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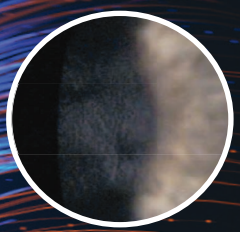

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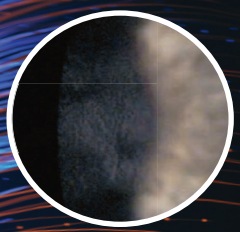

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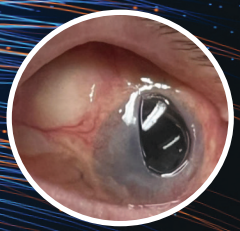

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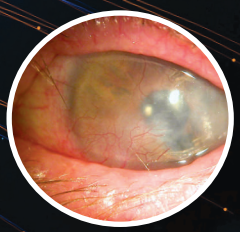

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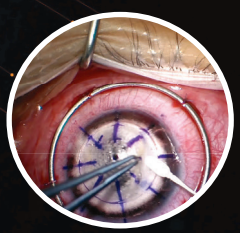

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CORNEA NEWS

META-ANALYSIS HIGHLIGHTS LOW GLOBAL INCIDENCE OF *ACANTHAMOEBA* KERATITIS

New research, which sought to gain a better understanding of the prevalence of *Acanthamoeba* keratitis, found that it has a relatively low incidence in the general population but it remains strongly linked with contact lens wear.

While *Acanthamoeba* keratitis is a significant cause of infectious keratitis, a comprehensive assessment of the incidence of this condition remains lacking. To address this gap, an international group of researchers (representing institutions in the U.S., U.K., China and Italy) initiated a systematic review and meta-analysis to examine the incidence of AK using the currently available data from peer-reviewed literature.

In this analysis, researchers calculated the incidence of AK as the number of cases per health-care center per year (annualized-center-incidence). They also calculated the following meta-analytical ratios: (a) the ratio of AK eyes to the count of non-viral microbial keratitis (MK) eyes, and (b) the ratio of AK eyes to the overall population (i.e., the total number of subjects of a nation or region, as indicated by the authors in each study).

Overall, the study included 105 articles published between 1987 and 2022. Investigators identified a total of 91,951 eyes, with 5,660 affected by AK and 86,291 by non-viral microbial keratitis. Data showed that the median annualized-center-incidence was 19.9 new *Acanthamoeba* keratitis eyes per health-care center per year, with no statistically significant differences observed among continents. Risk factors did, however. "*Acanthamoeba* keratitis, in regions with high per capita incomes, primarily affects contact lens wearers," the authors wrote, "whereas elsewhere ocular trauma, often in agricultural workers, is the major association."

Additionally, the study authors found that the ratio of AK eyes to the total number of MK eyes was 1.52 percent. Comparatively, the ratio of AK in relation to the entire population was estimated at 0.0002%, or 2.34 eyes per 1,000,000 subjects, according to the study authors.

"Our analysis demonstrates AK as a relatively low-incident condition among the general population, with no major differences in terms of incidence among different continents," the study authors wrote.

"These studies will provide valuable insights for improving our understanding of *Acanthamoeba* keratitis epidemiology and implementing effective strategies for prevention, diagnosis and management," the research team concluded.

1. Aiello F, Afflitto GG, Ceccarelli F, et al. Perspectives on the incidence of Acanthamoeba Keratitis: A Systematic Review and Meta-Analysis. *Ophthalmology*. August 8, 2024 [Epub ahead of print].

HIGHER-ORDER ABERRATIONS IN FUCHS' PATIENTS STUDIED

A new analysis showed significant changes in high-order aberrations among Fuchs' endothelial corneal dystrophy patients with subclinical corneal edema. This data, recently published in the journal *Cornea*, highlight how tomographic analysis can support visual impairment assessment, disease progression and decision-making for early endothelial keratoplasty in these individuals.

This retrospective, single-center case series, which analyzed whether tomographic changes in Fuchs' dystrophy impact the higher-order aberrations in the early period of the disease, included a total of 78 eyes of 47 patients with Fuchs' endothelial dystrophy with slit-lamp biomicroscopically visible guttae, but no visible corneal edema. These patients were assigned to group 0 (no subclinical corneal edema) or 1 (subclinical corneal edema).

Group 1 was composed of 50 eyes of 33 patients with a mean age of 70.9 years and group 0 included 28 eyes from 18 patients with a mean age of 63.9 years. In group 0 and 1, 13 eyes and 34 eyes were pseudophakic, respectively.

Sixty-six healthy eyes of 38 patients were also included in the analysis as the control group. Of these, 58 eyes were phakic and eight were pseudophakic.

Study authors calculated mean values and standard deviations for the root mean square (RMS), coma, trefoil and spherical aberrations of the cornea, the anterior surface and the posterior surface.

Data demonstrated statistically significant differences in the RMS higher-order aberrations, coma and spherical aberrations of the posterior surface in group 1 eyes when compared to those in group 0. No statistically significant differences in high-order aberrations were observed between the control group and eyes without subclinical corneal edema (Group 0).

These findings showed statistically significant increases in high-order aberrations, particularly of the posterior corneal surface, in patients affected by Fuchs' endothelial dystrophy with subclinical corneal edema, according to the study authors, who noted, "Our study adds to the current literature by providing evidence of significant changes in high-order aberrations in patients with Fuchs' endothelial corneal dystrophy with subclinical corneal edema compared with those without.

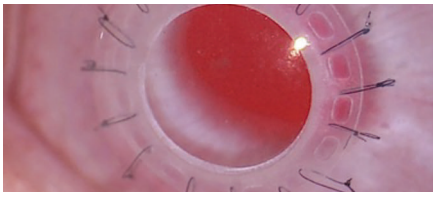
"Early tomographic analysis can, therefore, aid in detecting subclinical corneal edema with varying magnitude of high-order aberrations compared with patients with Fuchs' endothelial dystrophy without subclinical edema or healthy eyes," the authors added, "which, in turn, can help characterize the patients' visual impairment and decision-making for early endothelial keratoplasty." ◀

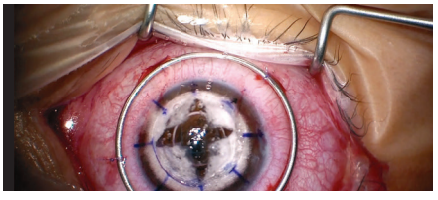
1. Blöck L, Son HS, Köppe MK, et al. Corneal high-order aberrations in Fuchs' endothelial corneal dystrophy and subclinical corneal edema. *Cornea*. July 30, 2024 [Epub ahead of print].

CONTENTS

*Editor's note: The staff would like to thank Wills Eye cornea specialist **Sadeer B. Hannush** for his invaluable assistance in planning this issue of **Review of Cornea and External Disease.***

FEATURES





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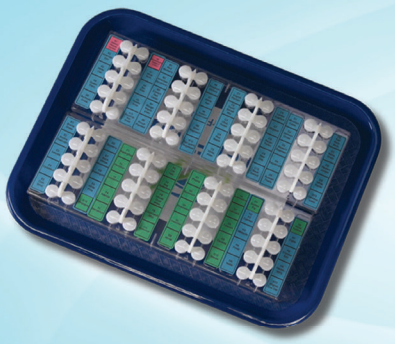

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A REVIEW OF PHOTOREFRACTIVE KERATECTOMY

Sarah Pajek, MA, BS, and Ellen H. Koo, MD
MIAMI

Photorefractive keratectomy received approval by the U.S. Food and Drug Administration in 1996, and quickly rose in popularity over incisional radial keratotomy. However, compared to LASIK, PRK remains a less popular procedure choice for primary refraction correction and represents about 10 to 15 percent of all laser refractive procedures performed in the United States.[1] That said, due to its unique advantages, PRK may be preferable in certain situations, and the procedure will continue to play an important role in refractive surgery. Here, we discuss the PRK procedure in further detail, including its indications as well as how to avoid and manage complications.

INDICATIONS AND PREOPERATIVE CONSIDERATIONS

Despite an association with more postoperative discomfort and a slower healing time than LASIK,[2] PRK can be the preferred refractive surgery in several instances. For patients who are considered suboptimal candidates for LASIK, PRK may be an option. This includes patients with thinner corneas, especially since a residual stromal bed of at least 250 µm is generally recommended with LASIK.[3-5] Certain eyes are deemed to be at higher risk for post-LASIK ectasia, based on tomographical findings and its derived indices.[6,7]

In addition, variations in anatomy may render the patient to be at higher risk for LASIK flap-related complications.[8] These include history of epithelial basement membrane dystrophy, history of recurrent erosions, very flat or very steep corneas, or anteriorly placed scleral buckles.[3,8] PRK would be preferable over LASIK in these situations.

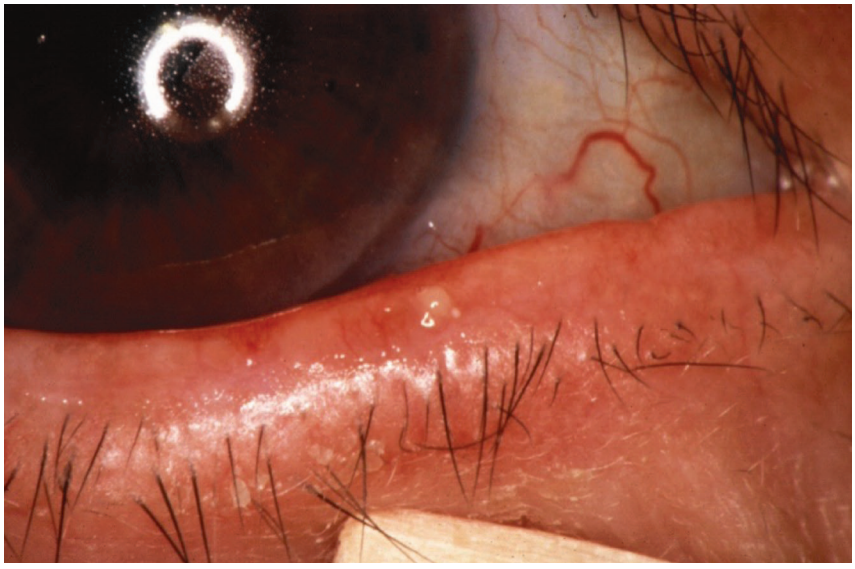
For patients with occupations that place them at higher risk for flap dislocation, such as athletes or military personnel, they may elect PRK over LASIK, as traumatic LASIK flap dislocation is a known complication that can occur several years after the procedure.[9] Finally, PRK is often used as a reliable means for refractive enhancement following prior cataract surgery or LASIK.[10,11]

Similar to other refractive surgeries, contraindications to PRK include uncontrolled or significant eye diseases, including severe ocular surface diseases and atopy.[3] Systemic connective tissue diseases and uncontrolled diabetes mellitus may be considered relative contraindications as these patients are at risk for delayed epithelial healing.[3] Furthermore, PRK should be postponed in patients who are currently pregnant, breastfeeding or who are taking medications that can affect their ocular health.[12] Patients with a history of herpes simplex keratitis should be treated with prophylactic antiviral medication for several months before the PRK procedure to reduce the risk of perioperative viral reactivation.[3] Meibomian gland disease and blepharitis must be treated and controlled prior to the procedure; measures include lid hygiene, surface lubrications and oral tetracyclines.

