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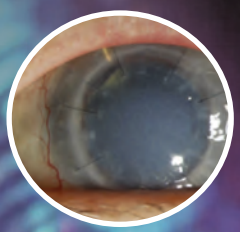

Management of Complex Penetrating Keratoplasty

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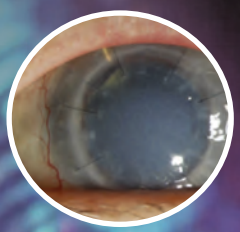
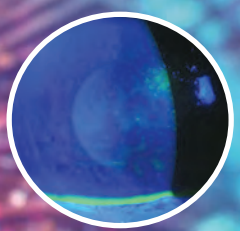


Management of Complex Penetrating Keratoplasty



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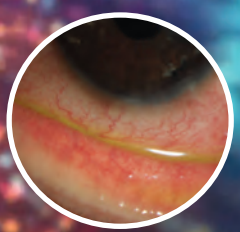

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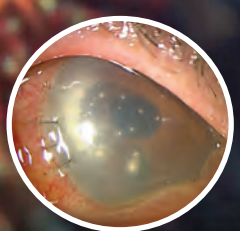

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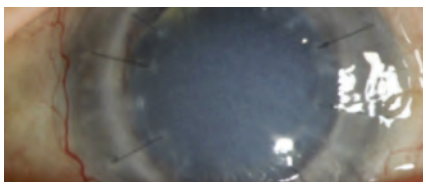
Editor's note: The staff would like to thank Wills Eye cornea specialist Sadeer B. Hannush for his invaluable assistance in planning this issue of Review of Cornea and External Disease.

FEATURES



MANAGEMENT OF COMPLEX PENETRATING KERATOPLASTY

By
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Jennifer Rose-Nussbaumer, MD
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Compared to lamellar keratoplasty, full thickness penetrating keratoplasty inherently has an elevated risk of immunogenic rejection, an issue that's exacerbated in higher risk clinical scenarios such as herpetic infection, autoimmune disorders and a history of multiple graft failures. In fact, indication for surgery is the most important predictor of graft survival after transplant; for example, keratoconus has been shown to have some of the highest graft survival rates,[1–4] while prior infectious keratitis portends a relatively lower graft survival.[5,6]

The last two decades have seen a shift away from PKP and towards lamellar keratoplasty. However, PKP remains the treatment of choice for combined endothelial and stromal pathology and still accounts for roughly one-third of corneal transplants performed in the United States, including most high-risk keratoplasty.[7] Careful preoperative planning, intraoperative considerations and postoperative care can improve surgical success and prolong graft survival. In this article, we discuss our approach to corneal transplant management in complex, high-risk scenarios.

MULTIPLE PRIOR GRAFT FAILURES/UVEITIS

Conditions including uveitis and multiple failed corneal transplants increase the risk of immunogenic rejection. Careful preoperative planning is essential to improve the chances of a successful surgical outcome. The differences in graft survival for each regraft can be stark, decreasing from 43-percent survival for the second regraft, to 25 percent by the third and fourth regraft.[8] Although not fully understood, factors such as a reduction in the blood-aqueous barrier[9] and neovascularization of the cornea, allow the immune system to become exposed to the foreign tissue.[2,10] Given the lower rates of survival, it's prudent to manage patient expectations, taking care to help them understand the more intensive postoperative care course and the reduced chances of graft survival.

Preoperatively, the surgeon should evaluate and address anatomic features that may accelerate endothelial decompensation. For example, stromal neovascularization leads to incremental increases in graft failure risk.[11–13] This is likely due to increased exposure of the immune system to foreign antigens. In light of this relationship, steps should be taken preoperatively to reduce corneal neovascularization. In certain situations, such as following a severe corneal ulcer, delaying surgery can help allow the eye become less inflamed. Preoperative topical steroids, and, potentially topical anti-VEGF therapies, may also be used. Vascular endothelial growth factor (VEGF)-A is a known promoter of neovascularization, and anti-VEGF-A neutralizing antibodies have been shown in experimental models to affect corneal angiogenesis.[14–16] In a recent pilot study, subconjunctival bevacizumab was shown to have a positive effect on endothelial rejection, though this wasn't statistically significant.[17] Vigilance should be maintained in the postoperative period, as patients can often require more potent immunosuppression with systemic medications.

Additional surgical intervention, such as glaucoma surgery, and postoperative complications can lead to higher graft failure rates. Therefore, as much as is possible, it's prudent to optimize glaucoma management and other ocular comorbidities prior to keratoplasty to minimize the necessity for subsequent surgical treatment. Careful surgical planning to address anatomical challenges such as peripheral anterior synechiae, an unstable anterior chamber intraocular lens, or a long glaucoma tube near the endothelium either prior to or concurrent with keratoplasty will improve outcomes. Ocular surface conditions such as severe aqueous deficiency syndrome (co-exist-

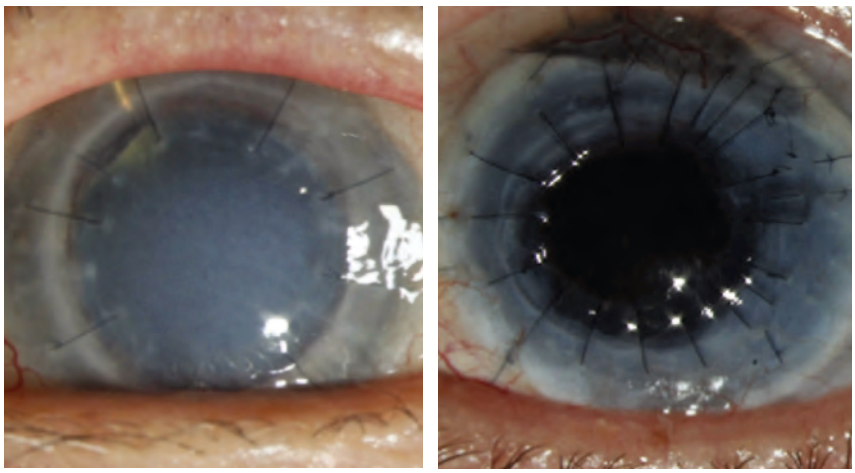

Figure 1. Left: A failed graft related to undiagnosed syphilis. Right: Penetrating keratoplasty for Mooren's ulcer on mycophenolate mofetil and Humira.

ing with rheumatoid arthritis), floppy eyelids and exposure keratopathy due to lagophthalmos, for example, are regularly overlooked, but must be addressed to ensure epithelial healing. Placing an amniotic membrane graft and temporary tarsorrhaphy can be helpful to promote epithelialization in the crucial immediate postoperative period.

In cases of uveitis or scleritis, the underlying etiology needs to be identified and adequately treated prior to considering surgical intervention. A thorough review of symptoms should be undertaken and a systemic work-up pursued, including evaluating for autoimmune conditions such as rheumatoid arthritis, granulomatosis with polyangiitis, sarcoid, and others as directed by the history and physical exam findings. In addition, infectious etiologies such as tuberculosis and syphilis should be ruled out. If there is latent tuberculosis or syphilis, infectious treatment is critical prior to proceeding with keratoplasty. This approach holds true even for cases of multiple graft failures, as undiagnosed systemic pathology may be the underlying cause of the repeat failures *(Figure 1)*. Once the uveitis has been adequately controlled for at least three months, the patient can undergo transplantation. We generally institute 1 mg/kg of oral prednisone starting three days prior to surgery and for the first week after surgery. In subsequent weeks, we'll taper the oral prednisone depending on the clinical response of the patient. In addition, we'll give the patient intraoperative methylprednisolone of 500 mg to 1 gm intravenously. Following the surgery, these patients will also require more frequent and stronger topical steroids (such as difluprednate), to control inflammation.

Because the cornea is an immunologically privileged site, topical steroids are often sufficient for rejection prophylaxis in routine keratoplasty. However, in high-risk transplantation, alternative approaches and adjunctive therapies must be considered (*Table 1*). HLA matching was previously thought to have a positive effect on graft survival based on retrospective publications.[18–20] However, a randomized controlled trial found no evidence of a benefit in HLA matching to prevent immune reactions or graft survival.[21] This negative finding was, in part, attributed to a lack of biological relevance of HLA antigens in keratoplasty, specifically, that minor (H) transplantation antigens have stronger associations with graft rejection than the major histocompatibility complex.[22,23]

Topical tacrolimus has been shown to reduce graft rejection both in rat PKP models and in several human studies.[24–26] One retrospective cohort study of high-risk PKP grafts found that those treated with topical tacrolimus 0.03% in addition to topical prednisolone 1% had approximately 50 percent fewer irreversible graft rejections compared with topical prednisolone alone. Another randomized clinical trial of high-risk penetrating keratoplasty patients found a statistically significant reduction in graft rejection to 16 percent among those treated with topical tacrolimus 0.1% compared with 46 percent among those treated with topical cyclosporine 1%.[27,29]

Antimetabolites may also have some utility in this regard. Specifically, in a prior randomized controlled trial, mycophenolate mofetil (MMF) was relatively well tolerated and showed promise in preventing graft rejection and maintaining graft clarity and survival over a six-month period.[28] We'll often initiate systemic immunosuppression with an antimetabolite such as mycophenolate mofetil or methotrexate, both of which have a relatively good safety profile (*Figure 1*). These systemic medications take three months to reach therapeutic efficacy so should be initiated preoperatively with enough lead time prior to surgery. Adverse effects should be closely monitored and regular blood tests including liver function tests, creatinine, and CBC with differential performed regularly. Many ophthalmologists work closely with a primary care provider or rheumatologist to initiate these medications and monitor labs.

THERAPEUTIC PK (IK OR AUTOIMMUNE MELT)

As PKP performed emergently for microbial keratitis has a poor survival prognosis, we favor medical treatment first, resorting to keratoplasty only in severe cases refractory to medical management.[29] Despite appropriate anti-microbial therapy, however, corneal perforation or melt may necessitate a therapeutic PKP to preserve globe integrity, and to help eliminate infection *(Figure 2)*.[30]

These cases can be technically challenging, often requiring irregularly shaped crescentic or large diameter grafts.[31,32] A larger trephination into healthy tissue that encompasses the infected tissue improves the chances of clearing the infection while also ensuring wound integrity. Limbus to limbus grafts require a 360-degree conjunctival peritomy which may help preserve corneal limbal stem cells and prevent cornea-scleral sutures from loosening rapidly. A partial thickness trephination at the limbus can allow for a corneoscleral shelf to be cre-

Table 1. Treatment considerations for high-risk penetrating keratoplasty scenarios				
	Corneal Neovascularizton	**Glaucoma**	**Uveitis or Scleritis**	**Other considerations**
Preop	· Preoperative topical steroids · Preoperative anti-VEGF	· Preoperative optimization with medical therapy · Surgical planning to address anatomical challenges like PAS	· Thorough review of systems · Consider infectious etiologies · Control inflammation for minimum of three months prior to transplant · Oral prednisone 1mg/kg 3 days prior to surgery	· Optimize ocular surface
Intraop		· Tirm or move tubes to sulcus or pars plana to prevent corneal touch	· Intraoperative methylprednisone of 500-1,000mg IV	· Amniotic membrane graft for exposure keratopathy
Postop	· Sytemic immunosuppression		· Oral prednisone taper · Frequent postoperative topical steroids	· Systemic immunosuppression for uveitis, multiple graft failure cases

ated by entering obliquely with a crescent blade. This shelved architecture at the graft-host junction promotes a stable self-sealing wound and preserves the anterior chamber angle. In wounds involving the limbus we favor 9-0 nylon sutures.

