Cornea 2016
Advancements in Cornea and External Disease—Essential Tools for Success in 2016

Program Directors
Shahzad I Mian MD, Bennie H Jeng MD, Carol L Karp MD

In conjunction with the Cornea Society

McCormick Place
Chicago, Illinois
Saturday, Oct. 15, 2016

Presented by:
The American Academy of Ophthalmology

Sponsored in part by an unrestricted educational grant from Shire

2016 Cornea Planning Group
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Program Director
Bennie H Jeng MD
Program Director
Carol L Karp MD
Program Director

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2015  Stephen C Kaufman MD PhD
      Bennie H Jeng MD
      Shahzad I Mian MD
2014  William Barry Lee MD
      Elmer Y Tu MD
      Stephen C Kaufman MD PhD
2013  Kathryn A Colby MD PhD
      William Barry Lee MD
      Elmer Y Tu MD
2012  Anthony J Aldave MD
      Natalie A Afshari MD
      Kathryn A Colby MD PhD

2011  Christopher J Rapuano MD
      Natalie A Afshari MD
      Anthony J Aldave MD
2010  Michael W Belin MD
      David B Glasser MD
      Christopher J Rapuano MD
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On behalf of the American Academy of Ophthalmology and the Cornea Society, it is our pleasure to welcome you to Chicago and Cornea 2016: Advancements in Cornea and External Disease—Essential Tools for Success in 2016.

Shahzad I Mian MD
Program Director
None

Bennie H Jeng MD
Program Director
CoDa Therapeutics: C
Eyegate Pharmaceuticals: O
Jade Therapeutics: C
Kedrion: C | Santen Inc.: C

Carol L Karp MD
Program Director
None

2016 SUBSPECIALTY DAY ADVISORY COMMITTEE

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Kuldev Singh MD MPH (Glaucoma)
Abbott Medical Optics Inc.: C
Aerie: C
Alcon Laboratories Inc.: C
Allergan: C
Carl Zeiss Meditec: C
ForSight Vision S: C
InnFocus: C | Ivantis: C
Mynosys: C
National Eye Institute: S
National Space Biomedical Research Institute: C
Santen Inc.: C | Shire: C
Thieme Medical Publishers: C
Transcend: C
U.S. Food and Drug Administration: C

Nicholas J Volpe MD (Neuro-Ophthalmology)
Opticent Inc.: O

AAO STAFF
Ann L'Estrange
None
Melanie Rafaty
None
Lisa Romero
None
Debra Rosencrance
None
Beth Wilson
None
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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.

2016 Cornea Subspecialty Day Meeting Learning Objectives
Upon completion of this activity, participants should be able to:

- List common causes of corneal infections and best practices for management
- Discuss the role of keratoplasty in the management of corneal disease
- Review the role of imaging and in-office diagnostics for treatment of corneal disorders
- Provide a rationale for treatment of ocular surface disease and inflammatory disorders

2016 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.

2016 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.

Self-Assessment Credit
This activity meets the Self-Assessment CME requirements defined by the American Board of Ophthalmology (ABO). Please be advised that the ABO is not an accrediting body for purposes of any CME program. The ABO does not sponsor or endorse this activity, and the ABO does not endorse any particular CME activity. Complete information regarding the ABO Self-Assessment CME Maintenance of Certification requirements is available at http://abop.org/maintain-certification/part-2-lifelong-learning-self-assessment/sacme/

NOTE: Credit designated as “self-assessment” is AMA PRA Category 1 Credit™ and is also preapproved by the ABO for the Maintenance of Certification (MOC) Part II CME requirements.

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 Financial Interest
The American Academy of Ophthalmology is committed to ensuring that all 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.

The Academy requires all presenters to disclose on their first slide whether they have any financial interests from the past 12 months. Presenters are required to verbally disclose any financial interests that specifically pertain to their presentation.

Control of Content
The Academy considers presenting authors, not co-authors, 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, co-authors do not have control of the CME content and their disclosures are not published or resolved.

Attendance Verification for CME Reporting
Before processing your requests for CME credit, the American Academy of Ophthalmology must verify your attendance at Subspecialty Day and/or AAO 2016. In order to be verified for CME or auditing purposes, you must either:

- Register in advance, receive materials in the mail, and turn in the Subspeciality Day Syllabi exchange voucher(s) onsite;
- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting;
- Register onsite; or
- Scan the barcode on your badge as you enter an AAO 2016 course or session room.
CME Credit Reporting

Academy Resource Center, Booth 508 and South, Level 2.5
Attendees whose attendance has been verified (see above) at AAO 2016 can claim their CME credit online during the meeting. Registrants will receive an email during the meeting with the link and instructions on how to claim credit.

Onsite, you may report credits earned during Subspecialty Day and/or AAO 2016 at the CME Credit Reporting booth.

Academy Members: The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2016 credits entered onsite will be available to Academy members on the Academy’s website beginning Nov. 10, 2016.

After AAO 2016, credits can be claimed at www.aao.org/cme.

The Academy transcript cannot list individual course attendance. It will list only the overall credits spent in educational activities at Subspecialty Day and/or AAO 2016.

Nonmembers: The Academy will provide nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity. To obtain a printed record of your credits, you must report your CME credits onsite at the CME Credit Reporting booths.

Proof of Attendance

The following types of attendance verification will be available during AAO 2016 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

Visit www.aao.org/cme for detailed CME reporting information.
Faculty

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No photo available

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<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>James Philip Dunn Jr MD</td>
<td>Philadelphia, PA</td>
<td>Director, Uveitis Unit/Retina Division Wills Eye Hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Professor of Ophthalmology, Sidney Kimmel Medical College/Thomas Jefferson University</td>
</tr>
<tr>
<td>Bita Esmaeli MD FACS</td>
<td>Houston, TX</td>
<td>Professor of Ophthalmology, Director, Ophthalmic Plastic &amp; Reconstructive Surgery Fellowship Program M D Anderson Cancer Center</td>
</tr>
<tr>
<td>Pedram Hamrah MD</td>
<td>Boston, MA</td>
<td>Director, Anterior Segment Imaging Boston Image Reading Center Tufts Medical Center</td>
</tr>
<tr>
<td>Sadeer B Hannush MD</td>
<td>Langhorne, PA</td>
<td>Attending Surgeon Cornea Service, Wills Eye Hospital Assistant Professor Department of Ophthalmology Jefferson Medical College</td>
</tr>
<tr>
<td>Carol L Karp MD</td>
<td>Miami, FL</td>
<td>Professor of Ophthalmology Bascom Palmer Eye Institute University of Miami Miller School of Medicine</td>
</tr>
<tr>
<td>Lawrence W Hirst MD MBBS MPH DO FRACO FRACS</td>
<td>Graceville, QLD, Australia</td>
<td>CEO, The Australian Pterygium Centre Research Queensland Eye Institute</td>
</tr>
<tr>
<td>Bennie H Jeng MD</td>
<td>Baltimore, MD</td>
<td>Professor and Chair Department of Ophthalmology and Visual Sciences University of Maryland School of Medicine</td>
</tr>
</tbody>
</table>
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University of Michigan

Sonia H Yoo MD  
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Bascom Palmer Eye Institute  
Professor of Ophthalmology  
University of Miami Miller School of Medicine

Sonal S Tuli MD  
Gainesville, FL  
Professor and Chair  
Program Director  
University of Florida
Ask a Question Live During the Meeting Using the Mobile Meeting Guide

To ask a question during the meeting, follow the directions below.

- Access at www.aao.org/mobile
- Search Educational Sessions
- Select Program Search
- Filter by Meeting – Cornea Meeting
- Select Current Session
- Select “Ask the presenter a question (live)” Link
- Click Submit Question

In conjunction with the Cornea Society

## SATURDAY, OCT. 15

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speakers</th>
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<tbody>
<tr>
<td>7:00 AM</td>
<td>CONTINENTAL BREAKFAST</td>
<td></td>
</tr>
<tr>
<td>8:00 AM</td>
<td>Welcome and Introductions</td>
<td>Shahzad I Mian MD, Bennie H Jeng MD*, Carol L Karp MD</td>
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</tbody>
</table>

### Section I: Corneal Infections—Challenges in Diagnosis and Update on Management

**Moderator:** Bennie H Jeng MD*

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>8:02 AM</td>
<td>Introduction</td>
<td>Bennie H Jeng MD*</td>
</tr>
<tr>
<td>8:04 AM</td>
<td>What to Do About Antibiotic Resistance in the Setting of Bacterial Keratitis?</td>
<td>Eduardo C Alfonso MD</td>
</tr>
<tr>
<td>8:13 AM</td>
<td>Fungal Keratitis: What Is the Latest in Diagnosis and Management?</td>
<td>Jennifer R Rose-Nussbaumer MD</td>
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<tr>
<td>8:22 AM</td>
<td>Infections in the Setting of Endothelial Keratoplasty</td>
<td>Donald Tan MD FRCS FRCOphth*</td>
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<tr>
<td>8:31 AM</td>
<td>How Not to Miss the Diagnosis of Acanthamoeba Keratitis</td>
<td>Jeremy D Keenan MD MPH</td>
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<tr>
<td>8:40 AM</td>
<td>Is It VZV or HSV Keratitis?</td>
<td>Todd P Margolis MD PhD</td>
</tr>
<tr>
<td>8:49 AM</td>
<td>The Case of Infectious Keratitis That Wouldn’t Go Away</td>
<td>Deepinder K Dhaliwal MD*</td>
</tr>
<tr>
<td>8:58 AM</td>
<td>Discussion</td>
<td>Bennie H Jeng MD*</td>
</tr>
</tbody>
</table>

### Section II: The Evolving Role of Keratoplasty

**Moderator:** Shahzad I Mian MD

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>9:08 AM</td>
<td>Introduction</td>
<td>Shahzad I Mian MD</td>
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<tr>
<td>9:10 AM</td>
<td>Permanent Keratoprosthesis: Long-term Results</td>
<td>Anthony J Aldave MD*</td>
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<td>9:19 AM</td>
<td>Endothelial Disease: DSAEK as the Gold Standard</td>
<td>Terry Kim MD*</td>
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<td>9:28 AM</td>
<td>Role of Descemet Membrane Endothelial Keratoplasty as Primary EK</td>
<td>Mark A Terry MD*</td>
</tr>
<tr>
<td>9:37 AM</td>
<td>What’s the Issue With Donor Tissue? Transmission of Disease</td>
<td>Maria A Woodward MD</td>
</tr>
<tr>
<td>9:46 AM</td>
<td>Corneal Replacement: What Lies Ahead</td>
<td>Jodhbir S Mehta MBBS PhD</td>
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<tr>
<td>9:55 AM</td>
<td>Alternatives to Keratoplasty</td>
<td>Sonal S Tuli MD*</td>
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<tr>
<td>10:04 AM</td>
<td>Discussion</td>
<td>Shahzad I Mian MD</td>
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<td>10:14 AM</td>
<td>REFRESHMENT BREAK and AAO 2016 EXHIBITS</td>
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### Section III: Tools for Diagnosis and Treatment of Ocular Surface Tumors

**Moderator:** Carol L Karp MD

<table>
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<tr>
<td>10:44 AM</td>
<td>Introduction</td>
<td>Carol L Karp MD</td>
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<tr>
<td>10:46 AM</td>
<td>What to Do With Pigmented Lesions</td>
<td>Carol L Shields MD*</td>
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<tr>
<td>10:55 AM</td>
<td>Ocular Surface Squamous Neoplasia</td>
<td>Fairooz Puthiyapurayil Manjandavida MD</td>
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<tr>
<td>11:04 AM</td>
<td>Eyelid Lesions: When to Worry and When to Relax</td>
<td>Bita Esmaeli MD FACS*</td>
</tr>
<tr>
<td>11:13 AM</td>
<td>Iris Lesions: What Do I Do?</td>
<td>Arun D Singh MD</td>
</tr>
</tbody>
</table>

* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
<table>
<thead>
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<th>Time</th>
<th>Session Title</th>
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<th>Notes</th>
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<tr>
<td>11:22 AM</td>
<td>Pterygium: Evidence-based Management</td>
<td>Lawrence W Hirst MD MBBS MPH DO FRACO FRACS*</td>
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<td>11:31 AM</td>
<td>The Bump That Stumped Me</td>
<td>Kathryn A Colby MD PhD</td>
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<td>11:40 AM</td>
<td>Discussion</td>
<td>Carol L Karp MD</td>
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<td>11:50 AM</td>
<td>Advocating for Patients</td>
<td>Stephanie J Marioneaux MD</td>
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<td>11:55 AM</td>
<td>LUNCH and AAO 2016 EXHIBITS</td>
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<td><strong>Section IV: The Role of Imaging and In-office Diagnostics</strong></td>
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<td>Moderator: Carol L Karp MD</td>
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<tr>
<td>1:05 PM</td>
<td>Introduction</td>
<td>Carol L Karp MD</td>
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<tr>
<td>1:07 PM</td>
<td>Confocal: How This Helps Me</td>
<td>Pedram Hamrah MD*</td>
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<tr>
<td>1:16 PM</td>
<td>Tomography vs. Topography: What Do They Tell Me?</td>
<td>Michael W Belin MD*</td>
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<td>1:25 PM</td>
<td>OCT: Office Based and Intraoperative</td>
<td>Sadeer B Hannush MD</td>
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<td>1:34 PM</td>
<td>Pearls for Intraoperative Aberrometry</td>
<td>Sonia H Yoo MD*</td>
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<td>1:43 PM</td>
<td>In-office Diagnostics for Infection</td>
<td>Elmer Y Tu MD*</td>
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<td>1:52 PM</td>
<td>Case: “How Imaging Saved Me!”</td>
<td>Francis W Price Jr MD*</td>
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<td>2:01 PM</td>
<td>Discussion</td>
<td>Carol L Karp MD</td>
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<td><strong>Section V: Managing Ocular Surface Disease</strong></td>
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<td>Moderator: Bennie H Jeng MD*</td>
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<tr>
<td>2:11 PM</td>
<td>Introduction</td>
<td>Bennie H Jeng MD*</td>
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<tr>
<td>2:13 PM</td>
<td>New Developments in Dry Eye Diagnosis and Treatment</td>
<td>Anat Galor MD</td>
<td>39</td>
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<tr>
<td>2:22 PM</td>
<td>No, This Is Actually Not Dry Eye</td>
<td>Richard S Davidson MD</td>
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<tr>
<td>2:31 PM</td>
<td>How Do I Know if This Is Stem Cell Deficiency?</td>
<td>Sophie X Deng MD PhD</td>
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<tr>
<td>2:40 PM</td>
<td>How to Manage Stem Cell Deficiency</td>
<td>Virender S Sangwan MBBS</td>
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<tr>
<td>2:49 PM</td>
<td>Managing Ocular Surface Disease Before Cataract Surgery</td>
<td>William Barry Lee MD*</td>
<td>44</td>
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<tr>
<td>2:58 PM</td>
<td>Case: Not Your Ordinary Ocular Surface Disease Patient</td>
<td>Christopher J Rapuano MD*</td>
<td>45</td>
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<tr>
<td>3:07 PM</td>
<td>Discussion</td>
<td>Bennie H Jeng MD*</td>
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<tr>
<td>3:17 PM</td>
<td>REFRESHMENT BREAK and AAO 2016 EXHIBITS</td>
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<td><strong>Section VI: Inflammatory Conditions of the Ocular Surface</strong></td>
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<td>Moderator: Shahzad I Mian MD</td>
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<td>James Philip Dunn Jr MD</td>
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<td>Michael B Raizman MD*</td>
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<td>Closing Remarks</td>
<td>Shahzad I Mian MD</td>
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* Indicates that the presenter has financial interest.
No asterisk indicates that the presenter has no financial interest.
What to Do About Antibiotic Resistance in the Setting of Bacterial Keratitis?

Eduardo C Alfonso MD

Introduction

Bacterial keratitis is one of the most common forms of infectious keratitis, and worldwide second to viral keratitis as the most commonly seen cause of corneal infections. Antibiotic resistance is an emerging problem in the world, with fewer antibiotics being developed that can help eradicate infectious organisms and increasing use of antibiotics, causing those that are commonly available to become less effective.

Currently in the treatment of infectious keratitis due to bacteria most cases are treated empirically, meaning that for small peripheral ulcers or even early central ulceration, most ophthalmologists will use a topical broad-spectrum antibiotic drop on a frequent basis with good results. In the setting where microbiologic laboratory resources are available, studies will be done to elucidate the organism causing the infection. In these situations, approximately 50% of the time an organism can be identified. Antibiotics are then modified to and chosen based on the response to the treatment and the information obtained from the studies. Sometimes when there is slow response clinically, the antibiotic may be changed to an extemporaneously fortified one, or an additional one may be added. At times, slow response to initial antibiotic treatment may be due to prior treatment with a less effective antibiotic or the use of steroid drops.

