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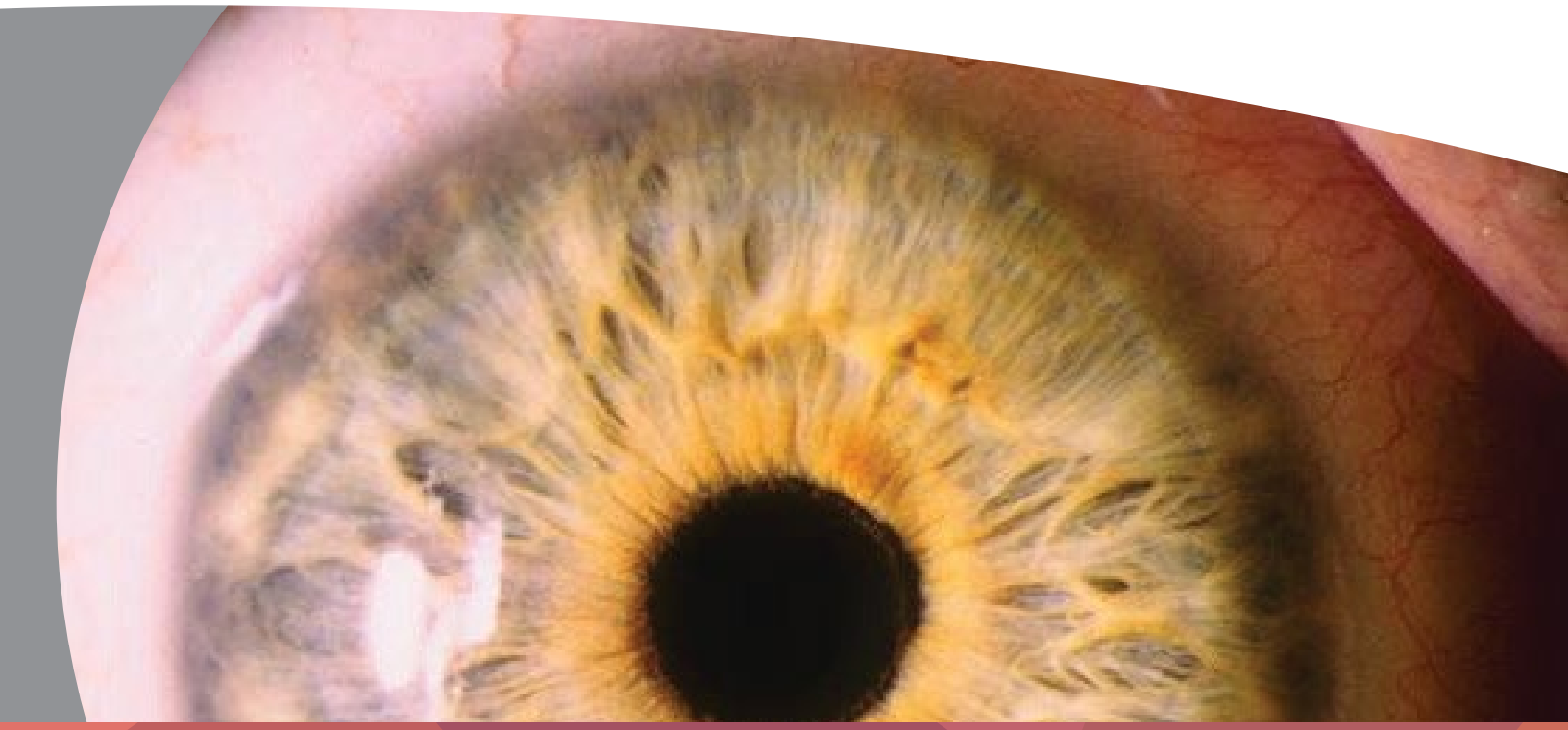

Cornea 2022

What's New in '22

Subspecialty Day | AAO 2022

Chicago | Oct 1

Protecting Sight. Empowering Lives.®

Cornea 2022
What's New in '22

Program Directors
Vishal Jhanji MD FRCOphth, Sonal S Tuli MD, and Christina R Prescott MD

In conjunction with the Cornea Society

Cornea Society
Advancing the treatment of corneal disease

McCormick Place
Chicago, Illinois
Saturday, Oct. 1, 2022

Presented by:
The American Academy of Ophthalmology

AMERICAN ACADEMY OF OPHTHALMOLOGY®
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On behalf of the American Academy of Ophthalmology and the Cornea Society, it is our pleasure to welcome you to Chicago and **Cornea Subspecialty Day 2022: What's New in '22**.

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Cornea 2022 Contents

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The Academy's CME Mission Statement

The purpose of the American Academy of Ophthalmology's Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement and change in physician practices, performance, or competence, thus enabling such physicians to maintain or improve the competence and professional performance needed to provide the best possible eye care for their patients.

Cornea Subspecialty Day Meeting 2022 Learning Objectives

Upon completion of this activity, participants should be able to:

- Understand how to use anterior segment imaging devices to assist with the diagnosis and management of corneal diseases
- Recognize ocular surface disorders that warrant surgical intervention and determine the ideal approach and timing of intervention
- Apply current best practices in the medical and surgical management of corneal infections and ocular surface inflammatory diseases
- Discuss complex keratoplasty techniques and alternative treatments in the management of patients with corneal diseases

Cornea Subspecialty Day Meeting 2022 Target Audience

This program is for cornea specialists and comprehensive ophthalmologists with an interest in anterior segment diseases and allied health personnel who are involved in the medical and surgical care of patients with corneal diseases.

Teaching at a Live Activity

Teaching instruction courses or delivering a scientific paper or poster is not an *AMA PRA Category 1 Credit*™ activity and should not be included when calculating your total *AMA PRA Category 1 Credits*™. Presenters may claim *AMA PRA Category 1 Credits*™ through the American Medical Association. To obtain an application form, please contact the AMA at www.ama-assn.org.

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Subspecialty Day 2022 CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

Friday Subspecialty Day Activity: Glaucoma, Pediatric Ophthalmology, Refractive Surgery, Retina (Day 1), and Uveitis

The Academy designates this Other (blended live and enduring material) activity for a maximum of *12 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Saturday Subspecialty Day Activity: Cornea, Oculofacial Plastic Surgery, and Retina (Day 2)

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Physicians registered as In Person and Virtual are eligible to claim the above CME credit.

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You do not need to track which sessions you attend, just the total number of hours you spend in sessions for each claim.

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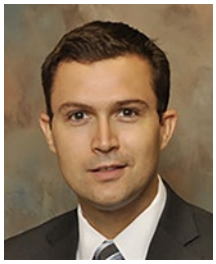

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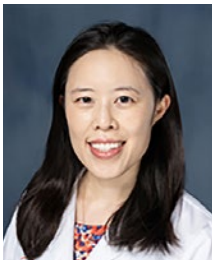

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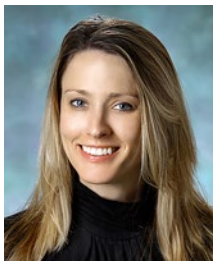

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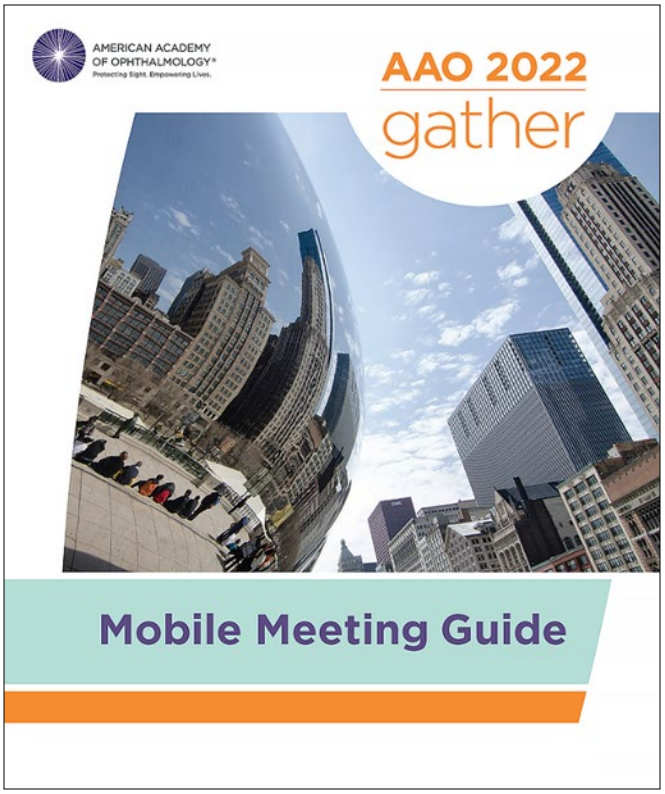

Cornea Subspecialty Day 2022

What's New in '22

SATURDAY, OCT. 1

8:00 AM	Welcome and Introductions	Vishal Jhanji MD FRCOphth Sonal S Tuli MD Christina R Prescott MD PhD	

Section I: Keratoplasty

Moderators: Christina R Prescott MD PhD and Sonal S Tuli MD

8:02 AM	Introduction	Christina R Prescott MD PhD	
8:03 AM	Deep Anterior Lamellar Keratoplasty, Superficial Anterior Lamellar Keratoplasty, and Variants	Massimo Busin MD	1
8:12 AM	Endothelial Keratoplasty: Staged, Triple, or Something Else?	Christopher S Sales MD	3
8:21 AM	Complex Penetrating Keratoplasty: Intraoperative and Postoperative Challenges	Irit Bahar MD	4
8:30 AM	Therapeutic Corneal Transplantation: When and How?	Tushar Agarwal MD	5
8:39 AM	Fungal Infections From Donor Corneas: Will This Ever End?	Mark A Terry MD	6
8:48 PM	Keratoprosthesis	Esen K Akpek MD	8
8:57 AM	Discussion		

Section II: Corneal Ectasias

Moderators: Christina R Prescott MD PhD and Vishal Jhanji MD FRCOphth

9:12 AM	Introduction	Christina R Prescott MD PhD	
9:13 AM	Update on Collagen Crosslinking for Corneal Ectasia	Beatrice E Frueh MD	9
9:21 AM	Post–Refractive Surgery and Post-Keratoplasty Ectasia	Kathryn Masselam Hatch MD	11
9:29 AM	Pellucid Marginal Degeneration	Jun Shimazaki MD	12
9:37 AM	Corneal Tomography and Corneal Biomechanics	Renato Ambrósio Jr MD	13
9:45 AM	Newer Diagnostics and Treatments for Ectasia	Farhad Hafezi FARVO MD PhD	14
9:53 AM	Discussion		
10:08 AM	In These Unprecedented Times . . .	Lee A Snyder MD	16
10:13 AM	REFRESHMENT BREAK and AAO 2022 EXHIBITS		

Section III: Keratitis

Moderators: Sonal S Tuli MD and Vishal Jhanji MD FRCOphth

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10:44 AM	Atypical Keratitis	Alex Mammen MD	18
10:52 AM	Recalcitrant Mycotic Keratitis	Lauren Jeang MD	20
11:00 AM	Herpetic Keratitis	Antoine Rousseau MD	22

11:08 AM	Parasitic Keratitis	Prashant Garg MD	24
11:16 AM	Infectious Etiologies of Ocular Surface Tumors	Carol L Karp MD	26
11:24 AM	Identification of Microbes and Susceptibility Testing	Thuy A Doan MD PhD	27
11:32 AM	Discussion		
11:47 AM	LUNCH and AAO 2022 EXHIBITS		

Section IV: Noninfective Keratitis

Moderators: Sonal S Tuli MD and Christina R Prescott MD PhD

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1:03 PM	Surgical Management of Scleral Necrosis	Sheraz M Daya MD	29
1:11 PM	Peripheral Ulcerative Keratitis: Rise of the "Rheumophthalmologist"	Ninani E Kombo MD	30
1:19 PM	Neurotrophic Keratopathy	Clara C Chan MD	31
1:27 PM	Drug-Induced Keratopathy	Jasmine H Francis MD	33
1:35 PM	Filamentary Keratitis	Ahmad Kheirkhah MD	35
1:43 PM	Case Presentation 1: Mystery Keratitis	Sarah Bonaffini, DO	36
1:44 PM	Case Presentation 2: Mystery Keratitis	Jason Frederick Miles MD	36
1:45 PM	Case Presentation 3: Mystery Keratitis	Farida E Hakim MD	36
1:46 PM	Case Presentation Discussion		
2:01 PM	Discussion		

Section V: Ocular Surface Disease

Moderators: Vishal Jhanji MD FRCOphth and Sonal S Tuli MD

2:18 PM	Introduction	Vishal Jhanji MD FRCOphth	
2:19 PM	Ocular Cicatricial Pemphigoid	Jennifer E Thorne MD PhD	37
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3:07 PM	Discussion		
3:22 PM	Diversity, Equity, Inclusion	Fasika A Woreta MD	
3:28 PM	REFRESHMENT BREAK		

Section VI: Exciting Discoveries in the Corneal World

Moderators: Vishal Jhanji MD FRCOphth and Christina R Prescott MD PhD

3:55 PM	Introduction	Vishal Jhanji MD FRCOphth	
3:56 PM	Corneal Cystinosis	Hong Liang MD	47
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4:12 PM	Novel Dry Eye Treatments	Gerami D Seitzman MD	49
4:20 PM	Mask-Associated Dry Eye Syndrome	Natalie A Afshari MD	51

4:28 PM	Deep Learning and Artificial Intelligence	Daniel Shu Wei Ting MD PhD	52
4:36 PM	Corneal Regeneration	May Griffith PhD	53
4:44 PM	Discussion		
4:59 PM	Closing Remarks	Vishal Jhanji MD FRCOphth Sonal S Tuli MD Christina R Prescott MD PhD	
5:00 PM	ADJOURN		

Deep Anterior Lamellar Keratoplasty, Superficial Anterior Lamellar Keratoplasty, and Variants

Massimo Busin MD

I. Background of Modern Lamellar Keratoplasty

II. Superficial Anterior Lamellar Keratoplasty (SALK)

A. Indications

B. Surgical technique

1. Superficial "free cap" 9 mm in diameter is cut from the recipient cornea using a 130-µm microkeratome head with a "zero" suction ring.
2. Anterior donor lamella is prepared by microkeratome-assisted dissection using a 90-µm microkeratome head.
3. Donor tissue is laid onto the host stromal bed without sutures.