Surgical efficiency is important to minimize open globe time and minimize risk of an expulsive hemorrhage or infectious seeding of the anterior chamber. Antimicrobial agents as directed by the underlying infection should be administered, such as intracameral moxifloxacin or voriconazole and subconjunctival antibiotics. Determining when to initiate topical steroids postoperatively is challenging and depends in large part on the underlying infection and the surgeon's confidence in infection elimination. For bacterial infections, we will often initiate topical steroids right after surgery to prevent worsening inflammation and melt. However, these patients must be monitored closely for signs of recurrent, or worsening, infection.

For PKP in cases of fungal keratitis, determining when and how much topical steroids to use is challenging and we would recommend using them with caution. Topical cyclosporine or tacrolimus may be considered instead, which have immunomodulating mechanisms of action, and also antifungal properties.[33] If there is suspicion for fungal spread into the anterior chamber, intracameral voriconazole may be considered. Even with these precautions and close monitoring, PKP in the setting of infectious disease is associated with higher rates of graft failure, and patients should be counseled to maintain realistic expectations, and that a subsequent optical keratoplasty is likely to be required.

In patients presenting for consideration of penetrating keratoplasty due to suspicion of autoimmune melt, a diagnostic work-up to evaluate for underlying conditions (such as rheumatoid arthritis (RA), polyangiitis granulomatosis, relapsing polychondritis, polyarteritis nodosa, etc.) is essential. Surgical intervention without inadequate immunosuppression is likely to significantly worsen the inflammatory response. In these scenarios, systemic therapy with a combination of high dose oral prednisone and steroid-sparing therapy is recommended. It's important to keep in mind that some of these medications can take time to reach efficacy; mycophenolate can take six to 12 weeks, and methotrexate up to 12 weeks. For these reasons, we often employ preoperative and postoperative courses of high dose oral prednisone, as well as intraoperative solumedrol.

GLAUCOMA

Glaucoma is both a serious postoperative complication, and a known risk factor for endothelial dysfunction[34–37] and graft failure.[38] High intraocular pressure not only accelerates the rate of endothelial cell loss, but can also, of course, lead to optic nerve damage and permanent vision loss. Patients with pre-existing glaucoma are known to have two times the rate of graft failure compared with those without.[39]

Glaucoma medications themselves have been shown to affect endothelial cells differently. Rhopressa, a rho kinase inhibitor, has been found in animal and nonglaucoma studies to enhance endothelial cell wound healing, increase endothelial cell density in animal models, and encourage resolution of corneal edema in patients with Fuchs' dystrophy.[40] Carbonic anhydrase inhibitors, such as dorzolamide, have been suspected to cause endothelial toxicity, though this has yet to be adequately studied.[41–43] On the other hand, glaucoma surgeries,[44–46] including phacoemulsification, trabeculectomy[47,48] and tube-shunt implantation,[49,50] have been shown to accelerate endothelial cell loss. Tube-shunt surgery is the most likely to accelerate endothelial cell loss,[51] perhaps due to intermittent tube-cornea touch or

increased disruption of the blood-aqueous barrier which allows for increased subclinical inflammation.[52,53]

In patients who had previous glaucoma surgery and have a tube in place, attention should be paid to the length and position of the tube. In cases where the tube is long, and appears to be in close proximity to the endothelium, we recommend trimming it shorter or, in a combined case with our glaucoma team, moving the tube to the sulcus or the pars plana. When possible, we favor pars plana tube repositioning which has been shown to minimize corneal endothelial loss compared to AC location.[54]

HSV/VZV/CMV KERATITIS

Viral keratitis is a common cause of corneal disease, and HSV is one of the leading causes of infectious corneal blindness in developed countries.[55] Corneal opacity from viral keratitis is a common indication for PKP; however, recurrence can impact the success of a graft. Herpes simplex virus is ubiquitous in the population, and thought to be latent in corneal tissue,[56–58] with rabbit models suggesting potential transmission between host and donor tissue.[59] In patients with a known history of HSV keratitis, it's our practice to start therapeutic doses of oral antivirals, such as 1,000 mg oral Valtrex three times daily or 800 mg oral acyclovir five times daily, starting a week prior to surgery and continuing for at least one month postoperatively. We maintain prophylactic doses of antiviral, such as 1,000 mg Valtrex daily or 800 mg of acyclovir twice daily for life. The Herpetic Eye Disease Study (HEDS) I demonstrated a significant benefit to using oral acyclovir and topical corticosteroids for stromal keratitis.[60,61] The HEDS II that followed showed that oral acyclovir decreased the recurrence of HSV keratitis (of any type) by about half.[62,63]

Some patients are thought to be at increased risk for HSV keratitis after receiving a corneal graft from an HSV positive host.[64] Case reports attributing graft failure to HSV are reported in the literature, and it's likely that HSV infection of endothelial cells can lead to corneal graft failure.[65] Cytomegalovirus has also been suspected as a cause of endotheliitis following PKP,[66] and donor corneas have been reported as a source of CMV inoculation in previously seronegative recipients.[67] Given these possible avenues of infection, particularly in the immediate postoperative period, we recommend vigilance, with a low threshold for starting antiviral therapy at the first signs of possible viral keratitis. For patients with history of prior HSV or varicella zoster virus flares, we recommend initiating a course of antiviral therapy prior to graft implantation, and in the immediate postoperative period.

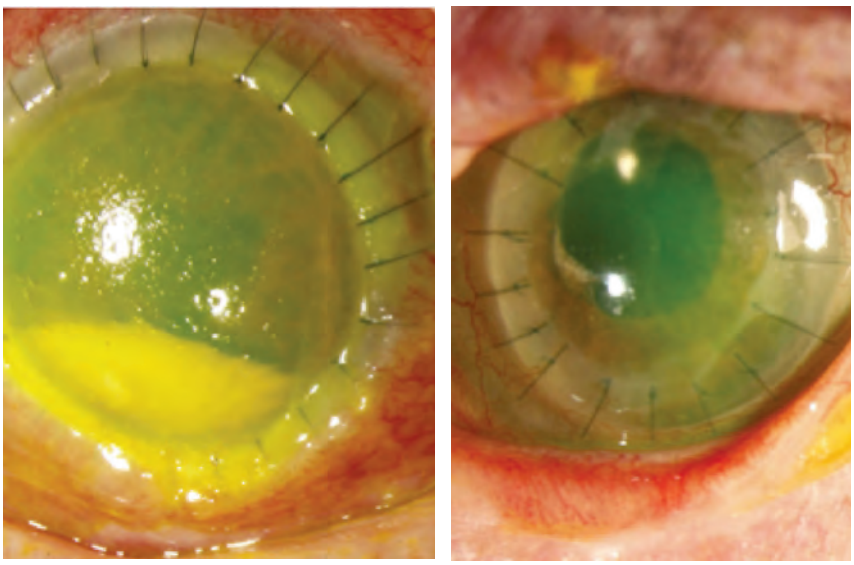

Figure 2. Left: Therapeutic penetrating keratoplasty for *Fusarium* keratitis resulting in perforation. Right: PK and lateral tarsorraphy lagophthalmos and neurotrophic keratopathy from herpes simplex virus.

In patients with acute HZO and ocular involvement, more than half have corneal involvement.[68] Decreased corneal sensation has been shown to be present in approximately 20 percent of patients presenting with HZO,[69] and occurs in nearly half of eyes within the first year.[70] With the loss of corneal sensation, the eye experiences tear dysfunction, lower blink frequency, exposure keratopathy and delayed epithelial turnover, making it a strong predictor of poor epithelial healing. For these reasons, we recommend checking corneal sensation in all patients with a history of HZO, and considering amniotic membrane graft and lateral tarsorrhaphy at the time of keratoplasty to promote epithelial healing (*Figure 2*). If patients have no corneal sensation, keratoplasty should be avoided if possible. We use an identical perioperative oral antiviral regimen as well as a prophylactic oral antiviral for life as described above for HSV. The Zoster Eye Disease Study (ZEDS) is currently underway to determine the effects of suppressive valacyclovir treatment in improving outcomes for patients with herpes zoster ophthalmicus.[71]

While complex PKPs have higher risks, they also offer the possibility of higher rewards. These transplants are often undertaken in patients with complex ocular disease who are facing severe vision loss and therefore there's also a high potential to improve vision-related quality of life. Managing patient expectations, ensuring a commitment to close follow up by both provider and patient, as well as a thoughtful approach to perioperative planning can optimize the chance of a satisfying and successful outcome. With these considerations, we have found that, while success in complex PKP isn't always guaranteed, it is attainable, and can be vision-restoring and life-changing for patients. ■

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Dr. Lin is a clinical associate professor of ophthalmology at Stanford.

Dr. Rose-Nussbaumer is an associate professor of ophthalmology at Stanford, and a researcher at the Francis I. Proctor Foundation at UCSF.

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SECRETS ON THE SURFACE

By
Liz Hunter
Senior Editor

Over the course of the last decade or so, considerable investments have been made on the topic of ocular surface disease. More than just "dry eye," ocular surface disease has proven to be a multi-faceted issue that plays a significant role in people's well-being. Studies have shown the prevalence of ocular surface disease is higher than previously thought—likely between 5 to 15 percent of the U.S. population[1]—meaning cataract and refractive surgeons in particular should be on high alert for ocular surface disease in their patients already in an effort to optimize surgical outcomes.

Read on to learn more about how to screen for, diagnose and treat ocular surface disease before proceeding with cataract or refractive surgery.

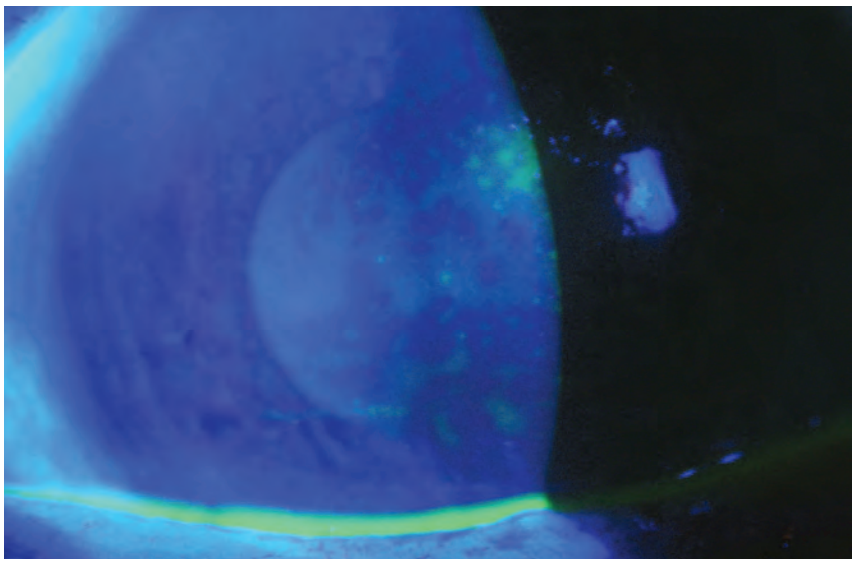
THE SCOPE OF THE PROBLEM

Ocular surface disease and dry eye became even more evident during the pandemic, where many people were sheltering remotely or working from home and screen time greatly increased, even among younger patients, says Terrence P. O'Brien, MD, a professor of ophthalmology at the University of Miami. "Evaporative dry eye was being seen even in people in their 20s as opposed to just in the typical older patients," he says. "Screen time on various devices and evaporative loss of tears is making the curves shift downward to even younger patients in whom we hadn't really been screening for dry-eye disease or ocular surface disease.

