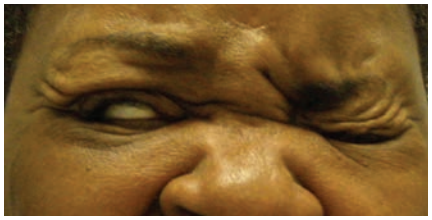
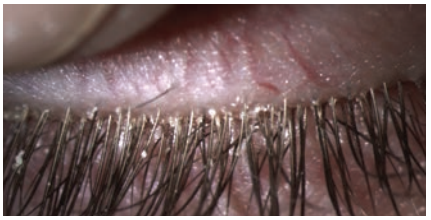
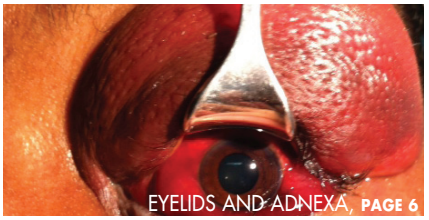
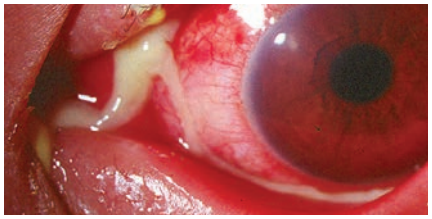
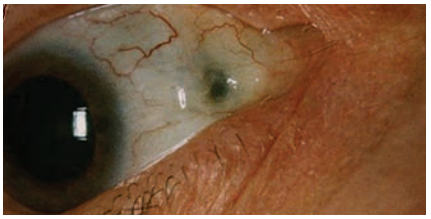
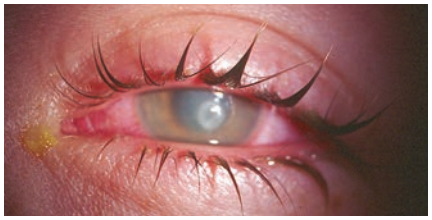
JOSEPH W. SOWKA, OD
ANDREW S. GURWOOD, OD
ALAN G. KABAT, OD

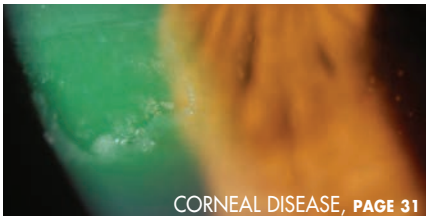




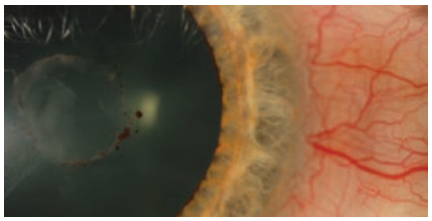






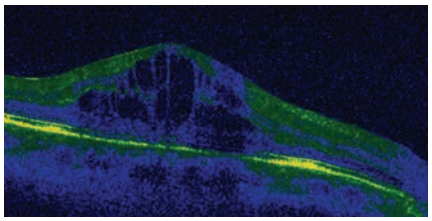
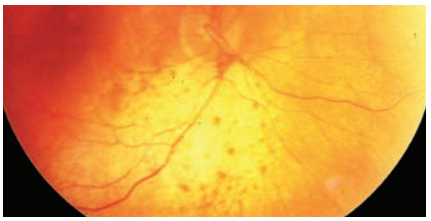


# THE HANDBOOK OF OCULAR DISEASE MANAGEMENT

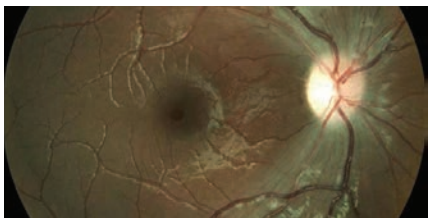








SUPPLEMENT TO
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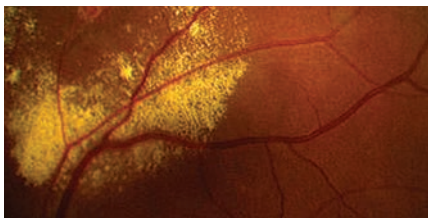

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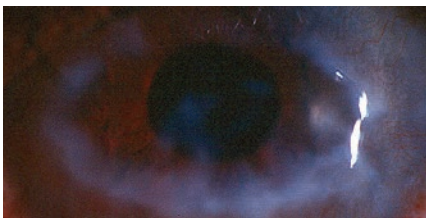

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24 HOURS OF OCULAR ALLERGY

# ITCH RELIEF IN ONE DROP


## New Once-Daily **PAZEO™ Solution** for relief of ocular allergy itch:

- The first and only FDA-approved once-daily drop with demonstrated 24-hour ocular allergy itch relief[1]
- Statistically significantly improved relief of ocular itching compared to **PATADAY® (olopatadine hydrochloride ophthalmic solution) 0.2%** at 24 hours post dose (not statistically significantly different at 30-34 minutes)[1]
- Statistically significantly improved relief of ocular itching compared to vehicle through 24 hours post dose[1]