C. Clinical outcomes

III. Deep Anterior Lamellar Keratoplasty (DALK)

A. Perceived barriers of DALK

B. Indications

C. Surgical technique (large-diameter 9.0-mm DALK with limited stromal clearance)

1. Initial partial-thickness deep trephination carried out by a guarded trephine calibrated within 100 mm from the thinnest anterior segment OCT pachymetry value at the 9-mm zone
2. Insertion of a DALK probe at the base of the trephination with centripetal advancement (1 mm)
3. Intracameral injection of an air bubble through a temporal paracentesis
4. Insertion of DALK cannula with further centripetal advancement (1 mm) through the same stromal track created by the probe
5. Injection of air to obtain a big bubble with displacement of the intracameral air bubble peripherally
6. Partial-thickness anterior keratectomy to approximately 80% depth
7. Incision of the bubble roof under viscoelastic protection with a 15 blade
8. Excision of the deep corneal stroma with corneal scissors
9. Limited stromal clearance at the 6-mm optical zone
10. Microkeratome-assisted dissection of 9-mm anterior lamellar graft
11. Suturing with 16-bite double-running diagonal cross-stitch suture

D. Clinical outcomes

IV. Two-Piece Microkeratome-Assisted Mushroom Keratoplasty

A. Indications

B. Surgical technique

1. 9-mm partial-thickness trephination centered on the corneoscleral limbus
2. Circumferential manual lamellar dissection from the base of the trephination toward the central 3-mm cornea
3. Removal of manually dissected tissue
4. 6-mm full-thickness trephination
5. Excision of 6-mm central button leaving a 1.5-mm posterior stromal crown of approximately 300 µm in depth
6. Donor graft transplantation with 6-mm posterior lamellae positioned within the central hole of the recipient bed without sutures and the 9-mm anterior lamella sutured onto the recipient bed with nylon 10-0 sutures

C. Clinical outcomes

V. Stromal Peeling: DALK in Post-Penetrating Keratoplasty (PK) Eyes

A. Ultrastructural changes in post-PK eyes

B. Surgical technique

1. 9-mm partial-thickness trephination
2. Creation of a corneal flap across the PK wound
3. Opening of the stromal component of the PK wound until a smooth, translucent natural plane is identified
4. Severing the attachment of the PK scar
5. Stromal peeling along the identified plane
6. Suturing of donor lamella

C. Clinical outcomes

1. Stromal peeling completed in 125 of 142 eyes
2. Baseline BSCVA (0.89 ± 0.31 logMAR) significantly improved, to 0.10 ± 0.09 logMAR at Year 2 ($P < .001$) and remained stable up to 5 years.
3. At 5 years, 91% of eyes were ≥20/40 Snellen; 71%, ≥20/25.
4. Endothelial cell loss: 6% ± 10% at 1 year, with an annual decline of 3% over 5 years
5. Recurrence of stromal disease: Not observed up to 5 years
6. Five-year cumulative risk for immunological rejection: 4%
7. Five-year cumulative risk for graft failure: 5%

Endothelial Keratoplasty: Staged, Triple, or Something Else?

Christopher S Sales MD

NOTES

Complex Penetrating Keratoplasty: Intraoperative and Postoperative Challenges

Irit Bahar MD

Corneal transplantation has been the most common type of organ transplantation over the last century. Although lamellar keratoplasty has gained popularity in the last decade due to its proven advantages, penetrating keratoplasty (PK) consists of 30%-40% of total corneal transplantations in the United States and remains a valid option for certain corneal pathologies and for complicated eyes with coexisting anterior and posterior segment problems. This lecture will review high-risk cases such as keratolenticular trauma, pediatric PK, keratopathy associated with aphakia and anterior segment derangement, significantly vascularized corneas, chemical injuries with limbal stem cell deficiency, combined PK with pars plana vitrectomy, and PK in patients with advanced glaucoma.

Intraoperative and postoperative challenges will be discussed.

Therapeutic Corneal Transplantation: When and How?

Tushar Agarwal MD

Therapeutic keratoplasty is the use of a corneal graft for terminating or improving an actively infectious corneal disease or for repairing an anatomical defect in cornea.

When to Perform Therapeutic Keratoplasty

A critical decision when managing a patient with a severe keratitis is to decide if and when a therapeutic keratoplasty should be performed. There are 3 possible scenarios a clinician may come across:

1. Therapeutic keratoplasty is indicated immediately: corneal ulcer with corneal perforation (>2 mm), limbal or scleral involvement of ulcer, large impending perforation
2. Therapeutic keratoplasty may be considered.
3. Therapeutic keratoplasty is not indicated.

How to Perform Therapeutic Keratoplasty

1. Manual trephination or freehand cut
2. Donor cornea oversized by 0.75-1.0 mm
3. Ancillary procedures including removal of membranes, peripheral iridectomies
4. Interrupted suturing to oppose the host-graft

Postoperative Complications and Outcomes

Selected Readings

1. Prajna NV, Krishnan T, Rajaraman R, et al; Mycotic Ulcer Treatment Trial Group. Predictors of corneal perforation or need for therapeutic keratoplasty in severe fungal keratitis: a secondary analysis of the Mycotic Ulcer Treatment Trial II. *JAMA Ophthalmol*. 2017; 135(9):987-991.
2. Sharma N, Sachdev R, Jhanji V, Titiyal JS, Vajpayee RB. Therapeutic keratoplasty for microbial keratitis. *Curr Opin Ophthalmol*. 2010; 21(4):293-300.
3. Ramamurthy S, Reddy JC, Vaddavalli PK, Ali MH, Garg P. Outcomes of repeat keratoplasty for failed therapeutic keratoplasty. *Am J Ophthalmol*. 2016; 162:83-88.e2.

Fungal Infections From Donor Corneas: Will This Ever End?

Mark A Terry MD

Tissue provided for corneal transplantation is *not* necessarily sterile!

Corneal transplantation is wildly successful in restoring vision, and due to the professionals of our eye banking community, the United States and other developed nations enjoy the luxury of plentiful tissue availability and scheduled transplant surgery. This has led many surgeons to view corneal tissue as a commodity, like an IOL. However, it is important to recognize that by its very nature, this precious living tissue is delivered to the operating room with no assumption of sterility. Every effort is taken by our eye banks to minimize the possibility of transmissible disease, but efforts to eliminate fungal contamination must be balanced by the efficacy, toxicity, and cost of the agents involved.[1]

What is the incidence of fungal keratitis/ endophthalmitis after corneal transplantation?

Despite the concern over increasing rates of fungal keratitis/ endophthalmitis following corneal transplantation, the occurrence of this dreadful complication remains exceedingly rare. The incidence of postoperative fungal keratitis reported in the literature is about 1 in 5000 transplants.[2,3] Most surgeons do not do 5000 transplants in their career and so are unlikely to ever encounter a case of post-transplant fungal infection.

What is the role of donor rim cultures in predicting postop fungal infections?

The utility of performing donor rim/transport media cultures at the time of transplantation remains controversial.[4] Only about 1.5% of all rim cultures will be positive for fungus, and of the positive cultures, only 6% to 10% will go on to clinical infection.[5,6] That is a ≥90% *false* prediction rate of your rim cultures! While there is one retrospective study[5] that showed that treating all the patients who had a positive rim culture prophylactically with systemic antifungals reduced (but did not eliminate) the rate of clinical keratitis, it must be kept in mind that if you choose this strategy, you will be treating ≥90% of patients who would never develop a postop infection, and you are using toxic systemic medications.

Of interest, it has been shown that if the donor rim is positive *and* the patient develops fungal keratitis, then there is a 75% chance that the mate cornea distributed for another patient will also be positive, and a 66% chance that that second patient will also develop keratitis.[7] Given that most fungal keratitis does not become evident until about 6 weeks or longer after surgery, the timing of the first surgeon "warning" the mate surgeon about a possible infection is problematic. In my opinion, the best that can be said about doing rim cultures for fungus is that they will make the surgeon "more alert" to the 6/100 eyes that are at risk of clinical disease, and so the surgeon may examine all 100 patients more frequently postop than usual.

What is currently being done to prevent transmission of donor fungus to the patient?

Eye Bank Association of America standards and the standard operating procedures of eye banks throughout that organization have allowed exclusion of donors at high risk of contamination, and the sterile processing of tissue has reduced clinical fungal infections to a rate of 1 out of 5000 cases. A 2019 paper[8] has also shown that a "double rinse" of 5% povidone iodine can significantly decrease the culture-positive rate of tissue, from 2.9% to 0.6%, and in their retrospective study of 1356 cases, their fungal keratitis rate went from 0.48% to 0%. Similar to the addition of the antibiotics gentamicin and streptomycin to storage media to reduce (but *not* eliminate) bacterial transmission from donor tissue, there have been efforts to add amphotericin B or other antifungals to storage media to reduce the rate of fungal keratitis/endophthalmitis. Laboratory studies have clearly shown that a concentration of 0.255 µg/mL of amphotericin B is ineffective in meaningfully reducing fungal counts, while a concentration of 2.5 µg/mL has shown >90% reduction over the critical time frame of storage.[9] However, the cost and efficacy of adding amphotericin B to every storage media (>79,000 vials a year) to try to prevent 1 out of 5000 cases of infection remains questionable.[10]

What should I do if my patient develops fungal keratitis after a corneal transplant?

First: Stop cursing/crying, and don't start blaming.

Second: Report this adverse occurrence immediately to your eye bank.

The vast majority of fungal keratitis after Descemet-stripping automated endothelial keratoplasty/Descemet membrane endothelial keratoplasty is *Candida* keratitis, and the infection usually manifests initially as a white spot in the interface of EK. When first recognized, these organisms are well established and sequestered from cure by topical, systemic, or injected antifungal agents, and they lie dangerously close to the aqueous. If the surgeon removes just the donor tissue, the aqueous is exposed to the fungus and a replacement graft should not be done until intracameral and systemic antifungals have completely eliminated the infection, usually weeks later, if at all. While there have been cures with this strategy, there is also the risk of losing the eye from endophthalmitis or extension of the corneal infection to the limbus. It is my opinion[4] that as soon as the interface infection is recognized, a penetrating keratoplasty should be performed quickly to completely remove the infected area and solve the problem. It is far easier to explain to a 20/20 patient the use of glasses or contacts for their astigmatism from PK than to explain that they lost all their vision from delayed extirpation of a devastating infection.

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Keratoprosthesis

Esen Karamursel Akpek MD

Loss of corneal clarity is the third leading cause of permanent blindness globally, behind only glaucoma and macular degeneration.[1] Corneal blindness is particularly sad, as it affects younger individuals and is disproportionately more prevalent in countries with lower socioeconomic status.[2] Currently, donor corneal transplantation remains the mainstay of restoring vision in the corneally blind because there are no medical therapies to reverse corneal opacification. Although corneal transplantation is known to be one of the most successful tissue/organ transplantations and leads to excellent outcomes in many individuals, two major challenges remain unmet: access and failure rates.

Availability of donor corneas is extremely limited outside of developed countries due to tissue perishability and requirements of the eye banking system, with only 1 donor available for every 70 who need a cornea.[3] Currently, approximately half of all corneal transplantations are performed in the United States.[4] The leading indication for surgery in the United States is Fuchs endothelial keratoplasty, which is not exactly a blinding condition as it is easily curable with endothelial keratoplasty. It is well known that preoperative diagnosis determines the ultimate outcomes of keratoplasty, with certain indications consistently associated with high rates of rejection and failure, such as dry eye and ocular surface diseases with conjunctival and corneal scarring. In the United States, of the approximately 40,000 donor corneal transplantations performed yearly, 3500 are repeat surgeries to replace previously failed grafts (Eye Bank Association of America Statistics). Keratoprosthesis, also known as artificial corneal transplantation, is infrequently offered to patients who have previously had a failed donor graft. Approximately 200 Boston type 1 keratoprosthesis (KPro) surgeries are performed yearly in the United States. Type 1 KPro is currently regarded as a last-resort surgery due to less than ideal clinical outcomes, particularly after the first few years, with permanent loss of vision due to the occurrence of postoperative complications.

Although yet to be invented, an ideal artificial cornea could potentially solve both the access and failure issues. The features of an ideal artificial cornea have been detailed previously.[5] This presentation will focus on the emerging artificial corneas, with particular emphasis on the 3 most important aspects: (1) biocompatibility/bioadhesion features of the material, (2) anatomical structure of the device, and (3) surgical technique for implantation. Comparison to the Boston KPro will be provided.

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Update on Collagen Crosslinking for Corneal Ectasia

Beatrice E Frueh MD

Corneal crosslinking (CXL) has proven to be effective in halting keratoconus progression. Minimal complications were reported in several studies,[1] even in children.[2] The original protocol from the Dresden group led by Theo Seiler is the gold standard,[3] as confirmed by prospective, randomized studies. The drawbacks of the Dresden protocol (epi-off, 0.1% riboflavin/20% dextran application for 30 min followed by 30 min UVA irradiation, 3 mW/cm^2, 5.4 J/cm^2) are the use of dextran in the riboflavin solution, which thins the cornea; the length of the procedure; and the need to abrade the cornea. This is why several attempts have been made to change the protocol. Most of these revised protocols have been published as stand-alone reports or as retrospective studies comparing the data with eyes previously treated with the standard protocol.

Transepithelial (Epi-On) CXL/Iontophoresis

Leaving the epithelium intact reduces postoperative pain and erosion-related complications. Because riboflavin cannot penetrate an intact epithelium (large hydrophilic molecule) and the epithelium blocks some 20% of the UVA administered, several approaches with special riboflavin formulation and use of iontophoresis have been developed. A recent meta-analysis[4] (based on 15 articles) showed that epi-off and epi-on CXL have comparable results in adults 1 to 2 years after surgery. There was a tendency to more flattening in epi-off CXL, but also a significant difference in epithelial healing and persistent stromal haze. The efficacy in the pediatric population as well as the long-term stability and efficacy of epi-on CXL is poorly investigated.

Accelerated CXL

Increasing the intensity of the UVA radiation (9-30 mW/cm^2) makes it possible to shorten the exposure time without altering the total energy delivered (5.4 J/cm^2). There is good experimental evidence that a higher UVA intensity results in a reduced stiffening of the cornea.[5] This is shown clinically in a shallower demarcation line,[6] which is the border between treated and untreated stroma. There are contradictory studies about the efficacy of accelerated CXL, using various accelerated protocols. A recent prospective study showed a failure rate of 7.6% for accelerated CXL of 9 mW/cm^2. This high failure rate suggests the use of the standard intensity of 3 mW/cm^2 for children.

CXL in Thin Corneas

Because of safety concern for the endothelium, CXL should not be performed in corneas thinner than 400 µm. To overcome this, a protocol for thin corneas to swell the stroma intraoperatively (with hypo-osmolar riboflavin) has been published.[7] For extremely "ultrathin" corneas, the so-called sub-400 protocol has been developed.[8]

Customized CXL

The rationale of customized CXL is to stiffen the cornea more in its weakest areas—that is, over the thinnest or the steepest sector. Our group centered the concentric treatment on the maximum of the posterior float.[9] It seems that customized CXL has a shorter epithelialization time, a stronger flattening, and a more regular corneal surface. Because of the paucity of studies and the different protocols used, the treatments remain experimental.