"One unique pre-selection factor in patients seeking refractive surgery is often contact lens intolerance, where they'd been wearing contacts successfully and then, because of ocular surface disease or dry-eye disease, their contact lens wearing time was reduced and comfort levels declined," Dr. O'Brien continues. "Thus, they're essentially pre-selected because they're coming in seeking refractive surgery due to the discomfort of wearing their contact lenses. That's a very well-understood reason for many patients to seek refractive surgery. We have to identify that and treat the dry eye or ocular surface disease that led to contact lens discomfort prior to even considering refractive surgery."

Dry eye is the top complaint among post-LASIK patients, with studies showing that 95 percent of them experience some manner of symptoms.[2] Due to its suspected ubiquity in the general population, many suspect that LASIK exacerbates previously undiagnosed ocular surface disease. "Active screening for ocular surface disease is perhaps even more important with refractive surgery—because it's an elective, voluntary procedure," Dr. O'Brien says. "If OSD isn't detected prior to an elective refractive surgery, the consequences can be even more significant for patient dissatisfaction and cause lingering ongoing problems."

Preeya K. Gupta, MD, FACS, a cornea and cataract surgeon in Durham, North Carolina, believes ocular surface disease should be suspected in a majority of cataract patients. She co-authored a study of cataract patients with a mean age of 69.5 years and found that upwards of 80 percent who came in for a cataract evaluation had some sort of ocular surface disease dysfunction.[3] "It's actually more common than not that patients will



Terrance P. O'Brien, MD

A 72-year-old female with cataract demonstrating a pattern of fluorescein staining consistent with aqueous tear layer deficiency.

present with dryness, though they may be asymptomatic," Dr. Gupta says. "That kind of leaves us to say, 'If I'm not seeing it in three out of four patients, maybe we're not looking for it the right way or we're not paying close enough attention to it.' "

Ocular surface disease increases with age, says Dr. O'Brien. "Since cataract is an age-related process and increases over time among that population, the two frequently overlap. It's not infrequent that patients will have significant ocular surface disease concomitant with advancing cataracts," he says. "Cataract surgeons really can't ignore this common correlation. They have to really be on the lookout and identify or detect significant ocular surface disease and preferably address it in advance to achieve better outcomes. The patient will be less likely to have protracted healing and worsening of OSD after the cataract surgery. Multiple factors related to the cataract surgery itself can often exacerbate pre-existing ocular surface disease."

WHY THE OCULAR SURFACE MATTERS

"The air-tear film is one of the most important refractive surfaces in the eye, in addition to the lens," says Dr. Gupta. "When we're performing cataract surgery, we're replacing the patient's lens but if we don't treat underlying ocular surface disease, we're not really going to be giving our patients the best quality of vision that they expect because the air-tear interface is critical in vision quality.

"With any ocular surgery, not just cataract surgery, we can actually worsen ocular surface disease by disrupting corneal nerves," she continues. "For some people, it's temporary, but for others it can be a persistent problem and becomes a source of dissatisfaction to patients because they came in asking for you to improve their vision, you performed cataract surgery, but they come back saying their vision is terrible. They might be seeing 20/20 on a chart but when you actually look at everything all together, it's their tear film that's gotten worse over time. That in itself is something that can lead to dissatisfaction after surgery, as well as blurred vision postoperatively."

The ocular surface's condition can also influence IOL calculations and refractive measurements. One retrospective case series found that epithelial basement membrane dystrophy and Salzmann's nodular degeneration altered the K measurements and affected the spherical and toric IOL power.[4]

"We know, when it comes to postoperative patient satisfaction, the precision of IOL calculations and refractive measurements prior to surgery, the ocular surface is increasingly important," says Christopher E. Starr, MD, an associate professor of ophthalmology and director of the refractive surgery service at Weill Cornell Medicine in New York. "Toric IOLs, premium IOLs, EDOF lenses—all these things do better when the ocular surface and the cornea in particular are pristine and optimized."

Defining ocular surface disease has been a challenge within the field. Bascom Palmer Eye Institute defines ocular surface disease as "disorders of the surface of the cornea" including "dry-eye syndrome, meibomian gland dysfunction, blepharitis, rosacea, allergies, scarring from glaucoma medications, chemical burns, thermal burns and immunological conditions such as Mucous Membrane Pemphigoid and Sjögren's Syndrome."[5]

More often than not, symptoms—which can include blurry vision, discomfort, pain, redness, itching—get lumped into the term "dry-eye," but it's much more complex. "For me, the distinction between the term ocular surface disease and dry-eye disease is an important one and it's a message I've been trying to get out there for years now," says Dr. Starr. "Stop calling all of this dry eye; dry eye is a subtype of ocular surface disease, and it's one of many that can have ramifications and implications on refractive outcomes."

SCREENING AND DIAGNOSTIC TOOLS

Since ocular surface disease can take so many different forms and severities, an OSD initiative was undertaken by representatives from the ASCRS Cornea Clinical Committee, including Dr. Gupta and Dr. Starr. "The idea was to create a protocol/workflow algorithm to help people navigate OSD and to help these practices adopt something that will help them to not miss this and instead manage this proactively," says Dr. Starr. The preoperative algorithm is freely accessible at www.ascrs.org.

• ***Questionnaires.*** One of the first steps in this algorithm is an ocular surface screening battery of questions. This isn't new to cataract and refractive surgeons, and there are various validated dry-eye questionnaires available, including the Ocular Surface Disease Index, Dry Eye Questionnaire-5, McMonnies Dry Eye Questionnaire, Symptom Assess-

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ment in Dry Eye (SANDE), and Standard Patient Evaluation of Eye Dryness (SPEED) questionnaires. These have been evaluated for their discriminative ability in a prospective, investigator-masked, diagnostic accuracy study[6] that found that the OSDI and SANDE scores had superior discriminative ability in detecting dry-eye signs compared with the others.

"A questionnaire is a great pre-screening tool that can often be sent even when the patient's making the appointment to come in for a cataract evaluation," says Dr. O'Brien. "The patient can receive this validated dry-eye questionnaire and upon arrival the team is even more alerted to the possibility or the actual likelihood of DED/OSD if the patient has a history of these conditions."

Common questions may include asking about frequency and severity of grittiness, burning, irritation or eye fatigue; if they use eye drops and how often; if they wear contact lenses and for how long; and if one eye seems more impacted than the other.

"Even if people aren't using a validated questionnaire from the National Eye Institute, or other questionnaires that have been shown to be validated, even just a few simple questions can be helpful," continues Dr. O'Brien.

One important question to ask is about fluctuating vision. "I very much like to ask them about their blurry vision, specifically if it's fluctuating or if it's constant," Dr. Gupta says. "Fluctuating blurred vision will often lead you to a diagnosis of dryness because cataracts do not typically cause fluctuation in vision, it's more of a fixed level of blur. Ocular surface disease will cause fluctuating blurred vision because patients will have a varied tear film blink to blink."

Dr. O'Brien notes that certain diseases and medications contribute to ocular surface disease, including Type 2 diabetes, hypertension and high blood pressure. "Those are often comorbid systemic conditions that contribute to dry eyes," he says. "A careful review of medications is essential because sometimes over-the-counter medications are omitted by patients who don't consider them to be medications because they're not prescribed by a physician. Examples include anti-allergy medications and decongestants. Those are very drying but frequently patients will forget to mention unless you really probe for all medications being used."

Dr. O'Brien says another class of medicines in use by many that are frequently ignored are sleep aids, such as benzodiazepines and soporifics that contribute to sleep. "Benadryl, which is an antihistamine, is taken by some to help go to sleep," he says. "A lot of people take a low dose of a sedative hypnotic to help go to sleep and those all really contribute to ocular dryness.

"Diuretics are another group of medicines about which to inquire," Dr. O'Brien continues. "Patients with high blood pressure are often on a diuretic and that's very drying as well. That's why high blood pressure is also frequently associated with dry-eye disease."

Cataract surgeons should also make sure to ask if the patient has had prior LASIK surgery. "If they had it 20 or 25 years earlier, they may have forgotten to mention it," Dr. O'Brien says. "That should be on our screening list because those patients may be more prone to develop dryness either prior to the cataract or certainly after the cataract because of their prior LASIK surgery. And of course, we want to know that because it can be more challenging to obtain an accurate determination of corneal power to select the desired intraocular lens power."

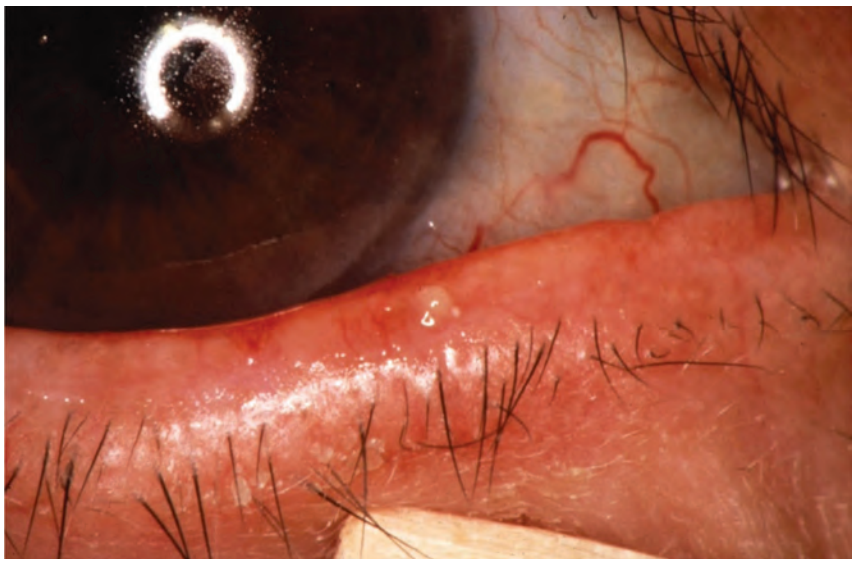
• ***Testing.*** Now that the surgeon is armed with knowledge about symptoms, when the patient arrives in the office, specific testing will look for signs of ocular surface disease. At this point, osmolarity testing is a beneficial tool, and there are in-office, point-of-care tests available. Dr. O'Brien says he believes the field is "on the cusp of a significant paradigm shift in screening patients for more efficient/robust detection of ocular surface and dry-eye disease using a 'multiplex' point-of-care testing options that have recently become available. I have actually been talking about this for many years with great hope that this would someday become a reality." He cites a tear lactoferrin assay that's become available and a future Tear IgE test that will look for ocular allergy in the clinic.

Tear osmolarity testing has been around for years, and has its pros and cons, physicians say. "Hyperosmolarity is a fundamental finding in dry-eye disease," says Dr. Gupta. "Osmolarity tests are readily available, but there's a cost associated with them. A lot of insurance companies will reimburse for them, but some will not, so it depends on your region. Osmolarity has a very high specificity. If it's abnormal, it's very likely that the patient has dry eye, but it's not necessarily a linear metric. We should know how the test works and be thoughtful about those aspects of it. But I do think it's a good screening tool for dry eye and it's easy to educate the patient when you tell them they have an abnormal number."