Prior to the procedure, patients are instructed to discontinue soft contact lenses for three days and hard contact lenses for two weeks in order to avoid corneal warpage, which can impact preoperative corneal measurements.[3]

PRK TECHNIQUE: A REVIEW

The procedure begins with epithelial debridement, which removes the epithelium without disrupting Bowman's layer. The debridement can be achieved by several methods, including mechanical removal via spatula, mechanical removal using a rotary brush, chemical removal using an alcohol solution, and removal using a femtosecond laser.[13-15] Among these various methods, removal of the epithelium using a diluted alcohol solution of 20% ethanol within a 6- or 7-mm corneal marker has been associated with the best long-term visual outcomes and



In a PRK candidate with meibomian gland dysfunction gentle expression of a blocked meibomian gland can help both diagnose the extent of the MGD as well as treat it.

a faster mean epithelial healing time.[13-18] Once the epithelium is debrided, a 193-nm argon fluoride excimer laser is used for the surface ablation of the stroma itself.[3] Additional pulses to the central 2.5-mm area may help to prevent central corneal islands. Patient fixation and cooperation throughout the procedure are important, in order to avoid decentered ablations, which can lead to poor visual outcomes.

POSTOPERATIVE PAIN AND CONSIDERATIONS

Acute postoperative pain typically begins soon after surgery, peaking at about 24 hours, and continues over the first three to five postoperative days until re-epithelialization is complete.[19-21] Most patients do report some level of acute pain after PRK, and self-reported pain severity can vary widely.[19] Several pain management strategies are available. Topical non-steroidal anti-inflammatory drugs such as ketorolac tromethamine 0.5% or diclofenac 0.1% may be used postoperatively, but these are associated with delayed epithelial regeneration; thus, patients are typically instructed to use these sparingly, i.e., for breakthrough pain.[17] Oral codeine/acetaminophen 30/500 mg administered four times per day for four days after PRK has been shown to be a safe and effective way to control post-PRK pain.[22]

Other pain management modalities for post-PRK pain include short-term oral gabapentin, ketorolac-soaked bandage contact lenses and chilled bandage contact lenses.[23-25] A bandage contact lens remains in place post-procedure, and is removed several days after the procedure. Topical fourth-generation fluoroquinolone drops such as moxifloxacin 0.5% and gatifloxacin 0.3% are prescribed to prevent infection during this period. While the epithelium is usually healed by day three, waiting to remove the bandage lens until day five may reduce the frequency of postoperative pain and discomfort, as well as epithelium-related complications (filamentary keratitis and recurrent corneal erosion).[26]

Postoperatively, patients may experience four to six weeks of halos or blurring while the epithelium regenerates and should be counseled on this to establish expectations.[3]

CORNEAL HAZE

Corneal haze is more likely to occur in PRK than in LASIK and occurs more frequently in hyperopic and large myopic or astigmatic corrections.[3,27,28] Mild early haze incidence peaks around two months, while severe late haze peaks at around four months.[27]

In regard to prevention of haze formation, the application of topical mitomycin-C has been shown to play an important role in preventing haze.[29,30] In a meta-analysis, the usage of MMC during PRK reduced both early- and late-onset haze, and improved the predictability of refraction and subjective postoperative visual acuity.[30]

While corticosteroids are commonly administered routinely after PRK, studies have demonstrated conflicting and controversial results, especially when it comes to its role in haze prevention.[31,32] A more recent systemic review and meta-analysis suggests that steroids can reduce postoperative corneal haze and myopic regression during the first six months after refractive surgery.[33] In addition, long duration of steroid administration (more than three months) post PRK appeared to be unnecessary in low and moderate myopia compared with high myopia.[33]

Ultraviolet-B (UV-B) has been associated with corneal subepithelial haze and abnormal stromal repair following PRK.[17,34] Patients should also be advised to wear UV-blocking sunglasses when appropriate for at least six months postoperatively.[17] Oral ascorbate has been shown to have a protective effect against haze formation following PRK.[35] A survey study showed that the most common regimen used postoperatively to prevent post-PRK haze were sunglasses, mitomycin-C, topical corticosteroids and oral ascorbate.[36]

MANAGEMENT OF POST-PRK HAZE

Clinically significant corneal haze post-PRK can be separated into the categories of early-onset haze (less than three months following PRK), versus late-onset haze (greater than three months following PRK). Early-onset haze typically responds well to topical steroids, whereas late-onset haze tends to be more resistant to them.[37-39]

For early-onset haze, topical prednisolone acetate 1% may be used five to six times daily and tapered over the course of three months. Adjunct serial imaging (such as slit lamp photography, anterior segment OCTs, epithelial maps, and Scheimpflug densitometry) along with slit lamp examinations performed over the subsequent weeks may be helpful in monitoring the response.[37] If haze persists beyond three months, it's considered to have progressed to late-onset haze, and further intervention is warranted.[37]

For late-onset haze, topical prednisolone acetate 1% may be initiated, similar to early-onset haze. However, unlike early-onset haze, if improvements aren't seen by four weeks, surgical intervention can be discussed with the patient.[37]

Surgical interventions for superficial cor-

More common with PRK than LASIK, corneal haze occurs more frequently in hyperopic and large myopic or astigmatic corrections.

neal haze refractive to medical therapy comprise mechanical debridement or superficial PTK for less than 15 µm.[38] If haze involvement is more than one-fifth of the corneal thickness or deeper than 15 µm, deep PTK or therapeutic myopic PRK ablation can be performed.[38] The laser ablation depth is set to the haze depth, after accounting for the thickness of the epithelial hyperplasia.[37]

Alternatively, based on surgeon preference, instead of deep PTK or therapeutic PRK, a beaver or crescent blade or a diamond burr can be used to remove the underlying stromal haze after epithelial debridement.[37] In either approach, 0.02% MMC (usually via a soaked sponge) is applied to the surface for two minutes,[37,39] followed by copious irrigation of the cornea with balanced salt solution.

REGRESSION

Regression is a risk of any refractive surgery. Refractive regression is defined as the gradual, partial or complete loss of the attempted correction, and affects the predictability of refractive surgery procedures; regression is deemed to be mainly due to epithelial hyperplasia and stromal remodeling.[41,42] Most cases of myopic regression develop over the first three months after surgery, with only a slight change after the first three months and up to 10 years.[41,42]

Higher refractive correction (>-5 D), small optical zone (<6 mm) and unstable fixation during laser ablation of PRK for myopia and myopic astigmatism were found to be associated with higher risk for regression.[43] Additionally, corneal haze post-PRK can also contribute to refractive regression.[28]

The main indication for retreatment is patient dissatisfaction with visual acuity due to the residual refractive error.[28] Compared to older studies, one study by Utah's Majid Moshirfar, MD, and his co-authors demonstrated that modern PRK enhancement after PRK has improved visual acuity and refractive outcomes.[44] While PRK enhancement isn't an FDA-approved procedure, the authors demonstrated that PRK enhancement meets or exceeds the FDA criteria for the correction of refractive error.[44]

When considering PRK enhancement, the surgeon should determine that there is stability of the refraction for at least six months.

ADDITIONAL COMPLICATIONS

Mildly decentered ablation is quite common and is of little clinical significance. Decentration, however, becomes clinically significant when the decentration is greater than 0.5 mm from the visual axis.[42] Decentered treatments may be associated with poor postoperative visual acuity and decreased quality of vision.[45] Topography-guided customized ablation can be an effective option for patients who underwent prior eye surgery that resulted in decentered ablation.[46,47]

The incidence of central corneal islands is higher in PRK compared to LASIK. Following PRK, most cases of central islands resolve by one month, and nearly all resolve by one year.[48,49]

Therefore, conservative management is generally recommended, especially in the early postoperative period, with regular monitoring using topography. Asymptomatic central corneal islands don't warrant treatment. Persistent, symptomatic central islands may need surgical intervention, but stability of the island (for at least six months) should be established prior to treatment. PTK is used to treat symptomatic and persistent central islands; at this time, there's no consensus regarding the best ablation algorithm to treat central corneal islands.[50,51]

Corneal ectasia may occur after refractive surgery, although the incidence is lower in eyes undergoing PRK than LASIK.[52]

In conclusion, given PRK's unique advantages, the procedure will continue to play an important role in refractive surgery, as it can serve as the preferred modality of vision correction in certain patients. By becoming familiar with the pearls and pitfalls surrounding the procedure, the surgeon can ensure that PRK is a safe and effective procedure that affords excellent visual outcomes and patient satisfaction. ◀

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Dr. Koo is an associate professor of clinical ophthalmology at the University of Miami Miller School of Medicine, and practices at the Bascom Palmer Eye Institute. Neither author has a financial interest in any product mentioned.