CXL Combined With PRK

The combination of a wavefront- or topography-guided PRK with CXL is still being debated. A simultaneous approach makes sense: the procedure weakening the cornea is followed by a stiffening procedure. But the disadvantage is the possible refractive effect of the CXL, such as a continuing flattening. One study with moderate keratoconus showed a loss of 2 lines of corrected distance VA in 3% of the eyes, but a gain of 2 lines or more in 20% two years after combined CXL/wavefront-guided PRK.[10]

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Post–Refractive Surgery and Post-Keratoplasty Ectasia

Kathryn Masselam Hatch MD

NOTES

Pellucid Marginal Degeneration

Jun Shimazaki MD

I. Introduction

Pellucid marginal corneal degeneration (PMD) is a rare, progressive ectatic disorder characterized by crescentic thinning of the inferior peripheral cornea and associated with progressive visual deterioration caused by irregular astigmatism.

II. Etiology and Epidemiology

The pathogenesis of PMD remains unclear; no genetic cause has been found. A male predominance has been reported. Unilateral cases constitute up to 25% of all patients. Allergic ocular diseases are rather commonly associated with PMD.

III. Visual Signs and Symptoms

Increasing against-the-rule irregular astigmatism causing a gradual reduction in visual acuity that typically commences in the fourth to fifth decades of life

IV. Examinations

A. Slit-lamp biomicroscopy:

On slit-lamp biomicroscopy, band-shaped peripheral corneal thinning associated with protrusion of the adjacent cornea is the classical hallmark of PMD. The ectatic zone lies above the point of maximum corneal thinning. Atypical superior, nasal, and temporal PMD have also been documented.

B. Corneal topography:

Corneal topography is required for early PMD detection. The "crab-claw" (or "butterfly") appearance is a valuable objective finding. It should be noted, however, that the "crab-claw" finding is not specific to PMD. Infants with PMD exhibit other corneal topographies, including inferior steepening or an irregular pattern.

C. Other examinations:

Anterior segment OCT and Scheimpflug images yield detailed information, especially in terms of pachymetric mapping.

V. Differential Diagnosis

PMD is most commonly misdiagnosed as inferior keratoconus. Involvement of the central two-thirds of the cornea, ectasia, corneal thinning at a characteristic location with the apex of the cone shifting inferiorly, and (topographically) an asymmetric bow tie with a skewed radial axis indicate keratoconus.

VI. Management

A. Medical management:

Most PMD patients are managed using spectacles or contact lenses. The fitting of contact lenses in PMD patients is more challenging than in those with other ectatic diseases, given the large inferior protrusion and the central corneal flattening. Hybrid contact lenses with soft skirts, and semi-scleral and scleral lenses, have been found to be useful.

B. Surgical intervention:

Several surgical procedures have been employed in attempts to improve visual acuity when contact lenses fail.

1. Collagen crosslinking (CXL): CXL effectively halts PMD progression and stabilizes vision. CXL may postpone or eliminate the need for corneal transplantation.
2. Corneal transplantation: Penetrating keratoplasty using a large or eccentric graft has been performed. However, the prognosis is poorer than that of keratoconus patients; the risk of rejection is higher. Crescentic and deep anterior lamellar keratoplasty have yielded variable results.
3. Other surgical methods: Intracorneal ring segments and peripheral corneal, concentric wedge resection have yielded encouraging results.

Corneal Tomography and Corneal Biomechanics

Renato Ambrósio Jr MD PhD, Alexandre Batista da Costa Neto MD, and Louise Pellegrino Gomes Esporcatte MD MsC

I. Why do we need an enhanced corneal diagnosis for corneal ectasia?

A. Paradigm shift related to the management of ectatic corneal diseases (ECD) and assessment of ectasia risk and progression to improve treatment[1,2]

1. An early indication of crosslinking and intrastromal corneal ring segments[2]

2. Screen for ectasia risk before laser vision correction (LVC).[3]

B. A biomechanical assessment is the ultimate tool to augment sensitivity. The goal is to characterize the inherent susceptibility to ectasia progression, in agreement with McGhee's two-hit hypothesis for keratoconus development[2] and the Dupps and Robert's biomechanical cycle of decompensation of corneal ectasia.[4]

II. Topography is an obligatory exam for screening ectasia risk before LVC.[5,6]

III. Advances in corneal imaging have allowed for tomography and segmental or layered tomographic (3-D) characterization with thickness mapping, epithelial thickness,[7] and Bowman layer.[8-10]

A. Beyond shape analysis, in the context of multimodal refractive imaging

B. Clinical biomechanical assessment augments the accuracy.

C. Artificial intelligence (AI) algorithms enhance data analysis and the efficiency of clinical decisions.[11,12]

1. Tomography of the cornea and corneal biomechanics integration due to the tomographic biomechanical index

2. Very asymmetric ectasia studies demonstrated the improved ability of corneal tomography to identify ECD. Some of these cases may be secondary unilateral ectasia.

IV. Future

A. Material stiffness using Corvis ST data (SSI-MAP)[13]

B. Brillouin microscopy[14]

C. Phase-decorrelation OCT[15]

D. Genetic testing[16]

V. Conclusions

A. Presently, the integration of Scheimpflug corneal tomography and biomechanical assessment provides the most advanced and accurate method.

B. Future advances in corneal imaging, including segmental or layered tomography for the epithelial thickness, may further add to the diagnosis of corneal ectasia.

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Newer Diagnostics and Treatments for Ectasia

Farhad Hafezi FARVO MD PhD

Introduction

The most common corneal ectasia is keratoconus, and historically, its prevalence has been greatly underestimated. Depending on the region of the world, its prevalence ranges from 0.2% to 4.8%. For many years, keratoconus was thought to affect 1:2000 people (0.05%),[1] but as corneal topography and tomography technology has advanced and become more commonplace, far more people with ectasias have been identified than ever before, as demonstrated recently in the global K-MAP study of keratoconus prevalence.[2]

Imaging Ectasia

Scheimpflug imaging, the current standard of care, provides very precise maps of the cornea. Considerable effort has been made to tightly integrate machine learning into the software of these instruments to improve their ability to detect and diagnose forme fruste/subclinical ectasias. One drawback of Scheimpflug imaging is that any disturbances in the transparency of the cornea can lead to the scattering of light, which can affect the accuracy of the maps and make it challenging to interpret the results. One method that can overcome this issue is combined corneal OCT–Placido disk topography. In our experience, we have seen several diopters of difference between each method during the healing period after PRK or CXL.

Expanding Access to Ectasia Screening

The other direction ectasia diagnostics has taken is to leverage consumer technology to expand the population that is able to be screened for corneal ectasias, particularly those in low-to-middle income countries (LMICs). Most people in LMICs live in rural regions, far from population centers with hospitals that have instruments that can perform screening, meaning that most people are never screened. Projects that make corneal topographical imaging portable, such as the Smartphone-Based Keratograph (SBK), may help change this. Combining a smartphone with a Placido disk–based adapter system, SBK can produce topographic maps of the cornea that can enable a reader to determine whether the cornea has pathologic features or not. This information can then be fed into a supervised machine learning model, with the intention of performing on-device screening/diagnostic support for ectasias like keratoconus and other corneal irregularities.

Biomechanical Assessments

Corneal biomechanical assessments are also an important component of ectasia diagnostics; not all corneas of the same thickness are equally strong. In vivo assessments come in 3 forms. The first involves high-speed recording of the deflection of the cornea to a puff of air (Scheimpflug tonometry), which reveals information about corneal biomechanical strength (stiffer, stronger corneas should be more resistant to deflection). This information can be combined with corneal tomography measurements to more accurately detect corneal ectasias,[3] and each individual eye's "biomechanical index" can be plotted against normative values in a manner that makes it easy to visualize how normal or abnormal the patient's corneal biomechanics are.[4] However, such an approach shows only the overall weakening effect on the cornea; focal weakening (such as those that cause the cone to develop in keratoconus) is not highlighted.

Brillouin microscopy involves measuring "phonon-phonon" interactions, which are a reflection of a tissue's viscoelastic properties. This technique involves shining a scanning confocal laser beam on the cornea and measuring the spectral shift of the refection to generate a 3-dimensional stiffness map. Technically, this is challenging to measure, as the frequency shifts are in the gigahertz range and have very faint signal strength, and other phenomena can cause light scattering too, which necessitates the use of an extremely advanced spectrometer detector in such an instrument. The acquisition can be slow, as only 1 small region of the cornea can be assessed, so numerous measurements are required to build up a biomechanical map of the cornea.[5]

OCT elastography uses corneal OCT imaging to measure the strain on the cornea caused by an external deformation stimulus, which can be achieved using many methods, including applanation, air puffs, and even pressure changes induced while the subject is wearing goggles. Displacement can be calculated by optical flow tracking, and strain over the entire stromal depth can be retrieved from the phase gradient of the complex interference signal. Early investigations have already revealed that there are fundamental differences in how the anterior and posterior corneas respond to strain.[6]

Latest Concepts in Crosslinking

Corneal crosslinking (CXL), the only intervention that can slow/halt the progression of ectasia, is also evolving. What was a slow technique—requiring epithelial debridement before riboflavin application and 30 minutes of relatively low intensity (3 mW/cm²) ultraviolet (UV) irradiation to deliver the required 5.4 J/cm² fluence in corneas no thinner than 400 µm—is now changing.

Thin corneas

Many ectatic corneas are thinner than 400 µm, but this thickness limit was imposed in the past to maintain a 70-µm un-crosslinked region at the base of the stroma to protect the endothelium from UV-related damage. Older protocols tried to artificially thicken the cornea, either using hypo-osmolar riboflavin or a riboflavin-soaked contact lens or leaving an epithelial island above the thinnest point. But each of these approaches involved compromises, which were, respectively, unpredictable swelling, suboptimal strengthening, and shallower CXL effects in the epithelium-on (epi-on) region.[7]

Our research group modelled the key components of the CXL UV-riboflavin-oxygen-cornea reaction and developed an algorithm, later clinically validated, that can predict the

depth of the CXL effect (the demarcation line) in individual eyes, based on pachymetry measurements of stromal depth, atmospheric oxygen, and UV irradiation time.[8] This information means that thin corneas can still be crosslinked and retain the 70-µm safety margin at the base of the stroma simply by customizing the UV irradiation time. This protocol, called "sub400," has been successfully used to crosslink corneas as thin as 214 µm with a 90% tomographic stability rate after 1 year, in eyes that would ordinarily have gone on to require keratoplasty.[9]

Epi-on CXL

Epithelial debridement was originally required to perform CXL, as riboflavin is too large a molecule to penetrate through the tight junctions of epithelial cells. However, removing the epithelium also necessitates careful handling of the defect in the weeks after the procedure until the epithelium regrows to close the defect, and corneal haze lasting up to 6 months is a frequent occurrence. These all mean that strict adherence to postoperative drug regimens to manage pain, inflammation, haze, and a small increase in infection risk is necessary. An epi-on CXL protocol would therefore be desirable.

Getting riboflavin through the epithelium and into the stroma is possible via either iontophoresis (electrostatically forcing riboflavin molecules through) or by using penetration enhancers that degrade the tight junctions between epithelial cells to achieve the same outcome. However, this alone is still less effective than epi-off protocols at strengthening the cornea. The epithelium absorbs some of the UV energy delivered to the cornea and restricts the diffusion of atmospheric oxygen into the stroma, which is a rate-limiting step in the UV-riboflavin photochemical reaction.

Protocols that moderately increase the fluence delivered and use fractionated (pulsed) UV dose delivery (to enable oxygen to diffuse in during the off-cycle of illumination) are helping overcome this issue, meaning that epi-on CXL that strengthens the cornea as effectively as epi-off protocols is becoming a reality.

Expanding access

Finally, the same issues regarding access to ectasia screening in LMICs mentioned above also apply to ectasia treatment: CXL is typically performed in operating rooms, which exist only in hospital settings, which in LMICs are concentrated in the major cities, whereas most of the population live in rural settings. However, CXL can be performed in an office-based setting; it does not need to be performed in an operating room.

The UV-riboflavin reaction results in the generation of reactive oxygen species. In addition to crosslinking molecules in the stroma together and thereby strengthening it, these species also directly attack pathogen cell membranes and intercalate with pathogen nucleic acids. CXL, in effect, sterilizes the cornea by the end of the procedure, so much so that it is used to treat infectious keratitis, where it is called photoactivated chromophore for keratitis-CXL (PACK-CXL). This negates the main advantage of the operating room: sterility, and this also avoids the associated costs of this setting. The development of battery-operated, rechargeable, portable CXL devices that can be operated at the near ubiquitous slit lamp opens up CXL to a far wider proportion of the global population who require CXL treatment for ectasia (and also infectious keratitis) but would otherwise not be able to access it.[10]

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In These Unprecedented Times . . .

Cornea Subspecialty Day 2022

Lee A Snyder MD

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During AAO 2022 in Chicago, invest in OPHTHPAC and Surgical Scope Fund at either of our two convention center booths (in the Grand Concourse and Lakeside Center) or online. You may also invest via phone by texting **MDEYE** to **41444** for OPHTHPAC and texting **SCOPE** to **51555** for the Surgical Scope Fund.

We also encourage you to support our congressional champions by making a personal investment to their re-election campaign via OPHTHPAC Direct, a unique and award-winning program that lets *you decide* who receives your political support.

Surgical Scope Fund contributions are completely confidential and may be made with corporate checks or credit cards. PAC contributions may be subject to reporting requirements.

Why Invest?

Academy Surgical Scope Fund contributions are used to support the infrastructure necessary in state legislative/regulatory battles and for public education. OPHTHPAC investments are necessary at the federal level to help elect officials who will support the interests of our profession and our patients. Similarly, state Eye PAC contributions help elect officials who will support the interests of our patients at the state level. Contributions to EACH of these three funds are necessary and help us protect sight and empower lives.

Protecting quality patient eye care and high surgical standards is a "must" for everybody. Our mission of "protecting sight and empowering lives" requires robust funding of both OPHTHPAC and the Surgical Scope Fund. Each of us has a responsibility to ensure that these funds are strong so that ophthalmology continues to thrive and patients receive optimal care.

OPHTHPAC for Federal Advocacy

OPHTHPAC is the Academy's award-winning nonpartisan political action committee, representing ophthalmology on Capitol Hill. OPHTHPAC works to build invaluable relationships with our federal lawmakers to garner their support on issues such as:

- Improving the Medicare payment system, so ophthalmologists are fairly compensated for their services
- Securing payment equity for postoperative visits, which will increase global surgical payments
- Stopping optometry from obtaining surgical laser privileges in the veterans' health-care system
- Reducing prior authorization and step therapy burdens

Academy member support of OPHTHPAC makes all this possible. Your support provides OPHTHPAC with the resources needed to engage and educate Congress on our issues, helping advance ophthalmology's federal priorities. Your support also ensures that we have a voice in helping shape the policies and regulations governing the care we provide. Academy member support of OPHTHPAC is the driving factor behind our advocacy push, and in this critical election year, we ask that you get engaged to help strengthen our efforts.