Dr. Starr uses tear osmolarity and matrix metalloproteinase-9 (MMP-9) with his patients. "I use these with all of my patients, not just my pre-surgical patients," he says. "Tear osmolarity is a fantastic test for dry-eye disease and it's quantifiable, however, it doesn't tell you a whole lot about other forms of ocular surface disease, whereas when MMP-9 is abnormal (the InflammaDry test measures this) then you know that the ocular surface is abnormally inflamed, and inflammation is certainly a result of chronic dry-eye disease. We know that inflammation is elevated in a lot of other ocular surface diseases that aren't dry-eye disease: allergy; pterygium; some forms of blepharitis; epithelial basement membrane disease that can sometimes elevate MMP-9; and conjunctivitis. There are a lot of other things that can cause elevations in MMP-9 that are all abnormal but not dry-eye disease."

One of the best tests that can be done is the tear-film breakup time, according to Dr. O'Brien. "We usually blink about every 12 to 15 seconds per minute," he says. "The tears should try to last until the next blink. However, in many patients the tears are breaking up much sooner than that. In some patients with severe dry eye it's almost instantaneous. In others, their tears break up after four to five seconds so they're not making it until that next blink and that's why they're symptomatic with evaporative dry eye. Tear-film breakup is a very simple test that any clinician can perform and should complete as part of the screening. It's very valuable information that's obtained quickly."

Dr. O'Brien cautions that these tests



The tried-and-true therapies of warm compresses and digital massage are very beneficial for eyes with meibomian gland congestion or inspissation.

should be performed on eyes in their natural state, free of any diagnostic drops. "If considering testing tear-film osmolarity, the results will be unfortunately marginalized if anesthetic drops or dilating drops are instilled. That's going to alter the osmolarity and affect other tear layer tests," he says. "It's better to observe the eye in its normal state."

• ***Clinical exam.*** Dr. Starr says the clinical exam is often an area that surgeons in general don't do because it can take up a lot of time. "As part of this algorithm, we needed to come up with a quick, pointed, catchy moniker for the ocular surface exam so that everybody does the steps with each visit," he says. "We came up with something called Look, Lift, Pull, Push (LLPP)."

"As doctors, we have limited time and it's hard for everybody to incorporate everything into their exam, so LLPP is meant to give people a framework and some guidance in how they can best approach screening their patients," adds Dr. Gupta.

Dr. Starr walked through the steps in detail:

• ***Look:*** "When I walk into a room and start talking to the patient, I am honed in on their eyes, their blink, their symmetry between the eyes, looking for signs of facial rosacea, looking for incomplete blinks or exposure, lagophthalmos, scleral show—these types of things tell you so much and are often overlooked," he says. "There's so much important information that can be gleaned just from talking and observing the eye. 'Look' is also look under the slit lamp, look at the eyelid margin, look at the lashes, look for signs of anterior blepharitis, bacteria, biofilms and telangiectasia. Look at the cornea for signs of subtle corneal dystrophy, such as epithelial basement membrane dystrophy and conjunctival issues, etc.

"We usually have the patient look up and we have the patient look down," Dr. Starr continues. "When the patient looks down, you can often see collarettes, and we now know collarettes on the eyelashes are pathognomonic for *Demodex* blepharitis. We know that when there are *Demodex* mites there's a higher chance of bacterial colonization or superinfection. In the pre-surgical patient, that's an important thing to identify, obviously, because of the risk of endophthalmitis and surgical infection."

• ***Lift:*** "Lift means lift up the upper eyelid, and we often don't do that. It's a quick and easy thing. You just lift it up and examine the superior conjunctiva and the superior cornea which is often blocked by the upper lid unless you lift it up," he says. "The reason why that's important is that there are things that reside up there that can cause problems and lead to visually significant ocular surface disease, such as superior limbic keratoconjunctivitis and corneal dystrophies like EBMD or map-dot fingerprint, which often lives on the superior cornea, and you might completely miss it unless you examine that area."

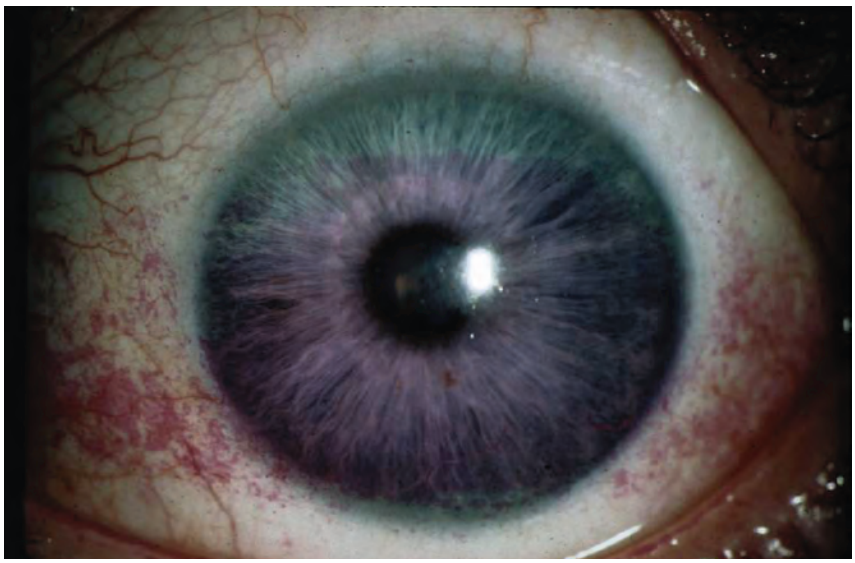
• ***Pull:*** "Pull the upper eyelid away from the eye to assess laxity. Floppy eyelid syndrome is a very common cause of ocular surface disease and chronic ocular surface issues and can have visual impact. Assessing that is important for everybody to do whether they're pre-surgical or not," Dr. Starr says.

• ***Push:*** "The final part of the exam is pushing on the meibomian glands. Meibomian gland expression is often not done and it's such important information," he continues. "If you push on the meibomian glands and nothing comes out then you know that you've got obstructive MGD and you're not going to have enough tear lipid and there's going to be evaporation."

Dr. O'Brien says meibography does help with looking at the health of the meibomian glands, but he stands by the practice of physically looking at the lids and manually expressing the meibomian glands as well.

During the clinical exam, Dr. O'Brien performs corneal staining. "There's fluorescein staining, which is beneficial, and even more beneficial is a vital stain such as lissamine green," he says. "Lissamine green will detect ocular surface disease earlier with cells that are devitalized from chronic dryness of the surface, punctate epitheliopathy, whereas fluorescein will only detect cells that have already died so you'll see erosions where cells have fallen out or dropped out. With lissamine green you'll see cells that are still alive but they're just not happy or healthy because of chronic dryness and inflammation of the ocular surface."

Dr. Gupta notes that corneal staining is a late-stage dry-eye disease finding. "Initially, when patients have dry eye they won't have corneal staining, and they may have higher symptoms than signs of dry-eye disease because they haven't had these cycles of inflammation that lead to corneal decompensation," she says. "Corneal staining can actually interfere with our measurements as well. We



A 59-year-old hyperope with decreasing tolerance to multifocal soft contact lens presenting for possible laser vision correction. Rose bengal demonstrates significant interpalpebral staining.

can sometimes get erroneous biometry measurements leading to inaccurate treatment plans."

In the past, Schirmer's testing was a common tool for ocular surface disease, but Dr. O'Brien says it became somewhat controversial due to difficulty interpreting results. "I agree that sometimes the value of the test may be limited or the validity may be questioned because in some patients there can be sort of a reflex tearing that's induced by the strip," he says. "The Schirmer I uses no anesthesia. I think that can be a better screening option than the Schirmer II, when you use anesthetic and then you test the amount of wetting on the little strip. On the Schirmer I, if you have next to nothing (zero or 1 mm only of wetting), the patient has severely aqueous deficient tears and that gives you some value. Sometimes with the Schirmer II, it's difficult to interpret the meaning or the value of the test. That's why a lot of doctors have abandoned Schirmer testing."

Advances in imaging technology have also helped in diagnosing ocular surface disease. "The machines we're using to get topography, such as the Oculus, can also measure the tear meniscus height," Dr. O'Brien continues, "and that can be a quantifiable measurement. If you have a low tear meniscus height then the person is at risk."

TREATMENT PLANNING

If a surgeon has discovered signs of visually significant ocular surface disease, this must be explained to the patient.

"Often all of these symptoms will get worse after surgery because of the incisions, drops, preservatives and all of the trauma of surgery," Dr. Starr says. "If you don't pick up on these before the surgery and discuss it with the patient and it worsens or becomes more visually symptomatic to the patient postoperatively, then they view it as a surgical complication. Having the discussion and instituting treatment makes sense on so many levels and will improve outcomes and reduce the perceived complication rates."

It's best to delay cataract or refractive surgery and begin treating the subtype of ocular surface disease. "Most of the time patients presenting are eager to have either cataract surgery or refractive surgery," Dr. O'Brien says. "The teams have been trained to be very efficient at screening. You have to make sure that there's a way to 'pump the brakes' prior to the patients just being rushed into the operating room. That's where some of the really unfortunate cases occur. Perhaps they could've been prevented if there was a slower, more robust screening and a slower-to-procedure process where treatment had a chance to work. Even for moderately severe ocular surface disease, surgery may have to be postponed for at least four to six weeks to allow the various therapies to have a chance to really bring the ocular surface disease under better control and to allow more accurate preoperative measurements."

Treatment depends on the severity of a patient's disease. A severity grading after performing this diagnostic testing can help guide treatment. The OSDI defines the ocular surface as normal (0-12 points), mild (13-22 points), moderate (23-32 points) or severe disease (33-100 points).[7]

"For most patients that fall into the mild or early group of dry-eye disease, treatment can sometimes be as simple as education about sleeping under a ceiling fan or if they have air conditioning blowing into their face because they're a truck driver," says Dr. O'Brien. "Or they work at a computer and that's almost everybody these days. They need education about screen time. We usually recommend the rule of 20-20-20: every 20 minutes the individual takes a break for 20 seconds and simply looks off in the distance for 20 feet. That interrupts the cycle of locking into the screen and blink rate going down and evaporation of tears going up. The 20-20-20 rule can be helpful.

"Also, educating about medications that they may be taking, over-the-counter, anti-allergy drugs, antihistamines, medicines for sleeping and antidepressants is useful," he continues. "We have a high number of people that have been prescribed these antidepressant medicines that have some anticholinergic effects so people's eyes become very dry with those as well. Behavior modification can help, such as drinking more water, especially if they work outdoors or exercise in warm places."

Tear replacement and lid hygiene are among other first-line treatments for those in the mild group. "Lid hygiene is very important so we recommend cleaning the eyelids and the eyelashes with some type of dilute shampoo," says Dr. O'Brien. "Even baby shampoos contain detergents so we prefer more of a commercially available foaming lid cleanser that would help remove tear debris from the lids and lashes that can end up in the

tear film. Then, especially for those with meibomian gland congestion or inspissation, the use of warm compresses for localized hyperthermia with accompanying massage is very beneficial."

Nutritional supplements such as Omega-3 fatty acids have also been shown to ameliorate dry-eye symptoms.[8]

There's no one perfect treatment, says Dr. Gupta, but for a lot of patients something that's very quick can be a topical steroid. "After patients are on the topical steroid for about two weeks, we'll have them back to repeat their testing and if things are better, we may be able to schedule the surgery, but they have to prove their surface is better before we go to surgery," she says. "If the patient has a risk of prolonged dryness postoperatively I have a low threshold to not only prescribe a topical steroid but to also put them on something like a chronic immunomodulating medication to help with their inflammation, which will help postoperatively as well."