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WHAT'S NEW IN ARTIFICIAL CORNEAS

Gavin Li, BS, and Esen Karamursel Akpek, MD
BALTIMORE

Since the first successful full thickness corneal transplantation was performed by Eduard Zirm in 1905,[1] the procedure has grown to become the most commonly performed transplantation globally. In the last 20 years, the field of corneal transplantation has been revolutionized by the development of partial-thickness transplantation techniques allowing less invasive approaches to treating corneal disease.[2,3] However, despite the significant technological and surgical advancements that have dramatically improved the clinical outcomes of corneal transplantation, there continues to be a significant shortage of available corneal tissue. Currently, only 1 in 70 patients who may benefit from the procedure eventually receive it.[4]

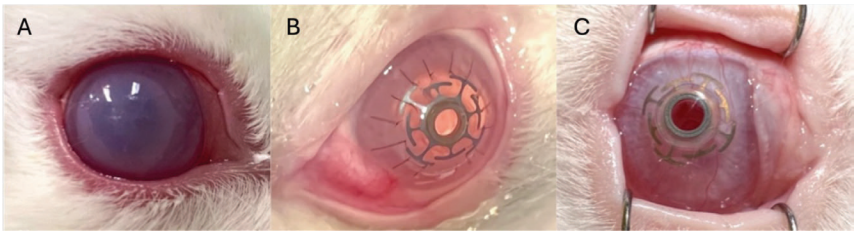
Artificial corneas, or keratoprostheses, have been proposed as a potential answer to the limitations of traditional donor keratoplasty. Fully synthetic corneas can be made readily available and be used to augment the supply of transplantable tissue by circumventing the need for costly eye banking infrastructure. However, artificial corneas have historically been used primarily as a last-resort option for patients who've experienced multiple graft failures or aren't suitable candidates for traditional donor keratoplasty, likely due to the frequent postoperative complications that may lead to loss of vision or loss of the eye.

Keratoprostheses that have been cleared by the United States Food and Drug Administration include the Boston type-1 keratoprosthesis (1992) (Massachusetts Eye and Ear Infirmary, Boston), the most widely implanted device globally with subsequent modifications including the click-on and Lucia models also gaining approval; the Boston type-2 keratoprosthesis (1992), and the AlphaCor (2003) (formerly Coopervision Surgical, Lake Forest, California) which was the first approved fully synthetic keratoprostheses. Recently, reinvigorated efforts in developing fully synthetic flexible devices have resulted in several prototypes now undergoing clinical trials. Here, we'll summarize these new developments.

BOSTON MI-KPRO

The Boston type-1 keratoprosthesis is the most extensively studied device; frequently referenced as the standard of care for artificial corneal transplantation. Newer models of the device including the click-on and Lucia models that consist of a two-piece design have likewise gained FDA approval and improved the accessibility issues outside of United States. However, long-term studies reporting increasing rates of complications including retroprosthetic membrane formation, sterile keratolysis and, most significantly, glaucoma, have limited the application of these devices.[5,6]

The minimally invasive keratoprosthesis



Eleftherios Paschalis, MD

Figure 1. A) Rabbit model of acid burn injury. B) One-month postop following mi-KPro implantation. C) One-year postop following mi-KPro implantation. Intraocular pressure, retina and optic nerve were normal at one year. Irido-corneal angle was open with no retroprosthetic membrane and clear optic.

Allan Slomovic, MD

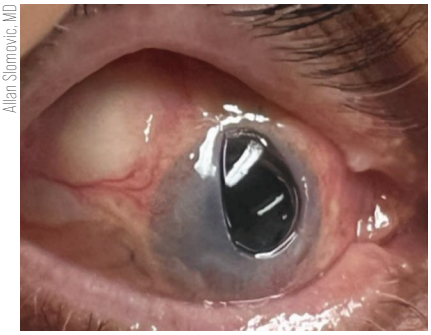


Figure 2. Slit-lamp picture showing postoperative month 12 following CorNeat implantation.

(Boston mi-KPro) was developed in an attempt to overcome these postoperative complications by decreasing the inflammation, post-implantation.[7] The device uses a new ultra-thin, flexible titanium backplate that's implanted anterior to Descemet's membrane similar to deep anterior lamellar keratoplasty.[7] There remains limited biointegration with the host cornea due to the titanium material. Only the optic penetrates the anterior chamber, resulting in less trauma compared to the Boston type-1 keratoprosthesis. The flexibility of the new backplate addresses the rigidity issue of the Boston type-1 keratoprosthesis, which caused a significant inflammatory response due to micro-trauma from blinking.

A poster presentation detailing an animal study compared the mi-KPro to traditional penetrating keratoplasty in alkali and acid burn models, reporting minimal complications in the mi-KPro eyes after 12 months. No mi-KPro eyes developed ocular hypertension or had significant optic nerve axonal loss, while half of the eyes receiving traditional keratoplasty showed significant optic nerve axonal loss.

CORNEAT

CorNeat keratoprosthesis (CorNeat Vision, Israel) features a unique design that consists of a central full-thickness optic made out of polymethylmethacrylate integrated with a polyurethane fiber skirt, representing a combination of traditional rigid keratoprostheses and novel flexible devices. The skirt is designed to integrate directly with the host conjunctiva rather than the optic with the host cornea, a novel approach that aims to enhance the bio-integration by taking advantage of the highly vascular conjunctival bed to ideally minimize the risk of device extrusion. The polymethylmethacrylate is a proven material with excellent optics.

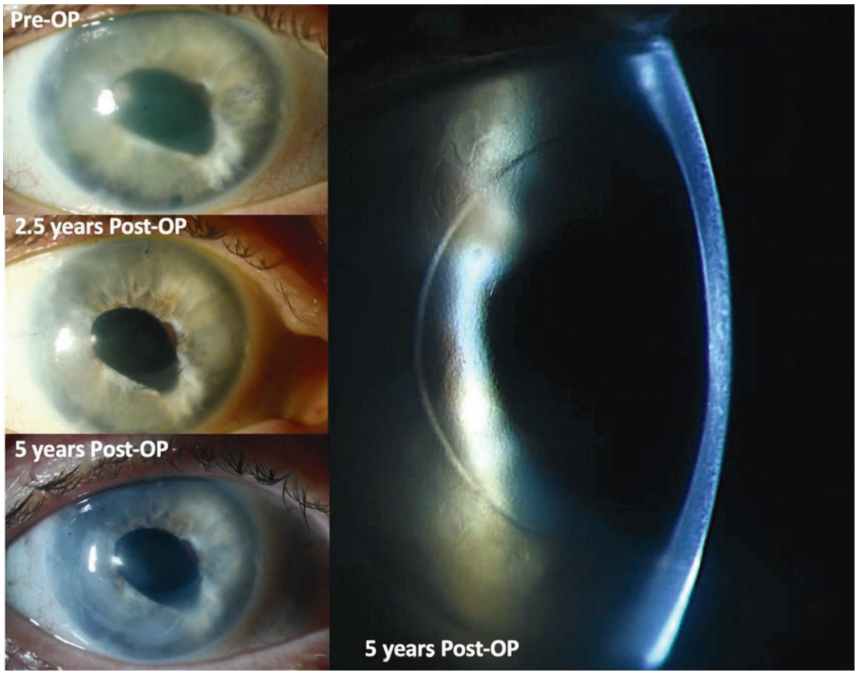
The surgical technique involves placement of the device skirt under the host conjunctiva with insertion of the optic into a central corneal trephination site. Although the biointegrating skirt is a novel way to improve the device retention, rigidity and lack of bioadhesion around the optic may pose known challenges that traditional keratoprosthesis devices have been associated with. This device is indicated for patients with a history of previous graft failure.

The first published in-human implantation in 2023 marked a milestone for the company.[8] One-year outcomes of the device in the first human implantation showed visual acuity improvement. The device remained in position with some regional conjunctival retraction over the skirt, and no anterior chamber inflammation was observed. Short-term rabbit studies reported a retention rate of over 80 at six months, with minimal anterior chamber inflammation. However, cataract developed in five of the eight eyes, as expected with any full-thickness device.[9] The ongoing multicenter clinical trial in Canada, France, Israel and the Netherlands will provide critical data on the device's longer-term performance in diverse populations and clinical settings.

ENDOART

The EndoArt (EyeYon Medical, Israel) introduces a 50-µm thick, flexible, synthetic partial-thickness disc with a diameter of 6 to 8 mm designed to function as an artificial corneal endothelium.[10] The device is made from a hydrophilic acrylic material and serves as a barrier preventing excessive hydration of the posterior stroma in cases of endothelial failure. The implantation technique is similar to that of donor corneal endothelial keratoplasty. After the Descemet's membrane and endothelium are removed from the host cornea, the EndoArt is injected, and an air bubble is used to facilitate adherence to the posterior stroma. The device is currently indicated for patients with multiple endothelial graft failures or as a bridge therapy until donor endothelial keratoplasty is available.

The first human implantations, with a follow-up up to 17 months, have shown promising results, with sustained reductions in corneal thickness and improved vi-



Gerd U. Auffarth, MD

Figure 3. A 58-year-old female status post cataract surgery complicated by endophthalmitis sustained corneal endothelial decompensation, despite aggressive management. She underwent a conventional DMEK which failed and led to end-stage bullous keratopathy. EndoArt device was implanted in 2019 which kept the cornea clear over the five years of follow-up.

sual acuity.[10–12] The common complication of device dehiscence requiring re-bubbling may be a concern, but the lack of sterile keratolysis or encapsulation reported thus far is encouraging. A clinical trial is currently being planned in the United States.

GORE SYNTHETIC CORNEA DEVICE

Developed jointly by W. L. Gore & Associates and Johns Hopkins University, the GORE synthetic cornea is a flexible, full-thickness, single-piece keratoprosthesis device that aims to mimic the biomechanics of the human cornea closely.[13] The device consists of a central optic and a peripheral skirt made from perfluoroalkoxy alkane (PFA), with expanded polytetrafluoroethylene (ePTFE) lining the skirt and optic wall to enhance bio-integration into the recipient corneal stroma.

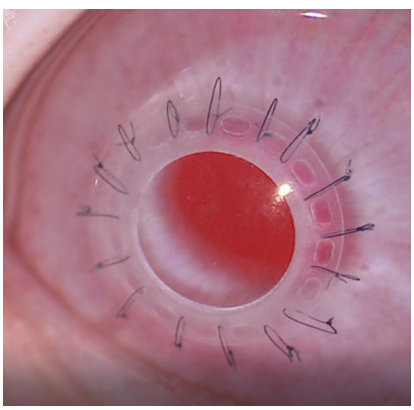
The implantation process involves placing the device's optic into a central corneal trephination and inserting the skirt into a circumferential stromal pocket.[14] The surgical technique along with the biomechanical design considerations aim to minimize the effect of shear forces at the optic-device junction, reducing inflammation and enhancing the stability of the device. Spoilation studies have shown that the GORE device doesn't experience the same issues with spoilation and debris deposition on the optic that may compromise visual acuity as previous flexible keratoprostheses.[13] These results highlight the device's potential for long-term compatibility with commonly used topical eye medications.