At the Academy's annual Mid-Year Forum, the Academy and the Cornea Society ensure a strong presence of cornea specialists to support ophthalmology's priorities. As part of this year's meeting, the Cornea Society supported participation of fellowship trainees via the Academy's Advocacy Ambassador Program. During Congressional Advocacy Day, they visited members of Congress and their key health-care staff—either in person or virtually—to discuss ophthalmology priorities. The Cornea Society remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund for State Advocacy

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies in support of their efforts to protect patient safety from dangerous optometric surgery proposals. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, have helped 43 state/territorial ophthalmology societies reject optometric scope of practice expansions into surgery.

If you have already made a SSF contribution, please go to safesurgerycoalition.org to see the impact of your gift.

Dollars from the SSF are critical to build complete cutting-edge political campaigns, including media (TV, radio, and social media), educating and building relationships with legislators, and educating the voting public to contact their legislators. This helps to preserve high surgical standards by defeating optometry's surgical initiatives.

Each of these endeavors is very expensive, and no one state has the critical resources to battle big optometry on their own. Ophthalmologists must join together and donate to the SSF to fight for patient safety.

The Academy's Secretariat for State Affairs thanks the Cornea Society, which has joined state ophthalmology societies in the past in contributing to the SSF, and looks forward to its 2022 contribution. These ophthalmic organizations complete the necessary SSF support structure for the protection of our patients' sight.

Surgical Scope Fund	OPHTHPAC®	State Eye PAC
To protect patient safety by defeating optometric surgical scope-of-practice initiatives that threaten quality surgical care	Support for candidates for U.S. Congress	Support for candidates for state House, Senate, and governor
Political grassroots activities, government relations, PR and media campaigns No funds may be used for campaign contributions or PACs.	Campaign contributions, legislative education	Campaign contributions, legislative education
Contributions: Unlimited Individual, practice, corporate, and organization	Contributions: Personal contributions are limited to $5,000. Corporate contributions are confidential.	Contribution limits vary based on state regulations.
Contributions are 100% confidential.	Personal contributions of $199 or less and all corporate contributions are confidential. Personal contributions of $200 and above are on the public record.	Contributions are on the public record depending upon state statutes.

State Eye PAC

The presence of a strong State Eye PAC providing financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates to the state legislature is critical, as scope-of-practice battles and many regulatory issues are fought on the state level.

Support Your Colleagues Who Are Working on Your Behalf

Two Academy committees made up of your ophthalmology colleagues are working hard on your behalf. The OPHTHPAC Committee continues to identify Congressional Advocates in each state to maintain close relationships with federal legislators to advance ophthalmology and patient causes. The Surgical Scope Fund Committee is raising funds used to protect Surgery by Surgeons during scope battles at the state level.

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Atypical Microbial Keratitis

Alex Mammen MD

I. Background
   A. Definition: uncommonly seen corneal pathogens
   B. Risk factors
      1. Contact lens wear
      2. Trauma with soil or vegetative matter
      3. Travel to areas with higher prevalence
      4. Ocular surface disease
      5. Previous ocular surgery
   C. Clinical presentation
      1. Indolent and chronic
      2. More difficult to diagnose, requiring high index of suspicion
      3. More difficult to treat
      4. Worse prognosis for vision and eye immunosuppression

II. Atypical (Nontuberculous) Mycobacterium
   A. Background
      1. Aerobic, nonmotile, non–spore forming, acid-fast bacilli
      2. Found in the soil, water, and air in wide range of climates
      3. Can colonize human skin and bodily fluids
      4. Opportunistic infections
         a. More commonly found in low- and middle-income countries
         b. Pulmonary, skin, soft tissue endocarditis, postoperative wound infections
         c. Associated with inadequate sterilization of surgical instruments/fluids contaminated by mycobacterial biofilms
         d. Most common ocular infection
            i. keratitis
            ii. 80% caused by rapidly growing mycobacteria like *Mycobacterium fortuitum* and *Mycobacterium chelonae-abscessus*
         e. Other ocular infections
            i. scleral abscesses
            ii. lacrimal drainage system infections
            iii. orbital cellulitis
            iv. endophthalmitis
   B. Clinical presentation with keratitis
      1. Days to weeks after insult, depending on rapid- or slow-growing mycobacterium, respectively
      2. Variable appearance, but due to indolence may lack an epithelial defect
      3. Milder inflammatory response
   C. Microbiologic diagnosis
      1. Classic tools
         a. Acid fast dye (Ziehl Neelsen) to stain slides and Lowenstein-Jensen media
         b. MacConkey agar
         c. Middlebrook 7H10 or 7H11 media to culture
      2. Slow-growing mycobacteria can take 6-8 weeks to grow.
      3. Rapid and sensitive molecular testing modalities (eg, PCR) are not yet broadly available.
   D. Treatment of keratitis
      1. Long-term treatment (weeks to months) required
      2. In vitro susceptibility has been shown to aminoglycosides (amikacin), macrolides (clarithromycin and azithromycin), and fluoroquinolones (ciprofloxacin, gatifloxacin, moxifloxacin).
         a. Species-dependent variability to treatment
         b. Combination therapy with 2 or more classes of drugs is recommended.
      3. Corticosteroid use is associated with worsening of infection.
      4. Refractory cases require lamellar or penetrating keratoplasty.

III. *Nocardia*
   A. Background
      1. Aerobic, gram-positive, nonmotile, filamentous bacteria
      2. Found in water and organic matter, especially in South Asia
      3. Can colonize tissue around teeth, but infection is usually from inhalation or trauma-related inoculation of external bacteria.
      4. Mainly causes respiratory infections in immunocompromised patients

5. Ocular infections are rare, usually from *Nocardia asteroides*.
    a. Keratitis (most common)
    b. Conjunctivitis
    c. Scleritis
    d. Lacrimal gland infections
    e. Orbital cellulitis
    f. Endophthalmitis

B. Clinical presentation with keratitis
1. Classic appearance: patchy, raised, pin-head sized infiltrates in a wreath-like pattern
2. Satellite lesions may mimic fungal keratitis.
3. Superficial infiltrates: epithelial, subepithelial, and anterior stromal

C. Microbiologic diagnosis
1. Gram-positive bacteria with beaded filaments (can also use Giemsa, KOH with calcofluor white or acid fast dyes)
2. Standard culture media: blood, chocolate, Sabouraud dextrose agar
3. Slow growing
4. Molecular testing modalities (eg, PCR) not yet broadly available.

D. Treatment of keratitis
1. Average reported treatment time required: 38 days
2. Drug of choice: fortified topical amikacin 2.0% to 2.5%
3. Corticosteroid use is associated with worsening of infection.
4. Refractory cases require lamellar or penetrating keratoplasty.

IV. *Microsporidia*

A. Background
1. Spore-forming, unicellular, opportunistic, waterborne pathogen previous classified as protozoa but more recently reclassified as fungi
2. Endemic to South and Southeast Asia
3. Can cause epithelial keratoconjunctivitis, deep stromal keratitis, scleritis, and endophthalmitis

B. Clinical presentation with keratitis
1. Multiple fine to coarse punctate, raised epithelial lesions with stuck-on appearance
    a. Variably stain with fluorescein
    b. Peripheral, paracentral, or diffuse
2. Invariably associated with conjunctivitis
3. Presentation with subepithelial punctate infiltrates may be indistinguishable from adenoviral keratoconjunctivitis.
4. Stromal keratitis may have relapsing and remitting course.
    a. Multifocal, mid to deep stroma, with intact overlying epithelium
    b. Associated stromal edema ± stromal vascularization
5. May have anterior chamber inflammation ± keratic precipitates

C. Microbiologic diagnosis
1. Gram-positive, oval-shaped, intraepithelial spores
    a. Stains well with gram stain, silver stain, and 10% KOH with 0.1% calcofluor white
    b. For deep stromal infiltrates, a corneal biopsy may be required.
2. Requires cell cultures to grow; does not grow on agar plates
3. Molecular testing modalities (eg, PCR) are not yet broadly available.

D. Treatment of keratitis
1. Epithelial debridement can be effective for superficial infections.
2. Anecdotal benefit with topical fluoroquinolones
3. Parasitistatic derivative of *Aspergillus*: *fumagillin*
4. Topical azoles
5. Biguanides like polyhexamethylene biguanide (PHMB) 0.02% and chlorhexidine gluconate 0.02% have been used, but with questionable benefit.
6. Topical steroids can be beneficial for inflammatory component.
7. The oral antiprotozoal drug albendazole effective against *Encephalitozoon* species

Recalcitrant Mycotic Keratitis

Lauren Jeang MD

I. Background

A. The global annual incidence of fungal keratitis is estimated to be approximately 1 million.[1]

B. Location plays a role in incidence, with more cases noted in tropical or subtropical climates.

1. Highest numbers in Asia and Africa
2. Lowest numbers in Europe

C. Microbial keratitis places a huge financial and time burden on patients and the health-care system.

II. Etiology

A. 95% of cases are caused by the filamentous fungi *Fusarium* spp and *Aspergillus* spp and the yeast *Candida* spp.[1]

1. Filamentous fungi are commonly seen in tropical and subtropical climates.
2. Yeasts are more commonly seen in temperate climates.

B. Vegetative trauma is considered the biggest risk factor in fungal keratitis, but contact lens use is now the primary cause in developed nations.

C. Other causes

1. Previous ocular surgery
2. Ocular surface disease
3. Contact lens use
4. Use of corticosteroids
5. Immunosuppressive states
6. Pre-existing herpes simplex virus keratitis

D. History may suggest type of fungal infection.

1. *Fusarium* is commonly seen with contact lens–associated cases.
2. Post–corneal transplant cases have a slightly higher incidence of yeast than molds.

III. Features of Fungal Keratitis

A. Often described as a "dry" appearance with feathery borders and/or satellite lesions[2]; pigmentation suggests dematiaceous fungi such as *Curvularia*.

B. Fungal infections can penetrate intact Descemet membranes and enter the anterior chamber without perforation: "fluffy" hypopyon, endoplaque

C. Epithelium may heal over active deeper infections, which can make it challenging to treat.

IV. Diagnosis

Diagnosis of fungal keratitis with clinical examination alone can be difficult, and adjunct testing is still useful.

A. Smears and cultures

B. Corneal biopsy

C. Polymerase chain reaction

D. Imaging

V. Treatment Strategies

A. Topical medication

1. Topical antifungal agents can be limited by fungistatic activity and poor ocular penetration.[3]
2. The Mycotic Ulcer Treatment Trial I (MUTT I) found better clinical outcomes with the use of natamycin 5% over voriconazole 1% in the treatment of filamentary fungal keratitis, especially for *Fusarium*.[4] Avoiding voriconazole monotherapy is recommended.
3. Amphotericin B (0.15%-0.5%) is the best option for treatment of yeasts. Natamycin and voriconazole also have efficacy against yeasts.
4. Compared to treatment for bacterial keratitis, treatment for fungal keratitis requires more time but less frequent dosing.
5. Steroids are contraindicated and should be discontinued if a fungal etiology is suspected.

B. Oral medication

1. MUTT II showed that concurrent oral voriconazole in addition to topical antifungals offered no benefit in the treatment of severe filamentous keratitis, though there was possibly some benefit for severe *Fusarium* keratitis.[5]
2. Oral voriconazole may be beneficial in case of limbal involvement or penetration into the anterior chamber in deep infections.
3. Periodic liver function tests need to be done due to potential liver toxicity.
4. High-dose oral posaconazole has been successful in a small case series of recalcitrant contact lens–associated fungal keratitis.[6]

C. Procedures

1. Intrastromal and intracameral amphotericin B (5 µg/0.1 mL) or voriconazole (50 mg/mL) can be effective for deeper corneal fungal infections.
2. Subconjunctival antifungals are no longer recommended but might be helpful in patients who demonstrate poor compliance or are unable to instill topical drops.
3. Cyanoacrylate glue can be used in cases of severe corneal thinning or small corneal perforations.

D. Surgical interventions

1. Surgical interventions in the acute period are mostly aimed at re-establishing globe integrity and/or debulking infectious material.[7]
2. Conjunctival flaps
3. Penetrating keratoplasty
   a. Typically has poor visual outcomes due to complications such as glaucoma, cataract, and graft rejection.[8]
   b. Glycerol-preserved corneas are an emergency option when no available fresh tissue is available.
4. Tectonic deep anterior lamellar keratoplasty (DALK) and lamellar keratoplasties

VI. Future Avenues

A. Collagen crosslinking (CXL)

1. Photoactivated chromophore for infectious keratitis CXL has shown mixed results in fungal keratitis.[9-11]
2. Risk of inflammation and perforations
3. Rose bengal photodynamic antimicrobial therapy is another method under investigation.[12]

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Herpetic Keratitis

Antoine Rousseau MD PhD and Marc Labetoulle MD PhD

Pathophysiology and Epidemiology of HSV1-Infection

Primary infection by herpes simplex type 1 (HSV-1) almost always occurs in the oral mucocutaneous tissues and is asymptomatic in more than 90% of cases. After local replication, viral particles migrate retrogradely along the trigeminal fibers to establish life-long latency in the neuron's somata of trigeminal ganglia (TG). Viral reactivation in the TGs (which occurs upon various stimuli, such as stress, inflammation, or surgery) are followed by viral replication and anterograde migration of viral particles that reach peripheral tissues, including cornea, to cause herpes simplex keratitis (HSK). In industrialized countries, HSV-1 seroprevalence increases with age, to exceed 60% among patients 50 years or older.[1] The annual incidence of HSK varies between 12 and 31.5 cases per 100,000 inhabitants, or approximately 75,000 to 150,000 in the United States.[1] Altogether, the approximate risk of developing HSK at least once in life is 1%. The first HSK episode may occur any time, including childhood, but is more frequent in the second and third decades. The risk of relapse is approximately 10% at 1 year and increases gradually to reach 70% at 20 years.[1]

Clinical Patterns and Their Underlying Pathophysiology

A striking feature of HSK lies in the unilaterality of lesions, despite the presence of HSV-1 genome in comparable amounts in both TGs. Another characteristic is the loss of corneal sensitivity, initially in the affected eye, due to alterations of the corneal nociceptors and the nerve fibers in the TG pathway,[2,3] which ultimately induce bilateral signs of dry eye, a consequence of decrease in the sensitive input from the affected eye to the brainstem areas involved in the regulation of the lacrimal functional unit (both eyes).[4] These features, plus anxiety of recurrence and associated visual consequences, have a major impact on the HSK patient's quality of life and social behavior.[5]

In HSK, corneal damage results from a combination of 3 main pathophysiological mechanisms—(1) viral replication and its direct cytopathic effects, (2) immune response, and (3) neurotrophic alterations—the relative importance of which varies according to the clinical subtypes.[6]

- **Epithelial HSK** (either dendritic or geographic) results from viral replication into the corneal epithelium.
- **Stromal keratitis without ulceration** is caused by the immune response triggered by HSV-1 replication (even at low grade). Innate immunity effectors such as natural killer cells, dendritic cells, macrophages, and neutrophils rapidly infiltrate the cornea, while T cells (eg, CD4+ T cells, CD8+ T cells, and regulatory T cells) orchestrate the immune response.
- **Stromal keratitis with ulceration** (also referred to as "necrotizing keratitis") results mostly from massive viral replication in deep corneal tissues.
- **Endothelial keratitis** is caused by a combination of viral replication, causing endothelial dysfunction and damage (corneal edema), with immune response, causing keratic precipitates and anterior segment inflammation.
- **Neurotrophic keratopathy** mostly results from long-term sensory corneal nerve alterations after repeated episodes of HSK.