Currently the most commonly used commercially available class of antibiotics for treatment of infectious keratitis are the topical fluoroquinolones (FQs). This class of antibiotics has excellent pharmacokinetics in the human cornea, with high concentrations achievable at the site of infection. However, there has been increasing pressure on the effectiveness of these antibiotics due to their widespread use in agriculture and medicine. Alternative options are the cefalosporins and aminoglycosides. The latter can also be obtained commercially for topical use, but their pharmacokinetics have not been as good as the FQs. Slow clinical response at times has been interpreted as resistance. Both the cefalosporins and the aminoglycosides can be fortified. In the setting of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin will be necessary due to the high level of resistance to all other antibiotics.

In addition to MRSA, other organisms are known to be less responsive to the FQs, like mycobacteria. For these organisms, fortified amikacin and clarithromycin are recommended. It is important to note that due to their slow growth, these organisms may develop resistance during treatment and require changes in the treatment, including use of newer classes of antibiotics like linezolid. This phenomenon can also be seen with other bacteria that are slow growing, and thus re-examination with cultures is important. At times, lack of clinical response may be interpreted as resistance. In these cases, it is best to continue treatment while other factors, such as patient compliance, are considered.

Epidemiology

Bacterial keratitis is the second most common form of infectious keratitis worldwide, second to viral keratitis. In the United States, approximately 30,000 cases are diagnosed yearly.

Diagnosis

Clinical diagnosis with history and slitlamp appearance can help, but studies have shown that the addition of laboratory studies enhances the accuracy of bacterial identification and the use of appropriate treatment. In addition to standard laboratory studies such as smears and cultures, other tests that may be helpful include chemical assays such as the Limulus lyase test, to identify the toxins, and molecular analysis. These studies may not only enhance identification but also provide more information on sensitivity to treatment options. Additional diagnostics studies may include confocal microscopy and high-resolution OCT. In cases where no etiology is defined on the initial studies, these should be repeated, including obtaining more tissue in a biopsy to be examined histologically.

Treatment

Treatment with broad-spectrum topical antibiotics, usually with a FQ antibiotic, is the first step. In cases of large central ulcers, a second fortified antibiotic such as a cefalosporin, vancomycin, or an aminoglycoside (tobramycin or gentamicin) may be added based on the suspected organism. Other options for treatment include crosslinking, iontophoresis, and surgical invention. Surgical options may be keratoplasty, lamellar or penetrating, as well as conjunctival flaps and amniotic membranes.

Selected Readings

I. Fungal keratitis is an important public health concern.
   A. Fungal keratitis is a major cause of monocular blindness in the developing world.1,2
   B. Approximately 50% of corneal ulcers in tropical regions are fungal in nature.3-5
   C. Fungal keratitis is often more severe than bacterial keratitis, resulting in worse visual acuity outcomes, higher rates of corneal perforation, and more frequent need for therapeutic penetrating keratoplasty (TPK).3,6
   D. While fungal ulcers are less common in the United States, they can occur after trauma, with contact lens wear, or after refractive surgery.7,8

II. Characteristics of Fungal Corneal Ulcers
   A. Different types of fungus
   B. Frequently isolated organisms in ulcers include *Fusarium* and *Aspergillus*.
   C. 10 characteristics of fungal ulcers
   D. Corneal experts are not good at differentiating between bacterial and fungal ulcers on exam alone.
   E. Diagnostic tools: culture, confocal, anterior segment OCT

III. Treatment of fungal keratitis has not been well characterized.
   A. Topical natamycin, a polyene, is the only antifungal agent approved by the Food and Drug Administration (FDA) for treatment of fungal keratitis.
   B. Voriconazole, a newer generation triazole, has gained popularity in the treatment of fungal keratitis.9,10
   C. The Mycotic Ulcer Treatment Trial I (MUTT I) demonstrated significantly better visual acuity at 3 months in patients with predominantly filamentous fungal keratitis randomized to topical natamycin vs. topical voriconazole, with fewer adverse events such as perforation.11
   D. Other randomized clinical trials and a recent Cochrane review have recently concluded that topical natamycin is superior to topical voriconazole in the treatment of filamentous fungal ulcers.10,11,13,14
   E. One of the limitations of topical administration of antifungals, and natamycin in particular, is bioavailability.12 Oral voriconazole may provide more steady-state drug levels compared with topical antifungals.
   F. The Mycotic Ulcer Treatment Trial II (MUTT II) is a randomized clinical trial in which smear-positive fungal corneal ulcers receiving topical antifungals were randomized to oral voriconazole vs. placebo.

References
Infections in the Setting of Endothelial Keratoplasty

Donald T H Tan FRCS FRCOphth, Jyh-Haur Woo MMed, Anthony J Aldave MD, Elmer Y Tu MD

I. Significant Growth Trend in Endothelial Keratoplasty (EK) vs. Penetrating Keratoplasty (PK) Over the Last Decade

Changing trends in post-keratoplasty infections noted, burgeoning case reports of predominantly fungal keratitis and fungal endophthalmitis occurring following EK

II. Post-EK Infections
A. Bacterial
B. Fungal (Candida)
C. Viral (cytomegalovirus endotheliitis)

III. Post-PK Endophthalmitis Rates
A. Meta-analysis of PKs (1975-2006) shows 14% positive donor rim cultures, but only 0.2% developed endophthalmitis.
B. Positive culture: bacteria = 1% risk, fungus = 3% risk

IV. Case Reports of Post-EK Infections
A. 2002: First report of post-endokeratoplasty interface keratitis reported—Mycobacterium chelonae
B. May 2009: First published report of donor-to-host transmission of Candida albicans after DSAEK; enucleation resulted
C. August 2009: Two cases of donor-related Candida keratitis after Descemet-stripping automated endothelial keratoplasty (DSAEK), from the same donor. Repeat surgery required in both cases. Since then 9 other publications of individual cases or case series. To date, 20 cases of post-DSAEK fungal keratitis in reported literature, mostly Candida keratitis, mostly from the United States but also from Asia and Europe.
D. 2010: We reported first case of fungal endophthalmitis following a repeat DSAEK procedure, originating from venting incisions.
E. Another 4 cases of post-DSAEK endophthalmitis reported: Candida sp, Mycobacterium abscessus, Streptococcus pneumonia

V. Rising Incidence of Post-keratoplasty Fungal Infections (EBAA 2015 MAB Subcommittee Report on Fungal Infection)
A. EBAA data 2007-1010: Fungal infections represented 63% of all cases of post-keratoplasty infections.
B. Fungal infections more commonly reported after EK (0.022%) than PK (0.012%), but not statistically significant (P = .076)
C. Increasing trend in annual incidence of post-keratoplasty fungal infection from 2005 to 2010 (mean 0.012%), but not statistically significant (P = .11)
D. 2013: Annual incidence of postkeratoplasty fungal infection = 0.039; this is a statistically significantly higher rate (P < .01).
E. Risk is higher with EK (0.084%) than PK (0.008%) (P < .01%).

VI. Relevance to Donor Tissue Cultures
A. If donor rim fungal cultures are performed, only 0.07% will be culture positive. However, 17.1% of recipients with positive fungal rim culture developed post-keratoplasty infection.
B. Donor rim fungal cultures should be performed in EK; useful to guide treatment of post-keratoplasty infection.
C. Prompt institution of antifungal therapy should be strongly considered when a donor cornea rim fungal culture is positive for Candida.

VII. Association of Fungal Infection With Eye-Banking Procedures
Increased risk of post-keratoplasty fungal infection related to eye bank tissue preparation of DSAEK donor tissue (0.11%), as compared to surgeon preparation in OR (0.02%) (P = .02)

VIII. Risk Factors for Fungal Infection Post-DSAEK
A. Donor tissue-related: repeated tissue warming cycles during tissue preparation in eye banks (Candida), no antifungal agents in storage media
B. Perioperative: venting incisions, bandage CL wear

IX. EBAA Medical Advisory Board Update
A. Donor rim fungal cultures for all eye-bank prepared DSAEK tissue
B. Additional studies needed on Candida risk factors in eye banks
C. Additional studies needed on antifungal supplementation of donor storage media
Selected Readings


How Not to Miss the Diagnosis of Acanthamoeba Keratitis

Jeremy D Keenan MD MPH

I. Acanthamoeba Biology

A. Life cycle

1. Trophozoite: motile, replicates by binary fission. Feeds on algae, bacteria, and other protozoans; also thought to feed on keratocytes in the cornea. Encysts when exposed to a harsh environment. Roughly 25-50 microns in size.

2. Cyst: dormant form; resistant to extremes in temperature and pH, desiccation, and chemicals. Does not require food. Excysts into the trophozoite form in the presence of food and other favorable conditions. Roughly 10-30 microns in size.

B. Species: 25 species have been identified based on morphological features. The most common causes of Acanthamoeba keratitis are Acanthamoeba castellanii and A. polyphaga. Most microbiology laboratories do not report the species.

C. Genotypes: 15 genotypes of Acanthamoeba (T1-T15) have been identified based on 18S RNA. Acanthamoeba keratitis is predominantly caused by T4.

II. Epidemiology

A. Incidence: Depends on country; in the United States the incidence has been reported as 0.15 per million in non-contact lens wearers and 1 per million in contact lens wearers, whereas in the UK the estimated incidence has been estimated as approximately 1 per million in non-contact lens wearers and 20 per million in contact lens wearers.

B. Contact lens wear: In western countries, approximately 85% of cases occur in contact lens wearers, although can also occur in rigid lenses, especially in orthokeratology lens wearers.

C. Water exposure: swimming in pools, hot tubs, fresh water, especially when water exposure happens in contact lenses.

D. Agricultural exposure to water and mud: This is the most common risk factor in India.

E. Seasonality: Acanthamoeba keratitis is more common in summer months, probably because of increased exposure to water (eg, swimming, boating).

F. Polymicrobial infection: Approximately 10%-20% of cases of Acanthamoeba keratitis may be polymicrobial or coinfected with herpes simplex virus (HSV).

III. Risk Factors

A. Contact lens wear: usually soft lenses (including daily disposable lenses), although can also occur in rigid lenses, especially in orthokeratology lens wearers.

B. Poor contact lens hygiene: washing lenses in tap water.

C. Water exposure: swimming in pools, hot tubs, fresh water, especially when water exposure happens in contact lenses.

D. Agricultural exposure to water and mud: This is the most common risk factor in India.

IV. Symptoms

A. Redness, photophobia, pain, tearing

B. Pain: Often severe pain, disproportionate to the clinical signs. However, pain is not universal and some patients have no pain at all.

C. Duration: Acanthamoeba keratitis is often not diagnosed promptly. Most larger series report a mean duration of symptoms of 4-6 weeks before the diagnosis is made. Acanthamoeba should be suspected when keratitis does not respond to other treatments (eg, treatment for viral, bacterial, or fungal keratitis).

V. Signs

A. Early (≤ 1 month)

1. Epitheliopathy: Often a punctate keratopathy, with a diffusely rough appearing corneal surface but no frank epithelial defect. In series from countries with a high prevalence of contact lens wear (ie, North America and Europe), 37%-46% of cases have only an epitheliopathy, without an associated stromal involvement. Lack of stromal involvement is less common in India and China (0%-2.5% of cases), perhaps due to delayed presentation.

Pseudodendrite: This is a form of epitheliopathy where the epithelium has linear staining reminiscent of a dendrite. This is different from a herpetic dendrite in that there is no epithelial defect and no terminal bulbs. Pseudodendrites are not commonly reported (3%-17% of cases), though this may be under-reported since the finding is often subtle.
2. Perineural infiltrate: Usually present in peripheral cornea, and often only 1-2 nerves will be affected. Look for a linear, radial structure, often only 1-2 mm in length, with indistinct borders indicative of a cellular infiltrate surrounding the nerve. This finding is not very sensitive, with studies finding the presence of perineural infiltrate in 3%-41% of cases. This finding is thought to be quite specific for *Acanthamoeba* keratitis.

3. Limbitis: Very common; may be less marked in eyes being treated with topical corticosteroids.

4. Patchy anterior stromal infiltrates: Often these are multifocal, diffusely scattered throughout the cornea. The infiltrates are usually not dense or purulent and often have no overlying epithelial defect. The differential diagnosis could include subepithelial infiltrates of epidemic keratoconjunctivitis or anterior stromal infiltrates associated with contact lens overwear.

5. Reduced corneal sensation: This is not unusual in *Acanthamoeba* keratitis and should always be assessed. Patients with reduced corneal sensation often have less or no pain.

B. Late (> 1 month)

1. Ring infiltrate: Usually a large ring involving the central cornea; often initially without an epithelial defect, but an epithelial defect usually forms over and within the ring. The infiltrate usually has deeper stromal involvement than the earlier patchy anterior stromal infiltrates. Ring infiltrates are present in 20%-60% of *Acanthamoeba* cases.

2. Frank ulceration: Large nonhealing epithelial defects with nonpurulent stromal infiltration are common. This is often accompanied by corneal vascularization and edema.

3. Uveitis and scleritis: Keratic precipitates, anterior chamber cellular reaction, scleritis usually worse near limbus. The scleritis can be very painful and is often relieved with oral nonsteroidal anti-inflammatory drugs.

C. Differential diagnosis: *Acanthamoeba* keratitis is often initially misdiagnosed. Consider *Acanthamoeba* before diagnosing the following:

1. Herpetic keratitis: Both can cause decreased corneal sensation, dendriform epithelial lesions, and a ring ulcer. Dendritic keratitis due to HSV has true dendrites, with fluorescein staining the base of the dendrite and terminal bulbs. Pseudodendrites due to *Acanthamoeba* usually do not have a frank epithelial defect. Interstitial keratitis due to HSV tends not to be multifocal and often affects the mid and deep stroma, whereas *Acanthamoeba* infiltrates are usually numerous and smaller multifocal anterior stromal infiltrates.

2. Subepithelial infiltrates (SEIs) from epidemic keratoconjunctivitis (EKC): Often SEIs will have punctate staining overlying the infiltrate, whereas *Acanthamoeba* often has a diffuse epitheliopathy, even over areas of the cornea without an infiltrate. Patients with EKC usually have a history of sick contacts.

3. Contact lens–related infiltrates: These are often in the peripheral cornea and usually consist of a small number of discrete small anterior stromal infiltrates.

VI. Tests

A. In vivo confocal microscopy

1. Features of images consistent with *Acanthamoeba* keratitis

   a. Cysts: Round, hyper-reflective bright spots and double-walled cysts measuring approximately 10-30 microns

   b. Trophozoites may be visualized, though the features are less well described than cysts, and probably should not be the focus when interpreting confocal images.

2. Sensitivity and specificity depend on experience of the grader.

3. Personal experience

   a. Both the operator and interpreter are important. The operator should start with central scans of the epithelium and anterior stroma, since cysts will often be visible here even in the absence of a frank central infiltrate. Then the operator should attempt to scan the edges of any infiltrates, focusing on the epithelium and anterior stroma.

   i. Heidelberg: Captures 400x400-micron images with 4-micron depth of field

      (a) Volume scan: Takes a cube of images, with each image 2 microns posterior to the previous image. Cysts can have different morphologies at different sections; volume scan can capture multiple scans of the same cyst, which might help in the determination of whether an object is a cyst or an inflammatory cell.

   (b) Sequence scan: The operator controls the X, Y, and Z coordinates manually. An advantage of this method is that it takes more images than the volume scan, and the images can traverse laterally as well as anterior-posterior.

   ii. Nidek: Captures 460x345-micron images with 8- to 25-micron depth of field

      (a) Semi-automatic full-thickness scan: Captures a volume scan of the entire cornea. The operator can do an initial central scan with this setting.
(b) Semi-automatic anterior setting: Cysts are most often located in the epithelium and anterior stroma, so this setting provides images that will be the most high yield. The operator can do several anterior stromal scans centrally and in the areas of infiltrate.

(c) Manual setting: This setting takes more skill than the semiautomatic settings described above. The manual setting is often necessary in eyes with corneal edema and dense infiltration. The manual setting can also be better for capturing the peripheral cornea.

b. Interpretation

i. Morphology: Double-walled structures greatly increase confidence in the diagnosis. In the absence of a double wall, very spherical and very hyper-reflective objects increase confidence in the diagnosis.

ii. Size: Cysts are usually 10-30 microns in size.

iii. Location: In a cornea that has not been treated with antiamoebics, cysts are usually located in the epithelium. Cysts can also be located in the stroma in these corneas, but be cautious giving a diagnosis of Acanthamoeba if the round structures are visible only in the stroma and not in the epithelium.

iv. False positives: Round structures that can look like cysts:

(a) Nuclei of epithelial cells: These are round structures in the superficial epithelium, regularly spaced, often without surrounding inflammatory cells.