**Study design:** Two multicenter, randomized, double-masked, parallel-group, vehicle- and active-controlled studies in patients at least 18 years of age with allergic conjunctivitis using the conjunctival allergen challenge (CAC) model (N=547). Patients were randomized to receive study drug or vehicle, 1 drop per eye on each of 2-3 assessment days. On separate days, antigen challenge was performed at 27 (±1) minutes post dose to assess onset of action, at 16 hours post dose (Study 1 only), and at 24 hours post dose. Itching scores were evaluated using a half-unit scale from 0=none to 4=incapacitating itch, with data collected 3, 5, and 7 minutes after antigen instillation. The primary objectives were to demonstrate the superiority of **PAZEO™ Solution** for the treatment of ocular allergy itch. Study 1: **PAZEO™ Solution** vs vehicle at onset of action and 16 hours. Study 2: **PAZEO™ Solution** vs vehicle at onset of action; **PAZEO™ Solution** vs **PATADAY® Solution**, PATANOL® (olopatadine hydrochloride ophthalmic solution) 0.1%, and vehicle at 24 hours.[1-3]

**Give your patients 24 HOURS OF OCULAR ALLERGY ITCH RELIEF with once-daily PAZEO™ Solution[1]**

## **PAZEO™ Solution:** Safety Profile

- Well tolerated[1]
- The safety and effectiveness of **PAZEO™ Solution** have been established in patients two years of age and older[1]
- The most commonly reported adverse reactions, occurring in 2% to 5% of patients, were blurred vision, dry eye, superficial punctate keratitis, dysgeusia, and abnormal sensation in eye[1]

## Once-daily dosing[1]

## INDICATION AND DOSING

PAZEO™ Solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis. The recommended dosage is to instill one drop in each affected eye once a day.

## IMPORTANT SAFETY INFORMATION

As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle to prevent contaminating the tip and solution. Keep bottle tightly closed when not in use.

Patients should not wear a contact lens if their eye is red. PAZEO™ Solution should not be used to treat contact lens-related irritation. The preservative in PAZEO™ Solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red should be instructed to wait at least five minutes after instilling PAZEO™ Solution before they insert their contact lenses.

The most commonly reported adverse reactions in a clinical study occurred in 2%-5% of patients treated with either PAZEO™ Solution or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia, and abnormal sensation in eye.

**For additional information on PAZEO™ Solution, please refer to the brief summary of the full Prescribing Information on the following page.**

**References: 1.** PAZEO™ Solution Package Insert. **2.** Data on file, 2011. **3.** Data on file, 2013.

*From Alcon, committed to providing treatment options for patients.*

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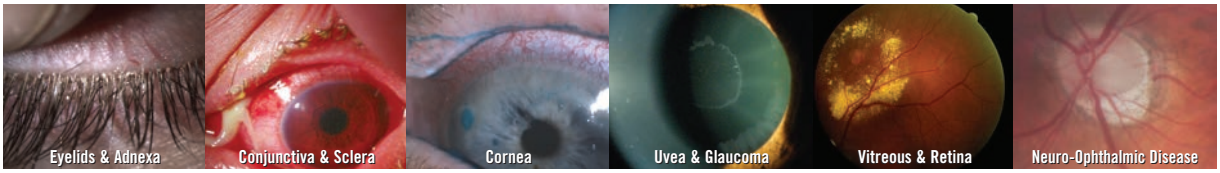
 5/15 PAZ15011JAD

Pazeo™
(olopatadine hydrochloride ophthalmic solution) 0.7%

# TABLE OF CONTENTS




## EYELIDS AND ADNEXA



## CONJUNCTIVA AND SCLERA



## CORNEA



## UVEA AND GLAUCOMA



## VITREOUS AND RETINA



## NEURO-OPHTHALMIC DISEASE



This publication addresses the management of various conditions with support from the best available peer-reviewed literature. This is done to provide the most up-to-date management of patients with various conditions and to indicate when patient referral is appropriate. In many cases, the management may necessitate treatment from a specialist or subspecialist. This manuscript does not recommend that any doctor practice beyond the scope of licensure or level of personal comfort. It is up to the reader to understand the scope of state licensure and practice only within those guidelines.

### A Peer-Reviewed Supplement

The articles in this supplement were subjected to *Review of Optometry*'s peer-review process. The magazine employs a double-blind review system for clinical manuscripts in which experts in each subject review the manuscript before publication. This supplement was edited by the *Review of Optometry* staff.

# Pazeo™

(olopatadine hydrochloride ophthalmic solution) 0.7%

## BRIEF SUMMARY

**PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7%. For topical ophthalmic administration.**

**The following is a brief summary only; see full prescribing information for complete product information.**

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

### Contamination of Tip and Solution

As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle to prevent contaminating the tip and solution. Keep bottle tightly closed when not in use.

### Contact Lens Use

Patients should not wear a contact lens if their eye is red.

The preservative in PAZEO solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least five minutes after instilling PAZEO before they insert their contact lenses.

## ADVERSE REACTIONS

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

In a randomized, double-masked, vehicle-controlled trial, patients at risk for developing allergic conjunctivitis received one drop of either PAZEO (N=330) or vehicle (N=169) in both eyes for 6 weeks. The mean age of the population was 32 years (range 2 to 74 years). Thirty-five percent were male. Fifty-three percent had brown iris color and 23% had blue iris color. The most commonly reported adverse reactions occurred in 2-5% of patients treated with either PAZEO or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia and abnormal sensation in eye.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

*Risk Summary*

There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 1,080 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD). There was no toxicity in rat offspring at exposures estimated to be 45 to 150 times that at MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Animal Data*

In a rabbit embryofetal study, rabbits treated orally at 400 mg/kg/day during organogenesis showed a decrease in live fetuses. This dose is 14,400 times the MRHOD, on a mg/m$^2$ basis.

