosthesis is now being used for unilateral or bilateral Stevens-Johnson syndrome: III; Insufficient; Discretionary.

Page 26: Keratoprosthesis is now being used for unilateral or bilateral congenital corneal opacification: III; Insufficient; Discretionary

Page 26: As corneal surgeons have gained a greater appreciation of the failure rate of repeat corneal transplantation, a role for a keratoprosthetic in cases of multiple graft failure has become clearer: II-; Moderate; Discretionary

Page 27: Frequent reassessment of the optic nerve and visual field studies are necessary to monitor these patients optimally and preserve their vision: II-; Moderate; Strong

Page 27: Patients with severe dry eye and autoimmune ocular surface diseases have had some success with a Boston type 2 keratoprosthetic designed to be used through the lid: III; Insufficient; Discretionary.

Page 27: Patients with severe dry eye and autoimmune ocular surface diseases have had some success with osteo-odonto-keratoprosthesis: III; Insufficient; Discretionary

Care Process – Follow-Up

Page 27: Frequent follow-up is necessary in many of these cases to reassess the underlying disease process and make adjustments to the medical or surgical treatment: III; Good; Strong

Page 27: For the management of corneal opacification, follow-up is required to monitor corneal clarity and the degree of surface irregularity: III; Good; Strong.

Page 27: Coexisting problems, particularly intraocular inflammation and IOP, need to be reassessed regularly: III; Good; Strong

Counseling and Referral

Page 28: Once a definitive diagnosis is made and the related work-up has been completed, a detailed discussion of the causes of the edema or opacity, and of various treatment options, becomes important: III; Good; Strong

Page 28: When more sophisticated diagnostic or medical management approaches (i.e., those exceeding the training or the level of comfort of the treating physician) are required, or if complex surgical treatments may be needed, referral for consultation is recommended: III; Good; Strong

Page 28: Referrals to retina, glaucoma, or pediatric ophthalmic subspecialists may be needed in some situations: III; Good; Strong.

Page 28: Once the condition has been resolved or has stabilized, referral back to the comprehensive ophthalmologist is appropriate: III; Good; Strong.

Page 28: A team approach is often of great advantage, particularly when geography makes subspecialist visits challenging: III; Good; Strong.

Page 28: The primary care physician should be included in the discussion, especially when surgery is being considered: III; Good; Strong

Page 28: When the disease process or its management is complex, every effort should be made to counsel the patient appropriately: III; Good; Strong

Appendix 4: IOP Determination in Diseased or Postsurgical Corneas

Page 40: Use of alternative and less subjective techniques for IOP determination in these diseased, abnormal, or surgically altered corneas is strongly advised: III; Good; Strong

Page 40: It is very important to use the same technique consistently, from visit to visit, to detect clinically significant and meaningful IOP elevations: III; Good; Strong

APPENDIX 4: DETERMINATION OF INTRAOCULAR PRESSURE IN DISEASED OR POSTSURGICAL CORNEAS

Intraocular pressure (IOP) assessment in diseased corneas may be very inaccurate when measured only by Goldmann applanation tonometry (GAT). This is due to a host of reasons, such as disease-induced and treatment-induced alterations in corneal thickness, hydration state, corneal curvature/astigmatism, an irregular corneal epithelial surface, or corneal stromal scarring. All of these factors can affect the estimation of the inherently subjective endpoint of GAT (i.e., the "just touching" inside edges of the semicircular mires viewed through the Goldmann applanation prism tip). Therefore, use of alternative and less subjective techniques for IOP determination in these diseased, abnormal, or surgically altered corneas is strongly advised. Electronic devices that assess IOP by less subjective techniques include the following:

- Applanation techniques, which are measured using the following technology:
  - Pneumatonometer. This technology uses a pneumatic sensor (consisting of a piston floating on an air bearing) with a 5 mm fenestrated silicone tip that conforms to the cornea. The balance between the flow of air from the machine and the resistance to flow from the cornea affects the movement of the piston, and this movement is used to calculate the IOP. This device generates 40 readings/second, and also measures ocular pulse amplitude. Topical anesthesia is required.
  - Non-Goldmann applanation tonometer. This technology utilizes a free-floating 1 mm micro-strain gauge transducer to detect transmitted IOP. The transducer is surrounded by an outer ring that flattens the adjacent cornea, reducing its influence on measurement. These devices measure 500 samples/second and average 8 or 10 readings for each IOP determination within confidence limits. Topical anesthesia is required.
  - Ocular response analyzer. This technology uses a collimated air pulse to cause the cornea to move inward and then outward, in a bi-directional applanation process, to measure the biomechanical properties of the cornea (i.e., hysteresis) and calculate a "corneal-compensated" and GAT-equivalent IOP. This technology also measures ocular pulse amplitude and does not require topical anesthesia.
- The contour-matching Pascal technique. This technology utilizes a piezoresistive sensor embedded into the tonometer tip to digitally sample IOP 100 times/second. The concave tip shape causes a relaxation of the cornea to conform to the DCT tip and minimizes any influence of corneal properties on IOP measurements. An internal microprocessor then analyzes this direct proportional signal, and extracts IOP and ocular pulse amplitude. As such, the device calculates an IOP independent of corneal properties. It requires 6 seconds or 6 ocular pulse cycles to determine the IOP, and it requires topical anesthesia.
- The rebound tonometry deceleration technique. This utilizes an induction coil to magnetize a small plastic-tipped metal probe, which is rapidly fired against the cornea (0.25 m/sec). Software analyzes the rate of deceleration and the contact time of the probe against the cornea (approximately 0.05 sec), the relative magnitude of which is proportional to IOP, and from which the IOP is calculated. Six measurements are required for accuracy. This technology does not require topical anesthesia.

Although applanation and rebound tonometers are more influenced by corneal properties compared with other devices, they are more objective than GAT. Therefore, they may more accurately and reproducibly estimate "true IOP" (relative to GAT) over the course of a patient's corneal disease state. Nevertheless, it is very important to use the same technique consistently, from visit to visit, to detect clinically significant and meaningful IOP elevations. Early detection of elevated IOP will allow timely initiation of IOP-lowering therapy before irreversible optic nerve damage occurs. These eyes are frequently subject to either disease-induced or treatment-induced secondary IOP elevation, which often goes undetected when relying on GAT alone to determine IOP.

RELATED ACADEMY MATERIALS

Basic and Clinical Science Course

External Disease and Cornea (Section 8, 2013–2014)

Focal Points

IOL Power Calculation in Patients with Prior Corneal Refractive Surgery (2013)
Pseudophakic Cystoid Macular Edema Module (2012)

Patient Education Brochure

Corneal Abrasion and Erosion (2011)
Cystoid Macular Edema (2011)

Preferred Practice Pattern® Guidelines – Free download available at www.aao.org/ppp.

Comprehensive Adult Medical Eye Evaluation (2010)

To order any of these products, except for the free materials, please contact the Academy's Customer Service at 866.561.8558 (U.S. only) or 415.561.8540 or www.aao.org/store.

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