(b) Inflammatory cells: These are round structures, without a double-wall, often with lobular forms within the round structure, often not perfectly spherical, often not as bright as a cyst, often smaller than a typical cyst, although macrophages are similar in size to a cyst. It can be difficult to differentiate inflammatory cells from cysts.

v. False negatives: In eyes already being treated with antiamoebics, cysts may not be present and confocal microscopy is likely less sensitive.

B. Corneal scraping

1. Smear: Giemsa, potassium hydroxide (KOH), calcafluor white, periodic acid Schiff, hematoxylin-eosin

2. Culture: Non-nutrient agar with E. coli overlay. In the presence of the E. coli food source, trophozoites will replicate and cysts will excyst then replicate.

3. PCR: Several different primers available; quantitative assays are more sensitive than qualitative assays.

C. Corneal biopsy: For cases where Acanthamoeba is suspected but corneal scrapings are negative and clinical course does not improve with antiamoebic therapy. Send half of tissue for pathology and half for culture, then scrape the bed of the biopsy and send for smear and culture.

References


Is It VZV or HSV Keratitis?

Todd P Margolis MD PhD

There is no one single sign, symptom, historical feature, or even test that will allow you to distinguish herpes simplex virus (HSV) from varicella zoster virus (VZV) keratitis with 100% certainty. If there are active corneal epithelial lesions, then the single best test is probably polymerase chain reaction (PCR) for viral DNA, assuming that you know your lab’s capabilities for handling ocular specimens. If there is an associated iritis, then PCR testing for viral DNA is probably your second-best option. Keep in mind that in both of these scenarios a positive test is very helpful, since these assays are very specific. However, a negative test does not rule out either an HSV or a VZV infection, since there are many factors that go into determining the sensitivity of a PCR-based assay.

Patient history can also be very helpful in distinguishing HSV from VZV keratitis, but it is not definitive. In a patient with a prior history of HSV eye disease, the diagnosis is most likely HSV. In a patient with a history of a zoster rash affecting the first division of the fifth cranial nerve, VZV is more likely. However, keep in mind that zoster keratitis can occur in the absence of a history of a zoster rash (zoster sine herpete). The age of the patient can also be helpful since the incidence of zoster increases with age. Finally, a history of neuralgia accompanying ocular disease favors VZV.

There are features of the ocular exam that can also help one in distinguishing HSV from VZV keratitis. Although both HSV and VZV keratitis can be associated with decreased corneal sensation, the loss of sensation with VZV can be quite profound, with total loss of sensation over the entire cornea and bulbar conjunctiva. I have never seen a case of HSV keratitis with associated loss of conjunctival sensation and have only rarely seen HSV keratitis with total loss of sensation over the entire cornea. As a result, neurotrophic keratopathy is much more common in cases of VZV keratitis.

The appearance of epithelial lesions can also help distinguish HSV from VZV keratitis. The classic dendrite of HSV keratitis is hard to miss, with its beautiful branching pattern, central ulceration, and end bulbs. The staining pattern of an HSV dendrite is similarly beautiful, with central fluorescein staining of the ulceration and surrounding rose bengal or lissamine green staining of the surrounding infected corneal epithelial cells. In contrast, the pseudodendrite of zoster is elevated or heaped up and appears pasted on, reflecting an epithelial to mesenchymal change of the cells on the ocular surface with extremely variable staining patterns. In contrast to the beautiful fractal quality of the HSV dendrite, the zoster pseudodendrite looks like it has been drawn by a five-year-old.

Both HSV and VZV can produce many different forms of stromal disease that can be hard to distinguish; however, in my experience there is one pattern of stromal keratitis that is highly suggestive of VZV but not HSV. This pattern occurs in the very anterior corneal stroma and extends from the limbus across at least a third of the diameter of the cornea in an ovoid pattern with very well-circumscribed edges.

Both HSV and VZV keratitis can be associated with iris atrophy, and both viruses have been associated with patchy, sectoral or diffuse iris atrophy. However, it has been my experience that VZV is more likely to cause diffuse atrophy. The atrophy of herpetic iritis can be associated with pigment and pigmented cells in the anterior chamber and along the trabecular meshwork. In my experience, the greater the degree of pigment, the more likely the infection is due to zoster, and the more likely that there is an active viral infection, not just an immune response, that needs aggressive antiviral therapy (and less corticosteroids).

Fortunately for the clinician, treatment of HSV and VZV keratitis is very similar. Treat actively replicating viral disease of the corneal epithelium or anterior chamber with an antiviral (I prefer oral antivirals for both locations), and treat inflammation with a topical corticosteroid under antiviral cover. Appropriate dosing of acyclovir, valacyclovir, and famciclovir is higher for VZV than for HSV, so when in doubt use the VZV dosing (acyclovir 800 mg PO 5 times/day; valacyclovir 1 gm PO t.i.d.; famciclovir 500 mg PO t.i.d.). The dosing for a topical corticosteroid is also very similar ... you rarely need more than q.i.d. with supervised reduction of the frequency to find the least dose required to keep the corneal stromal inflammatory reaction quiet.
The Case of Infectious Keratitis That Wouldn’t Go Away

Deepinder K Dhaliwal MD

Infectious keratitis can be challenging to treat for a variety of reasons. If the corneal ulcer is not responding to initial therapy after 2–3 days, the case must be reassessed. Poor response to therapy can be broken down into the following categories:

- Wrong diagnosis
- Wrong treatment
- Right treatment but “wrong” patient (poor compliance)
- Other factors: poor penetration / biofilm / CL

To get the correct diagnosis:

- Perform cultures / reculture / polymerase chain reaction / smears
- Think of atypical organisms: nontuberculous mycobacteria, fungus, ACA, Nocardia
- Could be a mixed infection and so only partially treated

Determining the etiology is of primary importance: if culture-negative, consider confocal microscopy or corneal biopsy. Also consider culture of CL, CL case, CL solution.

In terms of treatment, use the most potent agent available in its class. Cidal agents are preferred over static. Remember that corneal penetration is an important factor when considering choice of antimicrobial. Also, biofilms can modify the antimicrobial effect.

It would be ideal to take compliance out of the equation when treating severe corneal ulcers, since it is often difficult for patients to use drops around the clock and to instill properly. When patients are not responding to therapy even though diagnosis and treatment are correct, or when infection is located in the deeper layers of the cornea, we find corneal intrastromal injection of antimicrobials very helpful. Intrasceral injections can also be helpful if infection is extending beyond the cornea. Anterior chamber washout with culture / smear of hypopyon can help determine intracameral extension of infection, followed by antimicrobial injection into the anterior chamber.

**Dosage for Intrastromal / Intrascleral / Intracameral Injection**

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<th>Dosage</th>
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<td>Voriconazole</td>
<td>50 μg/0.1 mL</td>
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<tr>
<td>Amphotericin B</td>
<td>5-7.5 μg/0.1 mL</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 mg/0.1 mL</td>
</tr>
<tr>
<td>Amikacin</td>
<td>400 μg/0.1 mL</td>
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Therapeutic keratoplasty may be necessary in advanced cases. When performed, surgical instruments used to remove the infected cornea are removed from the field, and new sterile instruments are used to sew in the graft. Peripheral intrastromal antimicrobial injection of the host periphery can be performed at the end of the case if a proper clear zone is not achieved.
Permanent Keratoprosthesis: Long-term Results

Anthony J Aldave MD

Background

While a number of single-surgeon, single-center, and even multicenter studies have been published detailing the outcomes of the Boston type I keratoprosthesis, the average length of follow-up is relatively limited, typically less than 3 years. While most series that report on outcomes following keratoprosthesis surgery report the percentage of eyes that develop various complications after surgery, this percentage increases for each complication over time. Thus, while series reporting short-term follow-up of the Boston keratoprosthesis have provided encouraging data, the few series reporting longer term follow-up provide more realistic outcomes of keratoprosthesis surgery. In order to make evidence-based decisions regarding patient selection for keratoprosthesis surgery and the prevention and management of complications following keratoprosthesis surgery, it is imperative to have accurate data regarding the long-term outcomes of keratoprosthesis surgery.

This talk will present the long-term outcomes of 120 type I Boston keratoprosthesis procedures performed by a single surgeon between May 1, 2004, and May 1, 2011. The primary outcome measures following keratoprosthesis surgery that will be described are visual acuity, complications, and retention.

Patient Demographics and Surgical Indications

120 keratoprosthesis procedures were performed in 97 eyes of 93 patients. The mean (median) follow-up (by eyes) was 58.0 (64.6) months, with a range of 1.4 to 142.8 months. The most common comorbid disorder was glaucoma, present in 74.2% of patients, with 58.8% of patients having had glaucoma surgery prior to keratoprosthesis implantation. The most common indication for keratoprosthesis implantation (by procedure) was corneal transplant failure (56.7%), followed by Stevens-Johnson syndrome (10.8%) and chemical injury (10.0%). Even though two-thirds of keratoprosthesis procedures were performed in eyes with a history of 2 prior keratoplasties, in 17% of eyes the keratoprosthesis implantation was the primary corneal procedure performed.

Visual Acuity

Prior to keratoprosthesis implantation, VA was CF or worse in 88% of eyes and 20/200 or better in 6% of eyes. At intervals between 1 and 8 years after surgery, the percentage of eyes with visual acuity CF or worse varied between 18.2% (8 years) and 38.3% (5 years), and the percentage of eyes with visual acuity 20/200 or better varied between 55% (4 years) and 82% (8 years).

Complications

The most common postoperative complication following keratoprosthesis implantation was retroprosthetic membrane formation, occurring in 59.8% of eyes, requiring YAG membranectomy in 43.3% and surgical memranectomy in 9.3% of eyes. The other postoperative complications are shown in Table 1. Of note, endophthalmitis developed in only 1% of eyes.

Table 1. Postoperative Complications and Secondary Surgical Procedures

<table>
<thead>
<tr>
<th>Complication</th>
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<tbody>
<tr>
<td>Retroprosthetic membrane</td>
<td>58 (59.8)</td>
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<tr>
<td>YAG membranectomy</td>
<td>42 (43.3)</td>
</tr>
<tr>
<td>Surgical membranectomy</td>
<td>9 (9.3)</td>
</tr>
<tr>
<td>Persistent epithelial defect</td>
<td>40 (41.2)</td>
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<tr>
<td>Tarsorrhaphy</td>
<td>12 (21.6)</td>
</tr>
<tr>
<td>Sterile corneal stromal necrosis</td>
<td>25 (25.8)</td>
</tr>
<tr>
<td>Elevated IOP (&gt; 25 mmHg)</td>
<td>22 (22.7)</td>
</tr>
<tr>
<td>Tube shunt</td>
<td>6 (6.2)</td>
</tr>
<tr>
<td>CME</td>
<td>16 (16.6)</td>
</tr>
<tr>
<td>Intravitreal injection</td>
<td>11 (11.3)</td>
</tr>
<tr>
<td>Corneal infiltrate</td>
<td>15 (15.5)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>15 (15.5)</td>
</tr>
<tr>
<td>Repair of retinal detachment</td>
<td>12 (12.4)</td>
</tr>
<tr>
<td>Sterile vitritis</td>
<td>13 (13.4)</td>
</tr>
<tr>
<td>Vitreous tap and intravitreal injections</td>
<td>9 (9.3)</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

* 97 eyes total.

Retention

Thirty-nine of the 120 keratoprostheses implanted (32.4%) were removed during a cumulative 468.8 years of follow-up, leading to a retention failure rate of 0.083% per year. The mean time to failure was 32.8 months, with a range from 1.7 to 89.4 months. In the 28 eyes in which the initial keratoprosthesis was removed, a subsequently placed keratoprosthesis was retained at the final follow-up in 12 eyes, leading to an overall 83.5% of eyes (81 of 97) with a keratoprosthesis retained at the final follow-up.

Summary

The Boston keratoprosthesis provides significant visual improvement in the majority of eyes, with more than 50% regaining and maintaining visual acuity of 20/200 or better each year through 8 years after surgery. While postoperative complications are common, the incidence of each decreases over the first 10 years after surgery, and most can be managed with medical or minor surgical procedures. While almost one-third of implanted keratoprostheses were removed, over 80% of eyes retained a keratoprosthesis at the final follow-up.
Selected Readings


Endothelial Disease: DSAEK as the Gold Standard

Terry Kim MD

Descemet-Stripping Automated Endothelial Keratoplasty (DSAEK): A Proven Track Record

I. Historical Precedence of DSAEK
   A. Number of DSAEK procedures
   B. Longevity of DSAEK procedure
   C. Endothelial cell analysis
   D. Thick vs. thin vs. ultra-thin DSAEK

II. Surgical Procedure: Familiarity, Reproducibility, and Predictability
   A. Donor tissue preparation
   B. Donor tissue injection
   C. Donor tissue manipulation
   D. Donor tissue adherence
   E. Combined procedures (ie, cataract surgery)

III. Complications
   A. Graft damage
   B. Graft detachment
   C. Iatrogenic primary graft failure
   D. Pupillary block (need for inferior peripheral iridotomy, timing, YAG vs. surgical)

IV. Clinical Follow-up
   A. Intracameral air vs. gas (SF₆)
   B. Rebubbling rates
   C. Visual acuity/quality
   D. Graft rejection

V. Complex Patient Scenarios
   A. Glaucoma procedures (trabeculectomy, tube shunt, etc.)
   B. Advanced bullous keratopathy
   C. Anterior chamber (AC) IOL / shallow AC
   D. Iris abnormalities (ie, defects, mydriasis, etc.)
   E. Aphakia
   F. Post–pars plana vitrectomy

VI. Conclusion

Selected Readings


The Role of Descemet Membrane Endothelial Keratoplasty as a Primary EK

Mark A Terry MD

The evolution of endothelial keratoplasty (EK) has progressed at an astonishing pace. From the first deep lamellar EK (DLEK) procedure in the United States, over 16 years ago, to Descemet-stripping EK (DSEK) overtaking penetrating keratoplasty (PK) as the procedure of choice in 2011, we now have Descemet membrane EK (DMEK), with its ever-increasing popularity.

Each iteration of EK has had its own challenges and advantages over the prior surgical remedy of endothelial replacement. At each stage of development, surgeons have had to make the decision to either stay with the procedure they are comfortable with or go through another learning curve with the hope of offering something better to their patients.

In 2012 I published an editorial entitled “Why aren’t we all doing DMEK?” There I delineated the primary reasons surgeons did not want to transition from DSEK to DMEK, which were the exact same reasons surgeons initially did not want to embrace DLEK or DSEK over PK. The rationale for nonadoption was as follows:

1. DMEK is too difficult a procedure, with a long learning curve.
2. DMEK risks damaging or losing the donor tissue during the surgeon’s intraoperative prep, causing cancellation of the case, the loss of precious donor tissue, and payment of the substantial tissue processing fee despite an aborted case.
3. DMEK has complication rates that are much higher than those of DSEK, and so why change from a safe procedure with good results to one with a greater chance of complications?

Over the past few years, the advances in DMEK technique and the advances in eye bank preparation of DMEK tissue have largely answered each of these concerns, making the case for transition from DSEK to DMEK for routine cases of endothelial replacement even more convincing.

The Standardization of the DMEK Procedure for Easy and Safe Skills Transfer

The early reports on DMEK surgery included the learning curves of the procedure’s early adapters, with techniques and instrumentation that had not been fully worked out. This resulted in a difficult transfer of the unique skill set required for DMEK surgery. Several surgeons have now standardized the DMEK procedure with a step-by-step approach, so that the learning curve for DMEK is much shorter and easier than ever before. In addition, advances in the eye bank preparation of the donor tissue have removed some of the most difficult and dangerous aspects of the surgical procedure, making the learning curve even easier and safer. Indeed, in our own DMEK skills transfer courses at Devers Eye Institute, a recent survey of over 43 visiting surgeons to our individualized courses demonstrated that their complication rate in their first 25 cases was nearly identical to our low published complication rate. This demonstrated to us that the DMEK procedure is now standardized to the point of easy and safe skills transfer when done through individual teaching. The worry that DMEK represents a long and complex learning curve should now be largely mitigated.

The Risk of Preparation of the Donor Tissue

The risk of destroying the donor tissue when stripping has been transferred from the surgeon to the eye bank. Now that eye banks offer “prestripped” donor tissue, this major concern of surgeons has been eliminated. This eye banking innovation, similar to what “precutting” did for Descemet-stripping automated EK (DSAEK) surgery, has allowed much wider acceptance of the DMEK procedure. In addition, the development of new, safer injectors and devices for tissue delivery has eliminated another factor of intraoperative tissue loss.