An oral dose of 600 mg/kg/day olopatadine (10,800 times the MRHOD) was shown to be maternally toxic in rats, producing death and reduced maternal body weight gain. When administered to rats throughout organogenesis, olopatadine produced cleft palate at 60 mg/kg/day (1080 times the MRHOD) and decreased embryofetal viability and reduced fetal weight in rats at 600 mg/kg/day. When administered to rats during late gestation and throughout the lactation period, olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day. A dose of 2 mg/kg/day olopatadine produced no toxicity in rat offspring. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose.

### Nursing Mothers

Olopatadine has been identified in the milk of nursing rats following oral administration. Oral administration of olopatadine doses at or above 4 mg/kg/day throughout the lactation period produced decreased body weight gain in rat offspring; a dose of 2 mg/kg/day olopatadine produced no toxicity. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PAZEO is administered to a nursing mother.

### Pediatric Use

The safety and effectiveness of PAZEO have been established in pediatric patients two years of age and older. Use of PAZEO in these pediatric patients is supported by evidence from adequate and well-controlled studies of PAZEO in adults and an adequate and well controlled study evaluating the safety of PAZEO in pediatric and adult patients.

### Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

*Carcinogenicity*

Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 35 µL drop size and a 60 kg person, these doses are approximately 4,500 and 3,600 times the MRHOD, on a mg/m$^2$ basis.

*Mutagenesis*

No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test.

*Impairment of fertility*

Olopatadine administered at an oral dose of 400 mg/kg/day (approximately 7,200 times the MRHOD) produced toxicity in male and female rats, and resulted in a decrease in the fertility index and reduced implantation rate. No effects on reproductive function were observed at 50 mg/kg/day (approximately 900 times the MRHOD).

## PATIENT COUNSELING INFORMATION

• Risk of Contamination: Advise patients to not touch dropper tip to eyelids or surrounding areas, as this may contaminate the dropper tip and ophthalmic solution.

• Concomitant Use of Contact Lenses: Advise patients not to wear contact lenses if their eyes are red. Advise patients that PAZEO should not be used to treat contact lens-related irritation. Advise patients to remove contact lenses prior to instillation of PAZEO. The preservative in PAZEO solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 5 minutes following administration of PAZEO.

**Patents:** 8,791,154

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## HONORING JOSEPH C. TOLAND, OD, MD

He was a living legend to us—an optometrist who went back to medical school to become an ophthalmologist. As students, we remember his voice and manner always being to the point. As residents, we remember that he gave us enough independence to learn on our own while standing close enough to offer his skilled observations. His trademark was a series of clever one-liners that he would exclaim whenever the patient exhibited a classic ophthalmic sign, such as, *"A soft eye is a sick eye," "That eye is as red as a New Jersey road map," "That patient is in trouble, he's got one foot in the grave with the other on a banana peel," "That eye is so sick, even holy water wouldn't help"* and *"That eye is seeing lower than a well digger's heel."* We all still laugh when we think of those times.

He was the director of Medical Services at The Eye Institute of the Pennsylvania College of Optometry (now Salus University) for over 30 years. The sacrifices he made for that was beyond believable. He was a successful Philadelphia ophthalmologist, yet he was professionally ostracized—forced to endure skepticism and criticism from his ophthalmology colleagues—because he believed in the profession of optometry. He never once forgot where he came from or how he started. He never once claimed to be better or above the people he worked with. Imagine how empowered young residents (like us) felt when he stopped to ask for our opinion on an ophthalmic question or case.

*Our friend and mentor, Dr. Joseph Toland.*

Dr. Toland always had multiple copies of our *Handbook of Ocular Disease Management* with him as he saw patients on the floor, and he asked for a signed copy of his favorite edition. Joe always had your back. Joe always built morale and inspired the people around him to be better. He never failed to say thank you when you worked with him.

The drive for expanded scope of practice began to develop in the early 1970s, and Dr. Toland was there from the start. He loyally led the way as optometry amended its curriculum to match the parallel professions of dentistry and podiatry, both of which had achieved prescribing privileges. He boldly testified for optometrists to gain "as taught" scope-of-practice privileges and practice expansion. He relentlessly and selflessly spearheaded meetings with legislators, gave tours of the facility and hosted visiting dignitaries. He toured the country with an exceptional faculty (whom he trained) and expanded continuing education into the diagnostic and pharmacologic therapeutic areas that are now common tracks at all major optometry meetings. He lectured to students on ocular pathology. He willingly remained on call 24 hours a day, seven days a week to all Eye Institute patients, residents and faculty.

This "gentle" man supported the students, staff, colleagues, faculty and residents with every fiber of his being. Joe Toland, OD, MD, has since retired as the Eye Institute's medical director but still keeps regular hours. Recently the University honored him with the dedication of The Joseph C. Toland, OD, MD, Classroom, where all who enter can learn in the spirit of the man for whom it is named. This edition of *The Handbook of Ocular Disease Management* is dedicated to our mentor, colleague and friend, Dr. Joseph Toland, for all that he has done for us and our profession. — *Joe, Andy & Al*

Joseph W. Sowka, OD, FAAO, Dipl., is a professor of optometry, program supervisor of the Primary Care with Emphasis in Ocular Disease Residency, instructor in glaucoma and retinal disease, and chair of the Clinical Sciences Department at Nova Southeastern University College of Optometry. At the college's Eye Care Institute, he is the director of the Glaucoma Service and chief of the Advanced Care Service. Dr. Sowka is a founding member of the Optometric Glaucoma Society (and current Vice President), the Optometric Retina Society and the Neuro-ophthalmic Disorders in Optometry Special Interest Group. He is an American Academy of Optometry Diplomate in glaucoma. Dr. Sowka lectures nationally and internationally on topics in ocular disease. He can be reached at (954) 262-1472 or at jsowka@nova.edu.