Therapeutic Strategies

Curative treatments are adapted according to the clinical subtype of the recurrence, which may be combined. Epithelial keratitis is treated with either oral or topical antivirals and epithelial debridement, with an overall good short-term prognosis.

In stromal keratitis without ulceration and endothelial keratitis, interventions aim at both controlling inflammation (with topical or periocular steroids) and reducing the underlying viral replication. These 2 therapeutic components are tailored to the risk of definitive corneal opacification, neovascularization, and/or endothelial dysfunction.

As stromal keratitis with ulceration may rapidly evolve toward corneal perforation, high-dose systemic antiviral therapy is legitimate as a first-line option, and steroids are postponed until definite clinical improvement is observed.

HSV-1–associated neurotrophic keratopathy is managed in a stepwise manner, according to the severity. Severe cases may benefit from autologous serum (or platelet-rich plasma) eye drops, neurotrophic growth factor eye drops, and/or amniotic membrane patch/grafts. Scleral lenses can be a good option and may help to avoid vision-disabling surgery.

The strategy to prevent recurrences is based on the results of the seminal Herpes Eye Disease Study, which demonstrated that continuous antiviral prophylaxis (AVP) with oral acyclovir (ACV) reduces by 50% the frequency of recurrences.[7] Given their bioequivalence and/or pharmacodynamic properties, valacyclovir (VACV) and famciclovir (FCV) can advantageously replace ACV in this setting. However, antivirals alone may fail to prevent inflammatory recurrences in some patients, and adjunctive long-term control of ocular surface inflammation, using low potency steroids and/or other immunomodulatory eye drops (cyclosporine or tacrolimus),[8] topical lubricants and management of associated meibomian gland dysfunction, may help to further reduce the rate of HSK recurrences.

ACV-Resistant HSV-1 Keratitis as an Emerging and Concerning Challenge

Recent studies have alerted the community about the increasing proportion of ACV-resistant (ACV^R) isolates in tears from patients with recurrent HSK despite conventional AVP.[9] A prospective study investigating the causes of AVP failure in immunocompetent patients showed that genetic modifications of HSV-1 can arise with time and lead to resistance to usual AVP in some patients. Although still rare in everyday clinical practice, the emergence of ACV (of FCV)-resistant strains should be considered in patients receiving conventional AVP and presenting with a high rate of HSK recurrences, especially in case of immunosuppression history and/or a long history of HSK relapses.[10] To date, there is no consensus on the management of these rare but very challenging cases.

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Parasitic Keratitis

Prashant Garg MD

I. Introduction

A variety of parasites cause keratitis, either through direct invasion or indirectly by inducing inflammatory reaction. *Acanthamoeba* is one of the important causes of parasitic keratitis, with cases reported from all continents. But despite being an important cause, it accounts for only a small fraction (around 1%) of all cases of microbial keratitis. In this lecture I will cover primarily *Acanthamoeba* keratitis and will make a passing remark on other causes.

II. *Acanthamoeba* Keratitis (AK)

A. Epidemiology

1. *Acanthamoeba* are ubiquitous, found in every conceivable environment, from hot springs to under ice and everywhere in between.
2. Exposure to *Acanthamoeba* is common, as evidenced by presence of serum antibodies against *Acanthamoeba* antigens in nearly 90% to 100% of the population with no previous history of AK.
3. Although over 30 million people in United States alone use contact lenses and contact lens use is the most important risk factor, the frequency of AK in contact lens wearers is less than 33 cases per 1 million. Corneal abrasion is yet another risk factor.
4. Why is incidence of the infection is so low?

B. Clinical features

1. Classical
   a. Epitheliopathy
   b. Ring infiltrate
   c. Radial keratoneuritis
   d. Out-of-proportion pain
2. Nonclassical
   a. Nonulcerative stromal keratitis
   b. Ulcerative necrotizing keratitis
   c. Dry-looking infiltrate
   d. Nummular keratitis
   e. Keratouveitis
3. Complications
   a. Scleritis
   b. Chorioretinitis
4. In which clinical scenario should I suspect *Acanthamoeba* infection? Does presence of scleritis indicate widespread infection?

C. Diagnosis

1. Classical approach: Typical clinical features and documentation of the parasite in corneal scraping (microscopy, culture, or both)
2. Alternative strategies
   a. In vivo confocal microscopy (IVCM)
   b. Molecular diagnosis (real-time polymerase chain reaction [PCR])
3. What is the relative value of IVCM, PCR, and culture in the diagnosis of *Acanthamoeba* keratitis? Is there a role for microbiology in the workup of a case of scleritis in microbiology-proven *Acanthamoeba* keratitis?

D. Treatment

1. Classical anti-*Acanthamoeba* therapy: 0.02% biguanides and diamidines
2. Limitations of classical therapy
   a. Poor efficacy in advanced keratitis, delayed presentation, and prior therapy with corticosteroids
   b. Need for prolonged treatment
   c. Toxicity
   d. Effective in early cases; poor response in the presence of coinfection
3. Alternative drugs
   a. Antibiotics
   b. Antifungal agents
   c. Anticancer and anti-leishmaniasis drug miltefosine
   d. Other agents under investigation
   e. Role of vaccination or immunotherapy
4. Photodynamic therapy
   a. Riboflavin
   b. Rose bengal
   c. Other photosensitizers (porphyrin conjugated with mannose)
5. Role of corticosteroids and immunosuppressive therapy

6. Surgery
    a. Deep anterior lamellar keratoplasty
    b. Penetrating keratoplasty
7. Management of scleritis
8. When should I consider additive treatment in the management of *Acanthamoeba* keratitis? When and how to start corticosteroid therapy?

E. Prophylaxis
1. Modified contact lens cleaning solutions
2. Lens case modifications
3. What shall I advise to my contact lens wearers for protection against *Acanthamoeba* infection? Are there any new developments in this direction?

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Infectious Etiologies of Ocular Surface Tumors

Carol L Karp MD

Carcinogenesis is multifactorial, with both genetic and epigenetic factors. Exposure to ultraviolet rays, radiation, and other carcinogens may lead to cellular dysregulation and neoplasia. Interestingly, infections with certain bacteria, viruses, and parasites have been recognized as risk factors for several types of cancer in humans and linked to about 15% to 20% of cancers.

Infections can raise a person's risk of cancer by directly affecting the growth of cells, such as when viruses insert into cells and lead to uncontrolled growth. Another possible method of neoplasia is that some infections can cause long-term inflammation and metaplasia, which can eventually lead to neoplasia. Finally, any infections that can suppress the immune system (eg, HIV) can create a permissive effect for cancer growth.

Many viruses have been associated with cancers in the body. Human papilloma virus (HPV) can lead to cervical cancer but also anal, penile, throat, and oral cancer. Hepatitis B and C can lead to liver cancer and lymphomas, and human herpes virus 8 can lead to Kaposi sarcoma. In terms of bacterial infections, long-term infection of the stomach with *Helicobacter pylori* can lead to ulcers and lymphoma of the stomach. Parasitic infections have also been linked to bile duct cancer (*Opisthorchis viverrini* and *Clonorchis sinensis*). Schistosomiasis has been linked to bladder cancer.

In the eye, several infectious agents have been linked to conjunctival tumors. These include HPV 16 and 18, leading to ocular surface squamous neoplasia, and low-risk serotypes 6 and 11, causing conjunctival papillomas. As above, human herpes virus 8 leads to Kaposi sarcoma along with HIV infection. Conjunctival lymphoma has been concomitant with chlamydia and hepatitis C infections. These and other tumors will be discussed, with focus on etiologies and targeted therapies.

Identification of Microbes and Susceptibility Testing

Thuy Doan MD PhD

This section summarizes some of the commonly used techniques for outpatient testing and highlights new approaches for unbiased pathogen identification and susceptibility testing. This is not meant to be an exhaustive list of all pathogen identification or susceptibility testing methods. For that, please refer to a recent review by Singh et al.[1]

Pathogen Identification

I. Cultures are considered the gold standard, although they are mostly target dependent and sensitivity remains low.[2]

   A. Sample collection: Many ulcer patients now present on topical antibiotics. Some specialists discontinue antimicrobials for 24 hours before culturing. Preferably, proparacaine is used for anesthesia as it is less bactericidal than other topical anesthetics. Use either Kimura's spatula, 25-30 gauge needle, surgical blade, or a sterile polyester-tipped applicator (Puritan). Swab at both the edge and the base of the corneal ulcer. Use a new applicator/blade for each plate or glass slide. Streak the plates in rows of "C." This will help laboratory personnel to distinguish contamination from true growth.

   B. Common plates

      1. Blood: aerobic bacteria and some fungi
      2. Chocolate: *Moraxella*, *Neisseria*, *Hemophilus*
      3. Sabouraud and potato dextrose: fungi
      4. Non-nutrient with *E. coli* overlay: *Acanthamoeba*
      5. Thioglycolate broth: obligate and facultative anaerobic bacteria, some aerobic bacteria, some fungi
      6. Lowenstein-Jensen media: *Mycobacterium tuberculosis* and atypical mycobacteria

   C. Deep infiltrates: Pass a braided suture (ie, 8-0 Vicryl) and place the suture directly onto the plate. Cut the suture into fragments if more than one plate is used.

   D. Streak slides for Gram stain and KOH if those options are available. At some tertiary centers, this requires specialized laboratory personnel, and thus these options may not be routinely available.

II. In vivo confocal microscopy (IVCM) imaging can identify features of bacteria, fungi, or *Acanthamoeba* in some infectious corneal ulcers.[3]

   A. *Acanthamoeba*: bright spots (~15-20 µm in size),[4] double-walled cysts, signet rings, in clusters (after topical steroid use). At the Proctor Foundation, we mostly use IVCM to assess for *Acanthamoeba* and fungal keratitis.

   B. Bacteria-related keratitis: bullae in anterior stroma for severe cases of *Streptococcus. pneumoniae* or *Pseudomonas* or nonspecific inflammation without cysts or hyphae

   C. Fungal-related keratitis: filaments

III. Molecular approaches, such as nucleic acid amplification tests (NAATs), are more sensitive than culture-based assays, but they are limited for being pathogen-directed.[5] While one could interrogate for many pathogen targets at once, this generally comes at a cost of lower sensitivity. In addition, there is a finite amount of nucleic acids that can be extracted for any given sample.

   A. One can routinely send for herpes simplex virus, varicella zoster virus, and cytomegalovirus polymerase chain reaction (PCR).

   B. *Chlamydia trachomatis* (± *Neisseria gonorrhoeae*) PCR

   C. The University of Washington Molecular Laboratory and HealthTrackRx have a panel of other pathogen-directed PCRs. See www.medialab.com/dv/dl.aspx?d=871128&dh=2b267&u=110081&uh=a6e1e.

IV. High-throughput or deep sequencing has allowed for the unbiased and comprehensive interrogation of pathogens in any given clinical sample. This approach is particularly promising for minute samples such as corneal ulcer scrapings.

   A. Amplicon-based testing: 16S rRNA gene deep sequencing allows for the identification of all bacteria (assuming they are available in the reference database). The University of Washington Molecular Laboratory offers this assay.

B. Metagenomic sequencing: DNA-seq or RNA-seq. Both of these approaches are routinely used at the Proctor Foundation for corneal ulcers, conjunctivitis, or intraocular infections.

   1. DNA-seq allows for the detection of all pathogens with DNA genomes (bacteria, fungi, parasites, DNA viruses).[6] DNA-seq does not allow for the identification of RNA viruses such as SARS-CoV-2.
   2. RNA-seq allows for the detection of all replicating (or recently dead) pathogens that can be identified with DNA-seq, in addition to RNA viruses.
   3. Current limitations of DNA-seq and RNA-seq include cost and longer time to results. These methods might be best reserved for cases in which the suspicion of an infectious agent is high but conventional diagnostics have failed to identify a pathogen.

Susceptibility Testing

Antimicrobial susceptibility testing requires the successful growth of the organism. Most laboratories in the United States have adopted MALDI-TOF mass spectrometry for efficient microbial identification. Depending on the pathogen or the antibiotic, susceptibility testing can be done with either broth microdilution, disk diffusion (Kirby Bauer), gradient test (E-tests), or various semiautomated devices. For example, broth dilution is unsuitable for anaerobic bacteria, and gradient tests will fail with colistin. Please note that some minimum inhibitory concentration (MIC) breakpoints in the United States are set differently than those in Europe.

Antimicrobial resistance gene determinants (ie, *mecA*) can also be assessed using NAAT on cultured organisms. Please note that the presence of an antibiotic resistance determinant does not always correlate with phenotypic resistance, and neither genotypic nor phenotypic resistance correlate well with clinical outcomes.

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Surgical Management of Scleral Necrosis

Sheraz Daya MD

Introduction

Necrotizing scleritis is a severe and very painful condition that through loss of tissue can lead to ocular loss. It is associated with systemic diseases where vasculitis is prominent and both obliterative loss of vessels and inflammation result in collagenolysis and loss of tissue. Patients present early with pain and redness and sometimes photophobia if spill-over keratitis and anterior chamber inflammation are present. In 40% of cases the condition is bilateral, and it is more common in the fourth to sixth decades, peaking at the fifth decade. It can occur at any age and is associated with an identifiable systemic disease in 47% of cases.

Pathogenesis

The condition is associated with vasculitis from a type III immune reaction with immune complex deposition and surrounding inflammation. Scleritis may be anterior or posterior. In the anterior form, which is visible clinically at the slit lamp, it may present as:

1. Diffuse: deep and superficial dilation of vessels indicative of inflammation
2. Nodular: localized inflammation with nodule formation
3. Necrotizing: thinning and loss of tissue, noted to be avascular at the site of necrosis and surrounded by dilated episcleral vessels. The area of necrolysis increases progressively.