The Reduced Complication Rates of DMEK

In their initial publications, experienced DMEK surgeons reported their early experience with a complication rate that was as high as an 8% primary graft failure rate and a 60% rebubble rate. However, with further innovations in DMEK, multiple surgeons have presented a standardized DMEK procedure that has reduced the primary graft failure rate to 2% or less and the rebubble rate to the single digits. In addition, even though DMEK’s rebubble rate is still slightly higher than DSAEK’s, a rebubble in DMEK is far easier and faster to perform, is done at the slitlamp, and does not disrupt the flow of even the busiest clinic. Finally, the most common cause of primary graft failure in DMEK is an upside-down (inverted) graft, and this complication has been eliminated by the use of “prestamped, S-mark” tissue provided by the eye bank.

Three Reasons DMEK Should Be Used for All Routine Cases of EK

1. The visual results: Multiple studies, including contralateral eye studies, have now shown that the percentage of patients that achieve a visual result of 20/20 or better after DMEK is significantly higher than those after DSAEK or even “ultra-thin” DSAEK surgery. In addition, the quality of the 20/20 vision after DMEK is better than the quality of the 20/20 vision after DSAEK, likely due to less higher-order aberration after DMEK than DSAEK.
2. The lower rejection rate: Large studies from multiple centers have now uniformly demonstrated that the rejection rate after DMEK is less than 1%, even when using low-dose steroids in the first year. In addition, most DMEK surgeons have reported that the severity of a rejection that occurs after DMEK is extremely mild compared to the rejections of DSAEK grafts, and easily reversible. These findings not only allow for a better long-term survival prognosis for DMEK compared to DSAEK grafts, but also further our understanding of the mechanisms behind allograft rejection.
3. Less steroid-induced glaucoma: The lower antigenicity and lower rejection rate of DMEK compared to DSEK provides an important secondary benefit: a reduction in the need for strong steroids for prolonged periods. This ability to switch early in the postoperative period following DMEK surgery from a strong steroid such as prednisolone acetate to a weaker steroid such as fluorometholone allows the transplant surgeon to significantly reduce the incidence of steroid-induced glaucoma.19

Corneal transplant surgeons should embrace the advantages of DMEK surgery as their primary method of endothelial replacement in routine cases now that the procedure has been standardized, the learning curve has been reduced, and the safety profile rivals that of standard DSEK surgery.

The Complete Endothelial Transplant Surgeon: DMEK, DSEK, and PK

To transition to performing DMEK for all routine cases of endothelial transplantation is an additive transformation, not an exclusionary one. Surgeons will still need to keep their skill levels high for DSEK procedures in settings that are most appropriate, such as anterior chamber lenses that are retained, extreme iris loss, and aphakia. Also, surgeons may prefer DSEK in more complex eyes where the DMEK tissue may undergo severe trauma or there is poor postoperative bubble support, such as in eyes with prior extensive vitrectomy, large filtering blebs/tubes, and extensive iridocorneal adhesions. Finally, there will always be cases where the endothelium, stroma, and topography are not normal and require total corneal thickness replacement, with PK as the best procedure. Today’s transplant surgeon should be able to apply the best procedure for any given circumstance. These are exciting times!

References


What’s the Issue With Donor Tissue? 
Transmission of Disease

Maria A Woodward MD MS

I. Background (EBAA 2015 statistical report)
   A. In 2015, 66.3% of recovered corneas were used for corneal transplantation.
   B. Several indications, related to the donor’s health, that recovered tissues are not released for transplantation:
      1. In 2015, 29.5% not released for transplant were because of + serology
      2. In 2015, 23.1% not released because of medical record or autopsy findings
      3. In 2015, 8.2% not released because of the medical/social interview
      4. Remaining tissues not released related to the quality of the tissue

II. Donor Screening: Diseases Resulting in Contraindication to Transplantation (see Table 1)
   A. Infectious etiologies
   B. Noninfectious etiologies: Malignant melanoma case

III. Screening Methods by EBAA Eye Banks (see Table 2)
   A. Diagnoses in medical chart
   B. Risk factors
   C. Clinical factors
   D. Physical evidence

IV. Prevalence of Disease in Potential Donors
   A. Variability in eye bank practices
   B. Impact on surgical tissue availability

V. Dynamic Standards Development in Response to Changing Conditions and Knowledge
   Transnational and emerging infections (Chagas, Zika, etc.)
### Table 1. Contraindications to Transplant

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious Diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Viral disease</td>
<td>Rubella (congenital)</td>
</tr>
<tr>
<td></td>
<td>Reye syndrome within 3 months</td>
</tr>
<tr>
<td></td>
<td>Viral encephalitis (subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, etc.)</td>
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<tr>
<td></td>
<td>Viral meningitis</td>
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<tr>
<td></td>
<td>Rabies</td>
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<tr>
<td></td>
<td>Ebola virus disease</td>
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<tr>
<td></td>
<td>Human immunodeficiency virus(^b) (by anti-HIV-1, anti-HIV-2 or combination test)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B (by hepatitis B surface antigen [HBsAg])(^b)</td>
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<tr>
<td></td>
<td>Hepatitis C (by anti-HCV)(^b)</td>
</tr>
<tr>
<td></td>
<td>West Nile virus</td>
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<tr>
<td></td>
<td>Vaccinia</td>
</tr>
<tr>
<td>Bacterial disease</td>
<td>Bacterial meningitis</td>
</tr>
<tr>
<td></td>
<td>Bacterial endocarditis</td>
</tr>
<tr>
<td></td>
<td>Syphilis (Treponema pallidum)(^b)</td>
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<tr>
<td>Fungal disease</td>
<td>Fungal endocarditis</td>
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<tr>
<td>Prion disease</td>
<td>Human transmissible spongiform encephalopathy (TSE) including Creutzfeldt-Jakob disease (CJD)</td>
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<td><strong>Systemic Diseases / Conditions</strong></td>
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<tr>
<td></td>
<td>Leukemia</td>
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<td></td>
<td>Lymphomas</td>
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<tr>
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<td>Malignant melanoma</td>
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<tr>
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<td>Parkinson disease</td>
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<tr>
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<td>Amyotrophic lateral sclerosis</td>
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<tr>
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<td>Multiple sclerosis</td>
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<td></td>
<td>Alzheimer disease</td>
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<td></td>
<td>Down syndrome</td>
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<tr>
<td><strong>Eye Diseases</strong></td>
<td></td>
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<tr>
<td></td>
<td>Retinoblastoma</td>
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<tr>
<td></td>
<td>Malignant anterior segment tumors</td>
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<tr>
<td></td>
<td>Adenocarcinoma in the eye of primary or metastatic origin</td>
</tr>
<tr>
<td></td>
<td>Active ocular or intraocular inflammation</td>
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<tr>
<td></td>
<td>Congenital or acquired disorders (eg, keratoconus)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
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</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Death of unknown causes</td>
</tr>
</tbody>
</table>

\(^a\) EBAA and FDA standards, combined

\(^b\) Diseases where donor blood testing is required

Source: 2015 Eye Bank Association of America (EBAA) Medical Standards; 1013 18th Street, NW, Suite 1010, Washington, DC 20036, USA; www.restoresight.org.
<table>
<thead>
<tr>
<th>Method</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnoses</td>
<td>Medical chart review reveals a condition not listed on problem list.</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Diagnosed with dementia of unknown etiology</td>
</tr>
<tr>
<td>Clinical evidence</td>
<td>Indication of sepsis: Temp &gt; 100.4°F; HR &gt; 90 beats/min; RR &gt; 20 breaths/min; or WBC &gt; 12,000 cells/mm³ (If 2 of 4 signs)</td>
</tr>
<tr>
<td>Physical evidence</td>
<td>Evidence of nonmedical percutaneous drug use (e.g., needle tracks)</td>
</tr>
</tbody>
</table>

*a Tissues determined to be ineligible any potential donor who exhibits one or more of the following conditions or behaviors.

Source: 2015 Eye Bank Association of America (EBAA) Medical Standards; 1015 18th Street, NW, Suite 1010, Washington, DC 20036, USA; www.restoreight.org.
Corneal Replacement: What Lies Ahead

Jodhbir S Mehta MBBS PhD

There has been a significant advancement in corneal replacement over the last 15 years. We have seen a re-emergence of lamellar keratoplasty procedures—both automated lamellar keratoplasty (ALK), in the forms of automated lamellar therapeutic keratoplasty (ALTK) / hemi-automated LK (HALK) and deep anterior LK (DALK), for anterior lamellar procedures and Descemet-stripping automated EK (DSAEK) / Descemet membrane EK (DMEK) for posterior lamellar (endothelial keratoplasty) procedures. Growing evidence from the literature also supports the use of these partial-thickness procedures over conventional full-thickness corneal transplantation with respect to better outcomes in terms of visual acuity, reduced complications, and better long-term graft survival.

Despite this, however, there are also reports in the literature of poorer outcomes with these procedures, and in certain countries they have not been widely adopted. Many factors can affect the adoption of a surgical procedure in a country, but the ease with which it can be performed is a major one. Procedures with a very steep learning curve are likely to be performed in only a very few centers internationally, hence limiting their utility for most of the population who may benefit from them.

Thus in the immediate future what lies ahead is improvement on what we are currently doing and what we know works well, while also leveraging current technology. For DALK the literature tells us the deeper the dissection, the better the visual acuity results, but also the higher the rate of complications. The most difficult part of the procedure is achieving a deep dissection and achieving a big bubble. The use of intraoperative OCT can help guide surgeons during the surgery with respect to the depth during the procedure. The use of integrated intraoperative OCT can help surgeons with the placement of the needle to an optimal depth, away from the Descemet membrane, in order to achieve a higher probability of success. Illustrations of its use in DALK surgery will be shown.

For EK several studies have shown conflicting results with respect to long-term outcomes. Some studies have shown worse outcome for DSAEK and DMEK vs. PK. The majority of the endothelial damage during EK occurs during donor insertion. With DSAEK this has been shown to be reduced using insertion devices (eg, Endoglide); however, for DMEK this has not been shown. Using in vivo confocal angiography and a corneal adapter, we have developed an imaging system that can assess any immediate damage to a donor cornea following DMEK insertion. This will allow surgeons to practice their techniques and to assess their outcomes prior to performing clinical cases. This use will also be demonstrated during the presentation. Currently this is available only for research use, but it can be adapted to clinical use.

What lies ahead in the near future may be a move away from heavy reliance on donor tissue by using tissue-engineering approaches. For anterior lamellar surgery the use of bioengineered corneas has already undergone proof-of-concept studies. Likewise for endothelial surgery the use of cultured corneal endothelial cells is already undergoing clinical trials in the form of cell injection therapy.

Further down the line, more work will concentrate on prevention of scar development in the stroma by the possible injection of keratocytes or corneal stroma stem cells. By modulating the wound healing process by cell therapy, one could circumvent the need for anterior lamellar procedures. For endothelial disease it is likely that different diagnoses will develop different therapies. For bullous keratopathy, where there is widespread destruction of endothelial cells, tissue-engineered cell therapies will be the way forward. Using tissue-engineered cells one can consistently produce grafts with cell counts of > 3000 cells/mm². For Fuchs endothelial corneal dystrophy (FECD), there has been a vast improvement in the understanding of the disease in the last 5 years with regard to its genetic basis. The use of selective Descemet stripping without transplantation, possibly in combination with Rho-associated kinase (ROCK) inhibitors or pure Descemet membrane transplants with ROCK I, offers an exciting approach to remove patients’ guttata. Further upstream for patients with CTG repeat sequence, oligonucleotide silencing offers an interesting approach to slowing down the disease process. For those with more advanced disease, we will still be able to perform cell therapy or conventional EK surgery.

In conclusion, corneal transplantation has come a long way in the last 2 decades. However, making our current surgical techniques more consistent and reproducible so more patients worldwide will benefit from the current surgery is important to widespread adoption. There are interesting times ahead, and the prospect of performing more minimally invasive surgery and treating patients early, hence avoiding the need for corneal transplantation, is a real option. Personalized bespoke medical therapy may be available for patients with FECD.
Alternatives to Keratoplasty

Sonal Tuli MD

I. Reasons to Do a Keratoplasty

A. Optical
   1. Corneal scarring
   2. Corneal dystrophies including keratoconus
   3. Bullous keratopathy

B. Therapeutic
   1. Infectious keratitis
   2. Painful bullous keratopathy
   3. Neurotrophic keratitis

C. Tectonic
   1. Central corneal melts and perforations
   2. Peripheral ulcerative keratitis (PUK)

II. Nonkeratoplasty Approaches

A. Optical
   1. Contact lenses
      a. Typically, rigid gas permeable or scleral
      b. Provide a smooth interface to replace warped air-corneal interface
      c. Soft contact lenses may help with microcystic edema.
   2. Debridement
      a. Limited to epithelial or basement membrane irregularities
      b. Rotating brush, blade, or diamond dusted burr
      c. Remove unhealthy tissue to allow healing
   3. Phototherapeutic keratectomy (PTK)
      a. To smooth cornea with masking agents
      b. To remove scars or opacities in dystrophies
      c. Limited to superficial stroma
   4. Manual lamellar keratectomy
      a. Similar indications to PTK but not as precise
      b. Higher risk of scarring

B. Therapeutic
   1. Bandage contact lens
      a. Provides protection and structural support to allow healing underneath
      b. Although may act as barrier to medications, may also act as depot of medications
   2. Stromal puncture:
      Causes scarring and allows increased adherence of epithelium to irregular basement membrane to prevent bullous keratopathy
   3. Amniotic membrane
      a. Provides growth factors and anti-inflammatory agents
      b. May act as sink for infectious organisms
      c. Protects the surface from trauma
      d. Provides a scaffold for healing
   4. Gunderson flap
      a. Provides serum-based growth factors
      b. Provides structural support
      c. Fibrovascular tissue resistant to ulceration and infection
   5. Pedicle graft
      a. Similar to Gunderson flap but for peripheral pathology
      b. Vision may be retained if limited to peripheral.
   6. Tarsorrhaphy

C. Tectonic
   1. Corneal gluing
      a. Tamponades the defect to allow the tissues to heal underneath
      b. Prevents growth of infectious organisms
      c. Acts as barrier for proteases in PUK, preventing further melting
      d. Inflammatory and acts as stimulus for vessels
      e. Could be definitive treatment for peripheral ulceration but usually temporizing measure for central ulceration
   2. Multilayer amniotic membrane:
      As above but additional structural support provided
   3. Pedicle graft
      a. As above but useful only for very small perforations
      b. Contraindicated in active PUK
What to Do With Pigmented Lesions
Conjunctival Pigmented Lesions
Carol L. Shields MD

I. Racial Melanosis
   A. Terminology: Also termed “complexion associated melanosis” (CAM)
   B. Clinical features
      1. Flat with microfolds
      2. Bilateral, limbus
      3. Dark complexion
   C. Management
      1. Observation
      2. Resection
      3. Cryotherapy
      4. Laser photocoagulation
   D. Prognosis: No transformation into melanoma, but note that primary acquired melanosis can occur in dark complexioned patients and can simulate CAM.

II. Primary Acquired Melanosis (PAM)
   A. Also termed “conjunctival melanoma in situ” and “intraepithelial melanocytic proliferation with/without atypia”
   B. Clinical features
      1. Flat, patchy pigmentation without cysts
      2. Usually white / European descent
   C. Management
      1. Surgical excision using no-touch technique
      2. Cryotherapy
      3. Mitomycin C 0.04% q.i.d. for 1 week on, 1 week off, 1 week on, 1 week off
   D. Prognosis
      1. Transformation to melanoma at 10 years in 12%, particularly if severe atypia
      2. Each additional clock hour of PAM contributes 1.7 times risk for transformation to melanoma compared to 1 clock hour PAM.

III. Secondary Acquired Melanosis
   A. Clinical features: Flat pigmentation at site of exposure
   B. Management: Observation
   C. Prognosis: No risk for melanoma

IV. Nevus
   A. Clinical features
      1. Slightly elevated, multicystic mass, usually at limbus
      2. Pigmented or nonpigmented
      3. Whites > Non-whites
   B. Management: Observation or surgical resection
   C. Prognosis: Rare (1/300) risk for transformation to melanoma

V. Melanoma
   A. Clinical features
      1. Incidence is increasing. A study from the United States found rate of conjunctival melanoma significantly increased among white men, but not white women. In white men, the incidence rate increased 295% over 27 years, especially in men older than 60 years; probably related to solar radiation.
      2. Pigmented or nonpigmented mass, commonly associated with primary acquired melanosis
      3. Feeder and intrinsic vessels are prominent.
      4. Growth onto cornea or into fornix or orbit can occur.
   B. Management: Surgical resection
      1. Careful planning of approach is very important.
      2. No-touch technique
      3. Dry ocular surface without balanced salt solution
      4. The first surgery is the most important surgery as complete resection without disturbing the tumor or seeding the tumor is tantamount to preventing recurrence and metastasis.
      5. Do not perform incisional biopsy or cut through the melanoma as this can seed the tumor and lead to multiple recurrences, with need for exenteration.
Table 1. Classification by American Joint Committee on Cancer Classification (AJCC), 7th ed.

