

Cornea Subspecialty Day 2019

Keeping Disease at Bay

Program Directors

Jennifer Y Li MD, Sanjay V Patel MD FRCOphth,
and Sophie X Deng MD PhD

In conjunction with the Cornea Society

Moscone Convention Center
San Francisco, CA
Saturday, Oct. 12, 2019

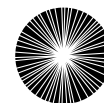
Presented by:
The American Academy of Ophthalmology

Cover photo courtesy of Sophie X Deng MD PhD

Supported by an unrestricted educational grant from Dompé.



Cornea Society
Advancing the treatment of corneal disease



**AMERICAN ACADEMY
OF OPHTHALMOLOGY®**
Protecting Sight. Empowering Lives.

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2019 Cornea Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the Cornea Society, it is our pleasure to welcome you to San Francisco and Cornea Subspecialty Day 2019: Keeping Disease at Bay.



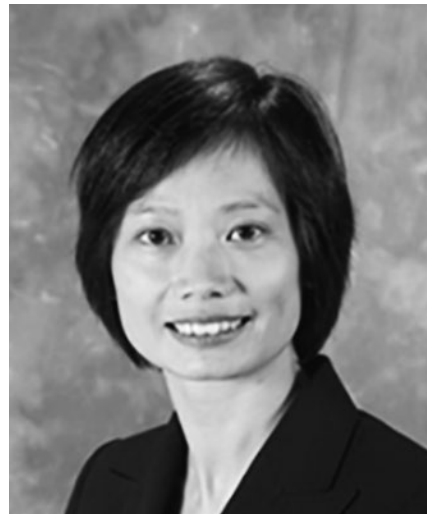
Jennifer Y Li MD
Program Director

None



Sanjay V Patel MD FRCOphth
Program Director

None



Sophie X Deng MD PhD
Program Director

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National Eye Institute, Inc.: S
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CME Credit

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.

2019 Cornea Subspecialty Day Meeting Learning Objectives

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

- Understand current best practices for the management of corneal infections
- Discuss the role of keratoplasty in the management of patients with corneal disease
- Understand the role of imaging and in-office diagnostics in the treatment of corneal disorders
- Provide a rationale for treatment of dry eye and other ocular surface diseases and inflammatory disorders
- List management strategies for patients with keratoconus

2019 Cornea Subspecialty Day Meeting Target Audience

The intended audience for this program is cornea surgeons, comprehensive ophthalmologists with an interest in anterior segment, and allied health personnel who are performing or assisting with cornea surgery.

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.

Scientific Integrity and Disclosure of Conflicts of Interest

The American Academy of Ophthalmology is committed to ensuring that all continuing medical education (CME) information is based on the application of research findings and the implementation of evidence-based medicine. It seeks to promote balance, objectivity, and absence of commercial bias in its content. All persons in a position to control the content of this activity must disclose any and all financial interests. The Academy has mechanisms in place to resolve all conflicts of interest prior to an educational activity being delivered to the learners.

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The American Academy of Ophthalmology considers presenting authors, not coauthors, to be in control of the educational content. It is Academy policy and traditional scientific publishing and professional courtesy to acknowledge all people contributing to the research, regardless of CME control of the live presentation of that content. This acknowledgement is made in a similar way in other Academy CME activities. Though they are acknowledged, coauthors do not have control of the CME content and their disclosures are not published or resolved.

2019 Cornea Subspecialty Day CME Credit

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

The Academy designates this live activity for a maximum of 7 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Attendance Verification for CME Reporting

Before processing your requests for CME credit, the Academy must verify your attendance at AAO 2019 and/or Subspecialty Day. Badges are no longer mailed before the meeting. Picking up your badge onsite will verify your attendance.

Badge Scanning and CME

Getting your badge scanned does not automatically grant CME credit. You still need to record your own educational activities.

NOTE: You should claim only the credit commensurate with the extent of your participation in the activity.

CME Credit Reporting

Onsite, report credits earned during Subspecialty Day and/or AAO 2019 at CME Credit Reporting kiosks located in South Lobby, West Lobby, and in the Academy Resource Center, West Booth 7337.

Registrants whose attendance is verified at AAO 2019 will receive an email on **Monday, Oct. 14**, with a link and instructions on how to claim credit online. Attendees can use this link to report credits until **Wednesday, Oct. 30**.

Starting **Thursday, Nov. 14**, attendees can claim credits online through the Academy's CME web page, aao.org/cme-central.

Academy Members

The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2019 credits entered at the American Academy of Ophthalmology's annual meeting will be available to Academy members through the Academy's CME web page beginning **Thursday, Nov. 14**.

The Academy transcript cannot list individual course attendance. It will list only the overall credits claimed for educational activities at Subspecialty Day and/or AAO 2019.

Nonmembers

The American Academy of Ophthalmology provides nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity. To obtain a printed record of your credits, claim CME credits onsite at the CME Credit Reporting kiosks. Nonmembers choosing to claim credits online through the Academy's CME web page after Nov. 14 will have one opportunity to print a certificate.

Proof of Attendance

The following types of attendance verification are available during AAO 2019 and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

- CME credit reporting/proof-of-attendance letters
- Onsite registration receipt
- Instruction course and session verification

You must have obtained your proof of attendance at the CME Credit Reporting kiosks onsite located in South Lobby, West Lobby, and in the Academy Resource Center, West Booth 7337.

Faculty



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Philadelphia, PA



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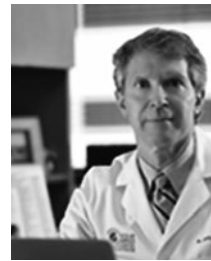
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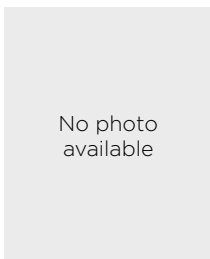
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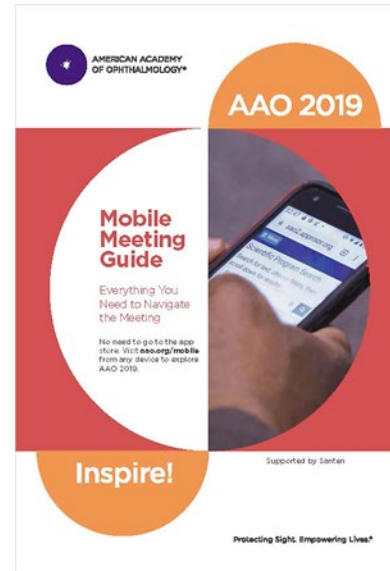


Maria A Woodward MD MS
Ann Arbor, MI

Ask a Question and Respond to Polls Live During the Meeting Using the Mobile Meeting Guide

To submit an answer to a poll or ask the moderator a question during the meeting, follow the directions below.

- Access at www.aao.org/mobile
- Select Program, Handouts & Evals
- Filter by Meeting – Cornea Meeting
- Select Current Session
- Select “Interact with this session (live)” link to open a new window
- Choose “Answer Poll” or “Ask a Question”



Cornea Subspecialty Day 2019: Keeping Disease at Bay

In conjunction with the Cornea Society

SATURDAY, OCT. 12, 2019

7:00 AM CONTINENTAL BREAKFAST

8:00 AM Welcome and Introductions
Jennifer Y Li MD
Sanjay V Patel MD FRCOphth
Sophie X Deng MD PhD*

Section I: Bent Out of Shape—Ectasia Update

Moderator: Sanjay V Patel MD FRCOphth

8:02 AM	Introduction: A Corneal Curiosity	Ivan R Schwab MD FACS	
8:04 AM	Imaging Keratoconus: Are We Progressing?	Michael W Belin MD*	1
8:12 AM	Crosslinking: Achieving Maximum Effect for Keratoconus	Vishal Jhanji MD	5
8:20 AM	Rigid Lenses: Expanding Options	Deborah S Jacobs MD*	6
8:28 AM	PK or DALK for Keratoconus: Do Long-term Outcomes Differ?	Bruce Allan MD*	7
8:36 AM	Management of Pediatric Keratoconus	Asim Ali MD*	8
8:44 AM	Managing Post-LASIK and Other Ectasias	Maria A Woodward MD MS*	9
8:52 AM	Interactive Case Presentation: Crosslinking	Anthony J Aldave MD*	10
9:02 AM	Panel Discussion		

Section II: Dry Eye/Ocular Surface Disease

Moderator: Sophie X Deng MD PhD*

9:12 AM	Introduction: A Corneal Curiosity	Christopher John Murphy DVM PhD	
9:14 AM	Management of Meibomian Gland Disease: Pulsing or Probing?	Joanne F Shen MD	11
9:22 AM	Update on the Medical and Surgical Management of Dry Eye Disease	Audrey R Talley Rostov MD*	13
9:30 AM	Diagnosis and Management of Neurotrophic Keratopathy	Francisco C Figueiredo MD PhD	14
9:38 AM	Diagnosis and Staging of Limbal Stem Cell Deficiency: What Did We Agree On?	Friedrich E Kruse MD*	16
9:46 AM	Management of Ocular Cicatricial Diseases: A Stepwise Approach	Clara C Chan MD*	18
9:54 AM	Managing Lump, Bumps, and Dumps on the Cornea	Christopher J Rapuano MD*	19
10:02 AM	Interactive Case Presentation: Is It Dry or Not Dry?	Anat Galor MD*	21
10:10 AM	Panel Discussion		
10:20 AM	Are You AT the Table or ON the Menu?	Stephanie J Marioneaux MD	22
10:25 AM	REFRESHMENT BREAK and AAO 2019 EXHIBITS		

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Section III: Infectious Keratitis

Moderator: Jennifer Y Li MD

10:55 AM	Introduction: A Corneal Curiosity	Sara M Thomasy DVM PhD	
10:57 AM	If Only It Were Simple: Managing Herpes Simplex Keratitis	Charles C Lin MD	24
11:05 AM	I'm Not Throwing Away My Shot! Management of Herpes Zoster	Sonal S Tuli MD	25
11:13 AM	Beating Back Bacterial Keratitis	Jennifer R Rose-Nussbaumer MD	26
11:21 AM	Fighting Fungal Keratitis	Namrata Sharma MD MBBS	27
11:29 AM	Not a Canned Approach: Management of Acanthamoeba Keratitis	Elmer Y Tu MD*	28
11:37 AM	Confocal Microscopy as a Diagnostic Tool for Infectious Keratitis	Pedram Hamrah MD*	29
11:45 AM	Don't Cross Me! Crosslinking for Infectious Keratitis	José Gomes MD*	30
11:53 AM	Interactive Case Discussion: Consider This Challenging Corneal Infection	Jessica B Ciralsky MD*	31
12:01 PM	Panel Discussion		
12:11 PM	LUNCH and AAO 2019 EXHIBITS		

Section IV: Keratoplasty and Keratoprosthesis

Moderator: Sanjay V Patel MD FRCOphth

1:26 PM	Introduction: A Corneal Curiosity	Sara M Thomasy DVM PhD	
1:28 PM	Practical Imaging Before and After Keratoplasty	Dipika V Patel MRCOphth PhD	32
1:36 PM	EK + DALK ≠ Panacea: When I Still Turn to PK	Mark A Terry MD*	34
1:44 PM	EK Alphabet Soup: Which Flavor to Choose?	Marjan Farid MD*	36
1:52 PM	Endothelial Graft Failure: Options and Outcomes?	Francis W Price Jr MD*	37
2:00 PM	Avoiding Keratoplasty: Descemet Stripping Only	Kathryn A Colby MD PhD*	38
2:08 PM	Keratoprosthesis Update: Indications and Long-term Outcomes	Geetha K Iyer MBBS	39
2:16 PM	Interactive Case Presentation: Choose Your Own Keratoplasty Adventure	Marian Sue Macsai-Kaplan MD*	40
2:24 PM	Panel Discussion		

Section V: Anterior Segment Tumors

Moderator: Jennifer Y Li MD

2:34 PM	Introduction: A Corneal Curiosity	Ivan R Schwab MD FACS	
2:36 PM	Is Tissue Still the Issue? Anterior Segment Imaging for Management of Ocular Surface Tumors	Carol L Karp MD	41
2:44 PM	Ocular Surface Squamous Neoplasia: Topical vs. Surgical Treatment for OSSN	Fairooz Puthiyapurayil Manjandavida MD	42
2:52 PM	There's Something Fishy Here: Diagnosis and Management of Lymphoproliferative Lesions	Bitá Esmali MD FACS	46
3:00 PM	Panicking Over Pigment: Management of Conjunctival Pigmented Lesions	Lauren A Dalvin MD	47
3:08 PM	Management of Pigmented Iris Lesions: When Should I Worry?	Carol L Shields MD*	48
3:16 PM	Interactive Case Discussion: It's Not a Too-mah ... Or Is It?	Shahzad I Mian MD*	50
3:24 PM	Panel Discussion		
3:34 PM	REFRESHMENT BREAK and AAO 2019 EXHIBITS		

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Section VI: Inflammatory Diseases of the Cornea

Moderator: Sophie X Deng MD PhD*

4:04 PM	Introduction: A Corneal Curiosity	Christopher John Murphy DVM PhD	
4:06 PM	Is This Infection or Peripheral Ulcerative Keratitis?	Natalie A Afshari MD*	51
4:14 PM	Scleral Melt: Too Hot to Patch?	Victor L Perez MD*	52
4:22 PM	What's New in Topical Anti-inflammatory Agents / Management of Atopic and Vernal Conjunctivitis	Stephen C Pflugfelder MD*	53
4:30 PM	Biologics: Are They Any Good for Ocular Inflammation?	Debra A Goldstein MD*	55
4:38 PM	Interstitial Keratitis: What Is the Best Treatment?	Roni M Shtein MD	56
4:46 PM	Interactive Case Discussion: Not Your Typical Red Eye	Deepinder K Dhaliwal MD*	57
4:54 PM	Panel Discussion		
5:04 PM	Closing Remarks	Jennifer Y Li MD Sanjay V Patel MD FRCOphth Sophie X Deng MD PhD*	

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Imaging Keratoconus: Are We Progressing?

Details on ABCD Progression Display

Michael W Belin MD

Table 1. ABCD Keratoconus Classification/Grading

ABCD Criteria	A	B	C	D
	ARC (3-mm zone)	PRC (3-mm zone)	Thinnest pachymetry (μm)	BDVA
Stage 0	>7.25 mm (<46.5 D)	>5.90 mm	>490 μm	$\geq 20/20$ (≥ 1.0)
Stage I	>7.05 mm (<48.0 D)	>5.70 mm	>450 μm	<20/20 (<1.0)
Stage II	>6.35 mm (<53.0 D)	>5.15 mm	>400 μm	<20/40 (<0.5)
Stage III	>6.15 mm (<55.0 D)	>4.95 mm	>300 μm	<20/100 (<0.2)
Stage IV	<6.15 mm (>55.0 D)	<4.95 mm	≤ 300 μm	<20/400 (<0.05)

Abbreviations: ARC, anterior radius of curvature; PRC, posterior radius of curvature.

The ABCD classification is measured at the cone.

- A: Anterior radius of curvature from a 3.0-mm zone centered on thinnest point
- B: Posterior (back) radius of curvature from a 3.0-mm zone centered on the thinnest point
- C: Minimal corneal thickness (not apical)
- D: Best spectacle-corrected visual acuity



Figure 1. Belin KCN Progression display II.

Graphical Display of ABCD Parameters

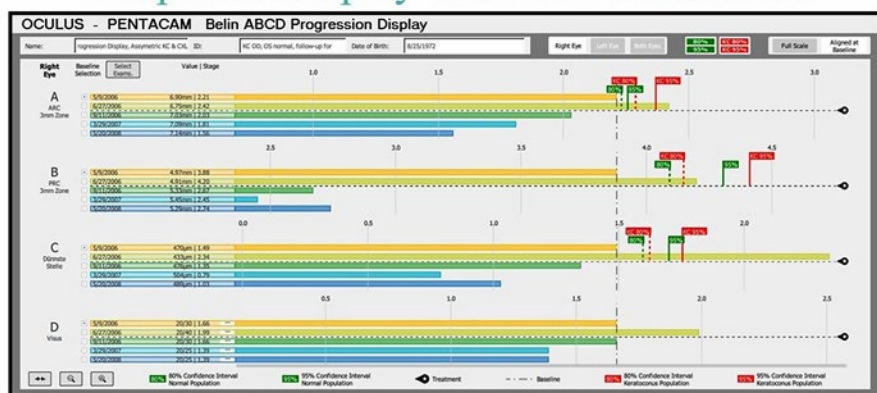


Figure 2. Graphical display of ABCD parameters (top), tabular format other progression parameters (bottom).