Dr. O'Brien says this includes cyclosporine drugs or lifitegrast. "Usually these patients are anxious to have their surgery and we want to try to get the ocular surface under control more quickly, and we may also give a brief pulse of a topical corticosteroid along with the immune modulation to try to accelerate the anti-inflammatory effects to bring the condition under control," he says.

"Those patients who have more significant disease, in addition to the corticosteroids and immunomodulatory agents such as cyclosporine or lifitegrast, we often will give a brief systemic course of doxycycline or minocycline as an immune modulator to help with ocular surface inflammation or meibomian gland inspissation," Dr. O'Brien continues. "For some patients where there's a significant evaporative component we may place punctal plugs. For people with very significant meibomian gland disease we might recommend even more aggressive treatment, for instance a pulsatile thermal physical therapy such as LipiFlow, iLux or a similar commercially available treatment."

"YOU HAVE TO CONTINUE TREATMENTS POSTOPERATIVELY TO HELP BRING THINGS UNDER CONTROL AND TO PREVENT THEM FROM GETTING WORSE."

— TERRENCE P. O'BRIEN, MD

For the very severe cases, treatment may even include autologous serum tears for at least six to eight weeks prior to being able to safely undergo the cataract procedure without creating a postoperative imbalance that could be very detrimental, he says.

If the patient is found to have other corneal diseases, those must be addressed prior to surgery. Salzmann's nodular degeneration is due to chronic inflammation of the eyelids and lashes, causing scar tissue to build up on the cornea (the nodules). "Those should be removed because they create a lot of irregular astigmatism and you'd get very abnormal readings," says Dr. O'Brien.

"Another common condition that may affect about 2 percent of the general population is epithelial basement membrane dystrophy or anterior basement membrane dystrophy," Dr. O'Brien adds. "That usually should be addressed prior to the cataract surgery by removing the epithelium either through excimer laser phototherapeutic keratectomy or manually, such as with a corneal burr, so that the cornea is smoother, otherwise it can affect the accuracy of biometry and intraocular lens power determination."

After giving these various therapies a chance to work, patients should be brought back to the office and surgeons should repeat the screening process to be sure the ocular surface disease is no longer visually significant.

However, Dr. O'Brien cautions that patients should continue their ocular surface disease treatments postoperatively. "You have to continue treatments postoperatively to help bring things under control and to prevent them from getting worse, because both cataract and refractive surgery leave the eyes drier for some time, about six to eight weeks—and maybe even up to three to six months with LASIK," he says.

Dr. O'Brien notes that several components of cataract surgery can contribute to postoperative dryness. "For example, there's the ocular anesthetics that are used, the multiple drops that contain preservatives, the incision itself—that's been looked at," he says. "If someone's having femtosecond laser-assisted cataract surgery the suction device of the laser can affect the ocular surface. The main and arcuate corneal incisions may affect corneal sensation. The ocular surface is prone to temporary or transient damage from dryness during cataract surgery, as well as the preservative-containing eye drops." ■

Dr. Gupta is a consultant to Alcon, Allergan, Sight Sciences, Novartis and Azura Ophthalmics. Dr. O'Brien reports no disclosures. Dr. Starr is a consultant for Trukera Medical and Quidel.

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MANAGING CORNEAL SIDE EFFECTS OF SYSTEMIC MEDICATIONS

By
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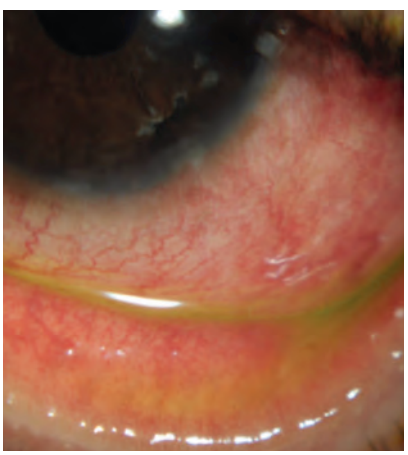
If you look hard enough most medications will have some ocular effects. Over time, as I've seen more unusual-appearing corneal deposits and edema patterns, I've become attuned to more thoroughly reviewing a patient's systemic medications. Since web searches for this topic can lead you down a rabbit hole of medications no longer in clinical practice (e.g., gold salts) or newly discontinued medications (e.g., belantamab mafodotin-blmf which was on an FDA REMS protocol)—I'd like to share with you cases I've compiled of patients presenting with corneal side effects of their systemic medications and presented in order of most frequent to least frequent that I've seen in my practice.

DUPILUMAB (DUPIXENT)

A 25-year-old patient was referred by his allergist for evaluation of chronic red eye accompanied by tearing. He was treated initially for nasolacrimal duct obstruction without relief. He only found relief while he was on oral prednisone. This patient had started taking dupilumab injections for his severe eczema and, though his skin condition was improving, his ocular redness and inflammation continued to worsen.

Dupilumab is a human monoclonal antibody that inhibits the action of IL-4 and IL-3. It's approved for patients over the age of 6 with refractory atopic dermatitis. Patients usually self-inject the medication every two to four weeks.

Dupilumab associated ocular surface disease has been reported in up to 34 percent of patients; sometimes this is directly drug related, and other times it's an exacerbation of pre-existing ocular surface disease. The mechanism of the ocular surface disease has been evaluated by impression cytology and is thought to be related to a reduction in goblet cells. Case reports have shown a myriad of findings, ranging from mild disease and conjunctivitis to severe ulcerative keratitis. Most patients showing this side effect usually have underlying atopic dermatitis.

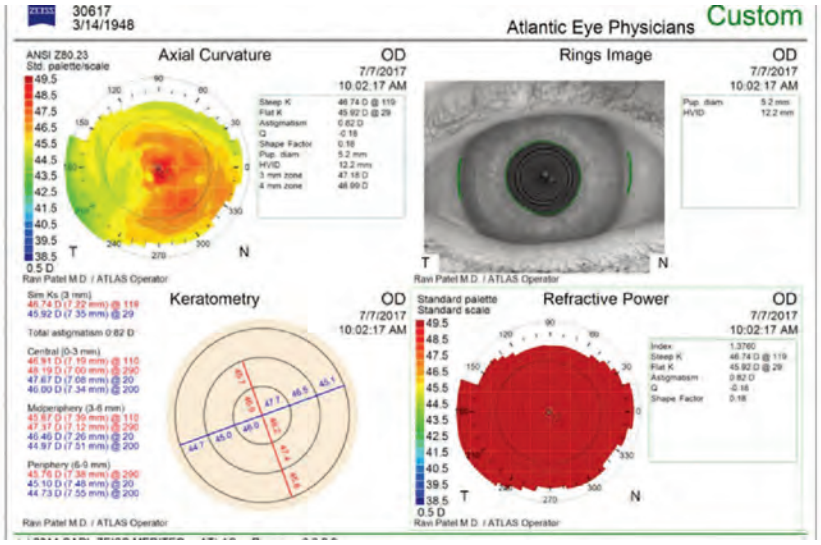


Ocular surface disease from dupilimab use is thought to be related to a reduction in goblet cells.

I vary the treatment based on the intensity of the symptoms. For milder disease profiles, I would consider topical ketotifen for the eye and topical tacrolimus for the lids. This usually helps to control the symptoms in most patients. Moderate intensity symptoms can be managed with topical cyclosporin (which has been shown to increase goblet cell density) and topical low-potency steroid (loteprednol 0.5% four times daily). If the disease course is more fulminant, then I'd favor starting crisaborole ointment for the lids with high-potency topical steroids (difluprednate 0.05% four times a day) and trying to taper the potency and frequency based on clinical response.

AMIODARONE (PACERONE, CORDARONE AND NEXTERONE)

A 72-year-old patient presented for consultation with worsening of blurry vision since bilateral cataract surgery. His BCVA was 20/30 with his spectacles. His past medical history was significant for seasonal allergies, hypertension and atrial fibrillation following ablation. The patient has many allergies and she reports allergies to all preservatives

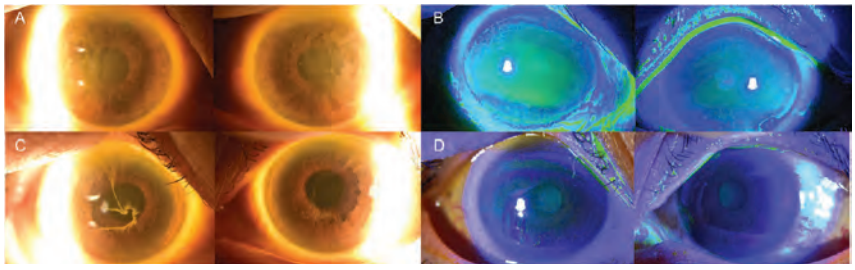


The whorl-like epithelial opacities often associated with the use of the cardiac drug amiodarone can result in irregular astigmatism and image blur.

as well as all hormones in meats. In the office, for many of these patients I'll perform a diagnostic RGP refraction, which in this case showed improvement to 20/20. The topography showed irregular astigmatism. Exam showed the typical vortex keratopathy and, upon further questioning, the patient was treated with amiodarone for several years prior to her ablation.

Amiodarone is an Class III antiarrhythmic medication used to treat numerous cardiac dysrhythmias including potentially fatal ones. It's part of ACLS life-saving protocols for cardiac arrest and can be used chronically for other arrhythmias. Besides the eye, it can deposit in the lungs, thyroid, liver, skin and peripheral nerves.

Amiodarone is an amphiphilic medication (which includes chloroquine, suramin, clofazimine, etc.), a class of drugs which has been long associated with whorl-like epithelial opacities. These were traditionally thought to be non-visually significant but I've seen many cases where these patients have irregular astigmatism and image blur from it. With improvements in technology to measure higher-order corneal aberrations, we're finding that symptomatic patients who have abnormal topographies or corneal aberrations often benefit from treatment. There are recent reports of using topical heparin successfully to remove amiodarone related deposits. But this can be difficult to get compounded. So, I'll offer these patients superficial keratectomy, particularly if they're now off the offending agent. For most patients this is an office procedure with a rapid recovery. I most certainly do warn patients that this can cause a shift in their refractive error and will likely need an update in their spectacles after the procedure.



Osimertinib (Tagrisso), an oral medicine for lung cancer, can cause serious side effects to epithelial cells. Lubrication, bandage lenses and amniotic membrane transplant can be useful in certain cases.

AMANTADINE (SYMMETREL)

A 58-year-old man was referred by his primary eye doctor for evaluation for possible endothelial keratoplasty due to progressive corneal edema. He was treated with hypertonic saline drops and prednisolone acetate 1% drops without any improvement. He was subsequently tried on oral valacyclovir presuming bilateral herpetic keratitis without improvement. The patient's wife noticed he developed extraocular edema and was prescribed neo-poly-dex ointment. He had no relevant ocular history. He's currently under the care of his neurologist for early-onset Parkinson's Disease and has a stent placed for coronary artery disease. His examination reveals diffuse stromal edema with endothelial folds and some asymmetry in both eyes. His visual acuity is 20/50 OD and 20/80 OS and his IOP is 20 mmHg OU.