Associated Systemic Conditions

- Rheumatoid arthritis
- Wegener granulomatosis
- Systemic lupus erythematosus
- Juvenile rheumatoid arthritis
- Polyarteritis nodosa (PAN)
- Relapsing polychondritis
- Rosacea
- Gout
- Psoriasis
- Syphilis
- TB
- Herpes simplex and zoster

Management of Necrotizing Scleritis

A diagnostic workup is essential to determine any systemic association that can be treated specifically. This consists of an immune profile including rheumatoid factor, ANA, and ANCA. Measures of inflammation include ESR and C reactive protein as well as complement C3 and C4 levels, which may be depressed in the context of vasculitis.

Aggressive medical management is necessary. While systemic nonsteroidal therapy is effective for diffuse scleritis and some forms of nodular (not Wegener PAN or relapsing polychondritis), systemic steroids are necessary to reduce inflammation as quickly as possible. The steroid regimen used depends on the condition. Bolus doses of between 125 mg and 1 g of IV methylprednisolone are used under supervision of an internist or rheumatologist, followed by prednisolone 1 mg/kg daily. Immunosuppressives cyclophosphamide, azathioprine, and methotrexate take a few weeks to have effect. Now with the advent of biologics, better agents are available: tocilizumab, rituximab, infliximab, abatacept, and tofacitinib, which are steroid-sparing and provide stabilization within 3 months. Rheumatologic oversight is vital. Pain management is a vital component that must also be considered.

Surgical Management

During the course of medical management, surgical intervention is often necessary, with the single objective of maintaining globe integrity. Necrosis can lead to perforation and in turn a bacterial superinfection and at worse loss of the eye from loss of contents and choroidal hemorrhage.

Replacement of tissue and reinforcement of the area of necrosis is the goal and will hopefully suffice until the condition is controlled medically. Options for tissue replacement include sclera, which is not likely to last in the context of severe inflammation as it is avascular and subject to collagenolytic agents from inflammation. Where there is adjacent keratitis and necrosis, a limbal horseshoe sclerocorneal graft is useful. Pericardium and fascia lata are more resistant to collagenases, and autologous periosteum or pericranium is arguably the most resistant, being strong tissue and highly vascular.

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Peripheral Ulcerative Keratitis: Rise of the "Rheumophthalmologist"

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NOTES

Neurotrophic Keratopathy

Clara C Chan MD

I. Definition
   A. Corneal epitheliopathy leading to frank epithelial defect with or without stromal ulceration associated with reduced or absent corneal sensations
   B. Classified as an orphan disease affecting 5 individuals or fewer per 10,000 patients

II. Sequelae
   A. Persistent epithelial defect
   B. Secondary infection
   C. Stromal thinning
   D. Scarring
   E. Vascularization
   F. Perforation
   G. Loss of eye

III. Etiologies
   A. Genetic
   B. Systemic (eg, diabetes)
   C. CNS pathway deficiency (eg, after neurosurgery, after retinal surgery)
   D. Post-herpetic infection
   E. Chemical/thermal burns
   F. Medication toxicity
   G. Chronic ocular surface disease
   H. Severe dry eye disease

IV. Mackie Classification

V. Principles of Treatment
   A. Restore corneal integrity to prevent progression of stages
   B. Stepladder approach based on staging/severity
   C. Medical, in office, and surgical options to consider

VI. Initial Medical Management
   A. Optimize ocular surface environment
      1. Preservative-free artificial tears, gels, ointments
      2. Avoid BAK preservatives
      3. Discontinue/avoid topical NSAID
   B. Prevent infection
      1. Topical fourth-generation fluoroquinolones
      2. Antiviral if active herpes simplex/herpes zoster virus
   C. Control inflammation: Cautious use of topical steroid, topical cyclosporine or lifitegrast, oral tetracyclines
   D. Nutritional healing support
      1. Autologous serum tears
      2. Platelet-rich plasma
      3. Recombinant nerve growth factor
   E. Physical protection of the ocular surface
      1. Soft contact lens, scleral contact lens, prosthetic replacement of the ocular surface ecosystem (PROSE)
      2. Tape splint tarsorrhaphy (see video at youtube.com/watch?v=ueVCwNDnUg0)

Table 1. Mackie Classification

Stage 1	Stage 2	Stage 3
• Inferior palpebral conjunctival staining • Decreased tear breakup time • Increased mucus viscosity • Punctate fluorescein staining	• Persistent epithelial defect (often oval, central/inferior cornea location, rim of loose epithelium, edges smooth/rolled) • Stromal edema with DM folds • Anterior chamber reaction	• Corneal ulceration • Stromal lysis and/or melting perforation
Initiate medical management	Maintain medical management and institute surgical intervention(s)	

VII. Surgical Management

A. Tarsorrhaphy: temporary or permanent with sutures vs. botulinum toxin–induced

B. Amniotic membrane transplant: dehydrated vs. cryopreserved vs. fresh frozen

C. Glue-patch to temporize thinning

D. Deep anterior lamellar keratoplasty/penetrating keratoplasty for treatment of perforation (perform tarsorrhaphy at conclusion of surgery)

E. Gunderson flap/conjunctival pedicle flap for eyes with poor vision potential and sterile surface

F. Corneal neurotization

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Drug-Induced Keratopathy

Jasmine H Francis MD

I. Introduction
   A. Recent expansion of cancer treatments beyond conventional chemotherapy to targeted agents and immunotherapy
   B. Brief review of corneal toxicity of conventional chemotherapy

II. Targeted Agents: Antibody Drug Conjugates
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Corneal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity

III. Targeted Agents: Other Small Molecule Inhibitors
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Corneal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity

IV. Immunotherapy
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Corneal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity

V. Conclusion

Table 1

Class	Drugs	Mechanism	Corneal Side Effects
Antibody drug conjugates			
	gemtuzumab (anti-CD33) inotuzumab (anti-CD22) brentuximab (anti-CD30) polatuzumab (anti-CD79b) enfortumab (anti-Nectin4) tisotumab (anti-Tissue factor) trastuzumab (anti-HER2) x 2 sacituzumab (anti-TROP2) belantamab (anti-BCMA) ioncastuximab (anti-CD19)	selective binding of antibody to tumor, internalization, lysosomal degradation and (cleavage of linker leading to) release of cytotoxic payload resulting in cell death	dry eyes keratopathy (MECs) refractive shift
Small molecule inhibitors			
	infigratinib erdafitinib	FGFR inhibitor, which can also work downstream to inhibit the MAPK pathway	epitheliopathy (severe punctate keratitis, recurrent corneal erosions) Descemet membrane haze ulcer
Immunotherapy			
	ipilimumab	monoclonal antibody targeting CTLA-4	conjunctivitis, episcleritis, keratitis (with or without uveitis), dry eyes
	pembrolizumab, nivolumab, cemiplimab, dostarlimab	PD-1 inhibitor	keratitis (with or without uveitis), dry eyes
	atezolizumab, avelumab, durvalumab	PD-L1 inhibitor	keratitis (with or without uveitis)

Abbreviations: MECs, microcyst-like epithelial changes; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death protein 1; PD-L1, programmed death ligand.

Filamentary Keratitis

Ahmad Kheirkhah MD

Filamentary keratitis (FK) is an ocular condition characterized by the development of filaments on the corneal surface. FK is often seen in certain ocular and systemic conditions. Of ocular conditions, FK is most common among those with dry eye disease, exposure keratopathy, and neurotrophic keratopathy. It can also be seen in superior limbic keratoconjunctivitis, viral keratitis, and following ocular surgery, particularly corneal transplantation. Various systemic diseases can be associated with FK, especially those with associated dry eye disease, such as Sjögren syndrome, rheumatoid arthritis, and graft versus host disease.

Although it is known that corneal filaments are composed primarily of epithelium, mucus, and cellular debris, their pathogenesis remains debated. Various theories have been proposed regarding the mechanisms of formation and progression of filaments, implicating the role of tear film, mechanical eyelid forces, corneal epithelium, and ocular surface inflammation.

Patients with FK may present with various symptoms, such as foreign body sensation, eye pain, grittiness, discomfort, photophobia, and blepharospasm. Symptoms may be worse with blinking and better when eyes are kept closed. Patients with filaments on a full-thickness corneal graft may be asymptomatic, possibly due to a limited innervation of the donor tissue.

Clinically, filaments appear as gelatinous protrusions or strands on the cornea. They may be seen as minute pinheads or freely movable strands with bullous ends. Filament location may depend on the associated conditions. Patients with dry eye disease mostly have filaments on the lower half to lower third of the cornea. Filaments in those with superior limbic keratoconjunctivitis are commonly found on the upper third of the cornea.

The diagnosis of FK is clinical, though appropriate testing for conditions associated with FK may help in differentiating the etiology. Given the high prevalence of dry eye disease in patients with FK, providers should consider performing routine tests for dry eye disease in these patients.

Management of FK includes a variety of therapies to address acute or chronic underlying etiologies, alleviate symptoms, and restore the ocular surface. Reversing acute causes of FK may provide rapid resolution. More commonly, when associated conditions are chronic, FK is recurrent and requires a combined, prolonged therapeutic approach. Potential risk factors for FK should be addressed first. Initial steps may include addressing dry eye disease with the many treatments available.

In-office management to minimize patient discomfort may include filament removal and is recommended on presentation for patient's comfort. Care should be taken to remove the entire filament without further epithelial or basement membrane damage, which may slow resolution of FK. While filament removal may help in relieving symptoms, without adjunct treatment it rarely provides long-term benefits in preventing filament recurrence.

Various treatments options are available for FK. Artificial tears are commonly used as adjunct therapy in the management of FK. Preservative-free artificial tears are preferred. Furthermore, electrolyte-rich artificial tears with medium viscosity have been recommended for their favorable ocular residence time and to avoid shearing effects across the ocular surface during blinking.

Topical hypertonic saline is an effective first-line therapy for FK. However, those with dry eye disease respond less favorably to hypertonic saline than those with acute or traumatic disease of the cornea. N-acetylcysteine, a mucolytic agent that decreases the viscosity of mucus in the precorneal tear film, has also been used to treat FK.

Anti-inflammatory medications may help certain patients with FK, especially those with dry eye disease or superior limbic keratoconjunctivitis. Corticosteroids should be used in short-term "pulse" treatments for disease exacerbations. Low-potency corticosteroids are used when prolonged treatment is necessary.

Bandage contact lenses may be used alone or along with other topical therapies in FK and may provide relatively rapid symptom resolution. These lenses protect the cornea from shearing forces of the eyelids and protect denuded areas of the epithelial basement membrane from further trauma. FK has also been successfully managed with scleral lenses and collagen lenses.

Punctal occlusion with plugs or cauterization helps patients with FK and dry eye disease. Autologous serum eye drops have also been demonstrated to be an effective treatment for FK. Serum drops likely target various pathways leading to filament formation by providing lubrication, growth factors, and nourishment. In FK that is refractory to conventional treatments, botulinum toxin injection has also been studied. It works by relaxation of the orbicularis muscle, which would decrease eyelid pressure on the cornea, decrease blink frequency and force, and minimize the propagation of FK.

Although a variety of options are available for treatment of FK, not all patients respond equally. Treatment course and remission may also depend on associated risk factors. Treatment should be tailored to each patient by taking into consideration their comorbidities, symptoms, medication compliance, and follow-up time.

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Case Presentations: Mystery Keratitis

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NOTES

Ocular Cicatrial Pemphigoid

Jennifer E Thorne MD PhD

NOTES

Ocular Graft Versus Host Disease

Edgar M Espana MD

Background

Ocular graft versus host disease (GVHD) is the most frequent complication following hematopoietic stem cell transplantation, which is commonly used for a variety of hematological malignancies. Transplant recipients with GVHD have reduced quality of life and increased risks for long-term morbidity and mortality.

Clinical Presentation

GVHD presents in an acute or chronic form. A clear distinction between acute and chronic forms of GVHD as originally described is no longer used today.

Acute GVHD

Acute ocular GVHD manifests most commonly as severe membranous conjunctivitis in early few weeks after transplantation.

Chronic GVHD (cGVHD)

The chronic presentation of GVHD has features resembling autoimmune disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, and bronchiolitis obliterans.

Symptoms usually present within 3 years of transplantation. Manifestations of chronic GVHD may be restricted to a single organ or tissue or may be widespread and lead to debilitating sequelae such as joint contractures, decreased sight, end-stage lung disease, or mortality from profound, chronic, immune suppression–induced, life-threatening infections.

Ophthalmic Manifestations of GVHD

Ocular surface manifestations

Dry eye is the most frequent ocular symptom, usually occurring approximately 6 months after transplantation. In ocular cGVHD, inflammatory destruction of the conjunctiva and lacrimal gland with fibrosis occurs, resulting in aqueous and lipid tear deficiency.

Symptoms and signs

Ocular cGVHD clinical presentation is like other immunologically mediated inflammatory diseases of the ocular surface, and there are no specific symptoms or clinical signs. Ocular manifestations, present in 60%-90% of patients with cGVHD, primarily affect the anterior segment. Typical symptoms of cGVHD are dry eye, photophobia, foreign body sensation, irritation, burning, epiphora, redness, and blurriness.

Target Tissues

Lacrimal glands

The lacrimal glands are an important ocular target for the pathogenesis of GVHD. Fibrotic processes often affect both lacrimal glands, reducing their secretory capacity or causing complete stasis. Histological studies also show extensive tissue atrophy and fibrosis of the glands and ducts.

Conjunctiva

Pseudomembranous conjunctivitis can rarely occur in acute GVHD. Chronic conjunctival involvement with palpebral and subtarsal conjunctival scarring is frequently seen in cGVHD Punctal stenosis or closure is a common finding.

Meibomian glands

Besides aqueous tear deficiency, a progressive decline of conjunctival goblet cells and the dysfunction of meibomian glands contribute to the overall breakdown of the ocular tear film.

Cornea

Corneal findings include punctate keratopathy, mucus filaments, painful erosions, and eventually secondary corneal infections. Superior limbic keratoconjunctivitis is a common finding too. Sterile corneal stromal necrosis and perforations occur rarely.

Treatment of Established Systemic GVHD

Although many therapeutic options have been used in the management of systemic GVHD, adequate treatment remains challenging. The management is guided by a multidisciplinary approach, including adjustment of systemic immunosuppression. The treatment approach should include multiple strategies (topical and oral medications, surgery, environmental control, and systemic immunosuppression). Communication with the transplantation team is crucial.

Treatment of ocular cGVHD

Treatment is focused on improving surface moisture, eyelid anatomy and function, and decreasing ocular surface inflammation.

Topical lubricants

The traditional treatment for dry eye symptoms consists of topical lubricants. No data is available on the efficacy of specific artificial tears medications in ocular cGVHD.

Topical corticosteroids

Corticosteroids remain essential for controlling active cGVHD. Patients receiving topical corticosteroids should be monitored for adverse effects. In the presence of corneal epithelial defects, stromal thinning, or infiltrates, topical corticosteroids are contraindicated.