Tabular Format Other Progression Parameters

R	Date / Hour	Classification	Bed D	Prog Index Avg	ABTmax	K Max (D)	Q (VF) (Dmm)	Q (VF) (Dmm)	ISV	ISA	ISA	ISD	QS	Treatment
1	5/6/2006 12:25 PM	A2 B0 C1 D0	7.78	2.27	126	55.4	-0.78	-0.82	77	0.80	31.0	0.124	✓	
2	4/27/2006 10:21 AM	A2 B4 C2 D0	8.29	2.30	100	58.7	-1.17	-1.01	85	0.74	32.4	0.133	✓	
3	8/11/2006 14:53 PM	A1 B2 C0 D0	6.50	1.77	177	54.0	-0.69	-0.58	77	0.89	41.3	0.127	✓	
4	1/26/2007 1:56 PM	A1 B2 C0 D0	6.44	1.62	186	52.1	-0.30	-0.44	79	1.01	60.6	0.124	✓	
5	5/20/2008 9:20 AM	A1 B2 C0 D0	6.96	1.95	154	52.0	-0.64	-0.52	67	0.74	33.6	0.115	✓	

R	Date / Hour	Classification	Bed D	Prog Index Avg	ABTmax	K Max (D)	Q (VF) (Dmm)	Q (VF) (Dmm)	ISV	ISA	ISA	ISD	QS	Treatment
1	5/6/2006 12:25 PM	A2 B0 C1 D0	7.78	2.27	126	55.4	-0.78	-0.82	77	0.80	31.0	0.124	✓	
2	4/27/2006 10:21 AM	A2 B4 C2 D0	8.29	2.30	100	58.7	-1.17	-1.01	85	0.74	32.4	0.133	✓	
3	8/11/2006 14:53 PM	A1 B2 C0 D0	6.50	1.77	177	54.0	-0.69	-0.58	77	0.89	41.3	0.127	✓	
4	1/26/2007 1:56 PM	A1 B2 C0 D0	6.44	1.62	186	52.1	-0.30	-0.44	79	1.01	60.6	0.124	✓	
5	5/20/2008 9:20 AM	A1 B2 C0 D0	6.96	1.95	154	52.0	-0.64	-0.52	67	0.74	33.6	0.115	✓	

Figure 3. Graphical display: identify baseline and treatment (top); choose comparison population (bottom).

Identify Baseline & Treatment



Choose Comparison Population
(Defaults to Both)

Figure 4. Comparison results, normal vs. keratoconus population.

Normal Population



Keratoconus Population



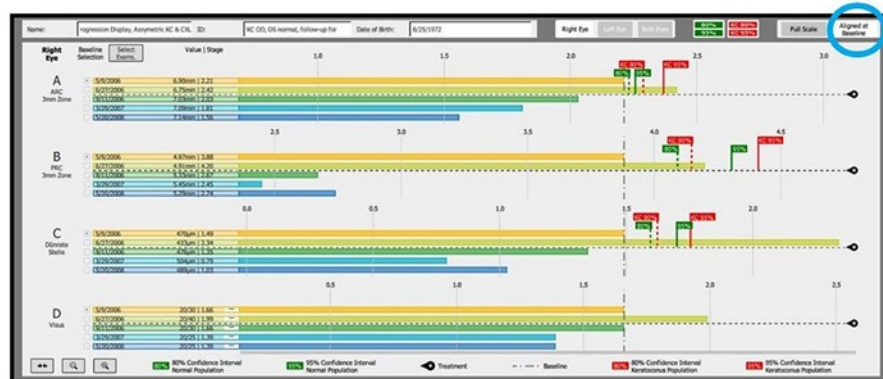


Figure 5. Aligned at baseline is best for determining progression—maximizes separation of the confidence intervals at the expense of losing the relative anatomical grading.

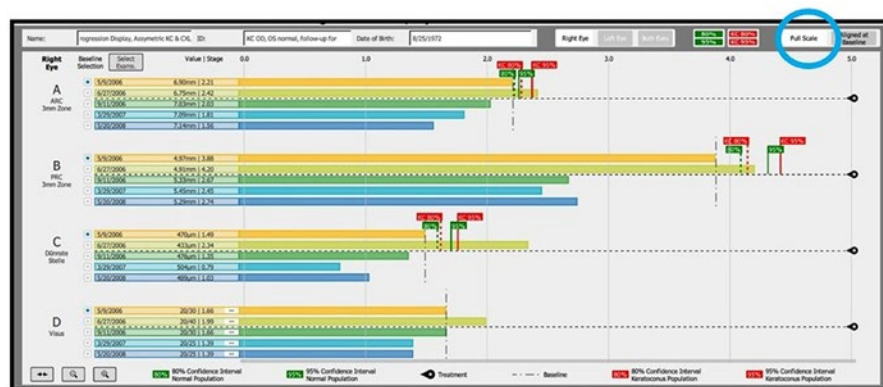


Figure 6. Full scale maintains the anatomical grading at the expense of confidence interval spacing.

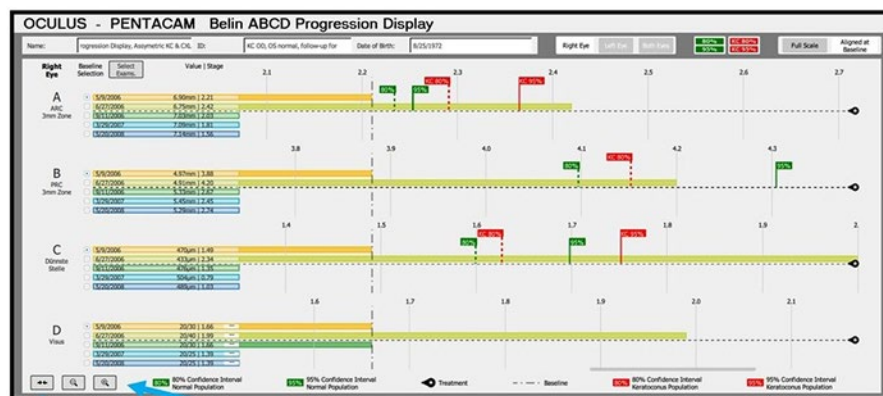


Figure 7. Ability to magnify areas of interest.

Combining Features Full Scale Plus Magnification



Figure 8. Combining features/full-scale plus magnification.



Figure 9. Bilateral display.



Figure 10. Features of Belin ABCD Progression II: confidence intervals removed after treatment.

Crosslinking: Achieving Maximum Effect for Keratoconus

Vishal Jhanji MD

Introduction

Collagen crosslinking is an established surgical intervention for progressive keratoconus. Multiple studies have shown that crosslinking is both safe and efficacious for keratoconus patients in all age groups. The U.S. Food and Drug Administration approved the conventional crosslinking technique. However, a multitude of alternative surgical protocols have been described. Furthermore, keratoconus corneas can respond differently in terms of keratometric flattening and improvement in visual acuity after crosslinking.

Observations

Previous studies have correlated severity of keratoconus and success rate of crosslinking. It has been observed that steep corneas show pronounced flattening after crosslinking. This is also true for transepithelial collagen crosslinking during which the corneal epithelium is retained. Other studies reported older age, thinner corneal pachymetry, and central cones to be associated with more flattening in keratometry.

This presentation will discuss the factors associated with maximum crosslinking effect in keratoconus corneas.

Rigid Lenses: Expanding Options

Deborah S Jacobs MD

- I. Specialty Contact Lens: A Growth Area in the Global Contact Lens Industry
- II. Expanding Number of Categories
 - A. RGP cornea → KC designs
 - B. “Sclerals”
 - 1. Anything “not corneal”
 - 2. Diameter and fit definitions
 - a. Corneoscleral/interpalpebral
 - i. Corneal touch
 - ii. Gross movement
 - iii. No seal
 - b. Miniscleral
 - i. Little movement
 - ii. Generally seals/settles/suction
 - c. True or full scleral
 - i. Sealing vs. fluid ventilated
 - ii. Bigger is better: Go larger to avoid seal.
 - C. PROSE (prosthetic replacement of the ocular surface ecosystem): A medical model
 - D. Innovations in design and manufacture
 - 1. Molding to 3-D printing: EyePrint Pro
 - 2. Image guided design and fit
 - 3. Wavefront-guided/-optimized optics
- III. Outcomes
 - A. Bigger is better. Size matters.
 - B. There is no cone that cannot be fit.
 - C. Scleral lens is an option after hydrops.

- IV. New Paradigm for Contact Lens in Keratoconus
 - A. Not a “contact lens failure” without trial of “true” scleral lens > 18 mm
 - B. PROSE treatment: An innovative approach to accommodate any cone
 - C. Penetrating or lamellar keratoplasty only for axial opacity limiting vision (in specialty lens)
 - D. No regrant for cylinder or recurrence of ectasia without trial of specialty lens

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PK or DALK for Keratoconus: Do Long-term Outcomes Differ?

Bruce Allan MD

In a recent global survey, 27% of all corneal transplants were performed for keratoconus.¹ Penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK) are the main forms of corneal transplantation used in cases of advanced keratoconus where patients are unsuccessful with contact lenses.^{2,3} Both procedures are relatively safe and effective. DALK preserves the host endothelium, eliminating endothelial rejection and dramatically reducing the risk of endothelial failure—the leading cause of graft failure after PK.^{4,5} Despite this apparent clear advantage, PK remains the most commonly performed type of keratoplasty for advanced keratoconus worldwide.¹

Corneal transplant failure is defined by repeat surgery or irreversible loss of transplant clarity.² While endothelial failure is unusual after DALK, primary failure (secondary to a persistent double anterior chamber) and stromal or interface scarring (secondary to transplant rejection) may be relatively common.^{2,6,7} Earlier case series and nonrandomized comparisons summarized in a 2011 American Academy of Ophthalmology report⁴ and limited randomized controlled trial evidence⁸ suggest similar graft survival and visual outcomes for PK and DALK in keratoconus. But recent corneal transplant registry reports from Australia² and the UK⁶ indicate that PK is superior to DALK in terms of corrected distance visual acuity (CDVA) and graft survival. These studies do not review recent data. Jones et al⁶ report results from the UK up to 2005. Coster et al² report on grafts performed in Australia between 1999 and 2012, but they include only a relatively low proportion of DALK cases, mostly performed later in the review period. The understanding of DALK techniques, and Descemet membrane-baring DALK techniques in particular, has evolved significantly since then.

Recent reports^{5,9} from relatively high-volume single-surgeon series using Descemet membrane-baring DALK techniques suggest lower graft failure rates in DALK for keratoconus (<3%) than indicated by Australian (12%)² or UK (8%)⁶ registry studies. Our own recent multisurgeon results at Moorfields¹⁰ also demonstrate lower graft failure rates in DALK.

This presentation will examine changing techniques in DALK for keratoconus and ask whether a tipping point has now been reached.

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Management of Pediatric Keratoconus

Asim Ali MD

I. Keratoconus (KC) in Children

- A. Can present as early as age 4
- B. Associated with trisomy 21, Turner syndrome, vernal keratoconjunctivitis, eye rubbing, Leber congenital amaurosis
- C. More severe disease at presentation (Amsler-Krumeich grade 3-4), with faster progression than in adults

II. Diagnosis

- A. Diagnostic criteria same as in adults
- B. Obtaining reliable topography/tomography needs experienced staff.
- C. If suspected, follow closely (every 3 months) due to risk of progression

III. Corneal Crosslinking (CXL) in Children

- A. FDA approved for treatment in patients above age 14
- B. Criteria for treatment
 1. Criteria for progression and diagnosis vary between studies.
 2. Many authors advocate treatment after diagnosis, without waiting for progression.
 3. Minimum corneal thickness: Usually 400 microns in most studies, but down to 350 microns described with use of hypo-osmolar riboflavin
- C. Multiple techniques described in children
 1. Epithelium-on vs. epi-off: Mixed results, with comparative studies showing either equivalence or inferiority of epi-off technique. Perez-Straizota et al¹ recommend epi-off only in select patients (eg, trisomy 21 or with mild KC).
 2. Accelerated vs. standard ("Dresden") protocols: Studies generally show equivalent results.
 3. Iontophoresis: Early results, less effective in 1 study
 4. CXL + intracorneal ring segments: Rate of extrusion (6%-7%) is higher compared to adults.
 5. Single small case series describes success with use of topo-PRK and CXL in children.
 6. Most reports describe treatment with use of topical anesthesia and mild sedation.

D. Outcomes

1. Published case series are largely small with short-term follow-up (2 years or less)
2. Mazotta et al² found 24% risk of progression 10 years post-CXL and recommended long-term topographic monitoring in young patients.
3. Most studies report stable or improved BCVA, up to 0.15 logMAR, and improvement in Kmax by 1-2 D.
4. Decrease in thinnest pachymetry by up to 40 microns, which can reverse over time
5. Little published evidence on retreatments and on outcomes in patients with trisomy 21

E. Complications

1. Microbial keratitis, uncommon (1%-2%)
2. Sterile infiltrates described
3. Haze (6% or less)

F. Effect of atopy/vernal keratoconjunctivitis

1. Appear to be risk factors for progression after CXL and for microbial keratitis

2. Need to be treated aggressively in KC patients
3. May cause inaccurate topography when active; topography should be repeated when disease is well-controlled.³

IV. Surgical Management

- A. Penetrating keratoplasty and deep anterior lamellar keratoplasty both described with excellent results
- B. No head-to-head study in this pediatric age group
- C. Big bubble and manual techniques have both been successfully described in children with KC.

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Managing Post-LASIK and Other Ectasias

Maria A Woodward MD MS

I. Background

Corneal ectasia is a progressive steepening and thinning of the cornea. Patients experience increased myopia, with or without increasing astigmatism, and loss of BCVA. On examination, the cornea steepens and thins, as measured by topography and tomography.

Ectasia can occur immediately or years after refractive surgery. The incidence of ectasia is unclear, but it is likely between 0.04% and 0.6% of cases.

Screening for ectasia prior to refractive surgery has been developed, including an Ectasia Risk Score System. Other methods to screen for ectasia include modern tomographic and topographic imaging data, but these have not been formalized into a scoring system.

II. Ectasia Diagnosis

Patients with corneal ectasia can experience loss of visual acuity, positive dysphotopsias (eg, glare, halos), and image distortions (eg, multiple images, ghosting). Patients report loss of function and diminished quality of life as a result of their symptoms.

Diagnosing and evaluating corneal ectasia entails the following:

1. Assessing UCVA and BCVA
2. Performing a clinical examination of the cornea
3. Measuring image-based markers, especially keratometry values, using tomographic or topographic images. Image-based markers should be performed serially over several visits to assess progression.

III. Ectasia Management Strategies

Corneal ectasia should be managed according to the patient's degree of visual disability and needs. There are two goals of corneal ectasia disease management: (1) restoration of BCVA and (2) prevention of disease progression.

Restoring vision and minimizing symptoms

1. Eyeglasses: Eyeglasses are a mainstay of early or mild ectasia management. In case series, between 50% and 70% of patients could be corrected to $\geq 20/40$ with eyeglasses. While not ideal from a surgical-outcome perspective, prescribing eyeglasses is the least invasive management strategy.
2. Contact lenses: Contact lenses are the mainstay of management of corneal ectasia for the purpose of improving visual acuity. CTL options include toric contact lenses, rigid gas permeable lenses, custom wavefront-guided soft contact lenses, hybrid lenses, tandem soft contact lens–rigid gas permeable lenses, and scleral lenses.
3. Intracorneal ring segments (ICRS): Intracorneal rings can be surgically placed in the stroma of the cornea to improve visual acuity by altering the corneal shape. ICRS can be placed symmetrically or asymmetrically, depending on the nature of the ectasia. Surgical adjustments can be made to optimize ICRS use dependent on the corneal shape.