Initially, I was quite perplexed how this younger man with no ophthalmic history had progressive edema which was non-responsive to medical therapy. The referring doctor went down the pathway as I usually would, considering some traumatic event, hypotony (but his IOP was normal), viral illness (most are unilateral), inherited disease (Fuchs' endothelial dystrophy without guttata—very rare) and post-surgical sequelae. I finally reviewed his medication list and saw amantadine on the list.

Amantadine is a nicotinic antagonist/noncompetitive NDMA antagonist which was initially used a prophylaxis for influenza A. It was learned this medication can reduce dyskinesias from dopamine medications and therefore it has since been FDA approved for treatment of Parkinsonian dyskinesias. My initial treatment was to call the movement-disorder specialist to recommend cessation of amantadine. I added topical steroids and topical timolol to aid in his corneal recovery. As you can see by the attached OCT pachymetry maps his corneal edema and vision improved over two months back to 20/20 and 20/25. Since I initially saw this case, I've seen numerous patients with the same side effect both as outpatient and inpatient/emergency room consultations for blurry vision.

OSIMERTINIB (TAGRISSO)

A 63-year-old nonsmoker presented for evaluation of blurred vision. He had a history of retinitis pigmentosa and took brinzol-

amide three times a day. His past medical history was relevant for Stage 4 non-small cell lung cancer. His ocular surface showed a severe vortex keratopathy in both eyes. His visual acuity was limited by his retinitis pigmentosa to 20/80 and 20/40, but he was subjectively aware of a decline.

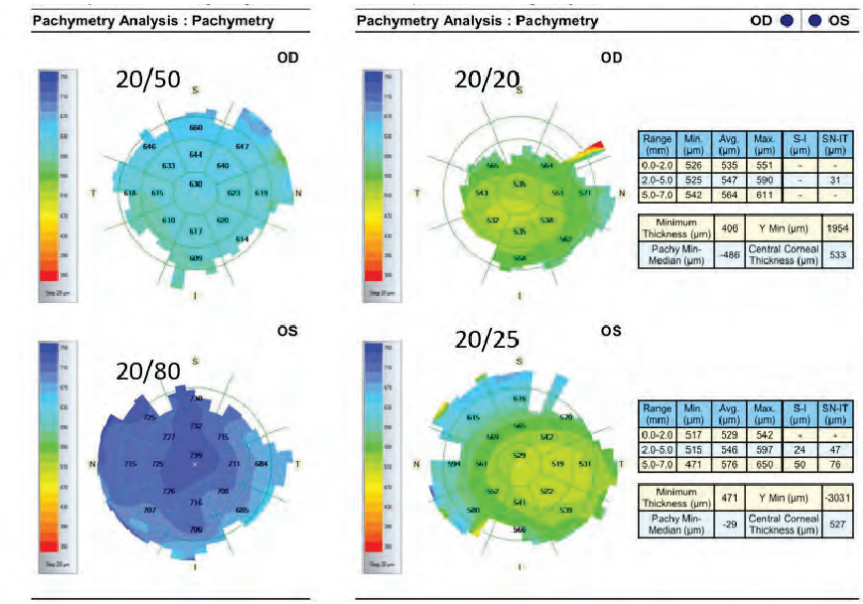
Osimertinib is a third-generation EGFR tyrosine kinase inhibitor which is used as a first-line therapy for T790M mutation EFGR-positive NSCLC. It's a daily oral agent capable of producing impressive improvements in progression-free survival.

Epithelial growth factor receptor (EGFR) inhibitors can cause side effects to any epithelial cells. Therefore, side effects include diarrhea, skin rash/inflammation, low blood cell counts and interstitial lung disease. Dry eye and whorl-like keratopathy are common in these patients. Since this is noninflammatory, steroids are of very limited use in the treatment of this condition. Many patients will become resistant to osimertinib within 10 months of treatment commencement and the condition is reversible with cessation of therapy. I have anecdotally found lubrication, bandage lens and amniotic membrane transplant can be helpful in select cases. Rarely, this class of medications can cause stromal deposits as well. As with any medication, this is one where it's especially important to balance the impact of drug cessation/modification weighed against the risk of systemic disease progression.

ISOTRETINOIN (COMMON BRANDS: ACCUTANE, ZENATANE, ABSORICA)

A 22-year-old patient presented for consultation for laser vision correction. He had a stable refraction for several years, is mostly a spectacle wearer due to contact lens intolerance. He has no relevant family history and is a moderate myope with otherwise normal tomographies. He takes no medications and has no allergies. Careful examination of this eyelids showed severe meibomian gland dropout and you can see this on meibomography. Upon further questioning he admitted to isotretinoin use as a teenager for acne.

Isotretinoin is also known as 13-cis-retinoic acid and is used to treat severe acne which is refractory to other treatments. It's been used in a variety of other dermatologic conditions, and its side effects resemble Vitamin A toxicity. As a fat-soluble essential vitamin the effects are diverse throughout the entire body. Prescribing is highly restricted and monitored through a website called iPLEDGE due to is teratogenic effects.

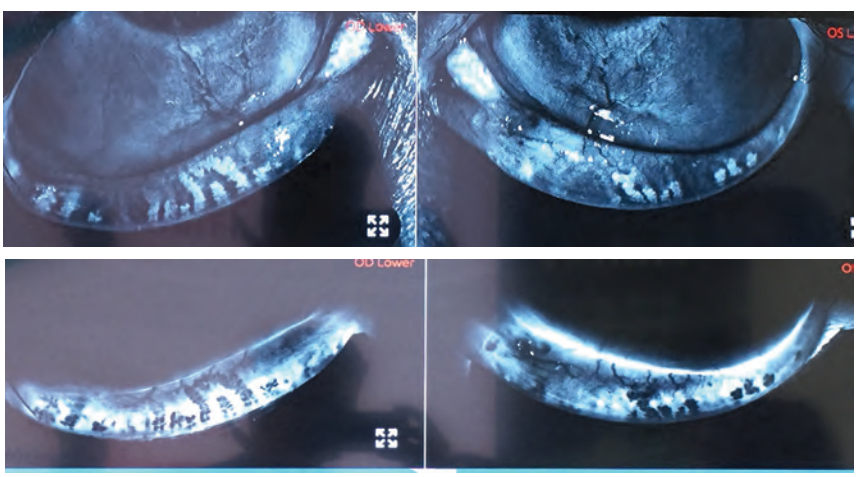


A patient on amantadine for Parkinson's had diffuse stromal edema and endothelial folds and some asymmetry bilaterally. His acuity was 20/50 in the right eye and 20/80 in the left (maps on the left). After cessation of the amantadine and the use of topical steroids and timolol, in two months the vision improved (right).

Isotretinoin is linked to blepharitis, conjunctivitis and dry-eye disease. Very rarely can it lead to cataract, color blindness, night blindness, contact lens intolerance, corneal opacification/keratitis and even papilledema. In this case the patient's reported symptom of contact lens intolerance and meibomography showing severe loss of meibomian glands is consistent with his previous use of isotretinoin. Unfortunately, there's no treatment to reverse this toxicity and conventional therapies for blepharitis are his only option.

RIFABUTIN (MYCOBUTIN)

A 74-year-old smoker with COPD presents with a recent diagnosis of mycobacterium avium complex pulmonary infection. He was started on ethambutol and is following up for his scheduled screening exam. He's pseudophakic and takes lifitegrast 5% topi-



Isotretinoin, used to treat severe acne, has been linked to blepharitis, conjunctivitis and dry eye. This patient showed severe loss of meibomian glands, most likely due to a history of isotretinoin use.

The antibiotic rifabutin can cause yellow-brown corneal deposits that are actually deep stromal lesions, and can involve the central cornea.

cally for dry-eye disease and has undergone SLT laser treatment for ocular hypertension. On exam his acuity was 20/30- and his IOP was 17 in each eye. He had normal color vision and no evidence of optic pallor on exam. His corneal exam showed peripheral circumferential yellow-brown deposits deep in the cornea. His entire medication list was reviewed and he was on a three-drug regimen which included ethambutol, rifabutin and clarithromycin.

Rifabutin is an antibiotic in the rifamycin family of medications which blocks RNA production in bacteria. It's typically used to treat tuberculosis and MAC, but is also employed in the treatment of *Bartonella* and *Babesia* colonies.

In the cornea, these yellow-brown deposits, which usually start peripherally then can progress to involving the central cornea, are actually deep stromal lesions. Confocal microscopy has shown they don't deposit in the endothelium, therefore they've not been associated with endothelial dysfunction. The prognosis of these lesions is unknown as they're rare and don't resolve with discontinuation of the medication. However, in an effort to prevent further progression, I spoke to the patient's infectious disease specialist about modifying his treatment and discontinuation of the rifabutin. Rifabutin has been linked to uveitis and retinal dysfunction, both of which are presumed to be reversible with discontinuation of the medication.

TAMOXIFEN (COMMON BRANDS: NOLVADEX, SOLTAMOX)

A 79-year-old woman's primary eye doctor referred her for evaluation of corneal changes. Patient's presenting complaint was progressive photophobia. Her past medical history included hypertension, osteoarthritis, breast cancer (and subsequent mastectomy) and radiation at age 62. Her visual acuity was 20/40 OU BAT to 20/100 OU. On examination she had refractile subepithelial deposits consistent with a drug-induced keratopathy. Tamoxifen was listed during a review of her systemic medications.

Tamoxifen is a selective estrogen receptor modulator used to prevent breast cancer. The most common side effects reported from its use are endometrial cancer, thromboembolism and hepatotoxicity. Most patients are treated for five years for secondary prophylaxis of breast cancer.

Tamoxifen is usually associated with dry-eye disease but rarely can cause keratopathy, retinopathy and cataracts. In this case, my patient had classic corneal findings which are rarely reported. This keratopathy is typically reversible with cessation of therapy. The patient was continued on the medication inadvertently as she had transitioned through oncologic care through relocation and retirement of her doctors. I spoke with her medical oncologist to ascertain if this was necessary for her ongoing treatment. Ultimately, since it has been more than 10 years of treatment, the patient was advised to discontinue the therapy. Her photophobia improved dramatically within the first three months. Over the following year most of her deposits resolved with surface lubrication and topical cyclosporin 0.05%.

INDOMETHACIN (COMMON BRANDS: INDOCIN AND TIVORBEX)

A 63-year-old patient was referred to see me for progressive corneal changes in both eyes with concern for monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma. Past medical history included lung cancer, skin cancer, hypertension, well-controlled diabetes mellitus type 2 and rheumatoid arthritis. The patient had visual acuity of 20/25- in both eyes and has been treated for dry-eye disease with topical lubricants. On examination he was found to have fine specks throughout the stroma. As a patient with a previous history of lung cancer his rheumatologic ailments were being managed with oral NSAIDs in lieu of biologic agents and of course he found the best relief with indomethacin.

Indomethacin is one of the most potent NSAIDs available for joint disease, headache, fever and most importantly pain relief. Indomethacin is used acutely in most cases and rarely are side effects from chronic use encountered. Indomethacin is unique from other NSAIDs in that in addition to its role as a COX inhibitor it's been found to reduce cerebral blood flow through vasoconstriction and nitric oxide pathways, making it helpful in treatment of certain headaches. It's a tocolytic that's helpful in delaying premature labor and it can cross the placenta and be used for treatment of polyhydramnios.