Topical cyclosporine A

Not enough data is available on the efficacy of topical cyclosporine emulsion in improving symptoms. Baptista Malta reported a retrospective study with 105 patients, of whom 43 developed ocular cGVHD. They concluded that cyclosporine is helpful in decreasing the incidence and severity of dry eyes in patients if started before the transplant.

Table 1. Organ Scoring of Ocular cGVHD

Score 0	Score 1	Score 2	Score 3
No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricating eye drops ≤3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricating eye drops >3x per day or punctual plugs), without new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain or unable to work because of ocular symptoms or loss of vision due to KCS)

Abbreviations: ADL, activities of daily living; KCS, keratoconjunctivitis sicca.

Topical tacrolimus

Not enough data is available on the efficacy of topical tacrolimus.

Punctal plugs

These patients have a high incidence of spontaneous punctal closure.

Autologous serum eye drops

Administration of serum eyedrops is one of the most effective therapies for symptom relief in our experience. The risk of contamination and subsequent infection are possible complications of autologous serum drops.

Contact lenses

In patients with cGVHD affecting the ocular surface, 2 different types of lenses can be used: bandage soft lens and scleral lens. The fluid-ventilated, gas-permeable scleral lens has been effective in mitigating symptoms and in the treatment of moderate and severe ocular surface disorders of multiple etiologies. The fluid-filled reservoir shields the cornea from blink trauma, noxious environmental stimuli, and inflammatory mediators in the tears. High cost, inadequate fitting, poor tolerance, and discomfort with blinking in the presence of severe meibomian gland disease and keratinization discourage their widespread use. To our knowledge, no comparative prospective study has evaluated differences between available scleral lenses.

Cataract surgery in cGVHD

Posterior subscapular cataracts are common in patients with cGVHD due to radiation exposure and prolonged systemic corticosteroid use. Cataracts are considered the most common cause of decreased vision in patients with cGVHD. Retrospective reviews have shown that patients with cGVHD achieve good visual acuity after cataract surgery with aggressive pre- and postoperative treatment of surface disease. However, despite meticulous preoperative management, complications can still occur, including corneal ulceration with perforation. Shah et al reviewed 10 eyes of 6 patients with severe cGVHD and found 2 patients who developed corneal melt months after surgery. Saboo et al reviewed 62 eyes with cGVHD who underwent surgery and found that 8% developed corneal epithelial defects, which resolved within a week of treatment. Additionally, 6% developed filamentary keratitis, and 16% developed corneal punctate keratitis in the acute postoperative period. Preoperative measurements and imaging should show consistency on surface treatment to improve refractive accuracy.

Vernal Keratoconjunctivitis

Andrea Leonardi MD

Definition and Classification

Vernal keratoconjunctivitis (VKC) is a recurrent or chronic ocular allergic disease that affects mostly children and young adults living in warm climates worldwide. VKC may cause severe inflammation and, potentially, visual disabilities[1,2] and may interfere with the school performance, social interactions, and quality of life (QoL) of affected patients and families. Delays in diagnosis and treatment may have a serious impact on a young patient's QoL even if the disease improves or disappears after puberty. Recurrences in adulthood can be observed after complete remission of the disease. Adult onset of a VKC-like disease can appear as a new entity after puberty or in young adults, with signs and symptoms similar to those typical of VKC in children.

Epidemiology

VKC is a rare disease, with a prevalence in Western Europe of 1.16 to 10.55/10,000 inhabitants,[3] while the mean incidence in one case series was 0.1/10,000 new cases independently of gender and age and in the population up to 15 years of age.[4] Most VKC patients complain of symptoms from early spring to fall, with differences among climate zones. Perennial forms have been reported in approximately 20% of cases.

Clinical Forms and Manifestations

Although associated with asthma, allergic rhinitis, and eczema, VKC is frequently observed as a single entity, with predominant eye symptoms, itching, tearing, mucus discharge, eye irritation, and photophobia. On examination, giant/cobblestone conjunctival papillae and inflammatory limbal infiltrates, punctate epithelial keratitis, corneal erosions/ulcers, and subepithelial scarring can be observed. The disease may present in 3 clinical forms: tarsal, limbal, and mixed form. Large papillae of different shapes and sizes on the upper tarsal conjunctiva characterize the tarsal form, while Trantas dots, infiltrates and papillae on the limbus are typical of the limbal form. The mixed form is characterized by the presence of both forms in the same eye. The limbal and mixed VKC are predominant in Africa, whereas the tarsal phenotype is most frequent in Europe and America.

Corneal ulcer complicated the disease in 15% of patients, 68% of whom were affected by the tarsal form, 20% by the mixed form, and only 11% by the limbal form of VKC.[4] Exacerbations of the disease and acute episodes arise, triggered by allergen exposure or, more frequently, by nonspecific stimuli such as wind, light, and dust.

Various degrees of superficial corneal opacification and neovascularization may result from severe ulcers. Corneal microstructural changes associated with local inflammation have been described also in the absence of clinical signs of corneal involvement by in vivo corneal confocal microscopy.

In the adult form of VKC-like disease, signs and symptoms are similar to those typical of VKC in children, yet adults have a diffuse subepithelial thickening and fibrosis without giant papillae formation seen in the classic tarsal form of VKC in children, and a significantly lower rate of corneal ulcers.

Diagnosis

Through a comprehensive clinical history and ophthalmic examination, VKC is differentiated from other ocular allergic conditions, such as seasonal allergic conjunctivitis, perennial allergic conjunctivitis, atopic keratoconjunctivitis, ocular rosacea in children, and infectious conjunctivitis. While skin test and or specific IgE results may be positive, VKC is not always closely related to allergen exposure, and climate is an equally important factor. Conjunctival scrapings or tear cytology can be useful, revealing increased leukocytes in the conjunctiva, particularly eosinophils.

Evolving Concepts in VKC Pathogenesis

A variety of factors, including environmental allergens, climate, genetic predispositions, imbalance of the innate and adaptive immunities, and endocrine and neuronal factors, seem to be involved in the etiology of VKC. The predilection for males and the common resolution after puberty suggest a role of hormones in the development of VKC; however, the exact mechanisms behind this association are still unknown.

The seasonal incidence, association with other allergic manifestations, high number of tissue mast cells and eosinophils, high levels of total and specific IgE in serum and tears, increased tear levels of mast cell– and eosinophil-derived mediators, and the therapeutic response to mast cell stabilizers in mild cases are all evidence for an allergic, IgE-mediated condition. Nevertheless, the commonly observed lack of one or more of the above-mentioned characteristics confirms that a cellular hypersensitivity is also involved in VKC pathogenesis. Recent transcriptomic data confirmed that besides the prevalence of a type-2 immune response, several genes of the Th17-differentiation family are overexpressed in VKC.[5] VKC is thus classified as both an IgE- and non-IgE allergic disease, with multiple cytokines, chemokines, growth factors, and enzymes involved in the development of the disease.

Management of VKC

Patients and parents should be made aware of the long duration of disease, its chronic evolution and possible complications. Treatment should be based on the duration and frequency of symptoms and the severity of corneal involvement (see Table 1).[6] Mast cell stabilizers and antihistamines are effective for the treatment of mild to moderate forms of VKC. In the most severe cases, topical steroids must be used as rescue medication to reduce conjunctival and corneal inflammation, preferably at pulsed therapy.

Topical immunomodulators such as cyclosporine A (CsA) and tacrolimus can be used in severe VKC. Topical CsA has been proven to be an effective anti-inflammatory and immunomodulator agent for the long treatment of VKC, with significant steroid-sparing effect. CsA has been used at different concentrations (from 2% to 0.05%) and different vehicles. Tacrolimus ointments and creams are also used to treat eyelid dermatitis and can improve conjunctival symptoms. A new formulation as cationic emulsion (CE) 0.1% (1 mg/mL) eye drops is currently the first topical CsA licensed in Europe, Canada, and Asia for the treatment of severe VKC in children from 4 to 18 years of age and in the United States without severity and age limitations. This formulation has been shown to be significantly and clinically effective in reducing signs and symptoms of severe VKC in the short and long terms, with the higher benefit of CsA-CE administered 4 times daily.[7,8]

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Table 1. Practical Management of VKC

Make an accurate diagnosis.
Educate on avoidance of the offending allergens and nonspecific triggers (use sunglasses, hats with visors, and swimming goggles).
Stress the importance of nonpharmacologic treatments (lubricants, lid hygiene, cold compresses).
Recommend taking vacations in suitable climates.
Two or more topical, complementary drugs must be used in combination: mast cell stabilizers + antihistamines or multiple action components.
Recommend an adequate frequency of instillation of topical drugs (4-6 times per day).
Warn against use and abuse of decongestants/vasoconstrictors.
Recommend systemic antihistamines to reduce hyper-reactivity.
Use topical corticosteroid formulations as pulsed therapy (3-5 days) to reduce flare-ups.
Corticosteroids must be used in case of moderate to severe corneal epitheliopathy and ulcers in addition to the antiallergic treatments.
Avoid the continuous use and/or abuse of steroids.
Avoid corticosteroids as first-line treatment of VKC.
Consider topical immunomodulators in case of the frequent use of corticosteroids and/or in cortico-responder patients.
Topical on-label CsA can be considered in moderate to severe VKC and can be steroid sparing.
Removal of corneal plaques is the only surgical procedure recommended in cases of corneal complications.
Specific immune therapy is indicated only if extra-allergic manifestations are also present, when a specific offending allergen is clearly identified and clinically related to ocular manifestations.

Chemical Burns

Management of Ocular Chemical Injuries

Namrata Sharma MD MBBS

Ocular chemical burns are emergent situations that require close observation and intensive management right from the time the patient presents to a cornea specialist. Timely and optimal management of each stage of the injury is essential, since it determines the overall anatomical as well as the functional outcome. These injuries are usually work related, a proportion may be assault-induced, and a large subgroup of these patients are young children who get accidentally affected. Management has to be more aggressive in this subgroup since these patients are in the amblyogenic age group and carry a risk of permanent visual loss. Injury with alkaline agents are the commonest, followed by acids and alcohol-containing substances.

A detailed clinical examination should be done at the time of first presentation, and the severity of ocular surface damage should be assessed and documented in detail. Grading systems—such as the 4-step Roper-Hall classification system, based on the degree of corneal involvement and limbal ischemia, and the 6-step Dua classification system, which includes limbal and bulbar conjunctival involvement—help in prognostication and deciding further treatment strategy.[1,2]

A thorough irrigation of the ocular surface with either isotonic saline or ringer lactate is the first and most essential step in a case of ocular chemical burn. This allows removal of all residual chemical, thereby putting a halt to further destruction of ocular structures. Double eversion of eyelids combined with forniceal sweeping is recommended as it allows removal of tiny solid particles that might get entrapped in the fornices and subtarsal tissues, acting as a nidus for the constant release of chemical agent.

Pharmacologic therapy in the acute phase is primarily aimed to reduce ocular inflammation and promote epithelialization. Our standard medical therapy in a case of acute ocular chemical burn consists of topical corticosteroids to arrest the vicious cycle of inflammation and tissue destruction, broad spectrum antibiotics to prevent superadded infections, topical ascorbate and citrate for promoting stromal healing, antiglaucoma medications, cycloplegics, and preservative-free lubricants. In eyes with severe grade chemical injuries and in cases where the defect fails to heal after an initial observation period of 2 weeks, use of adjuvants such as autologous serum eye drops and umbilical cord serum (UCS) is preferred rather than simple tear substitutes due to the presence of various growth factors that help to promote healing of the ocular surface. In a randomized controlled trial by our group comparing UCS therapy with autologous serum and artificial tears in cases of acute ocular chemical burns, eyes receiving UCS eye drops epithelialized much faster compared to the other 2 groups.[3] A significantly large number of patients in the UCS group had clear corneas at 3 months follow up. In addition, platelet-rich plasma (PRP) has also been tested and used both as topical eye drops and as subconjunctival injections in patients with ocular chemical injuries. Due to a higher concentration of growth factors compared to autologous serum eye drops, this has been found more effective in promoting epithelial healing.

Among the surgical treatment options for acute phase burn management is amniotic membrane transplantation (AMT), which by virtue of its anti-inflammatory properties helps to accelerate ocular surface healing. Placing an amniotic membrane over a bare, inflamed stroma helps in stromal healing and prevents occurrence of melts. Compared to medical therapy alone, combined treatment with AMT and medical therapy in eyes with moderate ocular burns has been shown to result in significantly better epithelial healing.[4,5] We have observed and reported early epithelialization in eyes with severe grade burns, receiving UCS compared to AMT and medical therapy alone in both retrospective[6] and prospective randomized studies.[7] AMT combined with Tenon tissue advancement has also been proposed in cases with compromised limbal vascularity. Advancement of healthy Tenon capsule close to the limbal area helps in re-establishing limbal perfusion, thereby reducing the risk of anterior segment necrosis.[8]

The chronic stage of chemical burns is characterized by limbal stem cell deficiency, usually in association with extensive symblepharon formation and forniceal shortening. Optimization of the ocular surface should be taken as the first step before resorting to any procedure meant for visual rehabilitation. This is especially important in eyes in which a type I keratoprosthesis implantation is planned at a later date, as any amount of symblepharon is going to interfere with the placement of bandage contact lens.[10] The technique of cultivated limbal stem cell transplantation (CLET) involves obtaining a tiny limbal biopsy, either from the healthy contralateral eye or from an allogeneic source in cases of bilateral involvement, followed by expansion of stem cells in a laboratory setup. Favorable outcomes of both autologous and allogeneic CLET have been reported, with stability of ocular surface maintained for as long as 10 years following LSCT.[11-13] Simple limbal epithelial transplantation (SLET), on the other hand, involves direct transplantation of small limbal fragments over a denuded ocular surface, without requiring ex vivo expansion of stem cells. The results of this technique have now been replicated in various single-center and multicentric studies. In eyes with chronic ocular surface burns, SLET has been shown to successfully restore an epithelialized and avascular ocular surface.[14] Allo-SLET has also been performed as a means to achieve rapid epithelialization and prevent extensive long-term sequelae in eyes with acute phase chemical burns. The retrospective study by Iyer et al showed successful re-epithelialization in 94% of their study eyes with severe grade chemical burns, after a mean interval of 22 days, with reduced rates of symblepharon formation. This was found to be shorter than that reported following transplantation of amniotic membrane graft alone.

Cultivated oral mucosal transplantation (COMET) is yet another surgical technique for LSCT, with reportedly favorable results in eyes with chronic ocular surface burns.[16] The technique involves harvesting an oral biopsy specimen followed by transplantation of cultivated oral mucosal epithelial cell sheets over the denuded ocular surface. This is especially helpful in

patients who have suffered bilateral ocular surface damage and are at high risk for immunosuppressive therapy.