4. Corneal collagen crosslinking (CXL) with other treatment modalities: See below.
5. Keratoplasty: A penetrating or anterior lamellar keratoplasty is often the last option for visual rehabilitation, given the risks of surgery, long-term need for graft survival, and continued dependence on glasses or contact lenses. However, in cases of severe ectasia, a keratoplasty offers the best likelihood of good visual acuity.

Preventing ectasia progression

1. CXL: This is a viable, relatively new option for reducing or halting ectasia progression. However, CXL is not without surgical risk. The patient's degree of ectasia and other eye and health characteristics should be evaluated prior to CXL surgery.
2. Combination of CXL with refractive procedures: CXL is now being combined with procedures to improve UCVA and BCVA and minimize ectasia symptoms, including ICRS and with PRK.
3. Bowman layer transplantation: Transplantation of a Bowman layer tissue to the midstromal bed has been proposed to stabilize corneal ectasia and prevent transplantation.

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Interactive Case Presentation: Crosslinking

Anthony J Aldave MD

We present a case of a woman diagnosed with progressive keratoconus who was referred for corneal collagen crosslinking.

Management of Meibomian Gland Disease: Pulsing or Probing?

Joanne Shen MD

I. Introduction

Hyposecretory meibomian gland disease¹ (MGD; also called obstructive MGD) includes the finding of obliteration of meibomian gland ducts and orifice obstruction due to hyperkeratinization. Decreased lipid secretion can occur due to abnormal meibomian glands without concurrent observed obstruction.

- A. For symptomatic patients who fail to respond to conservative therapy:
 1. Automated thermal pulsation (LipiFlow)
 2. Intense pulsed light; sometimes paired with meibomian gland expression (MGX)
 3. Intraductal probing (Maskin probing)
- B. Efficacy and safety to determine recommendations

II. LipiFlow

- A. First described by Lane in *Cornea* in 2012² and funded by TearScience (bought by Johnson & Johnson; New Brunswick, NJ in 2017)
- B. Pubmed May 2019: 5 Level I (case controlled clinical trials), 5 Level II (prospective case series), 2 Level III (respective reviews)
 1. Lane et al, 2012²: 69 LipiFlow vs. 70 iHeat portable warming pack with crossover of iHeat to LipiFlow at 2 weeks. One-month follow-up: 76% LipiFlow vs. 56% iHeat improvement in symptoms.
 2. Finis et al, 2014³: 17 LipiFlow vs. 9 lid warming and manual massage b.i.d. at home with crossover at 3 months. Mean age 50 years. Six-month follow-up: 86% of patients had reduced symptoms. Improvement of bulbar redness, expressible glands, and lipid layer thickness. Meibography showed no change in atrophic glands.
 3. Blackie et al; LipiFlow Study Group, 2016⁴: 100 LipiFlow vs. 100 warm compresses and eyelid hygiene control. Mean age 56 years. Twelve-month follow-up: 86% LipiFlow group had just 1 treatment and improved meibomian gland secretion (MGS). Greater mean improvement in MGS associated with less severe baseline MGS and shorter duration of time between diagnosis and treatment.
 4. Yeo et al, 2016: 22 hot towel b.i.d. vs. 22 EyeGiene b.i.d. (EyeDetect; CA) vs. 22 Blephasteam b.i.d. (Thea Pharmaceuticals; United Kingdom) vs. 24 LipiFlow. Mean age 53 years. Three-month follow-up: symptoms, tear breakup time (TBUT), and corneal stain not improved in LipiFlow treatment group.

5. Zhao et al, 2016: 29 eyes LipiFlow (worse eye) vs. 29 eyes no treatment. Mean age 57 years. Three-month follow-up: Ocular Surface Disease Index (OSDI), meibomian glands yielding liquid secretion (MGYLS), corneal stain, and TBUT improved; meibomian gland dropout, partial blinking, and lipid layer thickness, no change. Schirmers 1 without anesthesia decreased.

III. Intense Pulsed Light (IPL)

- A. First link of IPL to meibomian gland disease treatment by Toyos in 2007 with IPL-MGX protocol on Quadra Q4 (Dermamed; Lenni, PA)
 - B. Pubmed May 2019: 6 Level I, 10 Level II, 4 Level III
 1. Craig et al, 2014⁶: 28 lower eyelids IPL (E-Eye, Eswin; Paris France) vs. 28 contralateral lower eyelids placebo (white light masking of IPL handpiece). No MGX. Mean age: 45 years. 1.5-month follow-up: Visual analog scale symptoms, lipid layer grade, noninvasive tear breakup time (NITBUT) improved in the treatment eye. Tear evaporation rate, tear meniscus were not different.
 2. Liu et al, 2017⁷: 44 upper eyelid and lower eyelids IPL (M22, Lumenis; Tel Aviv, Israel) + MGX vs. 44 contralateral flashlight light flicker simulation + MGX, 3 cycles total. Three-month follow-up: IL-17A, IL-6, and PGE-2 decreased, but these interleukin levels were not correlated with OSDI, TBUT, corneal staining. PGE-2 levels were correlated with corneal staining. IL-17 and IL-6 correlated with meibomian gland expressibility.
 3. Rong et al, 2018⁸: 46 patients. Mean age 46 years. 46 upper and lower eyelid IPL (M22) + MGX vs. 46 contralateral upper and lower eyelid placebo with setting of 0 joules + MGX, 3 cycles total. Three-month follow-up: Meibomian gland expressibility and TBUT improved in treatment eyes. However, 5 patients experienced mild burning and pain during IPL treatment, and 1 patient developed partial eyelash loss.
- Rong et al, 2018⁹: Published 9-month follow-up on 28 patients from the above cohort. Improved corneal stain and lower lid MG expressibility ended at 6 months. No difference in Standard Patient Evaluation of Eye Dryness (SPEED) score. Upper lid MG expressibility and TBUT improvement sustained to 9 months.

4. Arita et al, 2019¹⁰: 45 lower (M22) upper and lower eyelid IPL+MGX vs. 45 contralateral only MGX, 8 cycles total. Mean age 61 years. Eight-month follow-up: corneal staining, lipid layer grade, SPEED score, NITBUT, TBUT, lid margin abnormalities, meibum grade improved.
5. Zhang et al, 2019¹¹: Demodex blepharitis patients: 20 patients IPL (M22) ear-to-ear treatment x 3 cycles vs. 20 patients 5% tea tree oil (TTO) lid massage 15 min/day. Mean age 39 years. Three-month follow-up: OSDI, meibum quality, TBUT were improved. Demodex decreased 100% IPL vs. 75% in TTO group, not significant.

IV. Intraductal Probing

- A. Described by Maskin in 2010¹²: Maskin probes (Rhein Medical; Tampa, FL)
- B. PubMed May 2019: 2 Level I (neither used Maskin probes), 2 Level II, 4 Level III
 1. Ma and Lu 2016¹³: 25 patients 100-micron 2-mm stainless steel wire intraductal probing + fluoromethalone 0.1% t.i.d. (mean age: 58 years) vs. 25 patients fluoromethalone 0.1% t.i.d. only (mean age: 56 years). One-month follow-up: Meibum grade, lid margin abnormalities, TBUT, and fluorescein score improved.
 2. Incekalan et al 2018¹⁴: 20 patients conventional therapy (warm compress, eyelid massage, cleaning b.i.d., and artificial tears 5x day, ciprofloxacin drops 5x day for 2 weeks, omega 3 fatty acid 1000 mg b.i.d., oral azithromycin 500 mg daily for 3 days in a 7-day period x 3 cycles then first 10 days of each month) vs. 20 patients conventional therapy + intraductal probing 0.08 mm blunt tip 2 mm stainless steel wire at first visit. Three-month follow-up: OSDI and meibum quality were equally improved. No difference in the improvement of meibum expressibility between the 2 groups, but probing group was significantly faster.

V. Recommendations

- A. No comparative studies were found. Each technique improved MG parameters and symptoms. No reversal of atrophic meibomian glands was found with any treatment.
- B. The 2017 TFOS DEWS II report¹⁵ recommended LipiFlow and IPL as level 2 therapies after level 1 treatments such as hot compresses/hygiene, environmental, dietary changes, and artificial tears have been used.
- C. LipiFlow is well tolerated and appears to be more efficacious in younger patients with less severe hyposecretory MGD.
- D. IPL can be painful for some patients and cannot be performed on darkly pigmented skin. Repeated monthly applications are usually required. Proper

eye protection is needed for patient and user to avoid ocular injury.

- E. The long-term safety of the more invasive intraductal meibomian gland probing is not known based on the current Level I evidence.

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Update on Medical and Surgical Management of Dry Eye Disease

Audrey Talley Rostov MD

Dry eye disease is a prevalent disease affecting more than 16 million people in the United States. Prevalence is higher in women and is known to increase with age. There are algorithms that include many new modalities for the treatment of dry eye disease. These will be discussed, and options for medical, device, and surgical management will be presented.

I. Medical Management

A. Pharmacologic

1. Cyclosporine
2. Lifitegrast
3. Serum tears
4. Artificial tears
5. Topical steroids
6. Oral omega 3
7. Other compounded medications

B. Lid hygiene

1. Hypochlorous solutions
2. Choice of cosmetics

II. Procedure/Device Management

A. Meibomian gland expression

1. Thermal pulsation
2. Meibomian gland probing

B. Intense pulsed light (IPL)

C. Punctal plugs

D. Amniotic membrane

E. Nasal neural stimulation

F. Acupuncture

III. Surgical

A. Conjunctival chalasis repair

Diagnosis and Management of Neurotrophic Keratopathy

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Introduction

Neurotrophic keratopathy (NK) is a degenerative disease of the cornea caused by impaired or damaged corneal sensory nerves. A reduction in corneal sensitivity or complete corneal anesthesia is the main sign of this disease and is responsible for producing epithelial defects, ulceration, and sometimes even perforation.

Diagnosis

The diagnosis of NK is based on the clinical history, general examination, slit lamp examination, and associated diagnostic tests. Clinical examination and tests should be focused on the common features of NK and possible underlying condition.

1. Symptoms

Dryness, discomfort, pain, photophobia, and reduced visual acuity. Symptoms are worse in the morning and aggravated by external factors such as air conditioning, reading, and VDU use. Visual impairment is often worse in cases with central cornea involvement.

2. Signs on slit lamp examination

Rather like dry eye disease with reduced tear breakup time (TBUT), inferior corneal and conjunctival superficial punctate keratitis (SPK). Often accompanied by reduced blinking rate. The corneal epithelium is initially irregular, with erosions that with progression of disease would lead to an epithelial defect that is often slow to heal. A persistent epithelial defect (PED) with smooth and rolled edges is common. Mackie's classification has been traditionally used to grade NK, guide its management, and assess prognosis and response to treatment. It classifies NK into 3 severity stages in order of worsening severity and prognosis:

Stage 1: lissamine green staining of the lower palpebral conjunctiva, decreased TBUT, punctate corneal epithelial staining with fluorescein

Stage 2: punched out, round/oval epithelial defect with smooth edges and loose surrounding epithelium; stromal swelling with folds but without defect

Stage 3: stromal ulceration/melting that may lead to perforation

3. Investigations

Corneal esthesiometry: Reduced or absent corneal sensation should be measured in the center and the peripheral 4 quadrants and is essential for the diagnosis of NK. This can be measured qualitatively using a "wisp" of twisted cotton or quantitatively with a direct contact Cochet-Bonnet or the Belmont noncontact gas esthesiometer (BNGA). The Cochet-Bonnet is a device that contains a thin, retractable, nylon monofilament that extends from 0.5 cm up to 6 cm in length.

Variable pressure can be applied by adjusting its length. Corneal sensitivity is assessed observing the patient's subjective reaction to different lengths of the protruding nylon filament applied to the cornea. The shorter the length at which the patient feels the touch of the filament, the lower the corneal sensitivity. The BNGA is not commercially available.

In vivo confocal microscopy (IVCM): IVCM allows qualitative and quantitative assessment of corneal nerves in NK. Corneal nerve findings can vary from normal sub-basal plexus with mild preganglionic (trigeminal ganglion) NK to attenuated or lost sub-basal plexus nerves in postganglionic or complete ganglionic lesions.

4. Neurological examination

Full assessment of cranial nerves is very important.

Management

Management is titrated according to the grade of severity. The main goal is to arrest progression, promote epithelial healing, and prevent secondary bacterial infection. It can be divided into medical treatment, nonsurgical intervention, and surgical intervention according to NK severity stage; usually a combination of different treatments is required.

Stage 1: Unpreserved lubricants (ie, artificial tears and ointments) ± punctal occlusion. All other topical medication should be reviewed and possibly discontinued.

Stage 2: Main treatment aims are to promote epithelial healing and to prevent stromal tissue loss. In addition to stage 1 treatment, prophylactic unpreserved topical antibiotic is also recommended (eg, levofloxacin QDS). Eyelid closure can be achieved with lateral tarsorrhaphy, taping, pad, or botulinum toxin injection to induce ptosis, which may be effective in closing the epithelial defect. Additional treatment options include bandage contact lens, punctal occlusion, and amniotic membrane transplantation over the epithelial defect.

Despite our best management at stage 2, NK may still progress to stage 3 disease.

Stage 3: Main treatment aims are to stop further stromal lysis and prevent perforation. In addition to stage 1 and 2 treatments, matrix metalloproteinase inhibitors (ie, oral tetracyclines and topical acetylcysteine) are also recommended. Tissue adhesives should be considered in very thin corneas and in case of small perforation (<3.0 mm) combined with a bandage contact lens. In cases of larger perforations, a lamellar or penetrating keratoplasty may be the only treatment option.

Additional medical treatments

Regenerating agent (RGTA)-based matrix therapy such as Cacicol20 (applied once on alternate days) appears to be an effective therapeutic agent for PED resistant to conventional therapy. Cacicol20 facilitates the reconstruction of the extracellular matrix (ECM), which will help tissue repair and regeneration.

Recombinant human NGF (rhNGF, cenegermin, betaNGF): In July 2017, the European Medicines Agency (EMA) granted cenegermin 20 µg/ml (Oxervate) full marketing authorization for the treatment of moderate (PED) or severe (corneal ulcer) NK in adults. The efficacy and safety of cenegermin were evaluated in 2 independent, multicenter, randomized, double-masked, vehicle-controlled clinical studies comparing 2 different dosages of the medicinal product (20 and 10 µg/ml cenegermin) to vehicle, in Europe (NGF0212) and the USA (NGF0214) in patients with moderate or severe NK refractory to nonsurgical treatments. A summary of the results of the 2 studies has shown complete corneal healing of the PED or corneal ulcer after 8 weeks of treatment in more than 50% of the patients ($P = .002$ and $.006$, respectively) and remained healed after 1 year.^{1,2}

Additional surgical intervention

Surgery is often required in advanced disease refractory to medical management, in stages 2 and 3 NK. Medical and surgical therapy should be combined.

Corneal neurotization: Direct corneal neurotization aims to restore corneal sensitivity in patients with NK using the contralateral supraorbital and supratrochlear branches of the ophthalmic division of the trigeminal nerve. In 2009, Terzis et al³ described a novel surgical procedure in which the contralateral nerve branches are transposed to the contralateral anesthetic corneal limbus for sensory neurotization. Use of the sural nerve for this purpose has also been described.⁴

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Diagnosis and Staging of Limbal Stem Cell Deficiency: What Did We Agree On?

Friedrich E Kruse MD

Members from the supranational cornea societies have met several times to reach agreement on the definition, classification, and diagnosis of limbal stem cell disease (LSCD).

I. Definition of LSCD

LSCD is an ocular surface disease caused by a decrease in the population and/or function of corneal epithelial stem/progenitor cells; this decrease leads to an inability to sustain the normal homeostasis of the corneal epithelium.

The disease is characterized by conjunctivalization (ie, replacement of the normal corneal epithelium by conjunctival epithelium) and/or other signs of epithelial dysfunction, such as persistent or recurrent epithelial defects with or without neovascularization, ocular surface inflammation, and scarring. Frequent consequences are decreased vision and discomfort, leading to reduced health-related quality of life.