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
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<tr>
<td><strong>T</strong>0</td>
<td>No evidence of primary tumor</td>
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<tr>
<td><strong>T</strong>(is)</td>
<td>Malignant melanoma confined to conjunctival epithelium</td>
</tr>
<tr>
<td><strong>T</strong>1</td>
<td>Malignant melanoma of the bulbar conjunctiva</td>
</tr>
<tr>
<td><strong>T</strong>1a</td>
<td>≤ 1 quadrant</td>
</tr>
<tr>
<td><strong>T</strong>1b</td>
<td>&gt; 1 but ≤ 2 quadrants</td>
</tr>
<tr>
<td><strong>T</strong>1c</td>
<td>&gt; 2 but ≤ 3 quadrants</td>
</tr>
<tr>
<td><strong>T</strong>1d</td>
<td>&gt; 3 quadrants</td>
</tr>
<tr>
<td><strong>T</strong>2</td>
<td>Malignant melanoma of palpebral conjunctiva, fornical conjunctiva, and/or caruncle</td>
</tr>
<tr>
<td><strong>T</strong>2a</td>
<td>≤ 1 quadrant but not involving caruncle</td>
</tr>
<tr>
<td><strong>T</strong>2b</td>
<td>≥ 1 quadrant but not involving caruncle</td>
</tr>
<tr>
<td><strong>T</strong>2c</td>
<td>≤ 1 quadrant and involving caruncle</td>
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<tr>
<td><strong>T</strong>2d</td>
<td>≥ 1 quadrant and involving caruncle</td>
</tr>
<tr>
<td><strong>T</strong>3</td>
<td>Malignant melanoma with local invasion</td>
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<td>Globe</td>
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<tr>
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<td>Eyelid</td>
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<td><strong>T</strong>3c</td>
<td>Orbit</td>
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<td><strong>T</strong>3d</td>
<td>Paranasal sinus</td>
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<td><strong>T</strong>4</td>
<td>Malignant melanoma with intracranial invasion</td>
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<table>
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<td><strong>Nx</strong></td>
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<td><strong>N</strong>0a</td>
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<tr>
<td><strong>N</strong>0b</td>
<td>No regional lymph node metastasis, no biopsy done</td>
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<tr>
<td><strong>N</strong>1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M</strong>0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td><strong>M</strong>1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

C. **Prognosis**
1. Overall exenteration in 15%
2. Overall metastasis in 25%
3. According to AJCC, 5-year rate of metastasis is 11% for T1, 35% for T2, and 42% for T3.

VI. **Metastasis**
A. **Clinical features**
1. Usually known history of cutaneous melanoma
2. Can be unifocal or multifocal, unilateral or bilateral
3. Brown mass deep to surface epithelium within stroma

B. **Management**
1. Surgical resection
2. Evaluated for metastatic disease elsewhere

C. **Prognosis**: Poor survival, < 1 year

VII. **Scleral Melanocytosis**
A. **Clinical features**
1. Grey brown pigmentation on the sclera with 1/400 risk for uveal melanoma in whites
2. Can have associated ipsilateral cutaneous periocular, palate, orbit, meningeal, and tympanic membrane pigmentation

B. **Management**
1. Observation with dilated examination for uveal melanoma twice yearly
2. In some countries, the pigmentation is treated to depigment or remove the cells with YAG laser or surgical lamellar sclerectomy.
3. Consider other risks of orbital and meningeal melanocytosis that can lead to orbit and meningeal melanoma. Some clinicians perform MRI brain and orbits every few years.

C. **Prognosis**: If uveal melanoma develops, the risk for metastasis is twice the risk compared to melanoma without melanocytosis.

VIII. **Simulating lesions**
Several lesions including extraocular extension of uveal melanoma, mascara deposition, pigmented mycetoma, hemorrhagic cyst, oncocytoma, and others

**Selected Readings**


Ocular Surface Squamous Neoplasia

Fairooz P Manjandavida MD

Introduction

“Ocular surface squamous neoplasia” (OSSN) is a blanket term currently used for precancerous and cancerous conjunctival and corneal epithelial lesions. It is a spectrum including conjunctival dysplasia, intraepithelial neoplasia, and malignant squamous cell carcinoma (SCC).1-3 Previously used terms were “intraepithelial epithelioma,” “Bowens disease,” and “Bowenoid epithelioma.”4 It is recently broadly classified as conjunctival intraepithelial neoplasia (CIN) and invasive SCC. OSSN 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 The incidence of invasive SCC of the conjunctiva is much less than that of CIN, varying 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.7 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 There is a strong systemic association with xeroderma pigmentosum (XP) that may present as multiple recurrent lesions requiring long-term follow-up. Papillon-Lefèvre syndrome, a rare syndrome with palmo-plantar keratoderma, is also associated with OSSN in younger individuals.

It is mostly unilateral and is commonly seen in middle-aged and older patients, presenting as redness and ocular irritation. It may present bilaterally in immunocompromised individuals and in those with associated XP. Larger lesions encroaching the cornea may affect the vision. Characteristically, it appears as a fleshy, nodular, or sessile minimally elevated lesion with overlying keratin, feeder vessels, and intrinsic vascularity.1-3,6 Rose bengal staining is helpful in the diagnosis and assessing the extent of the tumor (see Figure 1).

In our experience, presence of keratin, feeder vessels, and positive Rose bengal staining has 97% and 98% sensitivity and specificity, respectively, in diagnosing OSSN (unpublished data). 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 SCC of the cornea is rare.

Table 1. Morphological Types

<table>
<thead>
<tr>
<th>Placoid</th>
<th>Gelatinous</th>
<th>Papilliform</th>
<th>Velvety</th>
<th>Leukoplakic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular</td>
<td>Diffuse</td>
<td></td>
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</tbody>
</table>

There are no consistent clinical criteria for distinguishing CIN from invasive SCC. Leukoplakia is usually absent or minimal in CIN; extensive leukoplakia raises the suspicion of malignancy. Nodular lesion causes suspicion of invasive SCC.8 A diffuse conjunctival OSSN can masquerade as chronic conjunctivitis.7 It is also important to evert the eyelid of patients with OSSN to detect the contiguous or multifocal involvement of the tarsal conjunctiva.

Figure 1. Left: An elevated nodular mass arising from temporal bulbar conjunctiva encroaching the cornea in the left eye of a 65-year-old male. Surface keratin and dilated feeder vessels are seen with pigmentation of the edges. Right: Characteristic clinical features of OSSN include keratin (solid arrow), feeder vessels (longer dotted arrow), and Rose bengal staining (shorter dotted arrow).
Advanced cases can infiltrate the cornea and sclera to have intraocular extension. Tumors extending into the orbit causes proptosis. Loco-regional lymph node and, distant metastasis may occur rarely.

The most aggressive variants include spindle cell squamous carcinoma, mucoepidermoid carcinoma, and adenoid SCC.

### Treatment

Primary management of OSSN includes complete surgical excision with cryotherapy. Recently, topical chemotherapy and immunotherapy have been widely accepted as a treatment modality in CIN. Complete surgical excision using a technique without touching the tumor, called the “no-touch” technique, is still considered the primary treatment of choice.

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 epithelectomy 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 one 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 SCC of the conjunctiva. However, with the protocol-based technique as described above, the recurrence rate can be limited to less than 5%. Cryotherapy of the conjunctival edge plays a major role in reducing recurrence.

Topical interferon therapy and chemotherapy have recently been considered as a mainstay of treatment in CIN. Currently, topical interferon alpha 2b is widely accepted in the management of CIN as immunotherapy for primary treatment, immunoreduction to reduce the size of large tumors to facilitate complete tumor excision, and immunomodulation in immunocompromised patients. 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. Combined topical immunotherapy and surgical excision provides excellent outcome with reduced recurrence rate. It has 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 intralesional injection.

### Table 2. Protocol for Interferon-Alpha 2b

<table>
<thead>
<tr>
<th>Method</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical eye drops</td>
<td>3 million IU 4 times a day for 3 to 12 months</td>
</tr>
<tr>
<td>Sublesional injection</td>
<td>5 to 10 million IU once monthly until resolution</td>
</tr>
</tbody>
</table>

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

### Table 3. Protocol for Topical MMC: Rule of 4

<table>
<thead>
<tr>
<th>Method</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical eye drops</td>
<td>0.04% (0.4 mg/ml)</td>
</tr>
<tr>
<td></td>
<td>Four times a day</td>
</tr>
<tr>
<td></td>
<td>Four days a week</td>
</tr>
<tr>
<td></td>
<td>Four weeks</td>
</tr>
<tr>
<td></td>
<td>Two weeks of treatment-free interval</td>
</tr>
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</table>

Other available drugs are 5-fluorouracil and cidofovir. Plaque brachytherapy is used to control gross or microscopic residual tumors. More extensive orbital invasion requires orbital exenteration. Plaque brachytherapy is indicated as primary modality or in those with scleral invasion.

### Table 4. 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 papillary axis
4. Positive margin after excision

### Prognosis

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

### References


Eyelid Lesions: When to Worry and When to Relax

Bita Esmaeli MD FACS

Clinical features of malignant lesions of the eyelid and periocular region will be highlighted through illustrative cases with the aim of preparing the general ophthalmologist to make the appropriate early diagnosis and interventions. Specifically, the following common eyelid lesions will be discussed with several illustrative cases:

1. Basal cell carcinoma
2. Squamous cell carcinoma
3. Sebaceous carcinoma
4. Eyelid skin or palpebral conjunctival melanoma
5. Metastasis
6. Intradermal nevus

Considerations about biopsy procedures and appropriate timing for referrals to specialists will be discussed.
Iris Lesions: What Do I Do?

_Arun D Singh MD_

I. Introduction

II. Iris Melanoma

A. Etiology and pathology
B. Clinical features
C. Variants
   1. Circumscribed iris melanoma
   2. Diffuse iris melanoma
   3. Tapioca iris melanoma

III. Differential Diagnosis

A. Iris and ciliary body nevus
B. Iris and ciliary body melanocytoma
C. Iris pigment epithelial (IPE) cyst
D. Iris stromal cyst
E. Iridocorneal epithelial (ICE) syndrome
F. Iris metastases
G. Non-melanocytic tumors

IV. Diagnostic Methods

A. OCT
B. Ultrasonography
C. Fluorescein angiography
D. Biopsy
   1. Fine needle aspiration biopsy
   2. Incisional biopsy
   3. Excisional biopsy

V. Conclusions
Ptɛrygium: Evidence-Based Management

Lawrence W Hirst MD MBBS MPH DO FRACO FRACS

Introduction

Over the last 100 years, pterygium surgery has been plagued by the problem of recurrence. Many methods have been advocated to reduce the recurrence rate, but the best method is still not widely agreed upon. In addition, many methods that do reduce the recurrence rate, such as beta irradiation and mitomycin, may cause vision-threatening complications. Until recently the issue of the postoperative aesthetic appearance has not been considered important in light of the recurrence rate and complication rate.

Discussion

A summary by the Ophthalmic Technology Assessment on pterygium surgery (2012), which reviewed 51 randomized controlled trials, suggested that the use of a conjunctival autograft together with mitomycin resulted in the lowest recurrence rate but reserved judgement on the route and dose for the mitomycin.

I have reviewed 85 published studies (Group A), including RCTs involving conjunctival autografts, mitomycin C, and amniotic membrane transplantation, as well as the OTA (Group B), to understand the role of 5 factors that affect recurrence rate outcomes and patient satisfaction.

1. Firstly, and most importantly, there needs to be a consistent and logical definition of pterygium recurrence. Forty-six percent of studies in Group A and 40% in Group B defined recurrence as “new growth more than 1 mm onto the cornea.”
2. Follow-up of a year, which is required to identify 97% of recurrences, was achieved in only 36% in Group A.
3. Cosmesis was considered in only 12% of Group A studies.
4. Assessment of short-term complications with mitomycin in Group A revealed granulomas in up to 25% of patients and delayed healing and avascular necrosis in a smaller number of patients. Long-term complications were not reported.
5. Many surgeries combine multiple modalities, including amniotic membrane grafts, tenonectomies, mitomycin, and steroid injections, making a persuasive argument for any one of these modalities very difficult.

An excellent cosmetic result after pterygium surgery implies no recurrence and is a higher level outcome than no recurrence alone.

In 2011, the cosmetic result of PERFECT for Pterygium (pterygium extended removal followed by extended conjunctival transplantation) was assessed in a randomized controlled trial; 94% of eyes were evaluated as of acceptable appearance, and graders were unable to distinguish between operated eyes and control eyes. In 2012, a prospective study of 1000 eyes that underwent PERFECT for Pterygium resulted in 1 recurrence and a very low complication rate. In 2013, a further study of PERFECT for Pterygium in 389 patients concluded that graders were unable to differentiate between eyes that had surgery and the unoperated normal contralateral eyes.

In view of the above studies, it would seem reasonable to suggest that any further randomized controlled trials of pterygium removal should use PERFECT for Pterygium as one arm of the trial.

References

The Bump That Stumped Me

Kathryn Colby MD PhD

Case Report

A healthy 53-year-old woman presented with a large amelanotic lesion extending from the conjunctiva onto the cornea for approximately 5-6 clock hours (see Figure 1). The lesion had been present for more than 5 years but recently had begun to grow. After a thorough discussion of the risks and benefits of various approaches, the patient wished to proceed with a trial of topical interferon to debulk the tumor. She was seen 4 weeks later with growth and appearance of new pigment on the lesion (see Figure 2). Ocular surface surgery was performed. The histopathology revealed malignant melanoma.

Discussion

Ocular surface tumors are one of the few ophthalmic diseases capable of causing death. However, with proper diagnosis, surgical removal, adjuvant therapies, and follow-up, most patients do well. Conjunctival melanoma (CM) is an uncommon tumor, with perhaps 200 new cases annually in the United States. Incidence appears to be increasing. Although most melanomas are pigmented, some can be amelanotic, as illustrated in this case. This is especially true of recurrent CM (even if the primary tumor was pigmented). Primary acquired melanosis (PAM) with atypia is the most common precursor lesion (75%). A smaller percentage arise from malignant transformation of a pre-existing nevus (25%). Rarely CM will arise de novo.

CM is a surgical disease. Complete removal, with margins of 2-4 mm, and adjuvant cryotherapy at the time of excision, is the preferred treatment. Adjuvant chemotherapy with topical mitomycin C (MMC) can be used in the setting of diffuse PAM that is too extensive for complete excision. MMC is a nasty but effective medication. Side effects include toxic conjunctivitis (universal), toxic keratopathy (less common), punctal stenosis (uncommon, punctal plugs reduce occurrence), and limbal stem cell dysfunction (uncommon). Scleral melting has been reported with MMC use in other settings, so one needs to be judicious in its use. CM shares common biology with skin melanoma and similar genetic mutations can be seen (BRAF). In the future, targeted therapy may be useful in management of CM.

Ocular surface squamous neoplasia (OSSN) is a spectrum of disease from dysplasia through intraepithelial neoplasia to frankly invasive carcinoma. It generally occurs on sun-exposed areas of the conjunctiva. Recurrences are common. Clinical appearance can vary from the typical amelanotic lesion with papillary vascularization to a flat leukoplakic lesion.

There is controversy about the optimal management of OSSN. Surgical management is the gold standard, but topical chemotherapy with interferon is very successful in OSSN. No randomized controlled trials have been done, but several case series indicate comparable efficacy. Surgery is quicker and provides a definitive diagnosis but costs more for the health care system. Topical interferon treats the entire ocular surface and avoids the risks of surgery (infection, scarring, persistent redness), but it can take several months to work and may not work for some tumors, does not provide a diagnosis, and is typically not covered by insurance so it is more expensive for the individual patient. High-resolution anterior segment imaging may help in distinguishing OSSN from CM and from benign lesions of the conjunctiva.

Selected Readings

2016 Advocating for Patients

Stephanie J Marioneaux MD

Ophthalmology’s goal to protect sight and empower lives requires active participation with and commitment to advocacy efforts. Contributions to the following three critical funds by all ophthalmologists is part of that commitment:

1. OPHTHPAC® Fund
2. Surgical Scope Fund (SSF)
3. State Eye PAC

Your ophthalmologist colleagues serving on Academy committees—the Surgical Scope Fund Committee, the Secretariat for State Affairs, and the OPHTHPAC Committee—are dedicating significant time to advocating for patients and the profession. The OPHTHPAC Committee is identifying congressional advocates in each state to maintain close relationships with federal legislators in order to advance ophthalmology and patient causes. The Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level. Both groups require robust funds from both the Surgical Scope Fund and the OPHTHPAC Fund in order to protect quality patient care.

These committed ophthalmologists serving on your behalf have a simple message to convey: “It takes the entire community of ophthalmologists” to be effective.