Optimal restoration of ocular surface also ensures favorable outcomes following a future keratoplasty. In a retrospective study by Basu et al, 47 patients with unilateral LSCD following ocular surface burns were treated by autologous CLET and penetrating keratoplasty either simultaneously or as staged procedure.[17] The clinical outcomes favored a staged approach compared to a combined procedure of LSCT and keratoplasty. Continued maintenance of a stable ocular surface with visual improvement has also been reported in pediatric patients undergoing deep anterior lamellar keratoplasty following a prior SLET.[18] Implantation of a keratoprosthesis is another means for visually rehabilitating patients with bilateral severe grade chemical burns, the choice of implant being guided by the wetness of the ocular surface.[19]

Among the various treatment options currently available, no single treatment option can address all types and grades of ocular surface burns. The treatment is individualized based on the stage at which the patients present, often requiring multiple surgical interventions in order to restore ocular surface homeostasis. Treatment options aimed at promoting regeneration of ocular tissues affected by primary insult, such as bone marrow–derived mesenchymal stem cell therapy, hold promise for the future.[20]

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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Chie Sotozono MD

Stevens-Johnson syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), are acute inflammatory disorders that affect the skin and mucous membranes. Both can affect anyone, and at any age, usually as the result of an adverse drug reaction. The mortality rate in cases of SJS and TEN is very high, ie, 1%-5% and 25%-35%, respectively. Moreover, ocular involvement is often easily overlooked in patients afflicted with SJS/TEN, primarily due to the serious general symptoms and the high lethality of these two diseases.

In SJS/TEN patients, ocular surface inflammation develops rapidly at the acute phase of the disease, and the extensive inflammation is often accompanied by pseudo-membranous formation and corneal and/or conjunctival epithelial defects. Of note, following the acute phase of SJS/TEN, the common course of the disease includes persistent epithelial defects (PED). Moreover, once corneal epithelial stem cells are lost at the acute stage of SJS/TEN, the corneal epithelium does not regenerate, thus resulting in conjunctival epithelial invasion into the cornea (ie, conjunctivalization) and cicatricial changes of the ocular surface. Permanent visual impairment or blindness remains and conjunctival inflammation is prolonged at the chronic phase.

I. Acute Phase
   - A. Epidemiology
   - B. Systemic findings
   - C. Ocular involvement
   - D. Risk factors of ocular sequelae
   - E. Management
     1. Systemic treatment
        - a. Corticosteroid pulse-dose and high-dose glucocorticoids
        - b. Intravenous immunoglobulin therapy
        - c. Plasmapheresis
        - d. Cyclosporine
        - e. Other
     2. Topical ocular treatment
        - a. Betamethasone eye drops
        - b. Antibiotics
     3. Surgical intervention
        - a. Amniotic membrane transplantation
        - b. Cultivated oral mucosal epithelial transplantation

II. Chronic Phase
   - A. Ocular sequelae
     1. Visual acuity loss
     2. Dryness of the eye
   - B. Ocular manifestations
     1. Lid involvement
     2. Conjunctival involvement
     3. Corneal involvement
     4. Bacterial flora
   - C. Management
     1. Medical treatment
        - a. Dry eye therapy
        - b. Anti-inflammatory agents
        - c. Antibiotics
     2. Surgical
        - a. Lid surgery
        - b. Mucous membrane grafting
        - c. Amniotic membrane transplantation
        - d. Cultivated oral mucosal epithelial transplantation
        - e. Keratoprosthesis
     3. Contact lens therapy
        - a. Scleral contact lens
        - b. Limbal-supported contact lens

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Limbal Stem Cell Deficiency

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NOTES

Corneal Cystinosis

Multimodality Imaging Analysis

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Introduction

As a rare lysosomal storage disease caused by the mutations of the cystinosin (CTNS) gene (17p13) coding for cystinosin, cystinosis is characterized by the accumulation of cystine crystals in all tissues, including brain, kidney, bone, and eyes.[1,2] The crystals can be observed in all the ocular structures: cornea, conjunctiva, anterior chamber, iris, choroid, retina, and even the optic nerve, and later induce severe complications.[3-5] The cornea has been named the "window of cystinosis" for its direct visibility of the hyperreflective crystal by slit lamp, sometimes even before the nephrologists' diagnosis of cystinosis.

Background Observations

Using direct slit-lamp examinations, the established Gahl score varies from 0 to 3, allowing for a semiquantitative analysis in the cornea crystals.[6] In recent years, anterior segment OCT (AS-OCT) and in vivo confocal microscopy (IVCM) were developed by our team for directly detecting corneal cystinosis at cellular levels by showing the feasibility of using the multimodal imaging system to investigate corneal cystinosis.[7-10] This multimodal analysis demonstrated the mechanisms of photophobia symptoms due to the presence of crystals, the corneal inflammation, and the corneal nerve damage during corneal cystinosis.[8] It would help to develop clinical trials for more effective local cysteamine eyedrops for treating corneal cystinosis, such as cysteamine gel formulation at the concentration of 0.55%.[9]

Case Presentations

Without appropriate management, the symptoms and signs worsened for the cystinosis patients. The photophobia symptoms increased with age, and the thickness of the crystals increased with age, as demonstrated directly by AS-OCT cystinosis thickness analysis and IVCM cystinosis scores. Severe corneal complications developed, such as corneal neovascularization, recurrent ulcer, bandelette keratopathy, and lastly blindness, and these were difficult to treat even by complicated corneal surgery, such as corneal graft.

Pro/Con Debates

Without a traumatic renal biopsy, the multimodal imaging system combining slit lamp, AS-OCT, and IVCM at the cellular level reflected a real advancement in our understanding of nephropathic cystinosis. We proposed treatment by cysteamine eyedrops as early as possible, even at the age of the 6 months. The treatment of the corneal cystinosis included not only the cysteamine eyedrops but also all cystinosis-associated corneal diseases. Lastly, to propose a better management of this rare pathology, as the specialist in analyzing "the window of cystinosis," the ophthalmologist has the duty to closely collaborate with the nephrologist, which requires a multidisciplinary group and communication with the patient, the family, and all medical groups.[10,11]

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Corneal Graft Delivery Devices

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NOTES

Novel Dry Eye Treatments

Gerami Seitzman MD

I. Lotilaner Ophthalmic Solution, 0.25%

A. Safety and efficacy of lotilaner ophthalmic solution, 0.25% for the treatment of blepharitis due to demodex infestation: a randomized, controlled, double-masked clinical trial[1]

B. Phase 2, randomized, controlled, double-masked clinical trial

C. 60 eligible participants with *Demodex* blepharitis were randomly assigned in a 1:1 ratio to receive either topical lotilaner ophthalmic solution 0.25% or control.

D. Study was conducted at the Asociación para Evitar la Ceguera en México I.A.P., Mexico City, Mexico.

E. Inclusion criteria: More than 10 collarettes present on the upper eyelid, at least mild lid margin erythema, and *Demodex* density of ≥1.5 mites per lash

F. Definition of "collarettes," "sleeves," and "scurf" will be reviewed.

G. One drop in each eye twice a day, morning and evening. Treatment was discontinued at Day 28.

H. "Improvement in collarette grade and mite density observed during the treatment period" in the medicated group, and this effect persisted for at least 2 months.

I. Clinically meaningful collarette cure (10 or fewer collarettes on the upper eyelid of the analysis eye) was achieved in 87.5% of subjects in the study group (21/24) at Day 28, compared to 22.2% (6/27) in the control group ($P < .001$).

J. Mite eradication (mite density of 0) was achieved in 66.7% of eyes in the study group at Day 28, compared to 25.9% in the control group ($P = .005$).

K. "The presence of collarettes is considered a pathognomonic sign of *Demodex* blepharitis." However, classic external disease teaching indicates the presence of sleeves is pathogenetic for *Demodex* and collarettes are pathognomonic for staphylococcal blepharitis.

II. Varenicline Nasal Spray

A. Efficacy and safety of OC-01 (varenicline solution) nasal spray on signs and symptoms of dry eye disease: the ONSET-2 Phase 3 randomized trial[2]

B. Randomized, multicenter, double-masked, vehicle-controlled, Phase 3 study

C. Patients ($N = 758$) were randomized in a 1:1:1 ratio to twice-daily treatment with 50-µl intranasal spray in each nostril of 0.03 mg ($n = 260$), 0.06 mg ($n = 246$), or vehicle (control; $n = 252$) for 4 weeks.

D. Inclusion criteria

1. Ocular Surface Disease Index score of 23 or more and
2. Schirmer test with anesthesia of 10 mm or less

E. Percentage of patients who had >10 mm on Schirmer test

1. 47.3% for the 0.03-mg group
2. 49.2% for the 0.06-mg group
3. 27.8% for the vehicle group

F. Improvement in the Eye Dryness Score (EDS), a 100-point scale of subjective discomfort

1. 20 points in the 0.03-mg group
2. 22 points in the 0.06-mg group
3. 15 points in the vehicle group

G. Sneezing

1. 95% of the 0.03-mg group
2. 97% of the 0.06-mg group
3. 29% of the vehicle group

H. Coughing

1. 19% of the 0.03-mg group
2. 22% of the 0.06-mg group
3. 2% of the vehicle group

I. Nasal route of administration is advantageous for avoidance of the ocular surface.

III. KPI-121 Ophthalmic Suspension 0.25% = EYSUVIS (Loteprednol Etabonate Ophthalmic Suspension) 0.25%

A. Safety of KPI-121 ophthalmic suspension 0.25% in patients with dry eye disease: a pooled analysis of 4 multicenter, randomized, vehicle-controlled studies[3]

B. Mucus-penetrating particles (MPP) technology evades the entrapment of drug particles by mucins.

C. 1430 subjects received KPI-121 0.25% q.i.d., and 1438 subjects received vehicle drops q.i.d. for 2 weeks.

D. "Significantly reduced signs and symptoms of DED compared with its vehicle"

E. At time of outline submission (June 2022), only the safety publication is publicly available, with publications detailing dry eye outcome efficacy not yet available. Will review details at meeting if this is updated.

F. EYSUVIS preservative: benzalkonium chloride 0.01%

IV. On the Horizon

A. NOV03 = inert and anhydrous semifluorinated alkane perfluorohexyloctane (F6H8)

1. Interacts with the lipophilic part of the tear film, preventing evaporation of the tears; may enter meibomian glands and dissolve meibum, and cools ocular surface

2. Randomized clinical study (SEECASE) to assess efficacy, safety, and tolerability of NOV03 for treatment of dry eye disease[4]

3. Improvements in corneal staining and VAS Dryness Score are reported.

B. AZR MD 001

1. An ophthalmic ointment being developed by Azura Ophthalmics

2. Contains selenium sulfide, a keratolytic agent

3. Other keratolytic agents are used to treat dermatological conditions involving hyperkeratinization.

4. One pathogenic mechanism in MGD is believed to include hyperkeratinization of the gland orifice.

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Mask-Associated Dry Eye Syndrome

Natalie Afshari MD

Face masks have been commonly used during the COVID pandemic. Health-care workers have been particularly impacted by the substantial increase in prolonged mask wear. Throughout the pandemic, many ophthalmologists have seen an increase in ocular dryness symptoms among mask users, introducing terms such as "mask-associated dry eye" or "MADE." We have studied mask-associated dry eye syndrome among 50 healthcare workers and have found mask use to be associated with increased ocular surface disease index (OSDI) and decreased tear breakup time (TBUT), possibly due to tear film evaporation. In this presentation we will review the literature and up-to-date evidence on masks leading to dry eye.

Selected Readings

1. Moshirfar M, West WB Jr, Marx DP. Face mask-associated ocular irritation and dryness. *Ophthalmol Ther*. 2020; 9(3):397-400.
2. White DE. BLOG: MADE: a new coronavirus-associated eye disease. Healio Ophthalmology. https://www.healio.com/news/ophthalmology/20200622/blog-a-new-coronavirusassociated-eye-disease. June 22, 2020.
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5. Scalinci SZ, Pacella E, Battagliola ET. Prolonged face mask use might worsen dry eye symptoms. *Indian J Ophthalmol*. 2021; 69(6):1508-1510.
6. Krolo I, Blazeka M, Merdzo I, Vrtar I, Sabol I, Petric-Vickovic I. Mask associated dry eye during COVID-19 pandemic: how face masks contribute to dry eye symptoms. *Med Arch*. 2021; 75(2):144-148.

Deep Learning and Artificial Intelligence in Ophthalmology

Daniel Shu Wei Ting MD PhD

The advent of computer graphic processing units, improvement in mathematical models, and availability of big data have allowed artificial intelligence (AI) using machine learning (ML) and deep learning (DL) techniques to achieve robust performance for broad applications in social-media, the internet of things, the automotive industry, and health care. DL systems in particular provide improved capability in image, speech, and motion recognition, as well as in natural language processing. In medicine, significant progress of AI and DL systems has been demonstrated in image-centric specialties such as radiology, dermatology, pathology, and ophthalmology. New studies, including preregistered prospective clinical trials, have shown DL systems are accurate and effective in detecting different eye diseases, including diabetic retinopathy, glaucoma, cornea diseases, etc. This talk will cover the basic principles of AI and DL application in ophthalmology, emerging domains, and future directions.

Corneal Regeneration

May Griffith PhD

I. Transplantation With Donor Corneas
   A. Only widely accepted treatment for corneal blindness
   B. There is a huge shortage in most countries, leaving an estimated 12.7 million patients on waiting lists, with 1 corneal tissue available for every 70 patients in need of surgery.
   C. Even if donated corneas were readily available, patients with inflammation and severe pathologies may be at high risk of graft failure or rejection.

II. Regenerating Human Cornea
   A. Use of cell-free, bioresponsive materials that mimic the collagenous extracellular matrix of the cornea
   B. In situ tissue regeneration by stimulating endogenous progenitor cells to affect regeneration

III. First-in-Human Successful Regeneration of the Human Cornea
   A. Clinical trial of 10 patients in early feasibility study
   B. Patients given anterior lamellar keratoplasty (ALK) with recombinant human collagen implant
   C. No rejection over 4 years; 1 rejection episode in control PK group
   D. Regeneration of epithelium, stroma, and corneal nerves
   E. No activation of dendritic cells in regenerated neocorneas; activated dendritic cells in allograft controls
   F. Problems with astigmatism due to soft implants and overlying sutures

IV. Successful Stable Regeneration of High-Risk Corneas
   A. Introduction of polymeric network of inflammation suppressing phosphorylcholine
   B. Clinical trial of 6 patients with active ulcers, scars from keratitis
   C. Best outcome in patients with intact corneal limbal stem cells

V. LiQD Corneas Promoting Regeneration
   A. Use of collagen analogs for liquid glue-filler
   B. Self-gelling in situ in 5-10 minutes
   C. Testing in rabbits, cats, minipigs confirms ability to seal perforations, act as alternative to ALK.

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I	Independent Contractor Contracted work, including contracted research.

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