LSCD may present alone as a single entity or associated with abnormalities of other components of the ocular surface, such as the conjunctiva, meibomian glands, lacrimal glands, tears, corneal nerves, and immune system.

II. Partial vs. Total LSCD

- A. Partial LSCD is characterized by incomplete conjunctivalization of the corneal surface and the presence of residual limbal and consequent corneal epithelial cells.
- B. Total LSCD is characterized by conjunctivalization of the entire corneal surface because of complete loss of corneal epithelial stem/progenitor cells.

III. Classification of LSCD

A. Acquired LSCD

1. Acquired nonimmune-mediated

- Chemical injury
- Thermal injury
- Radiation injury
- Contact lens wear
- Multiple surgeries involving the limbus
- Bullous keratopathy
- Infectious ocular disease
- Chronic lid disease
- Severe blepharitis–rosacea
- Trachoma
- Tumors of the ocular surface

- Severe pterygium
- Drug-induced
- Mitomycin C
- 5-fluorouracil
- Preservatives
- Systemic chemotherapy and immunotherapy

2. Acquired primary immune-mediated

- Stevens-Johnson syndrome/toxic epidermal necrolysis
- Mucous membrane pemphigoid
- Allergic ocular surface disease
- Vernal keratoconjunctivitis
- Atopic keratoconjunctivitis
- Graft-versus-host disease

3. Idiopathic

B. Hereditary LSCD

- Congenital aniridia
- Dyskeratosis congenita
- Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy/dysplasia
- Xeroderma pigmentosum
- Keratitis ichthyosis deafness syndrome
- Ectrodactyly–ectodermal dysplasia–clefting syndrome
- Lacrimo–auriculo–dental–digital syndrome
- Epidermolysis bullosa

IV. Diagnosis of LSCD

Total LSCD is characterized by conjunctivalization of the entire corneal surface because of complete loss of corneal epithelial stem/progenitor cells. The absence of the corneal epithelium phenotype or the presence of conjunctival epithelial cells (conjunctivalization) of the cornea produces clinical signs of LSCD.

A. Delayed fluorescence staining at slit lamp

Slit-lamp examination and fluorescein staining pattern could reveal signs of LSCD. Fluorescein staining of the ocular surface is a test that can differentiate between normal healthy corneal epithelium and abnormal pathologic epithelium. Under normal conditions, corneal epithelial cells on the surface are interconnected by tight junctions, which are

impermeable to larger molecules. By contrast, the conjunctival epithelium is characterized by relatively loose cell–cell contacts, which result in a permeability that is up to 40 times greater than that of the corneal epithelium. In LSCD, the epithelium on the corneal surface may be either conjunctival with neovascularization, a mixture of metaplastic corneal epithelial cells and conjunctival epithelial cells, or only conjunctival epithelial cells without neovascularization. The conjunctival epithelium, which is thinner and hazy, has a protein profile that differs from that of the healthy cornea.

In contrast to the epithelial defects that are immediately stained by fluorescein, the dye diffuses into the paracellular space of the conjunctivalized surface, and abnormal delayed staining is observed 10 or more minutes after fluorescein instillation. This abnormal staining pattern can be visualized even after rinsing with BSS or eye wash.

B. Cell sampling and application of dye or specific markers

Impression cytology or biopsy can be used to sample cells from the surface and to prove conjunctivalization of the corneal surface. Traditionally, histologic stains such as hematoxylin and eosin or periodic acid-Schiff stain are used to detect goblet cells collected by impression cytology or cell scraping. Because of the low sensitivity of goblet cells in the diagnosis of LSCD, specific markers of conjunctival epithelial cells have been sought to indicate the presence of these cells on corneal impression cytology specimens. Immunohistochemistry allows detection of intracellular proteins.

C. In vivo imaging

1. *In vivo confocal microscopy (IVCM)* has emerged as a diagnostic tool for LSCD, in part, because this method does not require the removal of corneal epithelial cells for the analyses. IVCM provides information about disease severity and can be used in both diagnosis and monitoring of LSCD. In addition, IVCM may be useful in evaluating the outcomes of cultured LSC grafts and recovery from trauma such as chemical injury. Corneal, conjunctival, and limbal epithelial cells can be distinguished on the basis of their different cell morphology. The absence of the corneal epithelium and/or the presence of conjunctival cells on the cornea is diagnostic of LSCD. Goblet cells can be detected by IVCM.
2. *Anterior segment OCT (AS-OCT)* has emerged as an alternative imaging technique for LSCD, allowing for both noninvasive imaging of the ocular surface, including the limbus, and a larger field of view at the expense of resolution. Although AS-OCT does not offer the

same degree of resolution at the cellular level as IVCM does, AS-OCT may prove useful in measuring epithelial thickness and pannus depth and assessing POV, limbal crypts, and the clear transition between the hyporeflexive corneal epithelium and hyperreflexive conjunctival epithelium in the limbal region.

V. Staging

LSCD can be categorized into 3 stages based on the extent of corneal and limbal involvement detected by clinical examination, as illustrated in Figure 1. Staging of LSCD is important in guiding therapeutic recommendations and surgical planning. The most important factors to be considered include whether the visual axis or central 5 mm of cornea is affected (stages II and III) and whether more than 50% of the LSCs are intact. The final stage (stage III) involves total LSCD, where the whole corneal surface is affected. Abnormalities of other components of the ocular surface such as the conjunctiva, meibomian glands, lacrimal glands, tears, corneal nerves, and immune system are important in the management of LSCD and will be addressed in a separate document on the global consensus of the treatment of LSCD.

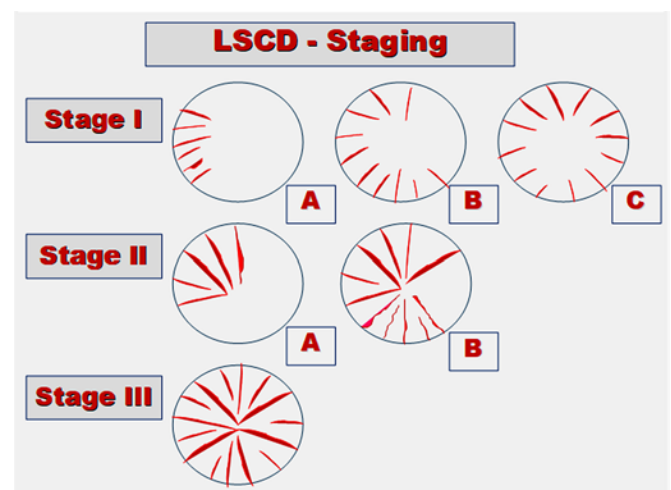


Figure 1.

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Management of Ocular Cicatricial Diseases: A Stepwise Approach

Clara C Chan MD

I. Introduction

- A. The conjunctiva allows for monitoring of ocular surface inflammation.
- B. Chronic conjunctival inflammation leads to mucin deficiency, limbal stem cell deficiency, symblepharon formation, fornix shortening/scarring/complete loss, and keratinization in the end stages.
- C. Eyes that suffer from chronic conjunctival inflammation and total limbal stem cell deficiency have the worst prognosis with any surgical intervention.

II. Stepwise Approach

- A. Determine the etiology for the conjunctival cicatricial changes and inflammatory status of the conjunctiva.
 - 1. Chronic inflammation persists (eg, Stevens-Johnson syndrome, mucus membrane pemphigoid, graft-versus-host disease, severe chemical injuries, atopic keratoconjunctivitis) vs. quiet eye after acute inflammatory process has resolved (eg, adenoviral epidemic keratoconjunctivitis)
 - 2. Important for prognosis and to help guide reconstruction process
 - 3. May need systemic immunosuppression to control inflammation
- B. Optimize the ocular surface with your “toolbox” of dry eye, lid margin disease, and exposure minimization strategies.
- C. Trial scleral contact lenses. If patient is intolerant, then you can consider ocular surface reconstruction.
- D. Lid and fornix reconstruction to correct for lash trauma, entropion, lagophthalmos, etc.

E. Optimize glaucoma, minimize glaucoma drops that cause worse ocular surface toxicity. A glaucoma drainage device is often needed.

F. Limbal stem cell transplantation (KLAL, Cincinnati procedure) with systemic immunosuppression

G. Optical corneal transplant (DALK/ PKP)

H. Keratoprosthesis if failed cornea transplant

I. Close monitoring for infectious keratitis, higher risk for fungal keratitis

III. Pearls

- A. Avoid ocular surface surgery if functional vision is achieved with scleral contact lenses.
- B. Refer to internal medicine specialist to rule out malignancy as underlying cause of paraneoplastic pseudo-OCP.
- C. If keratinization is present, contraindication to ocular surface stem cell transplantation and KPro
- D. Mucus membrane pemphigoid requires adequate systemic immunosuppression prior to any lid/fornix reconstruction, ocular surface stem cell transplantation.
- E. Stevens-Johnson syndrome patients are at risk for fungal keratitis after ocular surface stem cell transplantation.
- F. Amniotic membrane is useful to prevent recurrence of mild symblepharon after EKC (adenoviral epidemic keratoconjunctivitis).
- G. Keratolimbal allograft segment(s) may be used to prevent recurrent symblepharon formation.
- H. Biopsy unilateral symblepharon to rule out ocular surface squamous neoplasia (OSSN).

Managing Lumps, Bumps, and Dumps on the Cornea

Christopher J Rapuano MD

I. Cornea Surface Pathology

A. Affects comfort

B. Affects vision

1. Opacity

2. Irregular astigmatism:

If not diagnosed prior to cataract surgery, can cause unexpected poor vision post-op (even with “perfect” cataract surgery)

C. Affects corneal biometry prior to cataract surgery:

Inaccurate corneal curvature measurements can lead to incorrect IOL power and cylinder calculations. If corneal irregularities are then addressed postoperatively, may need refractive surgery or an IOL exchange.

II. Diagnostic Techniques

Careful slit lamp examination

A. Broad slit beam from a side angle:

A broad slit beam from a side angle can often identify mild epithelial irregularities due to epithelial basement membrane dystrophy. It can also be used to find mildly elevated creamy white nodules of Salzmann nodular degeneration.

B. Negative staining:

My rule of thumb is that if there is negative staining in the center of the cornea, typically in the central approximately 6 mm, then I believe it has a high chance of being visually significant. A few minor areas of negative staining way out in the periphery are probably not causing any issues with visual function.

C. Corneal topography:

I find those that use Placido disc type rings to be the best at evaluating corneal surface irregularities. This technology involves circular rings of light shined onto the cornea and imaged by a computer, which then calculates curvature and evaluates regularity. Most systems will show an image of the rings on the cornea in addition to a color-coded map of power and regularity. I find looking at the rings to be the best way to assess very small irregularities in the cornea because the color-coded maps often smooth out small but visually significant irregularities.

III. Epithelial Basement Membrane Dystrophy (EBMD)

A. Very common condition, especially as patients get older

B. Often an incidental finding and does not cause significant central negative staining or disruption of the corneal topography rings. Observe.

C. If the EBMD changes are causing central negative staining or irregularities in the corneal topography rings, then they may well be visually significant and it should probably be treated, especially prior to cataract surgery.

D. Treatments

1. Epithelial debridement alone: At the slit lamp or under a minor room operating microscope

2. Epithelial debridement combined with a diamond burr polishing procedure

a. A sharp blade (eg, #15 blade) or semisharp blade (eg, Tooke knife) is used to remove a large area, ~6-8 mm diameter, of central epithelium. It is critical to remove all the irregular reduplicated basement membrane overlying the Bowman layer, which is usually very smooth. When a diamond burr polishing procedure is being performed, then a large 5-mm diameter diamond-dusted drill is used to smooth out the cornea in a uniform fashion for about 5 seconds. The idea behind using the diamond burr is that it removes all the irregular basement membrane and perhaps allows for better adhesion of the new epithelium.

b. Over 90% successful in obtaining a smoother corneal surface

c. Complications include delayed epithelial healing, infection, corneal scarring, decreased vision, and of course, recurrent EBMD.

3. Excimer laser phototherapeutic keratectomy (PTK) ± mitomycin C (MMC): Not usually necessary for EBMD alone

IV. Salzmann Nodular Degeneration (SND)

A. Single or multiple, slightly elevated or severely elevated creamy white corneal opacities, usually in the peripheral cornea, although they can involve the central cornea. Even when peripheral, they can affect the central corneal topography, and thereby the vision.

- B. Bowman layer and anterior stroma may be involved, significantly increasing the chance of an irregular stromal bed after removal of the SND.

- C. Treatments

1. Lamellar keratectomy with a blade \pm diamond burr polishing procedure
2. PTK \pm MMC (mainly to decrease the chance of recurrence of the SND)
 - a. The nodules are removed manually with a sharp or semisharp blade, ideally down to a reasonably smooth Bowman membrane. If Bowman is fairly smooth, then large PTK ablation spots can be used to smooth it a little bit further. If Bowman is not smooth after the manual SND removal, then multiple small, medium, and large excimer laser spots need to be used to remove the irregularities and achieve as smooth a base as possible. After that, MMC on an 8-mm sponge is placed on the cornea for \sim 60 seconds and irrigated with 30 mL cold saline.
 - b. Success rate of PTK with MMC is \sim 90% successful in obtaining a smoother corneal surface.
 - c. Complications include delayed epithelial healing, infection, corneal scarring, decreased vision, and of course, recurrent SND.

- V. Pterygium

- A. Wing-shaped fibrovascular growth onto the cornea
- B. As a general rule, extension approximately 2-3 mm or greater onto the cornea has a greater chance of affecting vision.
- C. Corneal topography is very helpful in determining how visually significant a pterygium is. When the topography rings are irregular within the central 6 mm or there is significant irregular astigmatism on the color-coded maps, then the pterygium should be treated prior to cataract surgery.

- D. Treatments:

Pterygium excision with a conjunctival autograft is generally considered the treatment of choice. In cases where a conjunctival autograft is problematic, such as in patients after trabeculectomy or tube shunt surgery, then use of an amniotic membrane graft can also be very successful.

- VI. Band Keratopathy

- A. Calcium deposition in the cornea

- B. Numerous etiologies, often related to chronic inflammation; may be idiopathic

1. If central, can affect vision
2. If peripheral but elevated, can also affect vision
3. If elevated or irregular, can affect comfort

- C. Treatments: EDTA chelation

1. Remove all epithelium over the calcium deposition. Apply disodium EDTA 3% to affected area until all calcium is removed (usually takes 10-60 minutes, depending on the thickness of the calcium).
2. Success rate: EDTA chelation is \sim 98% successful in removing all the calcium.
3. Complications include delayed epithelial healing, infection, corneal scarring, decreased vision, and of course, recurrent band keratopathy.

- VII. Summary

Corneal lumps, bumps, and dumps commonly affect corneal clarity and regularity. They are often readily treatable with excellent outcomes.

Interactive Case Presentation: Is It Dry or Not Dry?

Anat Galor MD

I. Describe Case

A male with dry eye symptoms where both nociceptive and neuropathic components to the pain were found

II. Discuss How Nociceptive Parameters Are Addressed

III. Discuss When and How Neuropathic Parameters Are Addressed

IV. Describe Treatment Course and Follow-up Information

Are You AT the Table or ON the Menu?

Stephanie J Marioneaux MD

Ophthalmology's goal to protect sight and empower lives requires active participation and commitment to advocacy from every ophthalmologist. Contributions to the following three critical funds are a part of that commitment:

- OPHTHPAC®
- Surgical Scope Fund (SSF)
- State Eye PAC

Please join the dedicated community of ophthalmologists who are contributing to protect quality patient eye care for every-body.

The OPHTHPAC Committee is identifying Congressional Advocates in each state to maintain close relationships with federal legislators to advance ophthalmology and patient causes. At Mid-Year Forum 2019, we honored three of those legislators with the Academy's Visionary Award. This served to recognize them for addressing issues important to us and to our patients. The Academy's Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level.

Our mission of "protecting sight and empowering lives" requires robust funding of both the Surgical Scope Fund and OPHTHPAC. Each of us has a responsibility to ensure that these funds are strong so that ophthalmology can be represented "at the table."