- We need each member of the ophthalmology community to contribute to each of these 3 funds.
- We need each member of the ophthalmology community to establish relationships with state and federal legislators.
- We need each member of the ophthalmology community to make a commitment to protect quality patient eye care and the profession.

OPHTHPAC® Fund

OPHTHPAC is a crucial part of the Academy’s strategy to protect and advance ophthalmology’s interests in key areas, including physician payments from Medicare as well as protecting ophthalmology from federal scope of practice threats. Established in 1985, OPHTHPAC is one of the oldest, largest, and most successful political action committees in the physician community. We are very successful in representing your profession to the U.S. Congress. As one election cycle ends, a new one starts. OPHTHPAC is always under financial pressure to support our incumbent friends as well as to make new friends with candidates. These relationships allow us to have a seat at the table and legislators willing to work on issues important to us and our patients.

For the past year, the media and the country have focused on the U.S. presidential primaries. But the races most important to ophthalmology involve seats in Congress. The entire House of Representatives and one-third of the Senate is up for election. Several physicians need our help—and we have many new friends to make.

In order for ophthalmology to remain seated at the table, we need to be heavily invested in this year’s election. That takes investment by each member of the ophthalmology community, whether with time or money. Currently, only a minority of ophthalmologists have realized the vital importance of contributing to OPHTHPAC and the other funds. Right now, major transformations are taking place in health care and we need participation from the majority of ophthalmologists so that we have the resources to better our profession and ensure quality eye care for our patients.

Among the significant impacts made by OPHTHPAC are the following:
- Repealed the flawed Sustainable Growth Rate (SGR) formula
- Blocked the unbundling of Medicare global surgery payments
- Removed a provision in Medicare fraud and abuse legislation that targeted eyelid surgery
- Working to reduce the burdens from Medicare’s existing quality improvement programs, such as the EHR Meaningful Use program
- Working in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin
- Working to get the Centers for Medicare and Medicaid Services to revisit drastic Medicare fee cuts to glaucoma and retinal detachment surgeries
- Working to protect your ability to perform in-office ancillary services in your office

Contributions to OPHTHPAC can be made here at AAO 2016 or online at www.aao.org/ophtpac.

Leaders of the Cornea Society are part of the American Academy of Ophthalmology’s Ophthalmic Advocacy Leadership Group (OALG), which has met for the past nine years in January in the Washington, DC, area to provide critical input and to discuss and collaborate on the Academy’s advocacy agenda. The topics discussed in the 2016 OALG agenda included the impact of the Medicare Access and the CHIP Reauthorization Act (MACRA); the IRIS® Registry and quality reporting under Medicare; data transparency and public reporting, and a roundtable to discuss challenges for surgical specialties. At Mid-Year Forum 2016, the Academy, the Cornea Society, and the Eye Bank Association of America (EBAA) ensured a strong presence of cornea specialists to support ophthalmology’s priorities, and a record number of ophthalmologists visited members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The Cornea Society and the EBAA remain crucial partners with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund (SSF)

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their legislative, regulatory, and public education efforts to derail optometric surgery proposals that pose a threat to patient safety, quality of surgical care, and surgical standards. Since its inception, the Surgery by Surgeons campaign—in partnership with state ophthalmology societies and with support from the SSF—has helped 32 state/territo-
In 2016, thanks to Surgical Scope Fund support by Academy members and tireless advocacy by state ophthalmology society leaders, ophthalmology continues to champion surgical safety at state capitol across the country. State ophthalmological societies and the Academy’s Secretariat for State Affairs faced eight concurrent surgery by surgeons battles, in Alaska, California, Delaware, Illinois, Iowa, Massachusetts, Pennsylvania, and Puerto Rico.

In each of these legislative battles, the benefits from Surgical Scope Fund distributions are crystal clear. The fund has allowed for successful implementation of patient safety advocacy campaigns, which result in defeating attempts by optometry to expand their scope of practice to include surgery.

The Academy relies not only on the financial contributions to the Surgical Scope Fund from individual ophthalmologists and their practices, but also on the contributions made by ophthalmic state, subspecialty, and specialized interest societies. The Cornea Society and the EBAA contributed to the Surgical Scope Fund in 2015, and the Academy counts on their contributions in 2016.

Contributions to the SSF can be made here at AAO 2016 or online at www.aao.org/ssf.

State Eye PAC

It is also important for all ophthalmologists to support their respective State Eye PACs because PAC contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the Surgical Scope Fund. 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: ADVOCATE FOR YOUR PATIENTS

Academy Surgical Scope Fund contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. PAC contributions are necessary at the state and federal level 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. Surgical Scope Fund 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 Surgical Scope Fund, and your State Eye PAC. Please be part of the community advocating for your patients now.

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Kurt F Heitman MD (SC)
Confocal: How This Helps Me

Pedram Hamrah MD

I. Infectious Keratitis
   A. *Acanthamoeba* keratitis
   B. Fungal keratitis
      1. Filamentous fungi
      2. *Candida* species
      3. *Paecilomyces* species
   C. Role of confocal microscopy in management and assessment of therapeutic efficacy

II. Neurotrophic Keratopathy
   A. Relation to corneal sensation
   B. Role of confocal microscopy in diagnosis
   C. Role of confocal microscopy in long-term management

III. Dry Eye Disease
   A. Assessment of immune activation and inflammation
   B. Assessment of corneal nerves
   C. Role of confocal microscopy in diagnosis and management
   D. Role of confocal microscopy in assessment of therapeutic efficacy

IV. Corneal Neuropathic Pain
   A. Definition and pathogenesis
   B. Corneal nerve alterations by confocal microscopy
   C. Role of confocal microscopy in diagnosis
   D. Role of confocal microscopy in management
Tomography vs. Topography: What Do They Tell Me?

*Michael W Belin MD*

I. Placido-Based Topography

- Measures slope from the anterior tear film and from slope data computes curvature
- Limited to anterior corneal surface
- Reflective systems typically have limited corneal coverage.
  - Optical limitations
  - Anatomical limitations: Often stated as having superior accuracy compared to elevation-based systems

II. Axial Curvature (Sagittal)

- Most commonly used “curvature”
- All the centers of rotation fall on the VK normal.
- Does not represent peripheral data well
- Very close to refractive power in the pupillary area
- Maps tend to be smooth (not much noise)
- First-order equation

III. Tangential Curvature (Local)

- More sensitive to local curvature changes
- Centers of rotation do not fall on VK normal.
- Better in the periphery
- Does not reflect refractive power
- Points are all independently calculated.
  - Maps tend to be “noisy.”
  - Second-order equation

IV. Placido-Based Topography

- Useful in analyzing tear film quality
- Systems relatively inexpensive
- Have been in wide usage for over 25 years; Placido analysis over 200 years old

V. Curvature is analogous to measuring spectacle lens power.

- It may be accurate, but it tells you nothing about the shape of the lens (ie, multiple spectacle lenses [different shapes] can have the same power.)

VI. Curvature and power will change with orientation.

- Lens tilt and/or measurement axis
- The same lens (shape) can have multiple powers.
- This is true for all curvature regardless of whether it is Placido, Scheimpflug, or OCT derived.

VII. Comparisons have been based on measurements made on spherical test objects.

- Spherical test objects have the same curvature throughout, but constantly changing elevation.
- Curvature systems just need to average out their systematic error.
- This is a useless testing method with no clinical value.

VIII. Tomo/Topographic Comparison

A. Tomography

- Anterior and posterior surfaces
- Full pachymetric map
- Limbus to limbus coverage
- Less susceptible to false positives

B. Placido based

- Anterior only
- No measurement of thinning
- Coverage limited to < 9.0 mm
- High incidence of false positives

IX. Scheimpflug imaging (elevation)

OCT similar.

X. 3-Dimensional Analysis

- The major advance of complete anterior segment analysis is the ability to measure the posterior corneal surface and a full-corneal thickness map.

XI. Posterior Surface

- We have been told not to pay much attention to the posterior surface because it is less important as a refractive surface and in the past, information about it was unreliable.
- The posterior corneal surface is just as important as the anterior surface and serves as a more subtle or early indicator of potential pathology than any anterior surface parameter.

XII. How Is Elevation Data Displayed?

- Raw elevation maps are rarely shown/used.
- The most common method is to compare (amplify) the raw elevation data against some common shape.
- The most common shape used is the best fit sphere (BFS).
- Other shapes can be used: Ellipse / toric ellipsoid
XIII. Elevation Advantages
   A. Screening for refractive surgery: Early / subclinical keratoconus
   B. Diagnosis of peripheral corneal disease: eg, pellucid marginal degeneration (PMD)
   C. Toric IOL: Magnitude and axis orientation

XIV. Summary Evolution of Topo / Tomography
   A. Early qualitative and quantitative analysis was limited to a portion of the anterior surface.
   B. Newer technologies allow for examination of both the anterior and posterior corneal surface and for the generation of a full pachymetric map.
   C. Full anterior segment analysis allows for the identification of earlier disease (subclinical KCN), eliminates false positives seen with anterior curvature analysis (PMD), and allows for more accurate toric IOL placement.
Optical coherence tomography (OCT) is a noninvasive, noncontact, in vivo technique based on low coherence interferometry. It produces reproducible, cross-sectional images of ocular tissues.

I. Posterior Segment OCT for the Corneal Surgeon

A. Preoperative assessment of comorbidities: Macular edema, epiretinal membranes, and macular degeneration. This is especially useful when the view through the cloudy cornea does not allow clinical assessment.

B. Postoperative assessment: Usually identifying the etiology of suboptimal vision after corneal surgery as in the case of cystoid macular edema

II. Anterior Segment OCT (AS-OCT)

A. Preoperative

1. Assessing the depth of corneal pathology to determine candidacy for microkeratome-assisted or excimer laser phototherapeutic keratectomy, lamellar or deep anterior lamellar keratoplasty, and penetrating keratoplasty

2. Assessing the depth of the anterior chamber, angle configuration, and position of the crystalline lens before phakic IOL implantation or femtosecond laser-assisted cataract surgery (FLACS)

3. Determining the posterior corneal contour, especially at the graft–host junction, in failed penetrating keratoplasty to aid in decision making regarding secondary graft thickness and diameter (EK behind PK)

B. Intraoperative

1. In Descemet-stripping automated endothelial keratoplasty (DSAEK): Allows the accurate evaluation of the presence of any interface fluid between the host stroma and the DSAEK graft

2. In Descemet membrane endothelial keratoplasty (DMEK): Identifies the correct orientation of the DMEK graft before positioning it on the posterior surface of the host together with ensuring the absence of fluid in the interface

3. In deep anterior lamellar keratoplasty (DALK): Delineates the position and depth of the cannula in the host stroma before injecting air to create a big bubble (BB), identifies any perforations in the posterior stroma into the anterior chamber, and possibly distinguishes BB type 1 from BB type 2

4. In pre-Descemet DALK: Allows the measurement of the residual corneal stromal bed to help with the decision to remove more stroma before grafting the donor

5. In FLACS: Allows positioning of the laser for the performance of corneal incisions, astigmatic keratotomy, capsulorrhexis, and nuclear disassembly

C. Postoperative

1. Confirmation of graft attachment and ensuring the absence of interface fluid after DSAEK and DMEK: This is particularly important when it is difficult to determine the etiology of graft edema (poor adherence vs. endothelial failure) clinically.

2. Assessment of DSAEK graft thickness, contour, and eccentric trephination

3. Confirmation of DALK graft apposition, follow-up of pre-Descemet DALK (assessment of host posterior lamellar thickness and contour), and management of double anterior chamber

4. Assessment of LASIK flap thickness, interface fluid, and epithelial ingrowth

III. Ultrahigh-Resolution OCT (UHR-OCT)

Has an axial resolution below 5 microns and can be used to assess in great detail all layers of the cornea in normal and diseased entities: corneal dystrophies, degenerations, scars, and tumors

IV. Conclusion

OCT has become an important tool in the evaluation and management of corneal disease entities, especially perioperatively, in endothelial and lamellar keratoplasty.
Section IV: The Role of Imaging and In-Office Diagnostics

Pearls for Intraoperative Aberrometry

Sonia H Yoo MD

I. Clinical Pearls
   A. Confirm patient information.
   B. Keep IOP between 20 and 30 mmHg, wet cornea.
   C. Avoid causes for false astigmatism readings like parallax, drape, or speculum.
   D. Don’t rotate if within 5 degrees and/or < 0.5 D.

II. Clinical Case Example

III. Posterior Corneal Astigmatism
   A. Source of against-the-rule corneal toricity
   B. Mean value -0.30 D
   C. IOLMaster overestimates with-the-rule total astigmatism and underestimates against-the-rule total astigmatism.

Selected Readings


In-Office Diagnostics for Infection

Elmer Y Tu MD

Introduction
Infections of the ocular surface are one of the most common reasons for acute presentation to either a comprehensive ophthalmologist’s or a cornea specialist’s practice. While conjunctivitis is generally self-limited and produces limited ocular morbidity, it can result in significant loss of work days for both the patient and their contacts if not promptly managed. Corneal infections, on the other hand, will often result in both short-term and long-term ocular morbidity, representing a true ocular emergency where early, accurate diagnosis and treatment can significantly improve visual outcomes. In-office diagnostics can play a crucial role in directing the initial management of both of these disorders.

Importance of History and Slitlamp Examination
The history and slitlamp examination comprise the initial evaluation of any patient with an ocular infection. A detailed history of exposures, clinical course, and prior treatment is invaluable in narrowing down the list of differential diagnoses. For conjunctivitis, the slitlamp examination will define the eye’s inflammatory response. For infectious keratitis, numerous studies have confirmed the benefit of slitlamp examination in differentiating infectious from noninfectious forms of keratitis, but determining an actual pathogen from the clinical exam can be inaccurate.

In-Office Diagnostic Tools for Ocular Surface Infections
While culturing an infectious lesion is an in-office procedure, the results are generally not available during a patient’s initial visit. Culturing corneal lesions, in and of itself, can be helpful in providing tactile feedback to the clinician to further narrow the differential diagnosis. Clinical Laboratory Improvement Amendments (CLIA) has granted waivers to only two ophthalmology testing systems for in-office diagnostic testing: tests for adenoviral conjunctivitis and for matrix metallopeptidase 9 (MMP-9). The former clearly has some utility in differentiating an adenoviral conjunctivitis, while the latter may be elevated in patients with corneal ulceration but currently without a clear indication for ocular infection. Provider-performed microscopy can also be performed for wet mounts and KOH preps (potassium hydroxide preparations), only, and under specific CLIA rules.

For atypical infections where organisms are larger, ocular imaging devices may provide enough evidence to alter initial therapy. OCT devices provide corneal cross-sectional information about the level of involvement, but it is limited by corneal opacity and lateral resolution. Confocal microscopy provides en face images of the cornea with sufficient resolution to detect parasitic and fungal pathogens. Various studies have validated its utility for these forms of infectious keratitis.

Summary
Contemporaneous diagnosis of infections of the ocular surface can reduce morbidity and spread of corneal and conjunctival infections. A thorough history and slitlamp examination will properly direct other in-office diagnostics that can improve initial diagnosis and management of a myriad of infectious diseases.
How Imaging Saved Me  
(Or, Really, Saved My Patients)  

Francis W Price Jr MD

Great imaging devices make ophthalmology fun! However, the benefits have to justify your cost and time. The imaging devices I use routinely as an anterior segment surgeon are topography, tomography, OCT, specular/confocal microscopy, ultrasound biomicroscopy (UBM), and ray-tracing wavefront aberrometry/topography, or iTrace.

Topography is valuable for evaluating the quality of the ocular surface and quantifying the amount of irregular astigmatism from dryness or scarring. Topography also helps identify eyes not suitable for refractive surgery by detecting early keratoconus, and it allows us to evaluate the effect of scars and growths like pterygium on the central cornea. The primary reason that dry eye disease affects vision either after surgery (refractive, cataract, grafts) or in virgin eyes is that the ocular surface is disrupted and irregular. Topography quantitates this and helps us judge response to treatment along with visual acuity. The iTrace takes this a step further. To my knowledge no other instrument does this as effectively, and that is why this device is being noted specifically and not generically. The iTrace takes the calculated wavefront from the ocular surface topography and compares it to the overall total wavefront of the eye. This allows us to see what distortions are from the anterior surface of the cornea compared to the rest of the eye (typically the lens), so we can get an idea of how the vision is decreased by either the ocular surface or the lens.

Tomography provides a way to detect changes in the posterior corneal curvature in the early stages of either keratoconus or ectasia, before it is noticeable on the anterior surface of the cornea by topography. It also allows us to evaluate the thickness of the cornea in the midperipheral area, precisely where either intracorneal ring segments or transplant incisions will be placed.