Indomethacin can cause a whorl keratopathy as well as stromal deposits. There's some evidence that this drug can cause a pigmentary retinopathy, including bulls-eye retinopathy. In this case the findings were limited to the cornea and, though paraproteinemic keratopathy was in the differential for a patient with previous malignancies, I ordered an SPEP and UPEP to rule out MGUS and myeloma. I decided to first discuss alternative treatment options with his rheumatologist to see if we could reduce the dose or even stop the indomethacin. The patient was very reluctant since he knows how disabling his arthritis can become. Eventually he did a trial of corticotropin gel injection and there was some improvement of his deposits, but this was short-lived as he didn't like doing injections twice weekly, so he ended up back on indomethacin.

In summary, this list isn't exhaustive or even comprehensive, but is simply a cross-section of patient referrals I've seen in clinical practice. However, being familiar with it can be helpful: You might become a "zebra hunter" when looking for some of these conditions, but if there's evidence of an unusual finding in the cornea, a careful review the patient's systemic medications just may result in a surprise. ■

(References for the article appear in the online version on reviewofophthalmology.com.)

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HOW TO MANAGE DMEK COMPLICATIONS

By
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Sean Tighe, PhD Miami
Anny M.S. Cheng, MD Ft. Lauderdale, Fla.

Descemet's membrane endothelial keratoplasty is the selective transplantation of the Descemet's membrane and endothelium and is currently one of the most common surgical treatments for corneal endothelial dysfunction. Despite the already advanced status of the surgical procedure, DMEK is continuously being optimized to achieve positive outcomes, including a good functional outcome, relatively rapid visual recovery, low risk of hemorrhage and infection, reduced astigmatism, decreased corneal denervation and decreased rejection rates.[1] However, challenges of DMEK have been reported in the preoperative graft preparation, and complications may arise in the initial post-transplant weeks and are most evident at the initial postoperative clinic examination.[2] The diagnosis and successful management of these early complications are essential for the long-term survival of DMEK.[3] Studies show that the complication rate decreases significantly with DMEK surgeons' growing experience over the years.[4] Understanding the surgical technique and various nuances of DMEK surgery can be very helpful in obtaining an optimal result.[5]

In this article, we discuss the diagnosis and management strategies for complications of DMEK that occur intra- and postoperatively to achieve the goals of performing the procedure safely, reducing complications and making the procedure simpler for ophthalmic surgeons to reproduce.

DONOR TISSUE

The goal of corneal, surgical endothelial intervention is to usually replace the dysfunctional endothelial cells with healthy donor tissues and to provide optimal vision for the patient.

The donor tissue scrolls for DMEK surgery have been used in two varieties namely, endothelium-out and endothelium-in (trifold) orientation.[6] The outcomes being similar, it may then be a surgeon preference.[6]

Donor age can contribute to different behavioral patterns with regard to tissue scrolling and unscrolling, all of which can affect the surgical duration and intraoperative complexities of DMEK. When we look at donor age, the younger the donor, the more elastic the DM lamella, which allows the graft to coil up disproportionately, making unfolding in the anterior chamber, and fixing the graft to the recipient corneal bed, surgically challenging. Young donors have been found to scroll tighter than old donors.[7] Hence, it appears that an elderly donor is more suitable for unscrolling an endothelium-Descemet's membrane (EDM) disc, especially in eyes with a very deep or very shallow AC, that makes transplantation difficult. However, some older donor graft tissue may not scroll optimally and lead to additional surgical difficulties intraoperatively.[8]

Incorrect orientation of the EDM disc (endothelial-side-up) intraoperatively requires graft detachment by aspirating the AC air bubble and injecting balanced salt solution from a side port, and then injecting air or gas to reattach it in its proper orientation namely, endothelial-side-down. Postoperative detection of an upside-down DMEK requires timely surgical intervention[8] to establish correct orientation and re-establishment of the tissue anatomy between the donor and recipient tissues.

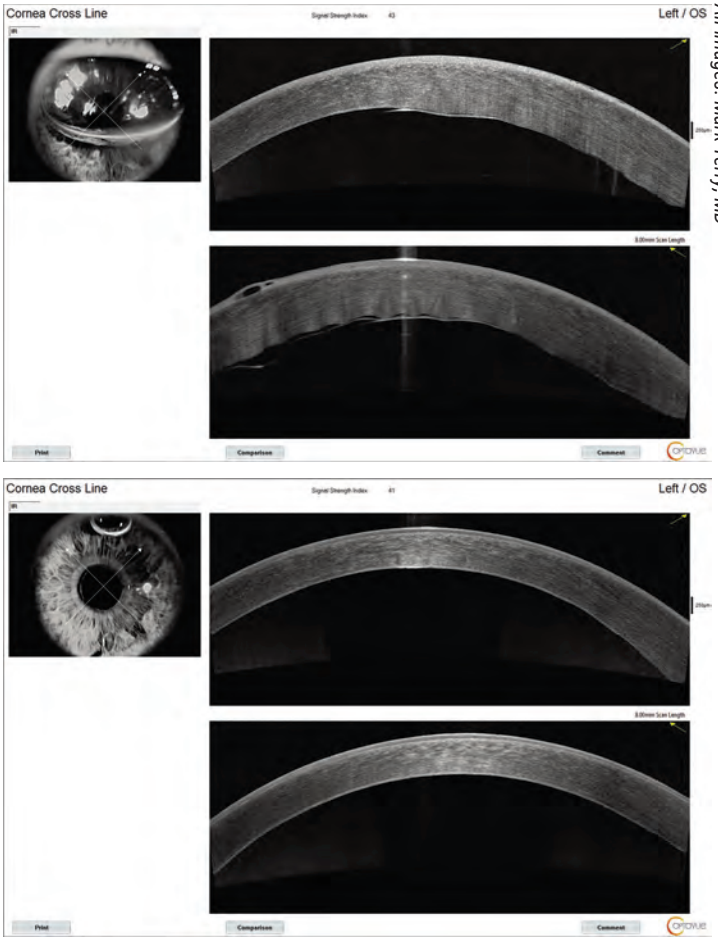
When comparing complication rates between younger and older donors, one study showed that younger donor age had comparable clinical outcomes and no difference in complication rate to older donor age in DMEK surgery within the first postoperative year.[9] It's also been

shown that donor age and endothelial cell density influence the properties of the DMEK grafts. Older donors and grafts with higher endothelial cell densities formed broader graft rolls.[10]

In addition to donor age and endothelial cell density, tissue characteristics such as the diameter of the graft, storage methods, methods of transplantation, and the recipient's AC status have also been reported as determining factors in the scrolling and unscrolling/unfolding of the DMEK graft. Therefore, it's important to consider these and other variables when optimizing for DMEK surgery.

Decreasing EDM disc unfolding time within the anterior chamber facilitates DMEK surgery and decreases potential iatrogenic donor endothelial cell loss. Pre-positioning the donor EDM disc prior to AC delivery of the donor tissue often facilitates easy and quick unfolding of EDM disc and shortens DMEK surgical time.[11]

While trypan blue greatly facilitates viewing the EDM disc within the recipient AC, it appears to have an effect on the DM elasticity. Trypan blue may decrease DM elasticity and consequently increase its stiffness.[12]



All images: Mark Terry, MD

Figure 1. (Top) Optical coherence tomography image of a donor EDM disc detachment treated with re-bubble. (Bottom) Same eye five days after rebubble, showing optimal attachment of DMEK donor graft and almost complete resorption of the air bubble.

CHALLENGES OF PREPARING A DMEK GRAFT

It's been noted that donor preparation problems can occur in individuals with systemic diseases such as diabetes mellitus, hyperlipidemia and obesity.[13] This may be due to glycosylation products, and oxidative stress may have induced increased cross-linking of corneal collagen fibers, resulting in ultrastructural factors such as difficulty separating adhesions between the stroma and DM.

Larger graft size has been recommended in patients with dysfunction of central and peripheral endothelium due to pseudophakic bullous keratopathy.[14] However, there's no definitive recommendation regarding the optimal graft size for DMEK, after failed penetrating keratoplasty. Some propose undersizing the DMEK graft diameter by 0.25 to 0.50 mm relative to the previously failed PK graft diameter,[15] whereas others find no difference in outcomes between oversized, same-sized and undersized DMEK graft diameters.[16]

Anterior chamber depth and posterior corneal profile have to be taken into account when sizing the DMEK graft in order to facilitate graft unfolding, graft attachment, and reduce endothelial cell (EC) loss.[17] A small graft can accommodate patients with small eyes, such as those with high hyperopia or a narrow AC, whereas a graft larger than 9.5 mm can accommodate patients with myopia and buphthalmic eye or a deep AC.[18] Patients who have previously undergone glaucoma drainage device surgery may benefit from a small graft size, not only to facilitate the unfolding and attachment of the graft but, more importantly, to avoid contact with the drainage tubing.[19]

Preparing a graft smaller than 5 mm or larger than 9 mm can be somewhat demanding. The difficulties of a small DMEK graft preparation include peeling, marking, loading and unfolding. Although multiple confounding factors have been reported to influence graft scrolling,[20] small grafts without enough peripheral area may not roll and stay flat. Specifically, a small-diameter graft often doesn't have enough area to be folded to maintain the tissue architecture in the preloaded DMEK device. Pre-loading EDM DMEK tissue with endothelium facing inwards (DM-endothelium complex folded as taco-like tissue with endothelium facing inwards) can be challenging, and the graft can lose orientation.[21] In contrast, an endothelium-outward, pre-loaded small EDM DMEK graft could be more feasible.[6]

A large-diameter graft may be needed in some DMEK cases as mentioned above. Corneal EC density is higher in the paracentral and peripheral regions compared with the central cornea.[22]

When preparing large-diameter DMEK grafts, peripheral or horseshoe-shaped tears are potential risks, as fragile tissues can tear at the periphery while stripping. One approach to handle an accidental peripheral tear is to make a decentralized, relatively smaller graft inside the large-diameter grafts after stripping.[23] The advantage of harvesting a decentralized graft of similar size is that it also provides more EC from the periphery. As the corneal EC density is higher in the periphery, transplanting larger or decentered grafts could potentially

provide more EC to increase overall graft survival. It's also important to avoid donors with previous cataract incision wounds at the mid-periphery of the cornea or with deep corneal scars. Similarly, a decentralized, relatively smaller-diameter graft can be obtained to avoid tissue wastage and provide a larger number of EC for transplantation.

THE KEYS TO PERFORMING A DESCEMETORHEXIS

A crucial step in DMEK procedures is descemetorhexis, the removal of the recipient's diseased DM and EC, before transplantation. Poor visualization of the recipient DM during descemetorhexis can result in too small or incomplete recipient DM removal, whereas a same-size or slightly larger descemetorhexis compared with the implantable graft diameter is the most desirable. Application of ophthalmic viscosurgical devices (OVDs) like Healon, trypan blue staining, and air in the AC have been reported to allow a better operative view.[24]

Descemetorhexis techniques such as initiating from the central area followed by enlarging it similar to a capsulorhexis or utilizing femtosecond laser have been proposed to prevent incomplete descemetorhexis. However, the paucity of comparative studies makes it difficult to determine the most effective method for descemetorhexis.

One of the important factors to keep in mind while performing a mechanical descemetorhexis is to maintain the proper plane of dissection with the blunt-tipped instrument without entering the recipient corneal stroma. If inadvertent stromal entry occurs, the instrument tip will usually be temporarily stuck in that location or cause increased tissue resistance. In such cases, it's best to withdraw, and then re-establish the proper plane to continue and complete descemetorhexis. Avoid the temptation to use additional force to overcome the resistance in such cases. Keeping the inner stromal surface of the recipient cornea in its pre-surgical state contributes to a better overall donor-recipient interface and potentially better vision.