OPHTHPAC®

OPHTHPAC represents the profession of ophthalmology to the U.S. Congress and operates to protect you and your fellow ophthalmologists from payment cuts, burdensome regulations, scope-of-practice threats, and much more. OPHTHPAC also works to advance our profession by promoting funding for vision research and expanded inclusion of vision in public and private programs—all of which provide better health-care options for your patients. OPHTHPAC is your federal voice in Washington, D.C., and we are very successful in representing your professional needs to the U.S. Congress.

Among OPHTHPAC's most recent victories are the following:

- Securing greater flexibility in the new Medicare Payment System
- Ensuring proper reimbursement of Medicare Part B drugs
- Blocking onerous administrative burdens on contact lens prescribers
- Preserving access to compounded drugs
- Preventing additional cuts to Medicare

However, ophthalmology's federal issues are a continuous battle, and OPHTHPAC is always under pressure to ensure we have strong political connections in place to help protect ophthalmology, its members, and their patients.

The support OPHTHPAC receives from invested U.S. Academy members helps build the federal relationships that advance ophthalmology's agenda on Capitol Hill. These relationships allow us to have a seat at the table with legislators

willing to work on issues important to us and our patients.

We also use these congressional relationships to help shape the rules and regulations being developed by federal agencies. Help strengthen these bonds and ophthalmology's legislative support.

Right now, major transformations are taking place in health care. To ensure that our federal fight and our PAC remain strong, we need the support of every ophthalmologist to better our profession and ensure quality eye care for our patients. Invest with confidence in the strongest PAC working to ensure your success as an ophthalmologist.

Contributions to OPHTHPAC can be made here at AAO 2019, online at www.aao.org/ophthpac, or by texting MDEYE to 41444.

At Mid-Year Forum 2019, the Academy and the Cornea Society ensured a strong presence of cornea specialists to support ophthalmology's priorities. Ophthalmologists visited members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The Cornea Society remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support 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 40 state/territorial ophthalmology societies reject optometric scope-of-practice expansions into surgery.

Thanks to the 2019 SSF contributions from ophthalmologists just like you, SSF has had a successful year, preserving patient safety and surgical standards in state legislatures across the country, including six critical wins in Alabama, Texas, Vermont, Wyoming, Maryland, and Iowa. The 2019 battle is far from over, though. For example, Pennsylvania and Massachusetts are under attack, and California and Illinois are facing threats.

If you have not yet made a 2019 SSF contribution, *contributions can be made at our booth at AAO 2019 or online at www.aao.org/ssf*. If you already have made that 2019 contribution, please go to www.safesurgerycoalition.org to see the impact of your gift.

Dollars from the SSF are critical to building 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 work helps to secure success in protecting patient safety by defeating optometry's surgical initiatives.

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

The Secretariat for State Affairs thanks the Cornea Society, which has joined state ophthalmology societies in the past in contributing to the SSF, and it looks forward to the society's

Surgical Scope Fund	OPHTHPAC® Fund	State EyePAC
To protect patient safety by defeating optometric scope-of-practice initiatives that threaten patient safety and quality surgical care	Ophthalmology's interests at the federal level 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, and organization	Contributions: Limited to \$5,000	Contribution limits vary based on state regulations.
Contributions are 100% confidential.	Contributions above \$200 are on the public record.	Contributions are on the public record depending upon state statutes.

2019 contribution. These ophthalmic organizations complete the necessary SSF support structure for the protection of our patients' sight.

State Eye PAC

It is increasingly important for all ophthalmologists to support their respective State Eye PACs because campaign contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the SSF. 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 all fought on the state level.

ACTION REQUESTED: Help Ophthalmology Ensure a "Seat at the Table"

Academy SSF contributions are used to support the infrastructure necessary for state legislative/regulatory battles and for public education. State PAC and OPHTHPAC contributions are necessary at the state and federal levels, respectively, to help elect officials who will support the interests of our patients. Contributions to *each* of these three funds are necessary and help us protect sight and empower lives. SSF contributions are completely confidential and may be made with corporate checks or credit cards, unlike PAC contributions, which must be made by individuals and are subject to reporting requirements.

Please respond to your Academy colleagues and be part of the community that contributes to OPHTHPAC, the SSF, and your State Eye PAC. Please be part of the community that ensures ophthalmology has a strong voice in advocating for patients.

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If Only It Were Simple: Managing Herpes Simplex Keratitis

Charles C Lin MD

- I. Diagnosis: Early and Correct Diagnosis Is Key to Preventing Complications
 - A. Viral culture and polymerase chain reaction of cornea scraping or aqueous humor performed off of antivirals
 - B. Metagenomic deep sequencing (research tool) for atypical cases
- II. HSV Epithelial Keratitis
 - A. Dendritic ulcer
 - 1. Epithelial debridement
 - 2. Topical antiviral: trifluridine, acyclovir ointment 3%
 - 3. Oral antiviral: acyclovir, valacyclovir, famciclovir
 - B. Geographic ulcer
 - 1. Longer treatment is usually required than for dendritic ulcer.
 - 2. Additional measures as for neurotrophic ulcer may be needed.
- III. HSV Stromal Keratitis
 - A. Immune-mediated stromal keratitis. Also known as interstitial keratitis
 - 1. Oral antiviral: acyclovir, valacyclovir, famciclovir
 - 2. Topical steroids are integral to preventing complications such as neovascularization and lipid keratopathy: prednisolone 1%.
 - 3. Chronic cases require maintenance prophylaxis with oral antiviral and topical steroids.
 - 4. Goal of therapy: Titrate to minimum dose required to suppress inflammation
 - B. Necrotizing stromal keratitis
 - 1. Rare, aggressive form less responsive to conventional treatment and characterized by corneal thinning
 - 2. Additional measures such as amniotic membrane and tarsorrhaphy may be indicated.
- IV. HSV Endotheliitis
 - A. Subtypes: disciform, diffuse, and linear
 - B. Oral antiviral: acyclovir, valacyclovir, famciclovir
 - C. Topical steroids: prednisolone 1%
- V. Complications Associated With HSV Keratitis
 - A. Neurotrophic cornea and ulcer
 - 1. Oral antiviral needed for therapeutic and prophylactic purposes
 - 2. Rule out secondary infection with corneal cultures and treat with topical antibiotic.
 - 3. Topical steroids may be needed if inflammation is preventing healing.
 - 4. Bandage contact lens, tarsorrhaphy, serum tears, amniotic membrane for nonhealing ulcers
 - 5. Cenegegermin (nerve growth factor) shows promise.
 - 6. Corneal neurotization procedure is under investigation.
 - B. Corneal thinning
 - 1. Cornea glue if risk for perforation
 - 2. Temporary tarsorrhaphy
 - 3. Anterior lamellar keratoplasty

I'm Not Throwing Away My Shot!

Management of Herpes Zoster

Sonal Tuli MD

Herpes zoster ophthalmicus (HZO) incidence is increasing, and the age at which it occurs is decreasing, which may be related to the widespread vaccination of children against chickenpox. Zoster is caused by the decline in cell-mediated immunity (CMI), which allows latent herpes zoster virus in the trigeminal ganglion to reactivate. Unfortunately, ocular involvement by zoster can cause long-term effects due to the live virus, as well as immune reaction to the residual viral DNA in the cornea even after resolution of the active infection.

Zoster can affect nearly all parts of the eye and visual system and cause significant morbidity. Acute effects such as corneal pseudodendrites are caused by live virus and treated with high doses of antiviral medications. Late effects, such as nummular keratitis, endotheliitis, and uveitis, are thought to be immunogenic and are treated primarily with steroids. The most problematic long-term complication is post-herpetic neuralgia, which is very difficult to manage and treat.

Two vaccines are commercially available for zoster and result in an increase in host CMI. Zostavax was licensed in 2006 and is a live attenuated vaccine. Its efficacy ranges from 70% in 50- to 59-year-olds to 34% in ≥ 70 -year-olds, rapidly declining over the next few years. A newer recombinant zoster vaccine, Shingrix, was licensed in 2017 and offers a significantly higher rate of protection, ranging from 97% in 50- to 70-year-olds and 91% in ≥ 70 -year-olds. It is effective longer but has been in short supply.

Whether to vaccinate individuals who have previously had HZO remains controversial. Both vaccines are labelled for use in patients with a previous history of zoster. However, there are several reports of reactivation of quiescent HZO after vaccination. Also, it is conceivable that exposure to a high load of zoster virus, as occurs in HZO, would be protective, at least for several years, so vaccination could be deferred.

To summarize: an ounce of prevention is better than a pound of cure. Get the vaccine before you get the zoster! If you can find it ...

Beating Back Bacterial Keratitis

Jennifer Rose-Nussbaumer MD

I. Bacterial Keratitis

- A. Although antibiotics are successful at achieving microbiological cure in infectious keratitis, outcomes are often poor because of corneal scarring.
- B. Randomized trials comparing different antibiotic treatments have not been able to demonstrate superiority of one antibiotic over another.¹
- C. Therapeutic penetrating keratoplasty has a poor prognosis compared with penetrating keratoplasty performed for visual rehabilitation.²⁻⁴
- D. The ideal treatment of corneal ulcers would address both the infection and the inflammation.

II. Steroids for Corneal Ulcers Trial (SCUT)

- A. SCUT investigated adjuvant topical steroids in addition to antibiotics to reduce the inflammatory response in bacterial ulcers.
- B. The trial failed to find benefit or harm overall.
- C. Prespecified subgroup analyses suggested that earlier steroid treatment of large, central, non-Nocardia ulcers led to better clinical outcomes.^{5,6}

III. Corneal Crosslinking (CXL) for Infectious Keratitis

- A. In vitro studies suggest that photochemically activated riboflavin is effective against common ocular pathogens.⁷
- B. CXL may also have anti-inflammatory effects and promote resistance of corneal tissue to enzymatic degradation.^{8,9}
- C. Randomized clinical trials to date have yielded mixed results (see Table 1).
- D. Crosslinking-Assisted Infection Reduction (CLAIR) is a randomized outcome-masked clinical trial evaluating the benefit of adjuvant corneal crosslinking in moderate to severe bacterial keratitis.

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Table 1. Relevant Randomized Clinical Trials Assessing Corneal Crosslinking

Trial	Question	N	Finding	Comment
Bamdad, et al., 2015 ¹⁰	Adjuvant CXL vs. standard therapy for moderate bacterial keratitis	32	Adjuvant CXL shortened the treatment course and resulted in improved outcomes.	Small sample size, investigator was partially unmasked, enrolled exclusively in Iran
Said, et al., 2014 ¹¹	Adjuvant CXL vs. standard therapy for bacterial, fungal, Acanthamoeba, or mixed keratitis	40	No benefit of adjuvant CXL	Inappropriate randomization, inclusion of multiple types of keratitis and mixed keratitis, small sample size, enrolled exclusively in Egypt
Uddaraju, et al., 2015 ¹²	Adjuvant CXL vs. standard therapy for deep fungal keratitis	13	Adjuvant CXL resulted in an increased rate of perforation.	Small sample size, inclusion of only severe fungal ulcers, enrolled exclusively in South India

Fighting Fungal Keratitis

Namrata Sharma MD MBBS

NOTES

Not a Canned Approach: Management of *Acanthamoeba* Keratitis

Elmer Y Tu MD

Introduction

The upsurge in cases of *Acanthamoeba* keratitis in the United States and other parts of the world starting in the mid-2000s continues unabated, affecting hundreds of patients a year in the United States. The infection masquerades as a number of other infectious and noninfectious diseases, which leads not only to a delay in diagnosis but also to unnecessary and ineffective treatment. Even as it becomes more commonly recognized, definitive diagnosis of the infection continues to be a challenge, with inadequate access and supply of diagnostic imaging equipment and microbiologic expertise. Access to traditional anti-acanthamoebal therapy has been significantly affected by stricter regulations on extemporaneous drug compounding and importation. Further, in high-volume treatment centers, both published and anecdotal evidence suggests that *Acanthamoeba* infections are not only occurring in greater frequency but are becoming more difficult to treat and are leading to poorer outcomes than just a decade ago.

Diagnosis

The most impactful management intervention remains early recognition and diagnosis of *Acanthamoeba* keratitis. Clinical suspicion for *Acanthamoeba* keratitis should be foremost in any contact lens wearer with a keratitis exhibiting either an atypical appearance or an atypical response to routine infectious keratitis treatment. Clinical signs are often nonspecific early in the disease, and diagnosis relies on a combination of diagnostic imaging (primarily confocal microscopy), microbiologic smear/culture, and, increasingly, molecular diagnostic methods.

The “Canned” Approach

There are no treatments approved by the FDA for the treatment of *Acanthamoeba* keratitis. The mainstay of therapy are the biguanides chlorhexidine 0.02% and polyhexamethylbiguanide (PHMB) 0.02%, given initially hourly until some sign of resolution. PHMB has become more difficult to dispense in some compounding pharmacies because of its absence from the U.S. Pharmacopoeia. Both agents have demonstrated widespread toxic effects for both trophozoites and cysts. Diamidines are next most commonly used, primarily as adjunctive agents. Neomycin is sometimes added, but it has only limited effects. Surgical treatment, in the form of penetrating keratoplasty or deep anterior lamellar keratoplasty, is generally avoided; because of the diffuse and infiltrative nature of *Acanthamoeba* keratitis, it can lead to a higher rate of recurrence without some measure of medical control.

The “Uncanned” Approach

Unfortunately, *Acanthamoeba* keratitis has increasingly defied a canned approach to therapy. Traditional therapy can still be successful, but it may be requiring longer and more intense regimens. Careful observation of these patients with contemporaneous or secondary bacterial or fungal infections is required. Secondary therapy often is dictated by what options the physician has available.

The simplest approach is to use increased concentrations of existing biguanides and/or combine their use (eg, PHMB + chlorhexidine). Few studies have assessed the value of this approach. Adjunctive use of secondary agents such as voriconazole (oral or topical), systemic pentamidine, caspofungin, and others have been described. The greatest interest has been the introduction of the orphan drug miltefosine, an anti-leishmaniasis drug, to the United States with an FDA designation for acanthamoebal infections, including *Acanthamoeba* keratitis, in 2015. A study has demonstrated that the drug is not effective in current topical compounded form but has some evidence of efficacy with systemic use in advanced or resistant infections. Although leading to poorer outcomes in patients prior to effective therapy, corticosteroids and other immunosuppressants are required to modulate an often exuberant and misdirected host immune response, which would lead to phthisis if left unchecked. While it is somewhat counterintuitive, studies demonstrate the safety and benefits of immune suppression in select patients with *Acanthamoeba* keratitis.

A great deal of interest has been generated around the application of collagen crosslinking to patients with *Acanthamoeba* keratitis. As with most atypical infections, the greatest effect may be in early forms of *Acanthamoeba* infections and for the vast majority of patients represents an adjunctive therapy. Other photoenhancers and wavelengths of light have been explored, both in vivo and in vitro, as alternatives to traditional crosslinking. In severely recalcitrant cases or those progressing to perforation, the timing and method of corneal transplantation requires modification because of the ill-defined borders of infection and potential for recurrence.