OCT is well established for retinal and optic nerve uses. What about OCT for the anterior segment and the cornea? In the clinic, OCT is very helpful in detecting endothelial keratoplasty detachment when the cornea is thick and edematous and slitlamp visualization is difficult. It lets us see not only if the graft is detached, but also if it is oriented in the correct position with endothelium toward the iris. In-office OCT can also show the epithelial vs. stromal thickness in eyes with advanced keratoconus and quantify the vault of a phakic IOL over the crystalline lens.

Intraoperative OCT is helpful for performing endothelial and anterior lamellar keratoplasty and phakic IOL placement. UBM is great for evaluating iris cysts: is the angle narrow from the lens pushing the iris forward or from iris cysts? It is also helpful for sizing posterior chamber phakic lens implants.

Finally, specular microscopy allows us to visualize the endothelial cells on the cornea to determine if edematous corneas are from low cell counts, or whether a low cell count is present and the cornea may decompensate if intraocular surgery is performed. Confocal microscopy allows not only evaluation of the endothelial layer but also evaluation of the stroma, with multiple cross-sectional views through the corneal tissue. Confocal microscopy can be invaluable in identifying the causative organism in chronic corneal infections that don’t seem to clear, such as Acanthamoeba or fungal infections.

My presentation will highlight specific examples of when imaging saved me, and my patients!
New Developments in Dry Eye Diagnosis and Treatment

Anat Galor MD

I. Overview
   A. What is dry eye?
   B. Definitions

II. New Developments in Dry Eye Diagnosis
   A. Biomarkers of ocular surface stress (eg, tear osmolality [TearLab])
   B. Biomarkers of inflammation (eg, matrix metalloproteinase 9 [InflammaDry, Rapid Pathogen Screening Inc.], IgE [Advanced Tear Diagnostics])
   C. New diagnostics for meibomian gland dysfunction (MGD) (eg, infrared imaging of meibomian glands)
   D. New diagnostics of somatosensory function (eg, quantitative sensory testing, confocal microscopy)

III. New Developments in Dry Eye Treatment
   A. New treatments for ocular surface stress (eg, environmental manipulation)
   B. New anti-inflammatories (eg, lifitegrast, Shire)
   C. New therapies for MGD (eg, manual debridement, probing)
   D. New therapies for somatosensory function (eg, topical and systemic therapeutic options)
No, This Is Actually Not Dry Eye

Richard S Davidson MD

Many ocular conditions masquerade as dry eye when, in fact, they are not dry eye at all. These conditions include but are not limited to the following:

- Blepharitis
- Meibomian gland dysfunction
- Conjunctivochalasis
- Floppy eyelid syndrome
- Unilateral or bilateral lower eyelid laxity
- Superior limbic keratoconjunctivitis
- Salzmann nodular degeneration
- Limbal stem cell failure
- Thyroid eye disease
- Exposure keratopathy
- Allergic conjunctivitis
- Infectious conjunctivitis

The purpose of this presentation is to discuss these and other conditions to help one approach these patients in a stepwise fashion and arrive at the correct diagnosis.
How Do I Know if This Is Stem Cell Deficiency?

Sophie X Deng MD PhD

Clinical Presentation of Limbal Stem Cell Deficiency

Clinical manifestations of limbal stem cell deficiency (LSCD) vary based on the severity and extent of involvement. LSCD can be sectoral or total. In sectoral, or partial, LSCD, in which only a segment of the limbus is involved, stippled late fluorescein staining is seen due to the loss of cell-cell tight junction that leads to staining of the basement membrane. The stippling fluorescein staining could follow a vortex pattern. There might be thinning of the epithelium layer. A clear line of demarcation may be visible between the corneal and conjunctival epithelial cells. The fluorescein dye tends to pool on the conjunctivalized area because of the relatively thinner epithelium. Additional features may include unstable tear film, filaments, or erosion over the affected area. Abnormal or absence of limbal palisade of Vogt could be an early anatomical change in mild cases of LSCD. However, absence of palisade of Vogt alone does not necessarily indicate LSCD. In moderate to severe cases, as the limbal function declines further, recurrent epithelial defects and superficial vascularization could occur. Persistent epithelial defect may lead to scarring, ulceration, stromal neovascularization, corneal thinning, or even perforation. If there is also the presence of tear deficiency, keratinization may occur. Total LSCD is characterized by a complete absence of limbal stem cell populations accompanied by conjunctivalization of the entire corneal surface. Neovascularization is often seen but might not present in some cases of LSCD.

Diagnosis of Limbal Stem Cell Deficiency

Diagnosis of LSCD remains challenging. LSCD can be detected clinically based on the presentation described above. However, some of the signs present in LSCD are also seen in other conditions that do not have a component of LSCD. In particular, signs in partial LSCD are often subtle and nonspecific. Severe LSCD can’t be distinguished from total LSCD based on the clinical exam alone. Diagnostic testing is necessary to confirm the presence of LSCD.

Impression cytology to detect goblet cells is the currently accepted diagnostic test for LSCD. However, goblet cell deficiency is also present in up to 36% of patients with LSCD. Hence the lack of goblet cells may lead to false-negative results. The epithelial morphology alone cannot distinguish conjunctival epithelial cells from corneal epithelial cells. Therefore, impression cytology has a low sensitivity.

In vivo laser scanning confocal microscopy (IVCM) provides high-resolution images of the ocular surface at the cellular level. Its use in ophthalmology has expanded tremendously over the last decade. Recently, IVCM has been used to study corneal and limbal microstructures. In normal cornea, wing cells have a dark cytoplasm, well-defined bright borders, and no visible nuclei. The deep basal epithelium layer cells are smaller in size, with no visible nuclei, and the cell border is still very well defined. In addition, palisades of Vogt may be detected as hyper-reflective, double-contour linear structures of the limbus. Significant microstructural changes in the corneal and limbal epithelium are seen in partial LSCD. The corneal epithelial cells in LSCD have less distinct borders and have prominent nuclei. The size of basal epithelial cells increases in both central cornea and limbus in the moderate stage. In severe LSCD, epithelial cells show significant metaplasia, and often corneal epithelial cells can not be detected. Epithelial thinning and a significant decrease of sub-basal nerve density are present even in partial LSCD. A combination of morphological changes in the corneal epithelium and a significant reduction in basal epithelial cell density, sub-basal nerve density, and epithelial thickness are signs of LSCD.

IVCM is the only method that can confirm the diagnosis of total LSCD. In eyes that present with clinically defined total LSCD (ie, epithelial opacity, neovascularization, and conjunctivalization of the corneal surface), normal limbal epithelial cells sometimes could be detected using IVCM. Therefore, IVCM is a more sensitive and specific method to make the diagnosis of LSCD.
How to Manage Stem Cell Deficiency

Virender S Sangwan MBBS

Introduction

The cornea is covered by a thin transparent layer of stratified squamous epithelium. This epithelial cover is renewed continuously as younger cells migrate inward from periphery and older cells are lost from the surface (just like skin epithelium and blood cells). The constant source of corneal epithelial cells is believed to be the limbus, which is annular ring of tissue between cornea and sclera. Corneal epithelial stem cells have been identified deep within a protected microenvironment or niche at the limbal palisades of Vogt. When the limbus is intact, corneal epithelial defects heal promptly. But when it is damaged because of either inflammation or injury, the normal corneal epithelial physiologic features are disrupted. This can result in delayed or nonhealing corneal epithelial defects and a condition called limbal stem cell deficiency (LSCD). The limbal stem cell deficiency (LSCD) consists of conjunctival encroachment onto the cornea, vascularization, and nonhealing of corneal epithelial defects. The LSCD is a rare but important cause of corneal blindness, and it could be unilateral or bilateral, partial or total, depending on the extent of involvement. The etiology of LSCD could quite varied, and it may be local or systemic, inherited or acquired, progressive or one-time damage, immune-mediated or traumatic.

Background Observations

Transplantation of healthy limbal tissue can reverse LSCD and restore a normal corneal surface. In the last 3 decades, both the understanding of limbal stem cell biology and the techniques of limbal transplantation have evolved considerably. Although direct conjunctival-limbal or kerato-limbal grafting continues to be practiced, the transplantation of ex vivo–cultivated limbal epithelial sheets (CLET, or cultivated limbal epithelial transplantation) has become popular in many centers worldwide. In February 2015 the European Medicines Agency (EMA) approved the first stem cell–based therapy for human application for LSCD induced by chemical and thermal burns. This product, called Holoclar, is developed and marketed byHolos of Italy.

Our Experience

We have been performing CLET since 2001, with over 1000 procedures, and have reported long-term outcomes comparable with those of other groups. The autologous CLET involves growing cells from a tiny limbal biopsy in a clinical grade laboratory; this technique reduces the risk of donor-site LSCD, which was associated with direct autologous conjunctival-limbal procedures. In the laboratory the cells can be expanded on a variety of substrates using either cell suspension or explant culture method (author’s preferred technique) with use of either animal-derived growth factors or completely xenofree cultivation techniques. We prefer completely xenofree methods and have been using autologous serum without using any animal-derived products, like mouse 3T3 fibroblasts. With autologous and allogenic CLET we have reported a success rate of over 70% with follow-up over 5 years. However, pediatric autologous CLET was successful was in only 45%. There are several limitations of CLET; for example, it needs a cGMP laboratory, which is quite expensive to maintain, makes the surgery expensive, and limits scaling up of new technology.

Keeping the above factors about CLET technology in mind, we have developed a new technique of growing cells on the ocular surface of the affected eye, thereby eliminating the need for an expensive clinical grade laboratory. It is a one-stage procedure, and surgery can be performed by any well-trained corneal specialist, reducing the cost of surgery significantly and bypassing the regulatory hurdles. This technique is called simple limbal epithelial transplantation (SLET). We recently reported long-term outcomes of SLET in 125 patients, and SLET has been replicated by several other groups; outcomes are better or at par with CLET outcomes. Specifically, SLET was found to be very useful in pediatric LSCD because CLET outcomes have been very poor in this population. Our results showed that SLET was successful in the long-term regeneration of the corneal surface in a large cohort of patients in unilateral LSCD caused by chemical burns, and this technique is as effective in children as it is in adults (76% in adults and 72% in children).

The unique features of SLET include following:

- SLET combines advantages of both traditional conjunctival-limbal auto transplantation and CLET, which means using a very tiny limbal biopsy for regenerating the entire damaged corneal epithelium and keeping epithelial-mesenchymal interactions intact, thereby enhancing clearing of scarring by stromal keratocyte stem cells. This advantage translates into reduced rates of penetrating keratoplasty after SLET as compared to CLET.
- SLET reduces the cost significantly, both to patients and to health care systems, as there is no need for expensive clinical grade laboratories and it is a single-stage procedure.
- SLET reduces the regulatory burden and oversight; because it is a surgical procedure, the surgeon is the key stakeholder in its application and further innovation.
- There is a real possibility of further simplification of procedures by introducing synthetic membrane instead of human amniotic membrane (AMG). We are working on a first-in-human clinical trial of PLGA membrane instead of AMG.

Selected Readings


Managing Ocular Surface Disease
Before Cataract Surgery
Maximizing Cataract Surgery Outcomes in Ocular Surface Disease

W Barry Lee MD

I. Ocular Surface Conditions
   A. Eyelid abnormalities
   B. Dry eye disease / dysfunctional tear syndrome
   C. Meibomian gland dysfunction / blepharitis
   D. Corneal degeneration

II. Eyelid Conditions to Tackle Prior to Cataract Surgery
   A. Entropion / trichiasis
   B. Ectropion / exposure keratitis
   C. Prior eyelid surgery (skin cancer resection / blepharoplasty)
   D. Lagophthalmia
   E. Cicatricial diseases

III. Dry Eye Disease
   A. Delayed vision recovery
   B. Persistent postoperative discomfort / pain
   C. Heightened risk of infection

IV. Pre- and Postoperative Management
   A. Lubricants with preservative-free liquid / gel / ointments
   B. Punctal occlusion
   C. Topical cyclosporine
   D. Topical lifetegrast
   E. Low-potency topical steroids
   F. New nontraditional procedures
      1. Thermal pulsation
      2. Eyelid scrubbing devices
      3. Intense pulse light laser
   G. Autologous serum
   H. Systemic immunosuppression (systemic autoimmune disease)

V. Management of Blepharitis
   A. Eyelid scrubs / warm compresses; tea tree oil lid scrubs (if Demodex suspected)
   B. Topical antibiotics
   C. Low-potency topical steroids
   D. Dietary supplements
   E. Oral antibiotics (cyclines)
   F. New nontraditional procedures
      1. Thermal pulsation
      2. Eyelid scrubbing devices
      3. Intense pulse light laser

VI. Corneal Degenerations
   A. Epithelial basement membrane dystrophy (EBMD)
   B. Pterygium
   C. Salzmann nodules

VII. Effects on Cataract Surgery
   A. Alters corneal surface
   B. May obscure visual axis
   C. Distorts biometry and topography / tomography

VIII. Treatment of Corneal Degenerations: Staged Procedures
   A. Epithelial debridement for EBMD, pterygium excision, or removal of Salzmann nodule prior to cataract surgery
   B. Remove cataract when biometry and topography normalize
   C. May take 6-8 weeks in some cases

IX. Pearls for Cataract Surgery in Ectatic Disease
   A. Consider preoperative collagen crosslinking.
   B. Make corneal incision on the steep axis.
   C. IOL planning: caution with toric IOLs
   D. Avoid toric IOLs when:
      1. Patient wears RGP's or scleral contacts and wants to return to them
      2. Younger patients
      3. High topographic irregular astigmatism
   E. Consider toric IOLs when:
      1. Older patients
      2. Spectacle-corrected patients prior to surgery
      3. Lower amounts of irregular astigmatism on topography
Not Your Ordinary Ocular Surface Disease Patient
Treatment of Partial Limbal Stem Cell Deficiency With Selective Epithelial Debridement

Christopher J Rapuano MD

CASE PRESENTATION

A 43-year-old African-American man presented with a 1-month history of slowly progressive decreasing vision O.S. He had worn soft contact lenses in the past; he had stopped for several years but restarted 1 year prior. He wore them as daily wear, keeping them in ~12 hours per day, disinfecting them nightly with cleaning solution (Opti-Free). He denied pain, redness, or discharge. He had no history of prior eye disease such as herpes keratitis, no prior eye surgery or trauma. He had been treated with cyclosporine 0.05% drops and loteprednol / tobramycin drops along with discontinuation of his contact lens wear for several weeks without improvement.

On presentation, his BCVA with glasses was 20/20 O.D. and 20/60 O.S. IOPs were normal. The external and slitlamp examinations were unremarkable except for mild superior whorl-like epithelial changes with punctate staining O.U. These changes reached ~2 mm from the superior limbus O.D. and ~8 mm from the superior limbus covering the pupil O.S. Dilated examinations were normal O.U.

A diagnosis of partial limbal stem cell deficiency (LSCD) O.S.>>O.D., most likely related to soft contact lens wear, was made. Numerous treatment options were discussed, including continuing his medical therapy and staying out of contact lenses, bandage soft contact lens, scleral contact lens, autologous serum tears, and placement of an amniotic membrane. Minor surgical treatments including silver nitrate solution application to the superior limbus and selective epithelial debridement along with the major surgical option of a limbal stem cell transplant (for cases of total limbal stem cell deficiency) were also discussed.

The patient continued medical therapy for the next month without improvement. He then underwent an in-office selective epithelial debridement O.S. After informed consent, topical anesthetic and antibiotics drops and an eyelid speculum were placed O.S. At the slitlamp, cellulose sponges and a #15 blade were used to gently remove the abnormal epithelium all the way to the superior limbus. The abnormal epithelium was quite loose, while the normal adjacent epithelium was quite adherent to the cornea. After the procedure the eyelid speculum was removed and the patient was treated with bacitracin ointment every 2 hours while awake and ice packs and narcotic pills for pain until the epithelial defect healed.

On postoperative Day 1 the vision with glasses was stable at 20/60 and the epithelial defect was healing nicely. On postoperative Day 3, the epithelial defect had resolved, although there was central superficial punctate keratopathy (SPK), and the vision with glasses had improved to 20/30. At postoperative Week 3, the central epithelium was well healed with no SPK and the vision with glasses had returned to 20/20. There was ~1 mm of irregular epithelium at the superior limbus consistent with mild LSCD, with mild underlying anterior stromal haze.

The patient was followed routinely and was last seen 2.5 years postoperatively. At that time, he had been wearing daily wear disposable soft contact lenses for a year with excellent vision and no complaints. He had no evidence of LSCD in either eye on slitlamp examination.