CHALLENGES OF DMEK GRAFT DELIVERY

Proper delivery and implantation of donor graft in the AC of the host is important to prevent donor tissue injury.

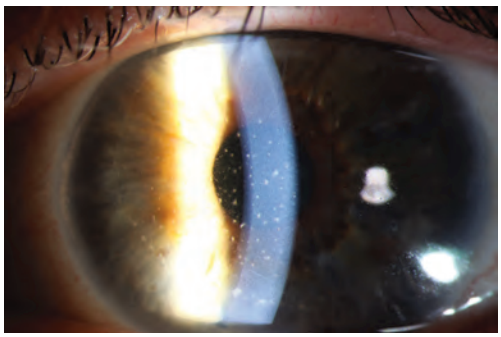


Figure 2. Slit-lamp photograph showing keratic precipitates in a DMEK graft, one year after DMEK surgery. Note that the KP are only on the area covered by the DMEK graft and aren't found outside of the graft edges, indicating that the area outside the edges is covered by recipient endothelium.

Various unfolding techniques are often based on the characteristics of the DMEK scroll in the AC, and most grafts are between 8 and 8.5 mm. Delivering and unfolding grafts sized more than 8 mm is reportedly challenging. However, they have the advantage of being easier to centralize due to their relatively large diameter. In contrast, small grafts are relatively more difficult, especially in cases with deep ACs. The AC needs to be kept shallow during all surgical maneuvers related to EDM disc unfolding.[25]

In general, the unfolding can be achieved through indirect manipulation with the aid of air, fluids, gentle tapping and sliding of cannulas on the outer corneal surface.

Specifically, the graft delivery and unfolding procedures can be somewhat complex in eyes that have undergone glaucoma surgery, especially those involving a glaucoma drainage tube.[26] Contact between the graft and the tube must be avoided to reduce the risk of graft detachment and EC loss. Also, injected air can partially escape through the opening in the seton tube within the AC, making the surgical procedure more difficult. Also, the graft has to unfold and attach above the tube, to the recipient inner corneal stroma. Also, repeated air injections are recommended to fill the AC adequately and pressurize the eye for an average of more than an hour, thereby reducing the rate of graft detachment.[26] Importantly, patent peripheral iridectomy should be done, preferably at the 6 o'clock position, to prevent potential pupillary block.

The unfolding and fixation of the EDM disc can be difficult in patients who are post-vitrectomy, have AC or iris-clip intraocular lens implants, or are aphakic or aniridic. Rarely, the donor DMEK graft tissue can pass through the pupil and land in between a PC IOL and an intact posterior lens capsule, giving the IOL a bluish appearance due to the trypan blue stained DM behind the PC IOL. When this occurred to one of the authors (TJ), no-touch fluidics was able to bring the DMEK graft back into the AC and it was attached to the recipient cornea with very good visual outcome.

The oil in a silicon-filled vitrectomized eye can get into the AC and impede the unfolding of the graft, which is associated with an increased risk of graft detachment.

In aphakic or vitrectomized eyes with a scleral- or iris-fixed intraocular lens, the injected air bubble can easily get behind the iris and lead to angle closure or even graft dislocation into the posterior segment. In such cases, the use of safety hammock sutures may be considered, which one of this article's authors (TJ) described at the 2017 meeting of the American Society of Cataract and Refractive Surgery in Los Angeles.

When the graft isn't visualized because of the cloudy cornea, gentle corneal epithelial scraping can improve the surgical view. Postoperative epithelial care is important to reduce the risk of infection and pain, and to achieve good visual results early on in the postoperative period.

CLINICAL COMPLICATIONS

Following are the complications to watch out for postoperatively in DMEK cases:

• ***Acute glaucoma.*** DMEK carries a risk of postoperative IOP elevation due to pupil blockage caused by the air or gas bubble in the AC, or angle closure due to anterior iris displacement caused by bubble migration to the posterior chamber.

A postoperative IOP rise occurs most frequently within the first two hours following DMEK. Such an increase in pressure may result in Urrets-Zavalia syndrome, characterized by iris sphincter muscle ischemia and atrophy. Temporary IOP elevation following surgery doesn't appear to influence functional or morphological outcomes, however.

To help counter possible risk of pupillary

block, you can perform a laser iridotomy prior to DMEK surgery in select cases. Typically, an inferior PI is performed intraoperatively to prevent pupillary block. If the PI isn't performed or if the air bubble in the AC is so large that it blocks the iridotomy, acute glaucoma attack remains a risk. The risk of pupillary block is greatest during the first 24 hours after surgery, before the bubble in the AC spontaneously absorbs.[27]

If the IOP is elevated due to posterior migration of the air bubble, air often can be displaced from the posterior chamber into the anterior chamber using a topical cycloplegic and mydriatic agent.

If pupillary block occurs, where the air bubble in the AC appears to cover the inferior PI, create a paracentesis with a 30-gauge needle on a 1-ml syringe to remove enough air and relieve the pupillary block.

• ***Endothelial graft detachment.*** Graft detachment is one of the most common complications after DMEK (*Figures 1A and 1B*). The detachment can be partial or total, depending on the contact area between the donor tissue and the recipient bed. The reported incidence of partial graft detachment ranged from 4 to 95 percent, with a rebubbling rate between 2.4 and 82 percent, whereas the incidence of total graft detachment is between 0.73 and 7 percent.[28]

Risk factors reported for graft detachment include graft preparation, learning curve, graft size, age, failed PK and endothelial keratoplasty (EK), history of glaucoma surgery (both glaucoma drainage device and filtrating surgery) and hypotony.

Pseudophakic bullous keratopathy has shown a higher rate of graft detachment compared with Fuchs' endothelial corneal dystrophy; however, the results of a three-year follow-up showed no statistically significant differences.

DMEK can be safely combined with cataract surgery or operated on sequentially, as graft detachment rates are similar. Abnormal anterior segment anatomy with peripheral synechiae, microphthalmos, aniridia or aphakia patients experienced high detachment and failure rates after DMEK.[29,30] SF6 20% as AC tamponade for DMEK significantly reduced the rebubbling rate and was associated with a lower rate of graft detachment, especially inferiorly and mid-peripherally, compared with 100-percent air. [31] However, the long-term visual and IOP results are comparable for both types of AC tamponade techniques. A large descemetorhexis with flat graft detachments can settle down over time, while a small descemetorhexis with a coiled graft detachment usually shows no improvement.[32]

A slit-lamp examination can diagnose post-DMEK detachment, which is typically characterized by the separation of the graft from the posterior recipient stroma. However, in some eyes, it may also be characterized by persistent corneal stroma edema over the area of DMEK graft detachment but clearing elsewhere. Optical coherence tomography and Scheimpflug imaging are useful for identifying graft detachment following DMEK. OCT can be a useful tool for pre- and postoperative corneal assessment to enhance the orientation assessment and increase the safety of the DMEK procedure, particularly in patients with poor graft visualization.

Most post-DMEK detachments are partial and nonprogressive; therefore, intervention may not be unnecessary. The postoperative treatment depends on the extent and location of the detachment. Numerous reports of spontaneous resolution of corneal edema, either through spontaneous reattachment of the graft Descemet's membrane or migration of proximal endothelial cells, have been published with promising visual outcomes.[33,34] However, detachments located in the center or involving the visual axis, comprising one-third of the graft's surface area, scrolled-in configuration, should be treated with repeated air or gas injection. The rebubbling procedure should be prompt in order to expedite visual rehabilitation and prevent wrinkling, fibrosis and contraction of the graft.

Despite the fact that the use of 20% SF6 as a tamponade is associated with fewer rebubbling procedures than air,[35] one study indicates that 10% C3F8 is an alternative when air or SF6 rebubbling fails.[36]

Animal studies show that all three gases exhibit a similar endothelial toxicity profile. Reattachment of the graft is between 79 to 92 percent of the time following rebubbling. If rebubbling isn't performed, corneal clearance typically occurs over a prolonged period of time (mean of six months), and only half of these eyes achieve 20/40 vision. Therefore, if the graft detaches but the cornea doesn't clear within a month, it's recommended to conduct a rebubbling. [37] Rebubbling can be approached in the inferior temporal quadrant or at a site where the DM is still attached. There are no reported differences in EC density in patients with single rebubbling or without rebubbling, whereas multiple rebubbling has a higher rate of EC loss.[38]

A complete detachment means that the post-DMEK graft has completely separated from the posterior corneal surface of the recipient and floats freely in the AC. The entire cornea remains edematous. It may be necessary to remove and replace the graft, or use a rescue technique as an alternative. The rescue technique involves staining the graft in the AC with trypan blue, performing a 20-gauge paracentesis and administering air promptly to prevent staining of the host stroma and to facilitate donor tissue attachment.

If the graft is completely attached after one week, then it usually doesn't detach. If any detachment is detected one hour after surgery, the patient should be carefully evaluated during the immediate postoperative period; if the detachment persists, it's unlikely that spontaneous reattachment will occur. If, however, no detachment is observed at one week postoperatively but not at one hour post-DMEK, spontaneous re-attachment is probable in nearly 90 percent of cases.[39]

• ***Graft rejection and Descemet's folds.*** One study showed that an endothelial immune reaction ("rejection") (*Figure 2*) over a period of four years occurs with a probability of around 2.3 percent, particularly in patients without long-term

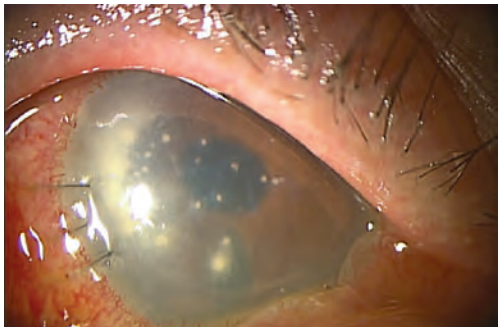


Figure 3. *Candida* infection of the interface following DMEK surgery. A penetrating keratoplasty and medical treatment resulted in an overall good outcome.

topical cortisone therapy, and that long-term administration of topical steroids is therefore recommended.[40] The range of graft rejection is about 1.4 to 5 percent, with an average of about 3.7 percent.[41] Since the immune reactions are often clinically asymptomatic, regular follow-up checks should be carried out at least in the first two years to detect subclinical immune reactions. Descemet's graft folds can occur in 1.9 percent of cases.[42]

LESS COMMON COMPLICATIONS

The following complications are possible, but less likely than those described above:

• ***Infection.*** Rarely, bacterial and fungal interface keratitis can occur after DMEK surgery (*Figure 3*).[43,44] Medical as well as appropriate, timely surgical management are important for preserving vision and optimizing outcomes.

• ***Other complications.*** The risk of pupillary block, hypotony, interface pigment deposits, subepithelial haze and anterior synechiae has been reported to be less than 1 percent.[42]

In conclusion, DMEK surgery provides a near-optimal anatomic procedure for endothelial transplantation in corneal endothelial dysfunction. It can provide the best visual outcome with the lowest endothelial graft rejection rate as compared to all other forms of corneal transplantation for corneas with compromised endothelium.

The continuous improvement process and our increased experience with the procedure lead to the optimization of the postoperative result and minimization of intra- and postoperative complication rates. ■

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