Confocal Microscopy as a Diagnostic Tool for Infectious Keratitis

Pedram Hamrah MD

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Don't Cross Me! Crosslinking for Infectious Keratitis

José AP Gomes MD

Corneal collagen crosslinking (CXL) was introduced in 2003 to stabilize the progression of keratoconus.¹ The procedure combines ultraviolet-A (UVA) light and riboflavin, inducing a photochemical reaction that increases corneal biomechanical stiffness.¹ In addition, CXL has been used in the treatment of other conditions such as bullous keratopathy, corneal melting, and infectious keratitis.^{2,3}

The rationale of using CXL to treat corneal infections can be explained through the effect of the 2 elements involved in the procedure.²⁻⁴ UVA light directly damages DNA and RNA in micro-organisms and inhibits them from replicating.²⁻⁴ Riboflavin also possesses its own microbicidal effect.² When it is photoactivated, it releases reactive oxygen species (ROS) that interact with the nucleic acids and cell membranes of the microbe.^{3,4} Additionally, CXL interferes with the enzymatic digestion caused by the pathogenic micro-organisms that induces corneal melting.⁴ The increasing number of publications on CXL treatment for infectious keratitis led cornea specialists to adopt the term "PACK-CXL," or photo-activated chromophore for keratitis-CXL.⁴

The antibacterial, antifungal, and antiparasitic efficacy of CXL has been challenged by experimental studies both in vitro and in vivo.^{3,4} A significant antibacterial action of UVA/riboflavin treatment was demonstrated against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*.²⁻⁴ On the other hand, the effect of CXL against fungi has been controversial, with poor results against *Candida* in vitro but good efficacy against *Fusarium solani* in vivo.^{3,4} The results of CXL treatment in experimental studies with *Acanthamoeba* keratitis have been much less encouraging, showing a poor antitrophozoite and cysticidal effect.⁵

The first clinical descriptions of PACK-CXL in treating bacterial infectious keratitis were promising, with a reduction of the corneal stromal infiltrates and melting.^{6,7} Similarly, other publications demonstrated good outcomes of adjunct CXL and antimicrobial topical medication in nonresponsive corneal infectious ulcers.^{6,7} Prospective randomized trials demonstrated a lower rate of perforation or recurrence of the infection in the PACK-CXL group compared to the control group.^{6,7} Corneal epithelial defect and infiltrate resolution also occur faster after the CXL procedure, especially in bacterial and superficial fungal ulcers.^{6,7} A few reports of good results of PACK-CXL in *Acanthamoeba* keratitis have also been reported.^{6,7} More recently, photodynamic therapy using rose bengal as the chromophore was introduced with good results for the treatment of resistant fungal keratitis.^{8,9} In contrast to these promising outcomes, disappointing results were reported with the use of CXL for the management of herpetic keratitis.¹⁰

In conclusion, PACK-CXL seems promising in the management of infectious keratitis, notably bacterial keratitis, and is not indicated in herpetic corneal disease. More evidence regarding its efficacy against fungal and parasitic infections and a better standardization of the procedure are needed to confirm its clinical relevance in the treatment of corneal infection.

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Interactive Case Discussion: Consider This Challenging Corneal Infection

Jessica B Ciralsky MD

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Practical Imaging Before and After Keratoplasty

Dipika V Patel PhD MRCOphth

- I. Background
 - A. A wide range of noninvasive imaging techniques is available.
 - B. Multiple research and clinical applications
 - C. Aim to optimize surgical outcomes
- II. Preoperative Ultrasound Biomicroscopy
 - A. Assess anterior segment status behind corneal opacities
 - 1. Anterior chamber (AC) depth
 - 2. Angle
 - 3. Lens and anterior capsule
 - 4. Membranes
 - 5. Adhesions
 - 6. Vitreous in AC
 - B. Advantages: Can image ciliary body and through corneal opacities
 - C. Disadvantages: supine position, water immersion, patient cooperation
- III. Preoperative Anterior Segment OCT (AS-OCT)
 - A. Assess depth of pathology
 - B. Advantages: noncontact, sitting position
 - C. Disadvantages: poor view of ciliary body, poor view through corneal opacities
- IV. Intraoperative OCT
 - A. Microscope-integrated OCT devices with images observed through:
 - 1. Surgeon's microscope
 - 2. External screen
 - B. Aims to improve surgical outcomes for lamellar keratoplasty
 - C. Deep anterior lamellar keratoplasty
 - 1. Evaluate needle/dissection depth
 - 2. Evaluate big bubble dissection plane
 - 3. Evaluate residual stromal thickness
 - 4. Detect microperforation
 - D. Descemet-stripping automated endothelial keratoplasty (DSAEK)/Descemet membrane EK (DMEK)
 - 1. Evaluate graft–host apposition
 - 2. Assess the extent of interface fluid
 - 3. Verify graft orientation (DMEK; avoids marking tissue)
 - 4. Faster graft positioning with less graft manipulation
 - E. DISCOVER study of feasibility and usefulness
 - F. Limitations
- V. Postoperative OCT
 - A. Assess DSAEK/DMEK graft
 - 1. Thickness
 - 2. Centration
 - 3. Location and extent of detachment
 - 4. Epithelial ingrowth
 - B. Influences management
 - 1. Graft reshaping
 - 2. Graft repositioning
 - 3. Rebubbling
 - C. Assess graft–host junction and graft interface
- VI. Postoperative In Vivo Confocal Microscopy/Specular Microscopy
 - A. PK late endothelial graft failure
 - 1. Preop donor endothelial cell density (ECD) not predictive
 - 2. Low ECD at 6 months post-PK
 - B. DSAEK late endothelial graft failure
 - 1. Preop donor ECD not predictive
 - 2. Low ECD at 6 months post-DSAEK
 - 3. Intraoperative difficulties

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EK + DALK ≠ Panacea: When I Still Turn to PK

Mark A Terry MD

The astounding evolution of corneal transplantation over the past 20 years has emphasized the selective replacement of whatever layer of the cornea is deficient.

For eyes where the endothelium is damaged or diseased and the overlying stroma is edematous, Descemet membrane endothelial keratoplasty (DMEK) provides pure anatomic replacement resulting in fast, high-quality visual recovery. For eyes where the endothelial layer is normal but the overlying tissue is damaged or warped, deep anterior lamellar keratoplasty (DALK) provides the tissue clarity and visual results of penetrating keratoplasty (PK) but without the risks of rejection or the complications associated with extended steroid use.

The overwhelming benefits of EK and DALK mandate not only that all corneal transplant surgeons have these techniques at their disposal, but that they utilize them for the majority of their cases.

But does this mean that PK is relegated to the bin of out-moded procedures? Hardly!

There are clinical situations where PK is the obvious choice and other situations where PK is preferred but not absolutely the only way to proceed. Here are clinical settings where I still consider PK as the best option for my patient.

Obvious Clinical Settings for a PK

Corneal edema with central stromal ulceration and/or scarring

This setting represents full-thickness disease and therefore requires full-thickness replacement. However, the eye with stromal opacity that results *solely* from chronic edema is still better off with an EK than a PK (eg, chronic pseudophakic bullous keratopathy, congenital hereditary endothelial dystrophy, etc.) because normal topography is more visually important than mild residual stromal haze.

Infectious keratitis with generalized endothelial decompensation or perforation

With a PK, the goal of saving the eye with a tectonic graft can be coupled to the visual rehabilitation of replacing all affected layers.

Failed, prior PK with edema and high irregular astigmatism and contact lens intolerance

An EK would return the patient to the same lousy situation he/she had prior to the onset of edema. Rule of thumb: If the patient was happy with the PK transplant before the edema, do an EK. If the patient was unhappy with the PK transplant before the edema, do a repeat PK.

Clinical Settings Where a PK Is One of the Options

Keratoconus with significant Fuchs corneal dystrophy

PK may be best. However, if the Fuchs has nonconfluent guttata, then a DALK is a better choice. If the patient was a successful CL wearer before edema set in, then an EK might be best. This is a judgement call. Use a rule of thumb similar to the one you use for treating failed PK.

Fuchs with mild to moderate keratoconus

If the keratoconus is mild but the Fuchs has confluent guttata/edema, then EK may be a better choice. This is a judgement call. Use a rule of thumb similar to the one you use for treating failed PK.

Severe scarring opacity of stroma, with healthy endothelium, but in a setting requiring anterior segment reconstruction (eg, subluxed cataract, iridoplasty, suturing of IOL, etc.)

If the view into the anterior segment is so poor that you cannot safely do complex lens or iris work, then a PK with an open sky approach to reconstruction is simpler.

Another option

Trephinate, do a deep cut-down DALK dissection, remove 90% of stroma, place a bandage contact lens cut 0.5 mm smaller than the trephination onto the 10% recipient bed, and this will provide excellent visualization for safer anterior segment work using a closed chamber.

Patient with new corneal stromal scarring/ulceration in setting of a successful EK years before

The conundrum is that the prior EK has endothelium that is now accepted (off steroids) by the body and is essentially antigenically neutral. Doing a PK is easier but introduces a new, antigenically active endothelium to the body, increasing the likelihood of rejection. A cut-down DALK may be a more rational choice if the current EK endothelium has sufficient endothelial cell density numbers.

Controversial Clinical Setting for PK: Interface Infections After DALK or EK

Although interface infections are exceedingly rare after DALK or EK (rate = 11 in 10,000 cases),¹ when they do occur, they are usually fungal, with *Candida* being the most common organism. By the time the infection is recognized, it is well established in a stromal interface that is sequestered from topical, intracameral, and systemic medical treatment. Medical treatment alone has been shown to have a dismal success rate,¹ and these interface infections can lead to endophthalmitis and loss of the eye.

It is my strong opinion that if an interface opacity is suspected to be infectious, then a PK should be performed. Simply removing an EK graft with an infected interface risks seeding the anterior chamber with fungal organisms. The decisive action of a PK will completely excise the interface organism with a block resection, preventing further spread of the interface infection to the rest of the eye.

Explaining to the patient about astigmatism after a PK is easy; explaining that you unfortunately left fungus in the eye after removing their infected EK tissue, and that's why they lost their vision, is difficult.

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EK Alphabet Soup: Which Flavor to Choose?

Marjan Farid MD

I. Advances in Endothelial Keratoplasty

- A. Move towards thinner grafts → speed and quality of visual recovery
- B. Surgical challenges have also increased.
- C. Which procedure is ideal?
 - 1. DSAEK: endothelium (endo), Descemet membrane (DM), stroma (>100 µm)
 - 2. Ultrathin DSAEK: endo, DM, stroma (60-100 µm)
 - 3. Pre-Descemet EK (PDEK): endo, DM, pre-DM (25-30 µm)
 - 4. DMEK: endo, DM (15 µm)
 - 5. Descemet stripping only (DSO)/descemetorhexis without EK (DWEK): no endo/no tissue

II. How Does the Tissue Thickness Play a Role in Outcomes?

Review of studies showing thinner grafts have faster and better visual recovery

III. DMEK

- A. Purest form of EK, replacing only DM and endothelium
- B. Slower in adoption than DSAEK
 - 1. Need older donor tissue
 - 2. Surgical technique for insertion and unrolling is challenging.
 - 3. Need good visibility of anterior chamber
 - 4. Increased challenges in eyes with glaucoma device, poor iris anatomy, phakic
- C. Differences between DSAEK and DMEK
 - 1. Rejection
 - 2. Surgical complexity
 - 3. Anatomy
 - 4. Visual outcomes

IV. PDEK

- A. Graft includes pre-DM, DM, and endo → 25-30 µm
- B. Slight increase in graft strength to allow for ease of manipulation and unfolding; can use younger donor tissue
- C. Graft preparation done by surgeon.
 - 1. Increased endo loss, risk of tissue loss
 - 2. Smaller diameter graft

V. DWEK/DSO

- A. Only for Fuchs dystrophy (central dense guttae)
- B. Central 4-4.5 mm DM stripped (not scored)
- C. Allows migration of endo cells and clearing over 1-6 months
- D. However, rate of recovery is variable.
- E. Surgical technique is important in visual recovery.
- F. Centration and stripping are essential for a good outcome; avoid scoring!

VI. Conclusion

- A. EK is now the standard-of-care technique for endothelial disease.
 - 1. DMEK provides better and faster visual recovery.
 - 2. DSAEK still has a role in complex eyes.
 - 3. DWEK's role in central Fuchs-related guttae shows promise.
- B. As surgical techniques and eye banking of donor tissues evolve, outcomes and safety will continue to improve.

Endothelial Graft Failure: Options and Outcomes?

Francis W Price Jr MD

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Avoiding Keratoplasty: Descemet Stripping Only

Kathryn Colby MD PhD

Fuchs endothelial corneal dystrophy (FECD) affects up to 4% of patients in the United States and is the most common indication for corneal transplantation, accounting for 35% of the 47,700 transplants done in the U.S. in 2018. Despite having been described over 100 years ago, FECD remains an enigmatic disease. Multiple different mechanisms have been suggested to play a role in its underlying pathophysiology, including oxidative stress, mitochondrial dysfunction, unfolded protein response, and epithelial-mesenchymal transition. Numerous genetic mutations have been associated with FECD, although the vast majority of cases in white patients manifest a trinucleotide repeat expansion on chromosome 18. Exactly how this repeat expansion causes disease in FECD is unproven. Interference with cellular homeostasis via nuclear RNA foci ("RNA toxicity") or by cytoplasmic translation products from the expanded repeats ("RAN peptides") have been suggested as possible mechanisms.¹

The surgical management of FECD has undergone a revolution in the past 20 years; selective endothelial replacement surpassed penetrating keratoplasty as the procedure of choice a number of years ago. Modern-day endothelial keratoplasties, including Descemet membrane endothelial keratoplasty (DMEK) and Descemet-stripping endothelial keratoplasty (DSEK), are safe and effective surgeries, with generally rapid visual recovery and low risks of immunologic rejection. A number of years ago, however, several lines of evidence suggested that the endothelium in FECD might be capable of self-rejuvenation. These included isolated case reports of corneal clearance after inadvertent removal of Descemet membrane,² after detachment of endothelial grafts,^{3,4} or after destruction of the corneal endothelium by cryotherapy.⁵ The first series of deliberate stripping of Descemet membrane as a treatment for endothelial dysfunction showed inconsistent results.⁶ Subsequently, we, and others, have shown that corneal clearance in FECD can be achieved after deliberate central Descemet stripping only (DSO), without graft placement.⁷⁻¹⁰ Recent work suggests that ripasudil, a topical Rho kinase inhibitor, can facilitate corneal clearance after DSO.^{8,10}

This talk will review the current state of DSO, the indications/contraindications for this procedure, and future directions for nongraft therapies for treatment of FECD.

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Keratoprosthesis Update: Indications and Long-term Outcomes

Geetha Iyer MBBS

Keratoprosthesis (KPro) forms the last resort for bilateral end-stage corneal blindness. Among all the KPros, the Boston Type 1 and 2 KPros, the modified osteo-odonto keratoprosthesis (MOOKP), and the osteo-KPro are the more frequently and commonly performed. Though the indications have significantly expanded over the years and the complications have been reduced with modifications in design and postoperative regimen, these are procedures that require an exclusive setup and a commitment to long-term follow-up and post KPro care. In order to be active in the field of KPros, it is important to understand the nuances of these surgeries and to make a judicious decision regarding patient and KPro selection and, more importantly, deferral.

Types of Keratoprosthesis/Design

The design of a KPro can be likened to some extent to that of an IOL, consisting of an optic (PMMA cylinder) and a haptic. It is the haptic of the KPro that determines the type of prosthesis, and these can be divided into the following groups:

- Biocompatible: Usually a PMMA skirt with the corneal graft as in the Boston Types 1 and 2 KPro
- Biointegrated: The Dacron mesh that forms the skirt around the PMMA optic in the Pintucci KPro
- Biological: The tooth or bone that forms an autologous biological tissue that supports the optical cylinder in the osteo-odonto and the osteo-KPro, respectively

The supporting cover tissue adds to the KPro complex.

Indications for Type 1 KPro

Good prognosis

1. Multiple failed grafts
2. Aniridia
3. Herpetic keratitis
4. Silicone oil-filled eyes

Guarded prognosis

1. Pediatric corneal conditions
2. Chemical injuries

Very guarded prognosis

1. Underlying immune conditions like Stevens-Johnson syndrome (SJS)/ocular cicatricial pemphigoid (OCP)
2. Severe chemical injuries with severe forniceal shortening and lid abnormalities

Indications for Type 2 KPros (MOOKP/Boston type 2/Osteo-KPro)

1. SJS
2. OCP/MMP
3. Severe chemical injuries
4. Severely keratinized surface

Brief Comparison of Techniques

Importance of Perioperative Care

Long-term Outcome

The outcome of each of the KPros over a 15-year period from a single tertiary eye care center in India will be compared with the global outcome, highlighting certain crucial timelines heralding the onset of complications specific to a particular type of KPro.

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Interactive Case Presentation: Choose Your Own Keratoplasty Adventure

Marian Sue Macsai-Kaplan MD

CASE PRESENTATION

A 50-year-old Italian female presents with blurred vision OD.

Past Medical History

At age 32 she underwent bilateral LASIK for -4.00 OU, with an outcome of 20/20. Two years later she was started on topiramate for migraines and was given the wrong dose by the pharmacy and developed IOP OU over 40. With discontinuation of the medicine the pressure normalized, but her right eye went on to develop progressive ectasia and underwent a full-thickness penetrating keratoplasty. She had 2 rejection episodes OD and eventually developed diffuse corneal edema with a dense cataract in the right eye.