Andrew S. Gurwood, OD, FAAO, Dipl., is a professor of clinical sciences, an attending optometric physician in Module 3 of the Eye Institute of the Pennsylvania College of Optometry at Salus University and a member of the clinical staff of Albert Einstein Medical Center Department of Ophthalmology. He is a Founding member of the Optometric Retina Society and a member of the Optometric Glaucoma Society. Dr. Gurwood has lectured and published nationally and internationally on a wide range of subjects in ocular disease. He can be reached at agurwood@salus.edu.

Alan G. Kabat, OD, FAAO, is a professor at the Southern College of Optometry in Memphis, Tenn., where he teaches courses in ocular disease and clinical procedures. He is an attending physician at The Eye Center as well as clinical care consultant at TearWell Advanced Dry Eye Treatment Center. A recognized expert in the area of ocular surface disease, Dr. Kabat is a founding member of both the Optometric Dry Eye Society and the Ocular Surface Society of Optometry. He is also Associate Clinical Editor of *Review of Optometry*. He can be reached at (901) 252-3691 or at alan.kabat@alankabat.com.

*The authors have no direct financial interest in any product mentioned in this publication.*

## MEIBOMIAN GLAND DYSFUNCTION

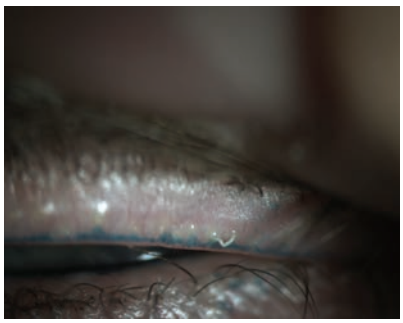
### Signs and Symptoms

Meibomian gland dysfunction (MGD) represents a chronic disorder of the lids, lid margins and preocular tear film. As a rule, the condition is bilateral, although there may be asymmetry in terms of severity. Patients with MGD may report a wide range of symptoms that are characteristically coincident with those of dry eye disease, including burning, dryness, grittiness, itching, foreign body sensation, heaviness of the lids and, in some cases, excessive tearing.[1] Fluctuating vision throughout the course of the day may also be among the complaints. Additionally, patients may express cosmetic concern regarding red and swollen lid margins. MGD demonstrates no proclivity toward a specific race or gender and can be seen at any age, although the prevalence does appear to be higher in elderly patients.[2]

The signs associated with MGD also vary considerably. In some cases, symptoms may precede signs to the point that nothing unusual is encountered on routine biomicroscopic evaluation. This has been dubbed "nonobvious obstructive MGD" by one group of researchers.[3] The earliest signs of MGD include foamy or frothy tears, which may be noted along the lower lid margin or at the canthal regions; this is likely due to saponification of tear lipids secondary to bacterial lipases.[4] In later stages, clinicians may observe inspissated or capped meibomian glands, as well as thickening, irregularity and hyperemia of the eyelid margins.[5] Meibomian gland orifices may demonstrate opacification, periductal fibrosis and posterior displacement toward the mucocutaneous junction.[6] Chronically inflamed lids may also display telangiectasis along the margin near the gland orifices and potentially extending to the lash line.

Testing for MGD must include manual expression to evaluate the consistency of the meibum. The clear oil that is expressed with minimal gland manipulation in normal patients becomes thickened and turbid in MGD, often with a buttery or toothpaste-like consistency. Sometimes, excessive pressure is required to liberate meibum from the glands.[1] As the disease progresses, obstruction of the glands may lead to structural damage, gland truncation and dropout.[7,8] Clinically, this can be observed as a loss of gland density on lid transillumination, infrared meibography, or both.[9] Other nonspecific clinical signs of MGD may include diminished tear stability in the form of reduced fluorescein break-up time, punctate corneal and conjunctival epitheliopathy and conjunctival hyperemia.

Capped and inspissated meibomian gland orifices in the upper lid.



"Toothpaste-like" secretions on gland expression in this patient with MGD. The blue areas represent lissamine green staining of the Line of Marx.

### Pathophysiology

The meibomian glands are modified sebaceous glands, localized within the tarsus of the upper and lower lid; they function to secrete the lipid component of the preocular tear film, commonly referred to as meibum. In normal individuals, there are 25 to 40 glands in the upper eyelid and 20 to 30 in the lower eyelid.[3] Current thinking suggests that MGD is primarily an obstructive disorder, rather than an inflammatory or infectious one as was once believed. Clinical and histopathologic studies reveal that terminal duct occlusion due to hyperkeratinization of the ductal epithelium within the glands is the most significant etiologic factor in the pathogenesis of MGD.[5,8,10,11] Obstruction leads to dilatation of the ducts as well as intraglandular cystic degeneration and loss of secretory meibocytes, resulting in downregulation of glandular function and progressive damage to the gland structure.[5] The obstructive process is believed to be influenced by both endogenous and exogenous factors, including age, diet, hormonal alterations and chronic use of topical medication.[8] Cumulative contact lens wear has also been associated with a decrease in the number of functional meibomian glands.[12]