Medium-term rabbit studies have shown no signs of intraocular inflammation, periprosthetic membrane formation, cataracts or glaucoma.[14,15] The evidence of bio-integration, including collagen deposition and fibroblast ingrowth into the skirt and optic wall, as early as six weeks post-implantation, is particularly promising. Currently, an early feasibility human study assessing the safety and efficacy of the device is being initiated in Mexico.

In conclusion, recent advances in the field of artificial corneal transplantation hold significant promise for patients who are poor candidates for traditional donor keratoplasty or reside in areas of the world with a scarcity of donor corneal tissue or eye banking. Newer devices seem less-invasive surgically and are showing fewer complications and better outcomes compared to earlier models. Notably, studies on newer flexible devices report significantly lower rates of glaucoma than the rigid Boston keratoprosthesis, although these findings are based on significantly shorter-term follow-ups.

Minimally invasive and/or partial-thickness devices such as the EndoArt and Gore synthetic cornea device offer an option for patients with repeated endothelial graft failure or an alternative for treating endothelial disease in areas where the donor supply isn't adequate to address patient needs. These innovations signify a shift towards more tailored approaches in corneal prosthetics. However, the challenge remains to develop a cost-effective device that can be widely adopted, particularly in resource-limited settings devoid of eye banking, where artificial corneas could provide substantial benefits.

Further research and extensive clinical studies are essential to optimize these devices, improve their outcomes and broaden their applicability. The ultimate goal is to enhance access to sight-saving treatments for patients with corneal blindness around the world, ensuring that advancements in biotechnology translate into real-world benefits for those in need. ◀



Esen Karamursel Akpek, MD

Figure 4. Gore synthetic cornea device implanted in a healthy rabbit eye. Photograph was taken 12 months following the surgery.

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CORNEAL NEOVASCULARIZATION AND LIPID KERATOPATHY

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Corneal neovascularization is a pathological condition characterized by the abnormal growth of blood vessels into the normally avascular cornea. This significant ophthalmologic condition not only disrupts corneal transparency but also poses a threat to visual acuity, potentially leading to blindness if untreated.[1] Intertwined with corneal NV is lipid keratopathy. Together, they significantly impact corneal transparency. Lipid keratopathy is characterized by the deposition of lipids within the corneal stroma, frequently following the development of neovascularization.[2]

Understanding the intricacies of corneal neovascularization requires a multifaceted approach that encompasses the pathogenesis, clinical manifestations, advanced clinical imaging techniques and contemporary treatment strategies. Here, we'll delve into the cellular and molecular mechanisms of corneal neovascularization, including the role of angiogenic factors and inflammatory cytokines,[3,4] and explore the pathological processes underlying corneal neovascularization. We'll also explain how this exploration is crucial for the development of targeted therapies aimed at modulating these pathways.

CELLULAR AND MOLECULAR MECHANISMS IN CN

There are several factors that contribute to corneal neovascularization:

• ***Angiogenic factors.*** Angiogenic factors produced by inflammation make up a key pathological process in the development of corneal NV. Corneal NV involves the activation of vascular endothelial cells (VECs) in response to hypoxia or inflammation. One of the key angiogenic factors is Vascular Endothelial Growth Factor.[5] VEGF promotes endothelial cell proliferation, migration and new vessel formation. The VEGF/VEGFR pathway is one of the most critical, with VEGF binding to its receptors on endothelial cells to activate downstream signaling cascades. VEGF exerts its effects primarily through three separate tyrosine kinase cell-surface VEGF receptors (VEGFR1-3), with VEGF-A, VEGFR-1 (Fms-like tyrosine kinase 1, Flt-1) and VEGFR-2 (kinase insert domain protein receptor, KDR/(fetal liver kinase 1, Flk-1) being strongly expressed in inflamed and vascularized human corneas and, thus, may play an important role in corneal NV.[5] In addition to VEGF-A and VEGFR2, other VEGF peptides play significant roles in NV. Aside from important functions in the NV of VEGF-A and VEGFR2, the activation of VEGFR1 leads to the loss of pericytes. One study showed that angiogenic defects caused by pericyte depletion are phenocopied by intraocular injection of VEGF-A or pericyte-specific inactivation of the murine gene encoding VEGFR1.[6]

VEGF is an important mediator of angiogenic signaling in inflammation to promote endothelial cell survival, proliferation and migration. It's upregulated in response to hypoxic cornea via the Hypoxia-inducible factor-1 (HIF-1) pathway.[7] Hypoxia-inducible factors (HIFs) are crucial regulators of angiogenesis in response to low oxygen levels. HIF-1α, in particular, is stabilized under hypoxic conditions and translocates to the nucleus, where it induces the transcription of VEGF and other proangiogenic genes. The interplay between HIF-1α and VEGF is a key driver of angiogenesis under hypoxic conditions in corneal NV. A study strongly implicated corneal HIF-1α as a component of the inflammatory and neovascular cascade initiated by hypoxia and further suggested that HIF-1α was a proximal regulator of VEGF expression in a mouse model of closed eye contact lens wear.[7]

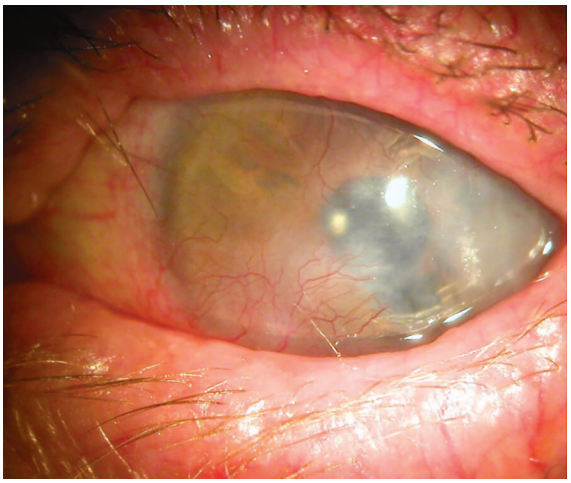
Basic fibroblast growth factor (bFGF) is another potent angiogenic factor implicated in corneal NV. The bFGF stimulates endothelial cell division and migration by binding to fibroblast growth factor receptors

(FGFRs), which activates downstream signaling pathways such as the mitogen-activated protein kinase (MAPK)/extracellular regulated kinase (ERK) pathway. A mathematical model validated FGF- and VEGF-induced MAPK signaling and phosphorylation of ERK, which promotes cell proliferation. Signaling is initiated by FGF binding to the FGFR1 and heparan sulfate glycosaminoglycans (HSGAGs) or VEGF binding to VEGFR2 to promote downstream signaling. [8]

Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are involved in the degradation of the extracellular matrix (ECM), facilitating angiogenesis.[9,10] During the formation of corneal NV, vascular endothelial cells traverse the basement membrane and ECM to enter the tissue. MMP-2 and MMP-9 bind to type-1 and 4 collagens, gelatins and laminin to degrade denatured collagens and gelatins and interfere with the proper functioning of the corneal epithelial barrier.

In a mouse model, the levels of MMP-2 and MMP-9 were elevated in the epithelial cells of neovascularized vessels in the corneal epithelium and stroma.[11] The presence of MMP-2 and MMP-9 was found before NV formation, and their levels rose alongside the accumulation of inflammatory cells and NV. This suggested that MMP-2 and MMP-9 have an important role in the production of corneal NV.[11,12]

Several signaling pathways are involved in the regulation of corneal NV. The PI3K/Akt signaling pathway inhibits angiogenesis in malignant liver tumors, melanoma, hemangioma and renal cell carcinoma by regulating vascular endothelial remodeling. [13–15] The PI3K/Akt signaling pathway is an important downstream pathway of the STAT3 protein. This pathway is critical in the regulation of NV through VEGF.[16,17] A study showed that the suppression of the PI3K/Akt signaling pathway, which is controlled by STAT3, effectively inhibits corneal NV.[18] The Notch signaling pathway also plays a significant role in angiogenesis. A bFGF-induced mouse study showed that the notch signaling pathway regulates VEGF expression to affect corneal angiogenesis.[19] The NF-κB signaling pathway is another important regulator of corneal NV. NF-κB is activated in response to various stimuli, including proinflammatory cytokines, and promotes the transcription of genes such as VEGF to promote corneal NV progression. [20]



Slit-lamp photograph showing corneal neovascularization extending into the central cornea with secondary intrastromal lipid leakage into the region of the visual axis. Also evident are anterior blepharitis and secondary bulbar conjunctival injection.