She now presents with a diffusely edematous graft with over 5 D orthogonal astigmatism and a dense cataract OD.

What should you do?

1. Repeat the PK and do open sky cataract surgery?
2. Descemet-stripping endothelial keratoplasty (DSEK) only, then cataract surgery?
3. Descemet membrane EK (DMEK) only, then cataract surgery?
4. DSEK with cataract surgery?
5. DMEK with cataract surgery?
6. Should you use a toric IOL?

Is Tissue Still the Issue? Anterior Segment Imaging for Management of Ocular Surface Tumors

Carol L Karp MD

Adapted from Karp CL. Evolving technologies for lid and ocular surface neoplasias: is optical biopsy a reality? JAMA Ophthalmol. 2017; 135(8):852-853.

Retinal imaging has revolutionized the management of posterior segment diseases. Imaging techniques provide outstanding visualization of the retinal anatomy and blood flow patterns. Finally, great advances in the field of imaging are now available for ocular surface lesions.

Lesions on the ocular surface can present a diagnostic challenge to eye care providers. While often a diagnosis can be made clinically, sometimes the pathology may be subtle, or the salient features can be obscured by concomitant skin and ocular surface diseases. In the arena of ocular surface and adnexal oncology, new advances in technologies of in vivo confocal microscopy (IVCM),^{1,2} optical coherence tomography (OCT),³ and high-resolution ultrasound biomicroscopy (UBM)⁴ can help detect and identify neoplastic lesions with greater sensitivity than is possible with clinical examination.

The idea of performing an “optical biopsy” in the office is indeed intriguing. IVCM, OCT, and high-resolution ultrasound are among the tools presently at our disposal. These new technologies can assist the ophthalmologist diagnose and manage ocular surface neoplasias.

High-resolution OCT shows promise for conjunctival lesions, in particular for squamous neoplasia.³ It has been shown to be helpful in the diagnosis and management of conjunctival lesions, even in the setting of complex ocular surface conditions. These devices provide resolution of 3-7 microns and provide a cross-sectional view of the lesion.³ It is noncontact and easily scans both corneal and conjunctival lesions. Most existing posterior segment devices can be used for the ocular surface with simple placement of an anterior segment lens. In comparison to IVCM, OCT technology is easy for the patient (noncontact/rapid image acquisition), has less need for an experienced operator, and is easier for health care providers to learn to interpret.³

Currently no imaging technique is perfect, and histopathology remains the gold standard. However, new imaging devices will continue to evolve as important adjuncts to clinical evaluation. This will help clinicians to target subtle lesions that need removal. These new techniques, in particular OCT, can also be useful in directing the biopsy location in ambiguous cases.⁵ This could potentially decrease the risk of false negative results.

As the pendulum swings toward treating more and more surface lesions with medical therapy, so also does our need for non-invasive surveillance techniques increase. These techniques can help the clinician monitor for resolution in medically treated lesions and avoid premature termination of therapy. Confirming resolution prior to termination of treatment is paramount to preventing recurrences. The ability to noninvasively evaluate the ocular surface is also a great advantage in the setting of coexisting ocular surface diseases.⁵

The time for noninvasive “optical biopsies” of ocular surface and lid tumors has arrived, and in vivo techniques are important adjuncts to clinical acumen. As technology improves, we can look forward to improved image resolution, ease of use, and expanded applications of imaging techniques for our patients with ocular surface tumors.

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Ocular Surface Squamous Neoplasia: Topical vs. Surgical Treatment for OSSN

Fairooz P Manjandavida MD

Introduction

“Ocular surface squamous neoplasia” (OSSN) is a blanket term currently used for precancerous and cancerous epithelial lesions of the conjunctiva and cornea that includes the spectrum of dysplasia, conjunctival intraepithelial neoplasia, and malignant squamous cell carcinoma.^{1,2} Previously used terms include “intraepithelial epithelioma,” “Bowens disease,” and “Bowenoid epithelioma.”³ It is recently broadly classified as conjunctival intraepithelial neoplasia (CIN) and invasive squamous cell carcinoma (SCC). It is confined to the conjunctival epithelium and accounts for 39% of all premalignant and malignant lesions of the conjunctiva and 4% of all conjunctival lesions.⁵ Invasive squamous cell carcinoma of the conjunctiva occurs with much less frequency than CIN, with incidence that varies from 0.02 to 3.5 per 100,000 population.⁶ Clinically, it is often difficult to differentiate between CIN and invasive SCC, but increased thickness and nodularity with feeder vessels are believed to be a sign of malignant transformation. However, there are thick tumors that may remain within the epithelium.

Predisposing factors for the development of OSSN, both environmental and systemic, include exposure to sunlight, HPV type 16 infections, and immunocompromised status.^{1,2,4,5} There is a strong systemic association with xeroderma pigmentosum that may present as multiple recurrent lesions requiring long-term follow-up. Papillon-Lefevre syndrome, a rare syndrome with palmoplantar keratoderma, is also associated with OSSN in younger individuals.

OSSN is mostly unilateral and is commonly seen in middle-aged and older patients, presenting as redness and ocular irritation. Larger lesions encroaching the cornea may affect the vision. Characteristically, tumor may appear as a fleshy, nodular, or sessile minimally elevated lesion with overlying keratin, feeder vessels, and intrinsic vascularity.^{1,2,5,6} Rose bengal staining is helpful in the diagnosis and in assessing the extent of the tumor. Corneal involvement may appear as a subtle, wavy, superficially advancing, greyish opacity that may be relatively avascular or may have fine blood vessels, whereas others may present as papilliform or diffuse gelatinous lesions usually encroaching the cornea. Primary corneal dysplasia affects the corneal epithelium with minimal limbal involvement.⁷ Primary squamous cell carcinoma of the cornea is rare.

Morphological Types

- Placoid
 - Gelatinous
 - Papilliform
 - Velvety
 - Leukoplakic
- Nodular
- Diffuse



Figure 1. Elevated nodular conjunctival-limbal lesion with surface keratin, feeder vessels, and intrinsic vascularity that stains positive with rose bengal. Corneal encroachment is noted. These are the clinical features of OSSN.

There are no consistent clinical criteria for distinguishing CIN from invasive squamous cell carcinoma. Leukoplakia is usually absent or minimal in CIN; extensive leukoplakia raises the suspicion of malignancy. Nodular lesion causes suspicion of invasive squamous cell carcinoma. A diffuse conjunctival OSSN can masquerade as chronic conjunctivitis.⁷⁻⁹ It is also important to evert the eyelid of patients with OSSN to detect the contiguous or multifocal involvement of the tarsal conjunctiva.

Advanced cases can infiltrate the cornea and sclera to have intraocular extension.⁷ Tumors extending into the orbit cause proptosis. Loco-regional lymph node and distant metastasis may occur rarely.⁹ The most aggressive variants include spindle cell squamous carcinoma, mucoepidermoid carcinoma, and adenoid squamous cell carcinoma.²

Types of Invasive Conjunctival SCC

- Spindle cell variant
- Mucoepidermoid carcinoma
- Adenoid squamous carcinoma



Figure 2. A 42-year-old immunocompromised male with conjunctival mass in right eye with extensive surface keratin presented with hypopyon and intraocular extension.

Diagnosis

OSSN is diagnosed clinically under slit-lamp biomicroscope with characteristic features as enumerated earlier. Anterior segment OCT is used as a diagnostic aid but may not be helpful in delineating the vertical extent in the presence of surface keratin and back scattering. Recently “optical biopsy,” a novel technology of ultrahigh-resolution spectral domain OCT, has proven useful in detecting epithelial lesions and in guiding the management of OSSN in the era of topical chemotherapy/immunotherapy.¹⁰ Ultrasound biomicroscopy (UBM) is found to be a useful tool in identifying the intraocular extension in advanced lesions. Orbit imaging with computerized tomography (CT scan) is advised in tumors with suspected orbital extension and indicate those that extend to fornix and caruncle.

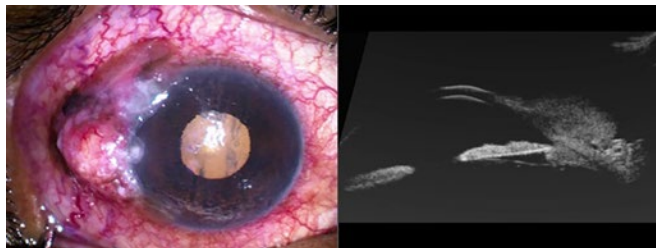


Figure 3. Nodular OSSN with corneal encroachment and scleral fixity shows scleral extension and ciliary body invasion in ultrasound biomicroscopy (UBM).

Treatment

Complete but gentle surgical excision using a technique without touching the tumor, called the “no-touch” technique, is the treatment of choice.^{1-3,5,11}

The steps of surgical excision include the following:

1. Conjunctival incision is made approximately 4 mm outside the clinically determined tumor margin. The incision incorporates full-thickness conjunctiva and Tenon fascia.
2. Dissection is carried out up to the limbus in the episcleral plane (if there is no episcleral adhesion).
3. Lamellar dissection of tumor-free sclera, 0.2 mm in depth and 2.0 mm outside the adherent conjunctival mass, is performed if the tumor is adherent to the episclera.
4. Absolute alcohol is applied with cotton-tipped applicator to the involved cornea to allow for controlled corneal epitheliectomy 2 mm outside the corneal component.
5. The corneal epithelium is scrolled off to the limbus using a controlled sweeping motion with a Beaver blade.
6. The tumor is removed in 1 piece along the limbus without touching the tumor.
7. Cryotherapy, double-freeze thaw cycle, is applied to the edge of the remaining bulbar conjunctiva and the scleral base if there was episcleral adhesion. Limbal cryotherapy should be limited to 6 clock hours.
8. Excision is followed by direct closure of the conjunctiva or with amniotic membrane graft.

Reported recurrence rate is 15%-52%. Lee et al reported a 17% recurrence after excision of conjunctival dysplasia, 40% after excision of CIN, and 30% for squamous cell carcinoma of the conjunctiva.² However, with the protocol-based technique described above, the recurrence rate can be limited to less than 5%.

Apart from surgical excision, topical immunotherapy and chemotherapy have recently been considered as a mainstay of treatment in CIN.¹²⁻¹⁴ Currently topical interferon alpha 2b is widely accepted in the management of CIN as immunotherapy for primary treatment, for immunoreduction to reduce the size of large tumors to facilitate complete tumor excision, and for immunomodulation in immunocompromised patients.^{15,16} It is also used in patients with surgical margin positive for tumor cells to prevent recurrence. Topically it is administered as 1 million IU, 4 times daily for 6 to 12 months. Extensive lesions are treated with 3 to 10 IU of monthly intralesional injections until resolution.

Indications for Topical Chemotherapy in Noninvasive OSSN

1. >2 quadrants of conjunctival involvement
2. >180 degree of limbal involvement
3. Clear corneal extension encroaching the pupillary axis
4. Positive margin after excision
5. Patient not fit for surgery

Protocol for Interferon-alpha 2b

- Topical eye drops 1 million IU 4 times a day for 3 to 12 months
- Injection sublesional 3 to 10 million IU once monthly until resolution
- Refrigeration required



Figure 4. Diffuse corneal OSSN with temporal limbal involvement in right eye of an 18-year-old immunocompromised female shows complete resolution with 4 months of topical interferon- alpha 2B.

Combined topical immunotherapy and surgical excision provides excellent outcome with reduced recurrence rate,¹⁵ also having the advantage of treating subclinical disease. However, clinical resolution is not immediate, often requiring months and strict patient compliance. It can also be used as a combination of topical and intra-lesional injection to reduce the treatment duration.

Topical mitomycin C (MMC) has similar indications but is less favored due to surface toxicity.¹⁷⁻¹⁹ There are several protocols, but a dosage of 0.04%, q.i.d., 4 days/week for 4 weeks works best, in our experience.

Protocol for Topical MMC: Rule of 4

- 0.04% (0.4 mg/mL)
- Four times a day
- Four days a week
- Four weeks
- * * *
- Two weeks of treatment-free interval
- Refrigeration required

Topical 1% 5-fluorouracil (5-FU) is an antimetabolite used in the treatment of OSSN. It is widely available and comparatively cheap.²⁰⁻

²⁵ Various studies have recently reported the effectiveness of 5-FU as a primary modality and postoperative adjuvant to reduce the recurrence.^{24,25} The advantage of 5-FU over the other topical

medication is that it does not require refrigeration or cold-chain to be maintained. In developing countries where there are financial restraints and resource limitations, 5-FU can be accepted as a valuable alternative.

Plaque brachytherapy is used to control gross or microscopic residual tumors. It is also indicated as primary modality or in those with scleral invasion.^{26,27} More extensive orbital invasion requires orbital exenteration.

Prognosis

Conjunctival squamous cell carcinoma has good prognosis. With protocol-based management, local recurrence rate is about 5% and regional metastasis is 2%.²² Prognosis is worse in mucoepidermoid or spindle cell variants and in patients who are immunosuppressed, particularly those with AIDS.

Protocol for Topical 5-Fluororacil

- 1% eye drops 4 times a day for 4 weeks (1 cycle)
- Two weeks of treatment-free interval
- Refrigeration *not* required

Table 1. Topical Chemotherapeutic Agents for OSSN: Summary

Drugs	Type	Mechanism of Action	Dosage	Adverse Effects
Mitomycin C	Alkylating agent	Under aerobic condition generates free radicals ↓ • Cytotoxicity • Lipid peroxidation • Inhibition of DNA and protein synthesis • Inhibits cell migration and production of extracellular matrix	• Topical • 0.02% to 0.04%	• Conjunctival hyperemia • Blepharospasm • Corneal punctate erosion • Punctal stenosis • Limbal stem cell deficiency
5-fluorouracil	Pyrimidine analogue	• Inhibits thymidylate synthetase • Inhibits production and incorporation of thymidine into DNA • Inhibits RNA synthesis	Topical 1%	• Eyelid erythema • Conjunctival hyperemia • Corneal punctate erosion
Interferon-α2b	Type 1 interferon	• Immune mediated suppression of IL-10, stimulates IL-2 and IFN-γ m RNA • Antiproliferative • Antiviral	• Topical or intralesional • 1 million IU/mL • 3 million IU/mL	• Superficial punctate keratopathy • Follicular conjunctivitis • Systemic • Flu-like syndrome • Fever/ myalgia

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There's Something Fishy Here: Diagnosis and Management of Lymphoproliferative Lesions

Bita Esmaeli MD FACS

In this talk I will discuss the clinical features of conjunctival/ anterior segment lymphomas and briefly review the role of biopsy and techniques, different histologies, risk of extraocular involvement, diagnostic steps, and treatment options for conjunctival lymphoma. Recent findings with the use of ultralow-dose radiation therapy will also be discussed.

Selected Readings

1. Kirkegaard MM, Rasmussen PK, Coupland SE, et al. Conjunctival lymphoma: an international multicenter retrospective study. *JAMA Ophthalmol.* 2016; 134(4):406-414.
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Panicking Over Pigment: Management of Conjunctival Pigmented Lesions

Lauren A Dalvin MD

I. Clinical Features of Conjunctival Melanocytic Lesions

A. Conjunctival nevus

1. Key clinical feature: presence of pseudocysts
2. Associated syndromes: Carney complex and dysplastic nevus syndrome

B. Complexion-associated melanosis (CAM)

1. Key clinical features: bilateral, flat, concentrated at limbus, more common with dark complexion

C. Primary acquired melanosis (PAM)

1. Key clinical features: unilateral/asymmetric, more common with light complexion, risk for melanoma
2. If severe atypia, 21% progress to melanoma

D. Malignant melanoma

1. Key clinical features: pigmented, elevated, feeder and intrinsic vessels, 25% risk for metastasis at 10 years, medical oncology referral required for systemic workup
2. Diagnostic tests: ultrasound biomicroscopy, anterior segment OCT
3. Atypical presentations of ocular surface malignancy
 - a. Amelanotic melanoma can mimic squamous cell carcinoma.
 - b. Pigmented squamous cell carcinoma can mimic melanoma.