Also contributory to the pathology of MGD, meibum secreted by these obstructed glands has been shown to be more saturated and contain less branched chain hydrocarbons and more protein.[13] This change results in more ordered, more viscous lipid secretions, which diminishes the flow and impedes the delivery of meibum to the lid margin. Stagnated meibum means that less lipid is available to form the tear film, resulting in diminished tear stability and increased tear evaporation.[14]

As a consequence of MGD, hyperosmolarity of the tear film may drive inflammation of the ocular surface, as well as increased growth of bacterial lid flora such as *Propionibacterium acnes* and

*Staphylococcus epidermidis*, which thrive in this environment.[15] These bacteria secrete lipases, which act directly on the meibum and initiate conversion of the lipids into free fatty acids and soaps. These unwanted elements in turn cause ocular surface irritation and further disrupt the tear film.[14] Recalcitrant forms of MGD may be associated with rosacea, a generalized dermatologic condition affecting the sebaceous glands of the face, particularly the nose, cheeks, forehead and periorbital regions.

## Management

There exists a broad range of treatment options for MGD, depending upon the severity of the disease and the disposition of the patient. *The Report of the International Workshop on Meibomian Gland Dysfunction*, published in 2011, delineated a staged treatment algorithm for MGD consistent with disease severity.[16] Among the recommendations were: patient education; eyelid hygiene with lid warming and gland expression; liberal use of ocular lubricants (particularly those with a lipid base) and lubricant ointments at bedtime; increased intake of omega-3 fatty acids; topical azithromycin; oral tetracycline derivatives; and anti-inflammatory therapies for dry eye in the most severe cases.

Eyelid warming—also known as lid hyperthermia—with concurrent or subsequent massage to help express the meibomian glands has long been considered the mainstay of MGD management. The direct application of heat (approximately 105˚F to 110˚F) to the lid margins helps to improve circulation in the lids and lower the viscosity of meibomian secretions, allowing them to flow more freely.[17,18] While numerous modalities can be employed as warm compresses, including hot soaked towels, hard-cooked eggs, rice socks and commercially available hot packs, it is important to use an item that can retain and generate consistent temperatures for at least five minutes.[19] With the addition of gentle pressure along the lid margins, sequestered meibum can be released from the glands to a significant degree. One study reported increases in lipid layer thickness of more than 80% after just five minutes of such treatment.[20] However, patients employing this form of therapy must be warned against vigorous rubbing of the eyelids, as that activity, on a chronic basis, holds the potential for corneal warpage.[21-23] Newer modalities such as intense pulsed light (IPL) therapy, LipiFlow vectored thermal pulse technology (TearScience) and MiBo ThermoFlo meibomian duct therapy (Pain Point Medical Systems) provide an option for in-office lid hyperthermia with concurrent or subsequent gland expression. Numerous studies have demonstrated the efficacy of these treatments for MGD.[24-28]

Ophthalmic lubricants may be quite helpful in MGD, particularly those that contain a lipid component; these products are typically labeled as emulsions or emollients. A recent open-label study of one such product in patients with MGD demonstrated not only improvement in subjective symptoms, corneal staining and tear break-up time, but also a mild but statistically significant improvement in meibomian gland expression scores.[29]

Diets or nutritional supplements rich in omega-3 essential fatty acids may also benefit the MGD patient by one or more proposed mechanisms. One hypothesis suggests that, since the metabolic breakdown of omega-3 fatty acids results in liberation of tear-specific anti-inflammatory prostaglandins, increasing omega-3s in the diet leads to diminished ocular surface and eyelid inflammation.[30,31] Another school of thought maintains that supplementation with omega-3 fatty acids may positively impact overall fat composition in the body, thereby improving the lipid properties of the meibum.[32]

Unfortunately, simply recommending nutritional modifications or supplements is not enough. Patients need to be directed toward appropriate products and dosing. The most readily bioavailable source of omega-3 fatty acids comes from cold-water fish such as mackerel, wild salmon, sardines and anchovies. Processed sources of fish oil should be in the triglyceride form, rather than the ethyl ester form, to maximize bioavailability.[33] A daily total of 2,000mg or more is typically required to instigate a positive effect on meibomian gland health; however, patients just starting on omega-3 supplements should be briefed on their side effects, notably increased urination and gastric distress. Patients may need to slowly build up tolerance to the product, beginning at 1,000mg/day and increasing slowly over two to three weeks. Patients taking systemic anticoagulant or antiplatelet therapy—such as aspirin, warfarin, Plavix (clopidogrel, Bristol-Myers Squibb) or Ticlid (ticlopidine, Roche Laboratories)—should check with their primary care doctor before starting omega-3 supplements, since there exists a potential dose-related risk for increased bleeding time.[34,35]

AzaSite (topical azithromycin, Akorn) has also demonstrated efficacy in this arena. Though the mechanism of action is poorly understood, a series of published studies involving AzaSite has shown distinct improvement in both signs and symptoms of MGD.[36-38] The typical regimen is one drop twice daily for two days, then one drop at bedtime for an additional four weeks. Patients are advised to instill the drop into the lower cul-de-sac, close their eyes gently, and then spread the residual medication along the lid margins with a clean finger. While this medication is not specifically FDA-approved for MGD, it has been shown to be safe and effective in its management.[36-38]