• ***Antiangiogenic factors.*** The cornea maintains its avascularity through the action of antiangiogenic factors, which counterbalance the effects of angiogenic stimuli. Pigment epithelium-derived factor (PEDF), a 50 kDa glycoprotein, is an important antiangiogenic factor, which inhibits endothelial cell migration and tube formation. Under normal physiological conditions, there's a dynamic balance between VEGF and PEDF, which prevents NV.[21] PEDF suppresses VEGF signaling angiogenesis and is used as a viable therapeutic agent for the treatment of corneal and other ocular NV.[22,23]

Corneal NV is closely linked to inflammation in the cornea, primarily caused by an imbalance between angiogenic and antiangiogenic elements. Tissue inhibitors of metalloproteinases (TIMPs) counteract MMP activity, thereby inhibiting new vessel formation. A study showed that TIMP3 binds to VEGFR-2 to suppress VEGF's binding and inhibit downstream signaling and angiogenesis.[24]

Thrombospondin-1 (TSP-1), a multifunctional extracellular matrix protein, is an antiangiogenic protein that inhibits endothelial cell proliferation and migration by interacting with receptor such as CD36. A mouse study showed that TSP-1 ligated with CD36 on monocytic cells inhibited VEGF. [25]

Endostatin, a proteolytic fragment of collagen XVIII, also plays a critical role in inhibiting angiogenesis by blocking the pro-angiogenic activity of VEGF and bFGF. Endostatin and its derivatives significantly inhibited vascular endothelial cell proliferation *in vitro* and suppressed corneal NV *in vivo*.[26]

• ***Cytokines***. Inflammatory cytokines play a crucial role in the initiation and progression of corneal NV. Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that promotes angiogenesis by upregulating VEGF and bFGF expression in corneal epithelial cells and fibroblasts. A study has reported that TNF-α promotes hemangiogenesis in the mouse trachea under inflammatory conditions.[27] In a wild type mice study, TNF-α enhanced VEGF and inducible nitric oxide synthase (iNOS) expression by peritoneal macrophage whereas the intraocular mRNA expression of angiogenic factors, including VEGF, iNOS was retarded severely in TNF receptor 1-deficient mice.[28]

TNF-α is a pivotal pro-inflammatory cytokine involved in CNV. It's primarily produced by macrophages, T-cells, and corneal epithelial cells in response to injury or infection. TNF-α exerts its effects by binding to its receptors to trigger downstream signaling cascades that promote angiogenesis. In a TNF transgenic mice study, TNF stimulated VEGF-C expression and increased nuclear factor kappa B (NF-κB) binding to an NF-κB sequence in the VEGF-C promoter.[29] NF-κB is a transcription factor that regulates the expression of various genes involved in inflammation and angiogenesis, including VEGF and IL-1β. The nuclear translocation of NF-κB related to the inflammatory response is inhibited by regulatory protein IkappaB (IκB), which prevents nuclear translocation of NF-κB by arresting it in the cytoplasm.[30] Upon TNF-α binding, the IκB kinase complex is activated, leading to the phosphorylation and degradation of IκB, an inhibitor of NF-κB. This allows NF-κB to translocate to the nucleus and induce the expression of pro-angiogenic genes.[31]

Interleukin-1 (IL-1) is another key mediator that enhances the production of pro-angiogenic factors. An IL-1 receptor antagonist

knockout mice study showed corneal NV with increased intracorneal macrophage infiltration and increased expression of VEGF and iNOS. [32] IL-1 also enhances the production of other inflammatory cytokines, amplifying the inflammatory response and promoting angiogenesis.

Conversely, anti-inflammatory cytokines such as interleukin-10 (IL-10) can suppress angiogenesis by downregulating the expression of proangiogenic growth factors. The multifunctional cytokine interleukin (IL)-10 is mostly known for its anti-inflammatory and regulatory effects on the immune response. Several studies have shown that IL-10 has antiangiogenic properties. [33,34] IL-10 promoted the production of antiangiogenic TIMPs [35] and augmented angiogenesis in IL-10-deficient mice that was accompanied by upregulation of proangiogenic MMP-2 and -9.[36] However, IL-10 has also been shown as a proangiogenic molecule in a murine model of inflammation-associated choroidal NV[37] and in the suture model for corneal NV.[38]

LIPID KERATOPATHY

LK can be classified as idiopathic or it can be secondary, resulting from ocular infection, inflammation or trauma. Idiopathic LK can be identified by the presence of neutral fat, glycoproteins, cholesterol and lipid deposits in the stromal layer of the cornea and the adjacent limbus.[39] The accumulation of lipids in idiopathic LK may result from an overproduction of lipids or a deficiency in fat metabolism. Typically, idiopathic LK manifests bilaterally and doesn't have a history of serum lipid problems or corneal NV. In contrast, secondary LK commonly arises from the accumulation of lipids in a cornea NV. As a result, any condition that causes corneal NV might potentially trigger LK.

Corneal NV can cause the accumulation of lipids and subsequently lead to LK through many mechanisms. During the formation of new blood arteries, increased amounts of lipoproteins can be transported to these regions, particularly when there are elevated levels of serum lipoproteins. Because there's less pericyte coverage, less basement membrane layering and fewer tight junctions in these newly formed vascular tissues, they are highly porous, which permits lipid and cholesterol leakage.[40] Fibroblasts endocytose this cholesterol-rich lipid, which is subsequently transported to lysosomes where it's deposited in droplets in the cytoplasm. Over time, these fibroblasts get encircled by lipid, resulting in cell necrosis and the accumulation of crystalline material in the corneal stroma.[41] Necrosis also triggers an inflammatory reaction, which worsens the process of NV and promotes the accumulation of lipids. Lipid deposition can produce NV as the condition worsens, and NV in turn can promote further lipid deposition, which further reduces visual acuity.

DIAGNOSIS

Patients with corneal NV often present with symptoms such as decreased visual acuity, photophobia and ocular discomfort. Accurate diagnosis of NV and lipid keratopathy relies on a combination of clinical examination and advanced imaging techniques. Slit lamp photography, *in vivo* confocal microscopy (IVCM), angiography, and optical coherence tomography angiography are the main diagnostic techniques used in clinic to assess the corneal surface.

On slit-lamp examination, corneal NV appears as fine, tufted blood vessels extending from the limbus into the corneal stroma. In lipid keratopathy, the cornea may exhibit yellowish-white opacities corresponding to lipid deposits, often in association with vascularized corneal scars. Slit-lamp biomicroscopy remains the primary tool for initial assessment, allowing for detailed visualization of the corneal structures and identification of NV and lipid deposits. While artificial intelligence algorithms have somewhat improved the diagnostic capabilities of slit lamp photography, the enhancement in diagnosability remains limited.

New imaging modalities have shown to be beneficial as adjunct methods. IVCM obtains sequential images across different corneal layers and offers insights into cellular changes within the corneal stroma. [42] It can visualize the presence of corneal vessels by detecting chemicals that are absorbed by the permeable vessels. Lipid deposits in LK may also be characterized with the use of IVCM. It frequently detects crystalline formations inside the stroma in cases of both idiopathic and secondary LK.[43] IVCM is a non-invasive method for imaging the cornea, while angiography relies on the use of particular dye agents. Fluorescein angiography can be used to assess the patency and leakage of corneal vessels.[44] Both fluorescein and indocyanine green leaking can indicate neovascular development and aid in the diagnosis. Fluorescein angiography and indocyanine green angiography facilitate early detection and precise mapping of NV.[45] They are reliable measures of the level of advancement of corneal NV with evaluation of the duration and direction of blood flow, even when corneal scars are present.[46]

Optical coherence tomography is now widely used for studying arteries because of the recent improvements in image capture and algorithms. OCT angiography has emerged as a new technique that enables the viewing of blood flow dynamics without the need for injecting contrast agents. Continuous imaging enables the visualization of ocular vessel blood flow through non-invasive OCTA, thereby avoiding the adverse reactions associated with invasive angiography.[47] The existing integrated software for OCTA enables users to perform sequential scans to create a three-dimensional assessment of the lesion and its related blood vessels.[48] This is valuable for determining the stage of the disease and devising treatment strategies. However, OCTA is unable to distinguish vascular activity and blood flow direction when compared to fluorescein angiography and indocyanine green angiography despite its advancements. AS-OCTA is another promising diagnostic tool for detecting abnormal blood vessel growth in the cornea. AS-OCT provides high-resolution cross-sectional images of the cornea, enabling precise measurement of corneal thickness and the extent of NV.[49] However, the scanning range of AS-OCTA is narrower compared to standard angiography procedures, requiring numerous successive scans to cover all corneal quadrants. While the acquisition speed is still poor despite the short scanning duration, involuntary eye movement might also impair clarity while assessing corneal NV.[50] As non-invasive AS-OCTA continues to advance, it's expected to replace invasive ocular examination methods for diagnosing corneal NV. This will allow for faster, more accurate and more efficient diagnosis.

THERAPEUTIC IMPLICATIONS

Understanding the molecular mechanisms underlying corneal NV and LK has significant therapeutic implications. Anti-VEGF therapies, such as bevacizumab, ranibizumab and aflibercept have been developed to inhibit VEGF signaling and are used to treat corneal NV, secondary LK and other angiogenic ocular diseases.[51,52] Similarly, inhibitors of bFGF and other proangiogenic factors

are being explored as potential treatments. Therapies aimed at enhancing the activity of TSP-1, endostatin or PEDF could help to restore the balance between angiogenic and antiangiogenic signals and inhibit pathological NV. Anti-inflammatory therapies targeting cytokines like TNF-α and IL-1β could be beneficial in reducing the inflammatory component of corneal NV. Drugs that inhibit NF-κB signaling or other proinflammatory pathways may help to decrease the expression of angiogenic factors and mitigate NV. However, most treatment options have resulted in a similar lack of long-term success. Although the primary approach to corneal NV is the treatment of the underlying infectious and inflammatory stimulus, topical corticosteroids have demonstrated little efficacy in reversing corneal vascularization.[53] Corneal transplantation alternatives, such as penetrating keratoplasty, have a significant likelihood of graft failure and a high risk of rejection in eyes with corneal NV.

Although the occurrence of corneal NV is increasing, there is still a lack of effective therapeutic techniques. Argon laser therapy has been suggested to induce vascular occlusion by focusing a focused beam of light into the abnormal blood vessels.[54] However, laser-induced tissue damage can exacerbate NV and hence LK by triggering inflammation and the release of angiogenic molecules. Fine needle diathermy (FND) was adopted by cauterization and elimination of the abnormal vessel. Nevertheless, complications may arise, such as temporary whitening of the cornea, bleeding inside the corneal stroma, recanalization or the development of collateral vessels.[55] Other vasodestructive treatments, such as photodynamic therapy, cautery, and suture ligation, have unsatisfactory long-term outcomes.