II. Treatment of Conjunctival Melanocytic Lesions

A. Surgical excision

1. Key techniques: no touch, alcohol keratectomy, partial lamellar scleroconjunctivectomy, 2-4 mm margins, double freeze-thaw cryotherapy
2. The first surgery is the most important.
3. Sentinel lymph node biopsy: Consider if malignant melanoma with tumor thickness >2 mm

B. Topical medications

1. Mitomycin C
2. Interferon alpha-2b

C. Radiotherapy

III. Role of Molecular Medicine in Conjunctival Melanoma

A. Biomarkers for prediction of metastatic risk and targeted therapy: BRAF, KIT, NF1, NRAS, PD-1, PD-L1, PTEN, TERT

B. Targeted systemic medications

1. BRAF inhibitors: vemurafenib (Zelboraf), dabrafenib (Tafinlar), encorafenib (Braftovi)
2. Checkpoint inhibitors: ipilimumab (Yervoy), pembrolizumab (Keytruda), nivolumab (Opdivo), atezolizumab (Tecentriq), avelumab (Bavencio), durvalumab (Imfinzi)

Selected Readings

1. Shields JA, Shields CL, Mashayekhi A, et al. Primary acquired melanosis of the conjunctiva: risks for progression to melanoma in 311 eyes. The 2006 Lorenz E Zimmerman Lecture. *Ophthalmology* 2008; 115(3):511-9.e2.
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Management of Pigmented Iris Lesions: When Should I Worry?

Carol L Shields MD

What Are the Various Types of Iris Tumors?

In 2012, Shields et al reviewed 3680 tumors of the iris referred to an ocular oncology practice and found that the spectrum of iris tumors includes cystic (21%) and solid (79%) tumors. The solid tumors included melanocytic (68%) and nonmelanocytic (11%). At all ages, the most common specific diagnoses were nevus (42%), iris pigment epithelial (IPE) cyst (19%), and melanoma (17%). Overall, the 3 most common specific diagnoses (children, young adult, mid adult, senior adult) were nevus (25%, 36%, 47%, and 47%, respectively), IPE cyst (28%, 30%, 15%, and 14%, respectively), and melanoma (8%, 16%, 20%, and 19%, respectively).

Of 2510 melanocytic iris tumors, the most common were nevus ($n = 1534$; 61%) and melanoma ($n = 645$; 26%). Throughout the 4 age categories, nevus and melanoma prevailed, but in children there was higher incidence of referral for melanocytosis and melanocytoma. Melanoma represented 17% (36/212 cases) of all iris tumors found in children, 27% (131/487) in young adults, 26% (258/981) in mid adults, and 27% (220/830) in senior adults.

What Do We Know About Iris Freckles?

In 1985, Kliman et al reviewed 213 patients with iris freckle, nevus, and melanoma and found a strong association with light-colored (blue or green) irides ($P < .001$).

In 2017, a report by Schwab et al reviewed 638 volunteers in Austria of mean age of 38 years and revealed 1 or more iris freckles in 76% of patients, usually in the inferotemporal quadrant. Iris freckles were associated with older age, more sunburn history, more sun-damaged skin, more skin freckles, and great skin total nevus count. They surmised that sun exposure can trigger formation of iris freckles. They further stated that iris freckles could be a biomarker for sun damage of the skin and risk for skin malignancy.

Can Iris Nevus Signify Eye Disease?

In 2009, Weis et al provided a meta-analysis of published reports to study the relationship between cutaneous and iris nevi with uveal melanoma. They found that atypical cutaneous nevi, common cutaneous nevi, cutaneous freckles, and iris nevi were all associated with risk for uveal melanoma. Meta-analysis of 825 cases in 4 studies found iris nevus with odds ratio of 1.53 for uveal melanoma.

In 2013, Shields et al studied iris nevus in 1611 cases monitored over a long period of time and found transformation into melanoma in 4% at 10 years and 11% at 20 years. Risk factors are listed in Table 1 and are remembered by the lettering "ABCDEF Guide."

Table 1. Melanocytic Iris Tumors in 2510 Cases Based on Age at Presentation

Diagnosis	All ages ($n = 2510$ tumors), n (%)	Children 0-20 years ($n = 212$ tumors), n (%)	Young adults, 21-40 years ($n = 487$ tumors), n (%)	Mid adults, 41-60 years ($n = 981$ tumors), n (%)	Senior adults >60 years ($n = 830$ tumors), n (%)
	111 (4)	8 (4)	20 (4)	33 (3)	50 (6)
Nevus	1503 (60)	108 (51)	271 (56)	606 (62)	518 (62)
Tapioca nevus	31 (1)	4 (2)	6 (1)	10 (1)	11 (1)
Melanocytoma	68 (3)	14 (7)	25 (5)	24 (2)	5 (<1)
Melanocytosis	64 (3)	22 (10)	14 (3)	18 (2)	10 (1)
Lisch nodules	70 (3)	12 (6)	17 (3)	29 (3)	12 (1)
Melanoma	645 (26)	36 (17)	131 (27)	258 (26)	220 (27)
Other	18 (<1)	8 (4)	3 (<1)	3 (<1)	4 (<1)

Table adapted from Shields CL, Kancherla S, Patel J, et al. Clinical survey of 3680 iris tumors based on patient age at presentation. *Ophthalmology* 2012; 119:407-414, table 3.

Table 2. Iris Nevus Growth to Melanoma: ABCDEF Guide for Predicting Nevus At Risk

Letter	Feature	Transformation into melanoma relative to feature presence/absence (n = 27)		Feature relative to presence/absence of transformation into melanoma (n = 1611)		
		Feature present, n (%)	Feature absent, n (%)	Growth into melanoma present, n (%)	Growth into melanoma absent, n (%)	Hazard ratio ^{a,b}
A	Age (≤40 yrs; n = 387)	13 (48)	14 (52)	13 (3)	374 (97)	3
B	Blood (n = 12)	3 (11)	24 (89)	3 (25)	9 (75)	9
C	Clock-hour inferior (n = 1147)	26 (96)	1 (4)	26 (2)	1121 (98)	9
D	Diffuse configuration (n = 6)	1 (4)	26 (96)	1 (17)	5 (83)	14
E	Ectropion (n = 300)	13 (48)	14 (52)	13 (4)	287 (96)	4
F	Feathery margin (n = 402)	14 (52)	13 (48)	14 (4)	388 (96)	3

a Rounded.

b Cox proportional hazard ratio.

Table adapted from Shields CL, Kaliki S, Hutchinson A, et al. Iris nevus growth into melanoma: analysis of 1611 consecutive eyes. The ABCDEF guide. *Ophthalmology* 2013; 120(4):766-772; table 6.

How Aggressive Is Iris Melanoma?

Iris melanoma can manifest as a circumscribed nodule or as a flat diffuse mass with extensive seeding. Treatment of iris melanoma includes resection for small tumors; plaque radiotherapy for small, medium, and large tumors or those with seeding; and enucleation for those with secondary glaucoma. A comparison of adults versus children with iris melanoma revealed children with smaller tumor size, less tumor seeding, lower incidence of glaucoma, and better prognosis. The American Joint Committee on Cancer (AJCC) classification can aid in prediction of metastasis. In 2012, Shields et al studied iris melanoma in 317 consecutive cases and found metastatic disease in 5% at 5 years, 9% at 10 years, and 11% at 20 years, much lower than the rates found with ciliary body and choroidal melanoma.

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Interactive Case Discussion: It's Not a Too-mah . . . Or Is It?

Shahzad I Mian MD

NOTES

Is This Infection or Peripheral Ulcerative Keratitis?

Natalie Afshari MD

The ocular surface can show the first sign of the systemic autoimmune disease, and since the peripheral cornea is vascularized, it can be the site of deposition of circulating immune complexes. The ocular findings in autoimmune disorders may be dry eye, peripheral ulcerative keratitis (PUK), episcleritis, scleritis, and uveitis. The most frequent ocular finding in autoimmune disorders is dry eye disease, and the most destructive ocular surface manifestation is PUK. The symptoms associated with PUK include pain, photophobia, corneal opacity, and even corneal perforation.

The exact pathogenesis of PUK is unknown, but studies indicate that both humoral and cell-mediated immunity are involved in the disease and matrix metalloproteinases lead to corneal melt. PUK often occurs in patients who have long-standing rheumatoid arthritis and positive serology for both rheumatoid factor and anti-cyclic citrullinated peptide antibody. The ulceration can be central or paracentral, and it is bilateral in 40% of cases. This fact, along with PUK's association with systemic disease and negative corneal cultures, helps in distinguishing this condition from infectious keratitis. Thus, in these cases a thorough history and review of systems, careful examination, and study of biomarkers are used as the diagnosis basis. Because of improved treatment options for rheumatoid arthritis with methotrexate or biologic disease-modifying anti-rheumatic drugs such as anti-TNF inhibitors, PUK is becoming less common.

Timely diagnosis and treatment of these patients is of utmost importance. Treatment should be initiated immediately after diagnosis and include systemic therapy such as nonsteroidals, corticosteroids, systemic immunosuppressive agents, biologics, and surgical therapy. Rheumatology assessment and comanagement of these patients is critical in the care and outcome.

Selected Readings

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Scleral Melt: Too Hot to Patch?

Victor L Perez MD

- I. Inflammation of the Anterior Segment
 - A. Tip of the iceberg of presentations of systemic autoimmune diseases and local infections
 - B. Case presentation
- II. Necrotizing Scleritis / “Scleral Melt”: Implication and Diagnosis
 - A. Scleral melt is an important inflammatory process of the anterior segment that cannot be missed.
 - B. Clinical implications from a systemic point of view: Increased incidence of morbidity and mortality.¹ Leads to ocular morbidity and severe damage = blindness.
 - C. Mechanism of action: Autoimmune vasculitis of deep episcleral vessels complex/plexus that leads to occlusion and ischemia. In infections, direct invasion of organism associated with severe inflammation.
 - D. Diagnosis
 1. Mainly clinical exam
 2. Photos of different presentations of scleral melt
 - E. Use of imaging modalities is complementary or helpful in treatment.²
- III. “To Patch or Not to Patch”
 - A. Do not panic: All scleral melts will look emergent, but surgical intervention may not be needed.
 - B. Photos of scleral melts: hot and not hot
 - C. Always culture and biopsy if necessary.
 - D. Scleromalacia is not an acute scleral melt.
- IV. Medical Therapy Is Always First Line of Therapy With or Without Patch
 - A. Use of steroids: Systemic prednisone is a very important medical therapy to understand and use.
 - B. Use of steroid-sparing therapies
 1. Anti-metabolites
 2. Biological therapies: anti-TNF therapies and anti-CD20 therapies
 3. Alkalating agents
 4. Others

- V. Surgical Approach to Patching
 - A. Control of inflammation first!
 - B. Scleral tissue: Patch graft or whole sclera (preferable)
 - C. Preparing scleral patch graft
 - D. Surgical technique video
- VI. Surgical Patching: Important Considerations
 - A. Need for healthy tissue around patch
 - B. Need to cover patch graft: conjunctiva, amniotic grafts, other mucosal tissue
 - C. What to do with infectious “hot scleral melts”
- VII. Conclusions
 - A. Scleral melts are dangerous manifestations of systemic autoimmune diseases or local infections.
 - B. Not every scleral melt needs a patch.
 - C. Surgical patching can be successfully done in hot scleral melts, but *inflammation needs to be controlled*.

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What's New in Topical Anti-inflammatory Agents/Management of Atopic and Vernal Conjunctivitis

Stephen C Pflugfelder MD

- I. Pathogenesis of Atopic (AKC) and Vernal (VKC) Keratoconjunctivitis¹⁻¹⁰
 - A. AKC: Increased expression of Th1 (IFN- γ) and Th2 (IL-4) cytokines and infiltration with eosinophils and neutrophils have been detected in the conjunctiva. IFN- γ concentration in tears is correlated with severity of corneal epithelial disease. Increased TGF- β expression promotes fibroblast activation, collagen deposition, and fibrosis.
 - B. VKC: Th2 cells, mast cells, and eosinophils are involved. Increased tear VEGF may contribute to corneal neovascularization and giant papillae formation.
- II. Clinical Trials on Clinicaltrials.gov
 - A. NCT003379311: Humanized Moab against siglec8 and inflammatory protein expressed by eosinophils. Phase 1b for AKC, active but not recruiting.
 - B. NCT00987467: CsA 0.05% for AKC. Completed.
 - C. NCT00884585: CsA 0.1% for AKC. Completed.
- III. Current Treatment Recommendations Include Anti-inflammatory Regimen Tailored to Symptoms and Severity of Clinical Signs
 - A. Itching: topical antihistamine/mast cell stabilizers^{4,11}
 - B. Conjunctival inflammation
 1. Pulse corticosteroid (dexamethasone, prednisolone, difluprednate) with taper to soft steroid at lowest frequency and concentration^{4,11}
 2. Consider supratarsal triamcinolone injection^{12,13}
 3. Calcineurin inhibitors: tacrolimus (0.03%-0.1%), cyclosporine (0.05%-0.1%)¹⁴⁻¹⁸
 - C. Corneal neovascularization: steroids, laser photocoagulation, and subconjunctival bevacizumab injection¹⁹⁻²¹
- IV. Other Therapies

Hydrogel or scleral contact lenses for severe epitheliopathy and nonhealing corneal epithelial defects²²
- V. Management of Dupilumab Conjunctivitis
 - A. Conjunctivitis has been reported to develop in 2%-23% of patients treated with dupilumab for moderate to severe atopic dermatitis (anti-IL-4 receptor alpha that blocks IL-4 and IL-13 signaling).²³⁻²⁶
 - B. Loss of goblet cells may contribute to disease.²⁴

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Biologics: Are They Any Good for Ocular Inflammation?

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Interactive Case Discussion: Not Your Typical Red Eye

Deepinder K Dhaliwal MD

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ClearView Healthcare Partners: C
CoA Therapeutics: C
CorNeat: C
Department of Defense: S
Dompé: C
Eye Bank Association of America: S
Gore: C
Guidepoint: C
Health Advances: C
Kala: C
KeraLink: L
LifeSciences Consultants: C
National Eye Institute: S
Shire: C
SightLife: L
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Dompé: C
Eyepoint: C
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Alcon Laboratories, Inc.: L,S
Allergan: C,L,S
Bausch + Lomb: C,L
CAPES: S
Cnpq: S
EMS: C
Fapesp: S
Genon: L
Mundipharma: L,C
Ofta: C,L,S

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Aerie Pharmaceuticals: C
 Allergan: C,S
 Bausch + Lomb: C,S
 Coopervision: C
 Dompé: C,S
 Eyegate Pharma: C
 GlaxoSmithKline: S
 Heidelberg Engineering: C
 National Eye Institute: S
 Santen, Inc.: C
 Shire: C,S
 Stealth: C,S
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AbbVie: C
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 Avedro, Inc.: C
 Eyevance: C
 Johnson & Johnson: C
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 Nutriceuticals: C
 Shire: L,C

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 National Eye Institute: S
 Novaliq: C
 Shire: C
 Trefoil: C,O
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 Immuneyez: O
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 Shire: C,S

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Aerie Pharmaceuticals, Inc.: S
 Alcon Laboratories, Inc.: C
 Allergan, Inc.: C
 EyePoint Pharmaceuticals: C
 Haag-Streit: C
 Interactive Medical Publishing: O
 Kedrion Biopharma: C
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 Bio-Tissue, Inc.: C,L
 GlaxoSmithKline: C
 Kala: C
 Novartis, Alcon Pharmaceuticals: C
 Rapid Pathogen Screening: O
 Shire: C,L
 Sun Ophthalmics: C
 TearLab: C

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 Immunocore, Inc.: C

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Alcon Laboratories, Inc.: C
 Allergan: C,L
 Avedro, Inc.: C
 Bausch + Lomb: C
 CorneaGen: L
 Shire: C,L
 Sightlife: C,S
 SUN: C

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Bausch + Lomb Surgical: P,S
 Envisia: C
 Gore: C
 Moria: S

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AbbVie: C
 Eversight: S,E
 Eye Bank Association of America: S
 Kedrion: C
 Okogen: C

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None

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Vortex Surgical: O
 Warby Parker: S

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