Oral tetracycline derivatives such as doxycycline or minocycline have

long been used as a treatment option for chronic or recalcitrant MGD. It is believed that these drugs hinder the production of bacterial lipases, which serve to alter the consistency of the meibomian lipids.[39] Additionally, tetracyclines are recognized to be potent anti-inflammatory agents, inhibiting the expression of matrix metalloproteinases and other cytokines.[40,41] A regimen of oral doxycycline 100mg BID for four weeks, then QD for another four to eight weeks, has been shown to be highly effective.[42] Therapeutic effects may be seen with as little as 40mg of doxycycline hyclate daily, though at this decreased dosage there is typically a delayed response, often taking up to six weeks for patients to have symptomatic improvement.[43]

Anti-inflammatory therapies are reserved for the most severe forms of MGD or those with concurrent ocular surface disorders such as aqueous deficient dry eye. Many clinicians prefer to use a combination agent with a concurrent steroid and antibiotic. Unfortunately, the long-term effects of corticosteroids must always be weighed against the benefit of any chronic disease. Most experts recommend corticosteroids for short-term use only—usually two weeks or less—in an effort to jump start therapy for moderate-to-severe disease.[44] Restasis (topical cyclosporin A, Allergan) may be substituted for long-term therapy in these cases. However, Restasis is nonspecific for MGD and may not provide the relief that patients seek quite as effectively as some of the therapies discussed.[44]

One of the recent interventions for MGD involves debridement scaling of the posterior lid margin. One report described a procedure in which researchers passed a golf-club spud firmly along the lower lid at the region overlying the meibomian gland orifices. After following these subjects for four weeks, the authors noted significantly reduced symptom scores and an increased number of glands expressing meibum, as compared to subjects in the control group.[45] In clinical practice, the BlephEx device (BlephEx) appears to provide a much more thorough and tolerable means to debride the obstructed meibomian glands, removing additional, toxin-laden debris from the lid margins. Another recent study demonstrated the efficacy of this device in treating patients with MGD. After a single BlephEx procedure, subjects exhibited significantly diminished MGD severity, increased tear break-up time and reduction of clinical symptoms by over 50% at four weeks post-treatment.[46]

## Clinical Pearls

- The epithelial lining of the meibomian ducts is naturally devoid of pigment. Subsequently, patients with darker skin may appear to have inspissated glands upon routine inspection, while fair-skinned patients may appear to have unobstructed glands. For this reason, it is crucial to perform diagnostic gland expression on all patients to ascertain what lies beneath the surface.
- Interferometric imaging of the ocular surface can be helpful in assessing the quality of the lipid tear layer, as a means to reveal evaporative dry eye and MGD. Two such devices that can perform this testing are the Keratograph 5M (Oculus) and the LipiView II (TearScience). These instruments are also capable of performing infrared meibography, in addition to other tests for ocular surface disease.
- The use of lid scrubs with surfactant cleaners is often employed in the treatment of anterior blepharitis, but may be of limited value in MGD. Because this disorder involves a lipid deficiency, and since surfactant cleansers function to remove oil, aggressive cleansing of the lid margin with baby shampoo or commercial detergent cleansers may be self-defeating. Rather, we recommend a nonsurfactant cleanser such as Avenova (NovaBay Pharmaceuticals), which addresses excessive lid margin bacteria and inflammatory mediators by incorporating a stable hypochlorous solution.
- Patient education is crucial to success in the management of MGD. A discussion of the progressive nature of this disorder as well as the need to alleviate meibomian gland obstruction helps patients to better understand the implemented therapeutic measures.
- Elements that additionally impact MGD include diet, the effect of work/home environments on tear evaporation and the possible drying effect of certain systemic medications; these should be communicated as well.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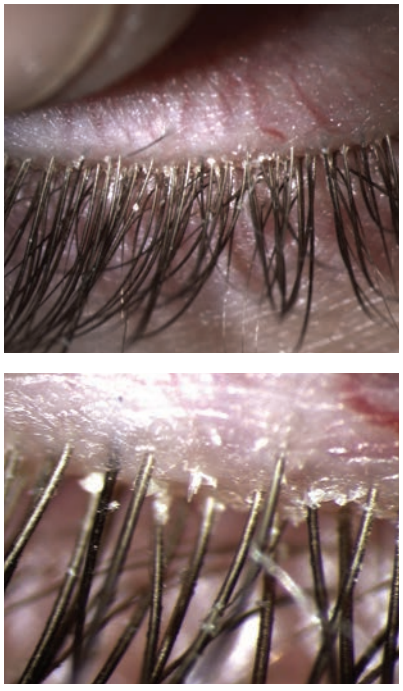
## OCULAR DEMODICOSIS

### Signs and Symptoms

Demodicosis refers to an infestation by mites of the genus *Demodex*. In humans, these mites selectively inhabit the skin of the face and head and have been associated with rosacea, steroid-induced dermatitis and seborrheic dermatitis, among other conditions.[1-4] When *Demodex* infest the eyelids and lashes, the condition is referred to as ocular demodicosis or *Demodex* blepharitis.