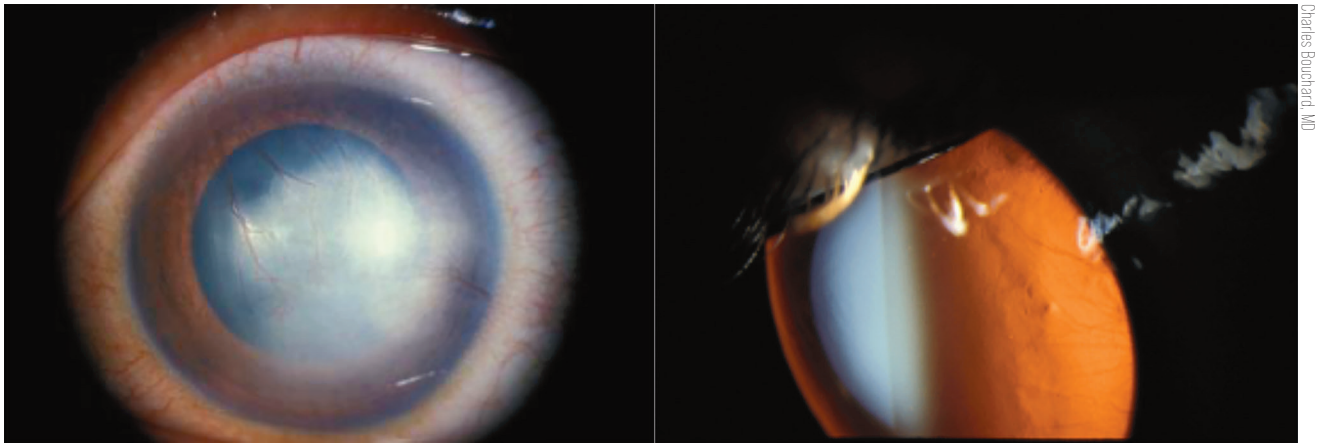
An optimal therapy should eradicate existing aberrant corneal NV and inhibit future vascularization. MICE, mitomycin-C (MMC) intravascular chemoembolization, is a newly proposed surgical method for addressing corneal NV and LK.[56] MMC inhibits the proliferation of vascular endothelial cells, hence impeding the development and regenerative potential of blood vessels.[57] Studies have reported MICE successfully treated corneal NV with LK,[56] and corneal vascularization prior[58] or after failed keratoplasty.[59]

In MICE, a 1.0 cc syringe is filled with MMC (0.4 mg/mL), which is then connected to a 33-gauge needle. The physician identifies the greatest lumen of a corneal vessel located just inside the limbus. Then the needle is positioned and inserted into the vessel at an approximate angle of 15 degrees relative to the corneal surface. A little amount of MMC (0.01 to 0.05 ml), with a maximum volume not exceeding 0.05 ml, is injected into the efferent and afferent vessels. The ocular surface is thoroughly irrigated using balanced salt solution to eliminate any remaining ocular surface MMC. One drop of moxifloxacin 0.5% and prednisolone acetate 1% is administered at the conclusion of the procedure.

Given the technical difficulty of this procedure, surgeons can confirm the intravascular injection of MMC by observing the blanching of blood vessels during the injection. If the needle's entire bevel isn't inserted through the stroma, the MMC will follow the path of least resistance, which is the ocular surface, rather than entering the vessel. In contrast, the administration of MMC into the anterior chamber could have catastrophic consequences, the surgeon must prevent the complete penetration of the full-thickness cornea. Some patients can achieve clinical success with one injection, but some may need a second MICE treatment to resolve the high-velocity blood vessels. It could be because the blood arteries were very deep and didn't receive effective chemoembolization, or MMC has entered the intrastromal space rather than the blood vessel. Surgeons can monitor the vessels blanching during the procedure. Particular attention should be paid to the needle's appropriate angling, which should be approximately 15 degrees, in order to successfully cannulate the vessel. When the injection is correctly positioned and angled, a tiny amount of MMC (0.01-0.05 ml) is sufficient to fill both the efferent and afferent vessels.

The MICE therapy resulted in remission of the corneal NV and later partial absorption of the LK in a reported case series.[56] Around one to three weeks after treatment, lipid and blood accumulated inside the corneal stroma which was absorbed within one to two months, resulting in a feathery appearance of the remaining lipid with decreased hyper-reflectivity on AS-OCT. The absorbed lipid may flatten the cornea, causing induced astigmatism. However, the corneal flattening and induced astigmatism were improved, and the visual acuity remained stable.

High dose (>0.05 ml of 0.4 mg/ml MMC) or injecting MMC toward the limbus may cause potential systemic adverse effects such as abdominal pain, nausea and



Charles Bouchard, MD

Left: Slit-lamp photograph displaying a significant amount of lipid keratopathy involving the central and mid-peripheral cornea. Also seen is corneal neovascularization. Right: Corneal neovascularization is clearly seen against this red reflex photograph.

vomiting. We suggest thoroughly irrigating the surface of the eye with balanced salt solution after the procedure to minimize the amount of MMC that comes into contact with the eye's surface. In the case of small vessels, the technical aspects of MICE can be particularly challenging. Consequently, it's advised to determine the biggest vessel. The hydrostatic pressure from the injection will fill the whole network with MMC, including the small vessels if properly placed.

In conclusion, corneal NV is a complex pathological process involving a delicate balance between pro-angiogenic and antiangiogenic factors, regulated by a network of cytokines and molecular pathways. VEGF, bFGF, MMPs are drivers of angiogenesis, counteracted by antiangiogenic factors like PEDF, TIMPs, TSP-1 and endostatin. The interplay of cytokines further modulates this balance. Key signaling pathways, including VEGF/VEGFR, Notch, HIF-1α, and NF-κB, coordinate the cellular responses leading to corneal NV. Understanding these mechanisms provides a foundation for developing targeted therapies to treat and prevent this vision-threatening condition.

Although the indications and procedure for MICE are undergoing changes, MICE is increasingly becoming one of the potential primary methods for treating corneal NV and LK. Performing MICE therapy is technically challenging, and large comparison studies with longer follow-up periods are warranted to evaluate its safety and effectiveness. ◀

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SUCCEEDING WITH DALK

Christine Yue Leonard, Senior Associate Editor

According to the 2023 U.S. Eye Banking Statistical Report, the domestic use of DALK tissue has been declining.[1] While penetrating keratoplasty, DSAEK and DMEK employ the lion's share of corneal tissue—28.9 percent, 32.4 percent and 34.2 percent, respectively—anterior lamellar keratoplasty represents just 1.2 percent of intermediate-term corneas.[1] Experts say there are a number of reasons for this, from the procedure's technical difficulty and availability of scleral lenses and cross-linking as early alternatives, to the good visual outcomes and relative ease of penetrating keratoplasty. Nevertheless, DALK is still a valuable procedure to learn, as it preserves the host endothelium and offers a number of safety advantages and good optical quality.

Here, corneal specialists share pearls for performing DALK, when to convert to a full-thickness transplant and the postoperative complications to watch out for.

STARTING OUT WITH DALK

The major advantage of performing DALK when indicated is the extremely low risk of graft rejection, according to Bennie H. Jeng, MD, chair of the Department of Ophthalmology and director of the Scheie Eye Institute at the University of Pennsylvania School of Medicine in Philadelphia. "You certainly eliminate all endothelial rejection, which is most cases of rejection since you're not replacing the endothelial cells," he says. "[DALK] is also safer [than PK] because it's an outside-of-the-eye procedure, if done successfully, so there's less risk of intraocular infection."

Since DALK involves replacing the stroma and superficial layers of the cornea, this procedure is suitable for any pathology anterior to Descemet's membrane provided the patient possesses a functional endothelium. Classic indications include keratoconus, corneal dystrophies and corneal scars. Eyes with endothelial disease such as Fuchs', full-thickness infection healed by scarring or non-functional endothelium aren't good candidates for DALK.

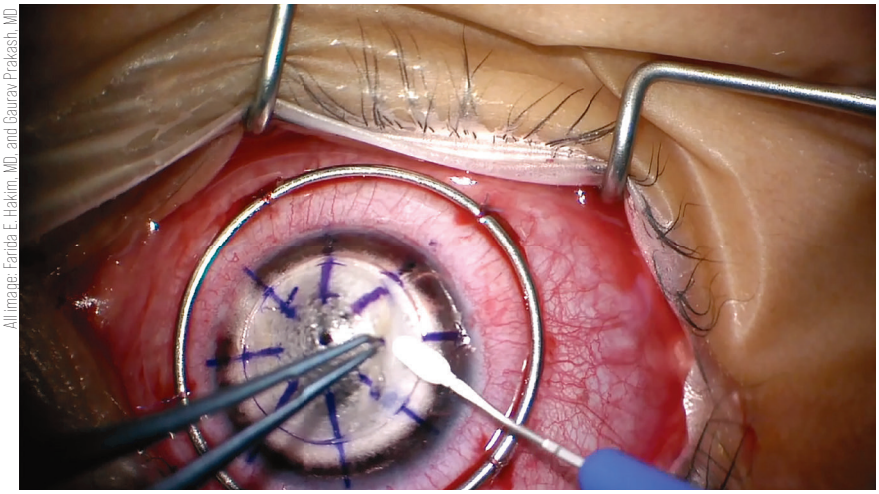
"DALK isn't that commonly performed nowadays because of the advent of scleral contact lenses for keratoconus, and the indications for it are much later [in the disease]," says Gaurav Prakash, MD, an assistant professor of ophthalmology at the University of Pittsburgh School of Medicine. "So, doing a DALK cleanly is definitely more challenging now compared to when we didn't have good quality scleral lenses or cross-linking and patients were sent for DALK earlier. All of these patients today come in with more advanced disease and are more challenging.

"The way to start doing DALK is to try to attempt a bubble in all the patients you're doing a penetrating keratoplasty," Dr. Prakash says. "Let's say you have a patient with a corneal scar, and this patient has to undergo PK. That's the best patient to attempt a big bubble in and see how your syringe is moving, how much air you're injecting and getting the feel of how you're going to get a bubble because eventually, you have to remove the endothelium in these patients, so the risk isn't there. It's definitely a more challenging procedure compared to normal LK, but the visual results are much more gratifying. This is what I recommend to new surgeons."

PRE-DESCEMET'S LAYER

Pre-Descemet's layer, first described by Professor Harminder Dua and colleagues in 2013, is a layer of stroma anterior to Descemet's membrane that provides a border to a cleavage plane in lamellar keratoplasty, explains Sadeer B. Hannush, MD, an attending surgeon on the Cornea Service at Wills Eye Hospital and a professor of ophthalmology at Sidney Kimmel Medical College of Thomas Jefferson University in Philadelphia. "The pre-Descemet's layer improves our understanding of DALK and makes it safer," he says. "This layer is about 5 to 20

All image: Farida F. Hakim, MD, and Gaurav Prakash, MD



Lamellar dissection is performed to debulk the cornea.

microns thick and is made of about five to 10 lamellae of collagen fibers. It's continuous with the trabecular meshwork. Many cornea specialists believe the pre-Descemet's layer to be acellular or paucicellular."