Partial LSCD that is not responding to medical therapy can often be treated successfully with a selective epithelial debridement procedure. This treatment is effective only when there is a reasonable degree of remaining healthy LSCs. Total LSCD requires replacement with healthy LSCs using a LSC graft or placement of an artificial cornea such as a Boston keratoprosthesis.
Scleritis: Evidence-Based Approach to Diagnosis

James P Dunn MD

I. Classification (Watson)
   A. Episcleritis
   B. Anterior scleritis
      1. Diffuse
      2. Nodular
      3. Necrotizing without inflammation
      4. Necrotizing with inflammation
   C. Posterior

II. Etiologic Classification
   A. Infectious (7% of all cases)
      1. Herpetic (zoster, 4.5%; herpes simplex virus, 1.5% of all cases)
      2. Post-surgical (bacterial, fungal)
      3. Post-traumatic (bacterial, fungal)
      4. Tuberculous
   B. Noninfectious
      1. Associated with systemic disease (44% of all cases)
         a. Rheumatic and vasculitis disease (37% of all cases)
            i. Rheumatoid arthritis (15% of all cases)
            ii. Antineutrophil cytoplasmic antibody (ANCA)-associated (granulomatosis with polyangitis [GPA]); Most common systemic vasculitis
            iii. Relapsing polychondritis
            iv. Systemic lupus erythematosus
            v. Other systemic vasculitides
         b. Inflammatory bowel disease
      2. Undifferentiated

III. Regional Classification
   A. Ocular
   B. Ocular/systemic

IV. Treatment-Based Classification
   A. Steroid sensitive (controlled with prednisone ≤ 7.5 mg/day)
   B. Steroid receptive (controlled only at prednisone dose ≥ 10 mg/day)
   C. Steroid insensitive (does not respond even to IV steroids)

V. Complications
   A. Scleral thinning/perforation
   B. Corneal thinning/perforation (more common than scleral perforation)
   C. Persistent epithelial defect
   D. Secondary infection
   E. Exudative retinal detachment
   F. Retinal vasculitis
   G. Optic neuropathy
   H. Chorioretinal folds
      I. Corneal scarring/interstitial keratitis (IK)
      J. Uveitis
      K. Astigmatism

VI. Workup
   A. Thorough review of systems is essential.
   B. Lab tests: Be parsimonious!
      1. ANCA: including anti-PR3 and –MPO
      2. CBC and comprehensive metabolic panel (if considering immunosuppression)
      3. Other tests based on review of systems and clinical findings
   C. Radiology and other imaging studies
      1. Chest x-ray / chest CT (TB; cavitary lesions in GPA)
      2. Sinus films (GPA)
      3. Consider GI workup through specialist if inflammatory bowel disease suspected
   D. Empiric therapy
      1. May be “diagnostic” in straightforward cases
      2. Possible herpetic scleritis
      3. Possible tuberculous scleritis
   E. Reasons for workup
      1. Don’t miss infectious cause
      2. Identify underlying disease
         a. Vasculitis may be life threatening
         b. Risk of development rheumatic disease: 4%/patient-year
      3. Nodular scleritis and IK most associated with infectious disease
4. Age > 50, female gender, diffuse scleritis, bilateral scleritis most associated with rheumatic disease

VII. Diagnostic Tests in Atypical Cases

A. Infectious (TB, viral, bacterial)
   1. Ask about:
      a. History of herpes zoster ophthalmicus
      b. From endemic area for TB
      c. Prior surgery with mitomycin (especially pterygium)
   2. Consider empiric treatment with antiviral or anti-TB therapy.
   3. Always perform cultures and stains if suspect fungal / bacterial infection.

B. Surgically induced necrotizing scleritis
   1. Usually ≥ 2 prior surgeries (extracapsular cataract extraction, vitreoretinal, strabismus, glaucoma)

   2. Consider anterior segment fluorescein angiography
   3. 40%-90% associated with underlying systemic disorder
   4. Responds to systemic steroids and immunosuppression, not NSAIDs

C. Malignancy
   1. B-scan for possible melanoma
   2. Biopsy for possible conjunctival lymphoma

D. Retained foreign body
   1. Ultrasound
   2. CT scan
   3. Electroretinography (iron toxicity)
Allergic Conjunctivitis: What’s New in Management

Michael B Raizman MD

I. Allergic Eye Conditions
   A. Seasonal allergic conjunctivitis
   B. Perennial allergic conjunctivitis
   C. Vernal conjunctivitis
   D. Atopic conjunctivitis
   E. Giant papillary conjunctivitis

II. Conventional Therapy
   A. Topical antihistamines
   B. Mast cell stabilizer
   C. Corticosteroid
   D. Calcineurin inhibitors
   E. Oral antihistamines
   F. Immunotherapy
      1. Injection
      2. Sublingual
   G. Leukotriene receptor antagonists

III. Modifications of Existing Therapy
   A. Drug delivery
      1. Delivery devices
         a. Contact lens
         b. Punctal plug
      2. Topical drop modifications
         a. Nanoparticles/micelles
         b. Liposomes
   B. Reformulation

IV. Potential Future Pharmacologic Agents
   A. Alternative calcineurin inhibitors
   B. Alternative glucocorticoids
   C. Rebamipide
   D. Anti-CCR7 (dendritic cells)
   E. Spleen tyrosine kinase (SYK) / Janus kinase (JAK) inhibitors
   F. Aldehyde trap
   G. Integrin / vascular cell adhesion molecule (VCAM) / intercellular adhesion molecule (ICAM) blockade
   H. Tumor necrosis factor-alpha blockers
   I. Oligonucleotides
   J. Antioxidants
   K. Lipid conjugates
   L. Chlorogenic acid
   M. cAMP stimulators
   N. Glucosamine
   O. Toll-like receptor (TLR) inhibition
   P. Interfering RNA
   Q. JAK-3 inhibitors
   R. Resolvins
   S. Interleukin (IL)-1 receptor antagonists

Selected Readings


Atopic Keratoconjunctivitis
Stephen C Pflugfelder MD

Clinical Features
Atopic keratoconjunctivitis (AKC) typically begins in the late teens and early 20s, although it has been reported as early as 7 years of age\(^1,2\) and can persist into the fourth and fifth decades of life, with a peak incidence between 30 and 50 years old.\(^1,3-5\)

It is usually perennial but can be associated with seasonal exacerbations.\(^1,3,5,6\) Although only 20% to 43% of patients with atopic dermatitis have ocular involvement, AKC is associated with atopic dermatitis in 95% of cases.\(^3,7\)

References

Table I. Summary of Symptoms, Signs, and Treatment\(^4,8-12\)

<table>
<thead>
<tr>
<th>Condition/Tissue</th>
<th>Symptom</th>
<th>Sign</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharitis</td>
<td>Redness, itching, crusting</td>
<td>Eczema, secondary staphylococcal infection, MGD</td>
<td>Eczema: emollients, corticosteroid, or tacrolimus 0.03% ointment, antibiotic ointment for staphylococcal infection, treatment of MGD</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Redness, itching, foreign body sensation, tearing, discharge</td>
<td>Papillae, tarsal thickening/scarring, Horner-trantas dots</td>
<td>Antihistamine and mast cell stabilizers, corticosteroids, cyclosporine, tacrolimus 0.03% ointment, systemic corticosteroids or cyclosporin for severe disease</td>
</tr>
<tr>
<td>Cornea</td>
<td>Irritation, blurred vision</td>
<td>Punctate erosions, epithelial defect, shield ulcer, scarring, neovascularization, secondary keratoconus HSV keratitis</td>
<td>Corticosteroids, tacrolimus 0.03% ointment, treat neovascularization, bandage CL or PROSE</td>
</tr>
<tr>
<td>Tear dysfunction</td>
<td>Irritation</td>
<td>Rapid tear break-up time, cornea and conjunctival dye staining</td>
<td>Artificial tears, corticosteroids, cyclosporine emulsion</td>
</tr>
<tr>
<td>Cataract</td>
<td>Blurred vision</td>
<td>Anterior subcapsular opacity</td>
<td>Cataract surgery</td>
</tr>
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Abbreviations: MGD indicates meibomian gland dysfunction; HSV, herpes simplex virus; PROSE, prosthetic replacement of the ocular surface ecosystem.
Management of Acute Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis

James Chodosh MD MPH

I. Acute Stevens Johnson Syndrome / Toxic Epidermal Necrolysis (SJS/TEN): Diagnosis and Clinical Features
   A. Presents with acute onset of flat atypical targets or purpuric macules predominantly on the trunk with involvement of at least 2 mucosal sites
   B. SJS and TEN represent a spectrum.
      1. SJS: epidermal detachment < 10% of body surface area
      2. SJS/TEN overlap: 10%-30% detachment of body surface area
      3. TEN: > 30% detachment of body surface area
   C. Published annual incidence rates for SJS/TEN range from 0.4 to 12 cases per million population (possibly higher in children)

II. General Concepts in Acute SJS/TEN
   A. Drug (or pathogen)-specific: Over 200 offending medications are implicated—probably almost any medication, from any drug class, can cause SJS/TEN in a susceptible individual.
      1. Common causes include sulfonamide antibiotics, aromatic anticonvulsants, beta-lactam antibiotics, NSAIDs
      2. Cross-reactivity for SJS/TEN exists between different classes of beta-lactam antibiotics (eg, penicillins and cephalosporins) and also within aromatic antiepileptics (eg, carbamazepine, phenytoin, and phenobarbital).
      3. Eye drop medications (!)
      4. Over-the-counter cold remedies
      5. Vaccinations and exposure to industrial chemicals and fumes
      6. After radiation therapy
      7. More common in the setting of HIV infection
   B. Mechanism(s)
      1. Drug metabolite builds to excess in persons lacking capacity for its breakdown, either due to genetic deficiency of a particular enzyme and/or ...
      2. Immune “type” (eg, HLA haplotype) determines faulty / excessive T cell recognition of antigen leading to aberrant immune response.
      3. Cytotoxic CD8 cells, natural killer cells, and activated monocytes all play a role.

   4. Mediators of disease include granzyme / perforin, Fas / FasL, and granulysin
   5. Histopathology characterized by:
      a. Full-thickness epidermal necrosis with minimal underlying dermal inflammation
      b. Keratinocyte apoptosis is prominent.

III. Ocular Involvement in Acute SJS/TEN
   Ocular mucosal epithelium is affected by the same processes as skin and other mucosal sites.
   A. Early ocular involvement is highly variable and ranges from conjunctival hyperemia to pseudomembranes to near total sloughing of the ocular surface, including tarsal conjunctiva and eyelid margins.
   B. Early conjunctival pseudomembranes with kissing epithelial defects lead to symblephara in the subacute stage.
   C. Eyelid margin necrosis (with concurrent meibomitis) leads later to eyelid margin keratinization and corneal limbal stem cell dysfunction as chronic sequelae.

IV. Early Intervention
   A. Early intervention by the ophthalmologist is critical to reduce long-term ocular complications and visual loss from SJS/TEN.
   B. Because SJS/TEN is a rare disease and hence not easily studied in randomized clinical trials, there is currently no proven effective treatment for the ocular surface manifestations associated with acute disease.
   C. However, published case series and case control studies suggest that specific windows of opportunity for intervention exist and must be recognized and acted upon (“If you see something, do something”).
   D. Systemic therapies
      1. High-dose glucocorticoids unproven and in some studies harmful; timing of systemic corticosteroids likely critical to harm/benefit ratio
      2. High-dose intravenous immunoglobulin (IVIG) probably not harmful, but of unproven benefit
      3. Systemic cyclosporine probably not harmful, but of unproven benefit
      4. Topical corticosteroids likely helpful
5. Amniotic membrane transplantation provides benefit, as shown in comparison to historical controls and in case-control studies; consider in acute SJS/TEN if:
   a. Ocular surface and/or eyelid margin epithelial defects
   b. Conjunctival pseudomembranes

V. Conclusions
   A. Ocular complications of SJS/TEN cause blindness.
   B. Early treatment is critical.
   C. Full examination with attention to epithelial defects and pseudomembranes (use fluorescein!)
   D. Use topical corticosteroids and consider amniotic membrane transplantation, the latter as early in the clinical course as possible.
Ocular Cicatricial Pemphigoid: Approach to Management

Esen Karamursel Akpek MD

Background

Mucous membrane pemphigoid (MMP) is a systemic autoimmune bullous disease that primarily affects mucous membranes. When localized to the conjunctiva, it is known as ocular cicatricial pemphigoid, a potentially blinding disease.

The true incidence of MMP is unclear but estimated to be about 1 in 1 million. A recent study from the United Kingdom demonstrated that ocular MMP accounted for 61% of the cases of newly diagnosed cicatricial conjunctivitis. MMP affects women more often than men, with a M/F ratio of 2:1. MMP mainly affects the elderly, between 60 and 80 years of age. Although rarely, children may also be affected. There is no known racial or geographic predilection.

The pathogenesis of MMP is complex. Circulating immunoglobulin G (IgG) and/or immunoglobulin A (IgA) autoantibodies against components of the basement membrane zone (BMZ) found in MMP patients’ serum indicate a humoral immune response. By use of immunoblotting and immunoprecipitation techniques, a variety of autoantigens—including the bullous pemphigoid antigen 1, the bullous pemphigoid antigen 2, integrin subunits α6/β4, laminin-332, laminin-332, laminin-6, and collagen type I—have been identified.

The ocular involvement manifests as a form of cicatrizing conjunctivitis that can result in blindness. To diagnose MMP, a specimen from the diseased tissue, including intact epithelium, should be submitted in formalin for light microscopic analysis using hematoxylin and eosin staining. MMP typically demonstrates the subepithelial split with an inflammatory infiltrate of eosinophils, lymphocytes, and neutrophils, similar to the changes seen in other forms of pemphigoid. A second specimen should be obtained for direct immunofluorescence (DIF) and submitted in a buffered hypertonic saline solution (Michel’s solution). The DIF typically shows a continuous, linear deposition of IgG and/or C3, and sometimes IgA along the BMZ. Indirect immunofluorescence (IIF) can be used to detect circulating autoantibodies in a patient’s serum. In a recent study from Canada, conjunctival biopsies were reported as positive in only 30%, negative in 63%, and inconclusive in 7% of the patients who were eventually diagnosed and treated for ocular MMP. Therefore, for as long as other causes of cicatrizing conjunctivitis have been ruled out, the institution of timely targeted treatment for MMP would be appropriate in a patient with progressive cicatrizing conjunctivitis.

Medical Treatment

Because of the rarity of the condition, large randomized controlled trials are lacking and the evidence supporting the therapies is limited to case series or expert consensus. Medications used for ocular MMP include corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, and various biologics. Intravenous immunoglobulin and tetracyclines in combination with other medications have also been shown to be of value. Particularly, the combination therapy of rituximab and intravenous immunoglobulin was reported to arrest disease progression and prevent total blindness in patients with recalcitrant ocular MMP. A recent analysis of published literature regarding treatment of MMP included 1 randomized clinical trial and 32 observational studies. The one randomized clinical trial with a high risk of bias in multiple domains found limited evidence that pentoxifylline + corticosteroid + cyclophosphamide was more effective than corticosteroid + cyclophosphamide for ocular MMP. Outcomes from 32 observational studies examining 242 patients across 19 unique treatments showed promise for rituximab and intravenous immunoglobulin. Of note, patients with inflammatory eye diseases treated with systemic immunosuppressive therapy are at increased risk of malignancy. However, the increase in absolute risk is believed to be modest. The types of malignancies observed are similar to those observed in solid organ transplant recipients and patients with systemic autoimmune diseases treated with systemic immunosuppression.

References


Rare Presentation of Red Eye: Lessons From the Expert

C Stephen Foster MD

I. General Categories of Things That Make an Eye Red
   A. Trauma
   B. Chemicals
   C. Infection
   D. Allergy
   E. Systemic conditions

II. More Specific Categories of Things That Make an Eye Red
   A. Generally not vision threatening
      1. Subconjunctival hemorrhage
      2. Stye
      3. Chalazion
      4. Blepharitis
      5. Conjunctivitis
      6. Episcleritis
      7. Dry eye
      8. Corneal abrasions (most)
   B. Vision threatening
      1. Corneal infections
      2. Scleritis
      3. Hyphema
      4. Uveitis
      5. Acute glaucoma
      6. Orbital cellulitis

III. Problems Often Misdiagnosed
   A. Herpes simplex virus conjunctivitis, episcleritis or scleritis
   B. Atopic conjunctivitis mimicking ocular cicatricial pemphigoid
   C. Sebaceous carcinoma mimicking chalazion
   D. Scleritis as first manifestation of systemic vasculitis
   E. Infectious uveitis

IV. Safeguards Against Misdiagnosis
   A. Take extreme care in history taking, especially review of systems.
   B. Always remember that rare things can and do occur.
   C. Suspect something uncommon if the chosen therapy is not making matters better.
   D. Consults, second opinions—even if that requires travel
   E. Biopsy anything that can be biopsied; plan ahead with pathology
      1. Skin
      2. Anything found on imaging studies (eg, lung nodule)
      3. Eye
         a. Conjunctiva
         b. Sclera
         c. Aqueous and vitreous
         d. Cornea
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