The typical patient with ocular demodicosis is over 50 years of age, with increasing prevalence in the elderly population.[5-7] There is no known racial or gender predilection.[6] Clinical symptoms of blepharitis—itching, burning, sandy or gritty feeling, heaviness of the lids or complaints of chronic redness—are often present in these patients, although a recent study indicates that nearly half of those individuals who harbor *Demodex* remain asymptomatic.[6] The classic sign associated with ocular demodicosis is the presence of collarettes, or scales that form clear casts around the lash root, a finding first recognized by Coston in 1967.[8] In 2005, Gao and associates coined the phrase *cylindrical dandruff* (CD), which is more descriptive of the eyelash sheathing encountered with *Demodex* infestation.[7] The study showed that lashes demonstrating diffuse or sporadic CD had a significantly higher incidence of *Demodex* organisms than those without CD.[7] Additional, nonspecific signs of ocular demodicosis include red and swollen lid margins, trichiasis, eyelash disorganization, madarosis, meibomian gland dysfunction (MGD), blepharoconjunctivitis and blepharokeratitis.[9,10] Recent studies also suggest a potential association between *Demodex* and pterygia and chalazia.[11,12]



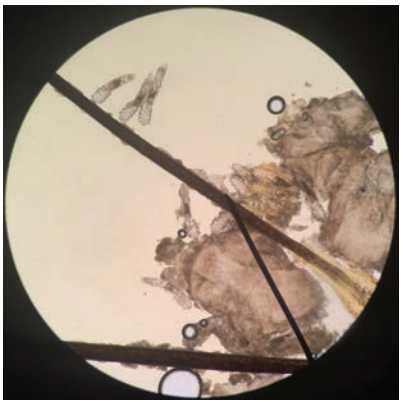
**Cylindrical dandruff at the base of the lash follicles is indicative of *Demodex* infestation (top). Following epilation, *Demodex* tails can be seen protruding from the lid margin (bottom).**

## Pathophysiology

Much controversy surrounds the role of *Demodex* in ocular inflammation. The organism is considered by many to be nothing more than a commensal saprophyte, inhabiting the skin of the host and feeding on accumulated oil secretions and dead epithelial cells.[13,14] Others, however, view the mites as parasitic—by definition, thriving in or on the host organism, offering no benefit and potentially causing harm. Judging by the recent literature, the latter view is currently more popular.

Two species of mites are known to inhabit the eyelids and eyelashes of the human host: *Demodex folliculorum* and the smaller, less prevalent *Demodex brevis*.[5-7,9,10,15] *D. folliculorum* tends to cluster superficially around the lash root, while *D. brevis* burrows into the deeper pilosebaceous glands and meibomian glands.[11,16,17] As *D. folliculorum* feed along the base of the lashes, follicular distention occurs, contributing to the formation of loose or misdirected lashes.[10] Cylindrical dandruff appears to result from epithelial hyperplasia and reactive hyperkeratinization around the base of the lashes, possibly due to microabrasions from the mite's sharp claws and cutting mouth-parts (gnathostoma).[7,10] *D. brevis*, in contradistinction, is believed to impact the meibomian glands either by mechanical blockage of the duct, a granulomatous reaction to the mites as a foreign body or as a vector for other microbes that incite the host's innate immune response.[10,11,18] The end result is MGD with associated lipid tear deficiency.[19]

Of course, not all individuals manifesting *Demodex* display these pathological changes. Studies have shown that infestation by *Demodex* induces an upregulation of tear cytokines, particularly interleukin-17, a potent mediator of inflammation.[20,21] Whether the symptomology and clinical manifestations associated with demodicosis are related to a critical number of organisms (with a pathological tipping point), concurrent pathogenic bacteria, age, environment or some other factor is yet to be determined.



**A microscopic slide showing numerous *Demodex* organisms residing along the lash follicle and in the accompanying debris.**

## Management

Because the eye is set back into the orbit, it does not lend itself to routine washing as readily as the rest of the structures of the face; this may in part explain why *Demodex* seem to flourish in this environment. Simple cleansing of the eyelids with baby shampoo or other surfactant cleaners has been advocated by some as a form of therapy, but studies have shown this to be ineffective as a standalone treatment modality.[7,19,22] Salagen (pilocarpine gel 4%, Eisai Pharmaceuticals) applied to the eyelids once or twice daily has also been recommended as a deterrent to mite infestation. This agent is theorized to interfere with the mites' respiration and motility via toxic muscarinic action.[23] However, studies have shown this intervention to be only partially effective, and the parasympathomimetic effects of pilocarpine on pupil size and accommodation must be weighed heavily against the clinical benefit.[22-24]

Tea tree oil (TTO), naturally distilled from the leaves of the *Melaleuca alternifolia* plant, appears to be the most widely accepted and most well-substantiated treatment for ocular demodicosis. Numerous derivatives of this essential oil have been advocated for application to the lid margins and lashes, including a 50% TTO in-office therapy, a 10% TTO home therapy, a 5% TTO ointment, a commercially available TTO shampoo and Cliradex (terpinen-4-ol, Bio-Tissue).[19,24-27] Cliradex is typically prescribed once or twice daily for three to six weeks. Sensitivity to these solutions tends to be dose and duration dependent, and while complete eradication of *Demodex* mites may be unattainable for all patients, subjective improvement is the rule rather than the exception. TTO can cause intense discomfort when applied to the delicate skin of the eyelids at full strength and can result in significant ocular toxicity if appropriate care is not taken. Diluting the solution with other natural oils (e.g., coconut oil, walnut oil or macadamia nut oil) is an intermediate step that can improve tolerability. In clinical studies, successful *in vivo* eradication of mites was seen in 73% to 78% of patients, while symptoms diminished dramatically in 82% of subjects after four weeks of therapy.[19,24]

While there are currently no studies to support the practice in terms of *Demodex* management, we have achieved great success with microblepharoexfoliation (MBE) using the BlephEx device (BlephEx). MBE provides ideal induction therapy for demodicosis by rapidly stripping away accumulated sebum, devitalized epithelial tissue, bacterial biofilm, cylindrical dandruff and even the more superficial mites themselves. In our experience, the combined use of MBE with ongoing hygiene efforts and specific, miticidal treatment modalities allows patients to achieve symptomatic relief much more quickly.