The pre-Descemet's layer is structurally strong. "If you only have Descemet's membrane between the anterior chamber and the outside world, you need about 30 mmHg of pressure in the anterior chamber to pop through Descemet's membrane," Dr. Hannush says. "But in the presence of pre-Descemet's layer, you need about 500 to 700 mmHg to pop through. This is a very unique property." In the big bubble DALK technique, the pre-Descemet's layer forms the posterior wall of the type-1 bubble and the anterior wall of the type-2 bubble (more below).

THE BIG BUBBLE TECHNIQUE

The big bubble technique uses air pressure to create a cleavage plane between the Descemet's layer and the stroma. "Patients that have a relatively clean stroma without any scarring are better candidates for the big bubble technique," Dr. Prakash says. "If patients have scarring or very thin corneas, we can do a manual deep LK rather than trying to do a big bubble. The big bubble technique requires blunt force to create a Descemet's detachment, so if there's a weak area of Descemet's (e.g., previous hydrops) and we try to make a big bubble, that will go through and through from that area. If the patient has any scarring, that's a potential area through which air can leak from the stroma into the anterior chamber, and then we can't do a big bubble in that situation."

Here are some pearls for performing successful big-bubble DALK:

• ***Invest in the best tools for the job.*** Using the right instruments such as blunt-tipped scissors, special blunt-tipped air cannulas and blunt lamellar dissectors "will pay dividends as it'll decrease the risk of inadvertent perforations," Dr. Jeng explains.

• ***Carefully evaluate preoperative corneal thickness.*** On preoperative tomography or OCT, examining peripheral corneal thickness is key. "Some of our keratoconus patients, which is one of the main indications for DALK, are very thin in the periphery and you really start cutting on your very first turn with the corneal trephine," explains Kourtney H. Houser, MD, an assistant professor of ophthalmology and director of the cornea fellowship program at Duke University. "So, knowing the thickness in those very steep corneas beforehand is helpful for judging the appropriate depth of your trephination. There are some guarded and measured trephines that can make it a little easier to control depth."

• ***Debulk the stroma first.*** "The big bubble technique works by creating an air cushion into the stroma, so the less stroma there is, the better," says Dr. Prakash. "Especially for new DALK surgeons, I want them to debulk at least two-thirds of the cornea before they start attempting the big bubble, because then we can control the amount of air injected. It's a very methodical approach."

• ***When injecting the air bubble, go as deep into the stroma as possible.*** "Put the cannula as far posteriorly in the stroma as possible without going through and through to the anterior chamber," Dr. Hannush says. "The opening of the cannula should point down toward the anterior chamber. Inject air. The pathway of least resistance for the air is to go posteriorly and split the stroma off of the pre-Descemet's layer."

"Correct depth is key," Dr. Prakash adds. "Around 90 percent of the initial depth is what we want to go in when doing the big bubble technique. Also avoid injecting air too fast and hard. This can blow Descemet's membrane."

• ***Don't use a needle to inject air.*** "Your chances of perforating are higher," Dr. Hannush says.

• ***Inject air in a soft eye***. "When you start injecting the air into the posterior stroma, you want the eye to be soft," Dr. Hannush says. "It's easier to get the cannula into the stroma in a firm eye, but once you get the cannula in, placement of a paracentesis to release some aqueous and soften the eye increases the likelihood of getting a big bubble."

• ***Familiarize yourself with the appearances of a big bubble type 1 vs. type 2.*** When a big bubble type 1 appears, there's no mistake about it, Dr. Hannush says. After a wave of intrastromal emphysema, the border of the bubble is smooth and expands from center to periphery. "You know that the bubble is anterior to pre-Descemet's layer and you're likely to be successful with your DALK after entering the bubble with a knife, a step known as the 'brave slash.' If it's a big bubble type 2, it means the bubble is between pre-Descemet's layer and Descemet's membrane. There is little intrastromal emphysema, and the bubble expands from periphery to center. This is a fragile situation. Some surgeons recommend not entering the bubble with a knife, but rather performing a layer-by-layer deep dissection followed by transferring the donor graft on to complete the keratoplasty.

• ***Use a small bubble to check your technique.*** While intraoperative OCT can be used to see where the bubble is, many surgeons don't have access to this instrument. "Another option is to place a small bubble on the periphery, which is called the double-bubble technique," Dr. Prakash explains. Basically, once you've created a big bubble, you make a peripheral, almost vertical stab incision and put in a small bubble. That bubble should not move to the center, because

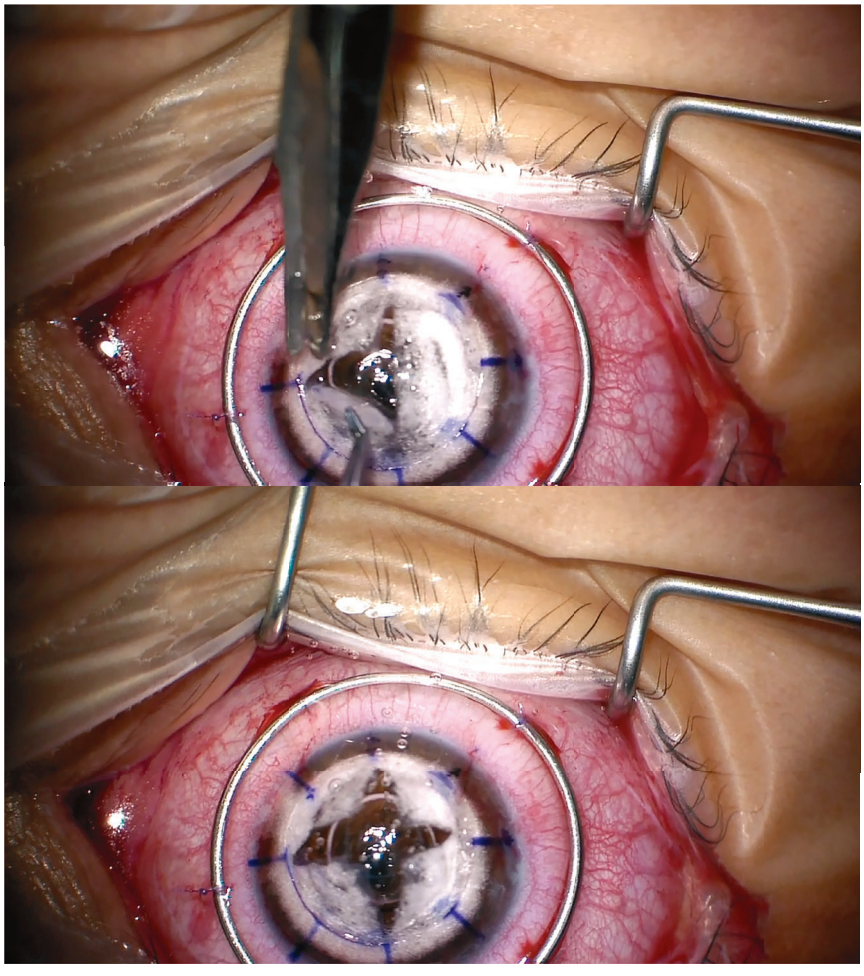
the center of the anterior chamber is already being involved by the Descemet's layer, which is pushed down by the big bubble. This gives you an idea of how good the bubble is."

• ***Avoid over-pneumatizing the stroma.*** "Another problem newer surgeons may encounter is not getting the full cleavage in the first bubble," Dr. Prakash says. "They may continue to put air in, which is okay up to a point. It's important not to pneumatize the stroma, otherwise it becomes difficult to get a clear dissection. The technique for this is to use a targeted approach in areas which aren't already pneumatized."

• ***Begin stromal removal through viscoelastic.*** "If a big bubble is achieved and we've reached a point that we have to rupture the central stroma so we can get bare Descemet's, I generally recommend that the surgeon put a blob of viscoelastic at the area where they're making a nick on the stroma at the center," Dr. Prakash says. "What happens is that once you make a nick in the central stroma, air releases and gushes out from the big bubble because it's under tension. The Descemet's isn't supposed to be that stressed and the sudden release can actually break the Descemet's when you're trying to remove the stroma. Once you have a blob of viscoelastic and you go through that to make a nick, the [air] leak is slow, and the bubble doesn't collapse as fast. The rate of hitting the bubble and creating a perforation is much less."

Similarly, he says that newer surgeons may find it easier to use a needle instead of a blade, since the track is smaller, allowing for less air to leap back. "It's always good to try a big bubble in a few animal eyes first to get an idea of how the air moves in your hand," he adds.

• ***Visualize first, then cut when dissecting out the cleavage plane***. "Once we've reached the bare Descemet's and are making four quadrants, it's important to make sure the nicks on the stroma are in to out," Dr. Prakash says. "Avoid hitting the Descemet's when you're trying to do quadrant removal of the stroma. Most perforations happen in the periphery, which happens because surgeons lose the guidance of how deep they have to go when they try to cut on the peripheral stroma. I always suggest visualizing first, then cutting—a basic tenet of lamellar keratoplasty. You should always lift up the cornea, which has to be dissected out to see where your scissors are going. Then, cut the periphery. This ensures you won't inadvertently catch the Descemet's membrane when you're trying to cut at the periphery."



Quadrant removal of the stroma is performed to expose Descemet's membrane.

• ***If a microperforation occurs, don't inject viscoelastic.*** "The tendency for surgeons when they perforate is to immediately grab viscoelastic to try to reinflate the eye," Dr. Jeng says. "This is a major mistake that can be avoided by injecting air instead. Air will tamponade the perforation, whereas viscoelastic will expand the perforation and make it bigger. Microperforations can be salvaged by carefully dissecting in other areas first and then leaving a little bit of stromal tissue over the perforation site if off axis."

• ***Ensure the posterior stroma is completely separated from pre-Descemet's layer.*** "When removing the posterior stroma, ensure the complete separation of the posterior stroma from Descemet's membrane all the way to the periphery, so that when you start cutting the posterior stroma to remove it, you don't nick pre-Descemet's layer with your scissors," Dr. Hannush says.

• ***Pay attention to depth when suturing.*** "When most surgeons do PK, they [pass the needle at approximately] 90-percent depth in the host and the donor," Dr. Prakash says. "[For DALK], one of my good friends and colleagues, Mayank A. Nanavaty, recommends suturing at 50-percent depth in the donor and 90-percent depth in the host to improve apposition of the donor with Descemet's membrane, which I have started doing after reading his work.[2] I agree that this makes operation much easier, which sounds counterintuitive for most. The reason is that it creates a tug and pulls the donor back into the host, which is what we want in these situations. That's what I've been teaching my fellows. So, rather than doing 90 percent on both sides, try to be more superficial on the donor and deeper on the host. This also reduces the risk of hitting the bare Descemet's membrane when you're putting in your

first few sutures."

• ***Don't give up.*** There's a learning curve with the big bubble technique, but practice pays off. "Most of us like to do the big bubble technique where we inject air and try to get a full cleavage of the plane between Descemet's and the stroma, but if you don't achieve a big bubble you can still be successful at DALK, you just have to be patient in a manual dissection," says Dr. Houser.

DALK VS. MANUAL DISSECTION

Surgeons may turn to manual dissection when a big bubble can't be achieved, or they may begin with manual dissection from the outset. "It's more laborious to remove the cornea layer by layer until we have a nice reflection back to the Descemet's," Dr. Prakash points out. "In fact, it's very difficult to get a bare Descemet's membrane in this situation and leaving about 25 to 30 or 50 microns may be better than trying to go deeper and potentially perforating."

Clarity is a key difference. "Bare pre-Descemet's layer is pristine, and its optical quality is excellent," Dr. Hannush says. "Manual dissection can't achieve as optically clear a situation as by baring pre-Descemet's layer. I get a big bubble about 80 percent of the time, and the other 20 percent of the time I perform manual dissection, always making an effort to retain the host Descemet's membrane and endothelium."

VISCOBUBBLE DALK

If air bubble formation fails, which is common even among experienced surgeons, manual dissection is often the next fallback, but recently another approach has shown promise. "Viscoelastic can also be used as a dissection force instead of using air," Dr. Prakash notes. "Surgeons who use this technique feel that it's a bit safer to use viscoelastic force [than air]."

A study of 140 keratoconus eyes on the outcomes of bubble formation with OVD after failed air bubble dissection for DALK reported that this approach increased the success rate of bubble formation from 75.71 percent to 95.71 percent.[3] They noted, however, that when bubble formation fails, the infiltration of OVD into the residual stroma complicates manual dissection, also resulting in interface haze and poor visual outcomes. No significant differences were noted between air and OVD bubble at later examinations.

FEMTO-ASSISTED DALK

Femtosecond lasers such as the IntraLase and the Z8 can be employed to make both the trephination and the posterior lamellar pass. "The posterior lamellar pass can be done predictably, so you can program the laser to do it at 100 to 120 microns from the endothelium," Dr. Hannush says. "What is the tolerance? Can there be error? Can you perforate? Sure. However, some surgeons feel that this can be done predictably and safely allowing a better chance for the creation of a big bubble."

Alternatively, the laser can also be used for trephination only followed by creation of the big bubble. "Once the laser makes a pass, you're committed to surgery at that level," Dr. Hannush points out. "You can still create a big bubble by injecting into the 100-micron-thick residual cornea. This is an alternative to the conventional approach for creation of the big bubble, but most surgeons won't use the femtosecond laser to make a horizontal pass."

Dr. Prakash says that femto-assisted DALK can be helpful for patients who have herpes scars or keratoconus with hydrops, where you don't want to destabilize the cornea by doing a big bubble. "We can make a femtosecond-assisted lamellar cut or make a partial trephination," he says. "The benefit of the femtosecond is that it's much more precise and it doesn't depend on how hard or tight you use the vacuum trephine. So, you can debulk the anterior two-thirds of the cornea with this technique, and the remainder can be done by manual dissection. That's one technique for deep LK."

WHEN TO CONVERT TO PK

"If [the big bubble technique is] done successfully, generally the DALK is able to be completed without any issues," says Dr. Jeng. "Surgeons may run into trouble when they can't get a big bubble and end up needing to do a manual dissection. As you try to dissect deeper and deeper into the stroma, there's a greater chance of getting too close and perforating [Descemet's layer].

"Conversion is only done when there's an intraoperative rupture of Descemet's membrane," he continues. "If it's a microperforation, then this can usually be salvaged and the DALK can be completed. If it's a macroperforation, sometimes it's not possible to continue because the hole is too big, and that's when most surgeons convert to a full-thickness transplant."

Surgeons have different thresholds for converting to full-thickness transplants, but in the United States, the threshold is relatively low compared with other countries. "[In the United States] we perform about 50,000 corneal transplants but have about double the amount of donor tissue," Dr. Hannush explains. "We export the rest. Since we have access to excellent corneas with healthy endothelium, a surgeon who doesn't have much experience with DALK or perforates early into the anterior chamber can easily convert to a full-thickness transplant knowing that the patient will do well with a full-thickness donor cornea. However, in many parts of the world, donor tissue with healthy endothelium is less readily available, so being able to perform a successful DALK is possible with tissue that may not be good for full-thickness transplantation.

"Some colleagues will order two corneas, one with borderline or poor endothelium, which they'll use if they're successful in creating a big bubble, and one with an excellent endothelium, which they'll use if they have to convert to a full thickness transplant," he continues. "This is a luxury that U.S. corneal surgeons have. The surgeon may then send back the unused full thickness donor tissue within a few hours, so it can be placed elsewhere."

Dr. Hannush says his threshold for converting is "when I have more than 3 to 4 clock hours of peripheral laceration of Descemet's membrane. If the perforation is central and small, there's no need to convert. A layer-by-layer dissection may be carried out, since it's difficult to create a big bubble in the presence of a full-thickness opening into the anterior chamber."

Dr. Houser says, "If I've penetrated the host endothelium and Descemet's on my trephination cut, then I'll usually convert to PK at that time because it can be very challenging to try to manually dissect off the stroma if you have a large penetration into the eye on your initial trephination. If there's a small break in Descemet's during the dissection after the trephination, and it's peripheral, I'll usually not convert and instead try to continue with a manual dissection to complete the DALK. I'll try to avoid that area during the manual dissection and then dissect around that area last, trying not to propagate the tear. Then I'll put a

bubble into the anterior chamber at the end of the case. But, if there's a very large, central perforation, or if I've penetrated on my original trephination, then I usually convert to PK."

How do surgeons talk to patients about the potential for conversion to a full thickness transplant? "I usually tell patients that if it's possible, I like to do a DALK because it may have a lower rejection rate, we can remove the sutures sooner and use less steroids [than a PK]," Dr. Houser explains. "There are multiple reasons why, if we can do a DALK, it may be favorable for them. But I tell patients that sometimes we're not able to do a DALK—their tissue may be too thin; we may penetrate into the eye and have to do a penetrating keratoplasty. I usually tell patients that we have everything ready to do both procedures. I usually order just penetrating keratoplasty tissue and then remove the endothelium should I be able to do a DALK. Some surgeons, and I've done this in the past as well, will order DALK tissue and PK tissue and send back the one they don't use. I'll assure patients that I have everything to do both procedures and whichever one seems to work best for their eyes is what we'll end up doing."

POSTOPERATIVE COMPLICATIONS

A double anterior chamber is the most common postoperative DALK complication. "A double anterior chamber is when there's either saline, aqueous fluid or viscoelastic material in the space between the donor and pre-Descemet's layer," says Dr. Hannush. "In that scenario an air bubble is placed in the anterior chamber and the fluid in the interface is burped out through the graft-host junction. This may be done at the slit lamp or in the operating room. Like with DMEK or DSAEK, the patient is then positioned supine for a short period of time, allowing Descemet's membrane and the pre-Descemet layer to be approximated to the donor graft."

Donor and host mismatch can also result in a double anterior chamber. "If you oversize the donor button, there can be a bit of a mismatch and you can have a hard time getting the host tissue to stick to the donor," Dr. Houser says. "Usually, your re-bubble works in those cases, but sometimes you have to incise the graft-host junction area and re-suture it. Or, if you have some sutures that are much tighter than others, you may need to replace those to make them a little more uniform."

The incidence of stromal rejection is low, but it can occur with DALK. "Because we haven't replaced the endothelium, the risk of endothelial rejection is decreased, but stromal rejection does happen in DALK," Dr. Prakash says. "If it's not reversed, it can lead to scarring. In that case, you could peel off the old graft and place a new one."

"In the event of stromal rejection, blood vessels may grow into the interface which can be problematic," Dr. Hannush says. "One way to manage that is to ensure the patient comes back for their scheduled visits. If you see edema of the graft or early vessels growing into the interface, frequent topical steroids may be initiated or an injectable steroid placed in the sub-Tenon's or subconjunctival space. If DALK was done for a herpes simplex scar, then make sure the patient is also on oral antivirals."

Interface haze can also occur, but experts say it's usually a small contributor to visual loss. "There are several ways to decrease haze," he continues. "You can use steroids and vitamin C like we do after PRK, and ensure the patient wears dark sunglasses if the surgery is done in summer to minimize exposure to UV light. There also may be a role for the antihypertensive losartan.

"Please consider DALK if the host corneal endothelium is healthy," Dr. Hannush says. "Consider it for corneal ectasias like keratoconus. Consider it for stromal scars and for most corneal stromal dystrophies. Don't abandon the option of DALK for penetrating keratoplasty without at least trying to do DALK. And if you fail, you can also always convert to a full-thickness transplant." ◀

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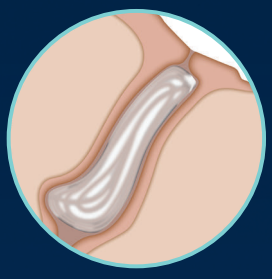

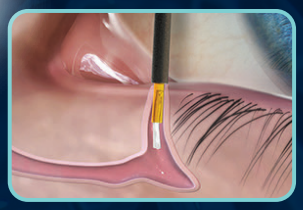

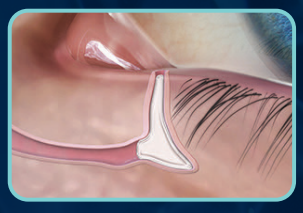

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