For more recalcitrant cases of demodicosis, or in those patients where compliance with topical therapy is unattainable, Stromectol (oral ivermectin, Merck) may provide some clinical benefit. Stromectol is an antihelminthic agent typically prescribed for the treatment of parasitic disorders such as strongyloidiasis or onchocerciasis. In terms of *Demodex* therapy, two 200mcg/kg doses given seven days apart represents the current standard.[28,29] As an example, an adult weighing 165 pounds would be prescribed five 3mg tablets to be taken in bolus form at the time of diagnosis, and an identical dose to be taken one week later. The most common side effects noted include nausea, diarrhea, dizziness and pruritus.[30]

Because *Demodex* inhabit various regions of the face and scalp, patients must remain vigilant even after a treatment for ocular demodicosis has been concluded. The patient should be advised to wash the face and hair regularly in order to reduce excess oils. Ideally, this should be done on a daily basis. The use of specialized facial scrubs or shampoos containing miticidal agents such as tea tree oil or permethrin may offer added benefit. Permethrin 5% cream, which is most commonly used for scabies treatment, may help to diminish stubborn *Demodex* reservoirs in patients with persistent or recurrent issues. This cream is typically applied to the face in the evenings, several times per week.[31] Due to toxicity, it should not be used on or near the eyelids.

## Clinical Pearls

• Clinical recognition of demodicosis can be challenging, as lid and lash debris are typically attributed to *Staphylococcal* or seborrheic blepharitis.

• *Demodex* mites are virtually impossible to view at the slit lamp due to their transparent nature, small size, aversion to bright light and tendency to remain buried within the lash follicle. Pulling two or three lashes and viewing them under a high magnification microscope can offer confirming evidence of these organisms in many cases. If a microscope is not available, lash rotation under the slit lamp can often help with the diagnosis. Rotating a lash in a circular fashion in the follicle can irritate the *Demodex* organisms and cause them, along with their debris, to evacuate the follicle.

• The hallmark finding of demodicosis is the presence of cylindrical dandruff at the base of the eyelashes.

• MGD may also be associated with demodicosis. *Demodex* mites have been identified as a risk factor for rosacea, and there may be a causative link.[4,32,33]

• Improved lid hygiene is the primary goal in managing any form of blepharitis, including ocular demodicosis.

• 50% TTO is generally used for in-office treatment only, while 10% solutions are recommended for home use. For those patients who cannot or prefer not to formulate their own concoctions, single-use commercial products such as Cliradex or Blephadex eyelid wipes are available.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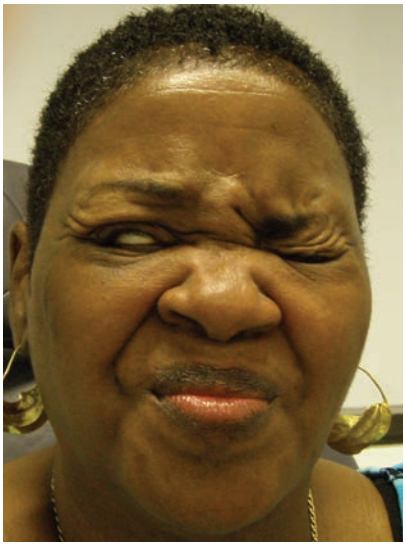
## BENIGN ESSENTIAL BLEPHAROSPASM

### Signs and Symptoms

Blepharospasm represents an eye-specific form of dystonia, a neurological condition marked by involuntary movements and extended muscular contractions.[1] Benign essential blepharospasm (BEB) refers to the tonic spasm of the orbicularis oculi muscle and associated musculature of the upper face, including the corrugator and procerus muscles.[1] In its earliest stages, patients with BEB experience intermittent bouts of uncontrolled blinking instigated by external stimuli, including such elements as wind, airborne pollutants, bright lights, loud noises or rapid head movement.[1] As BEB progresses, patients may experience more forceful closure of the eyelids lasting for longer periods, resulting in temporary functional blindness. Long-standing blepharospasm may lead to the development of lid and brow ptosis, dermatochalasis or entropion. In advanced stages, involvement of adjacent facial musculature becomes likely.

When blepharospasm is associated with dystonia of the platysma, muscles of the lower face and muscles of mastication, it may be referred to as Meige syndrome or segmental craniocervical dystonia.[1,2] Patients with Meige syndrome characteristically demonstrate pronounced bruxism (clenching of the jaw), as well as difficulty with speech, eating and swallowing.

The onset of BEB most often occurs in middle age, with 53 years being the median age at the time of diagnosis.[3] Women are affected nearly three times more frequently than men.[1,3,4] A majority of patients report some type of life-altering or emotionally stressful event immediately prior to the development of symptoms, according to one study.[3] The subsequent development of clinical depression and feelings of social isolation is also common.[1]



Severe, bilateral blepharospasm.

### Pathophysiology

Since the motor division of the seventh cranial nerve (CN VII) is responsible for delivering the voluntary motor innervations to the muscles of facial expression (and to the stapedius muscle of the inner ear, which dampens loud sounds), any irritation by adjacent or direct infection, infiltration, inflammation or compression of cranial nerve VII nuclei or its fascicles can produce involuntary contracture of the affected region.[5-7]

BEB is poorly understood and in most cases, despite extensive laboratory testing and neuroimaging, there is no clearly identifiable etiological factor.[8] As such, BEB must be considered a diagnosis of exclusion. Abnormal levels of neurotransmitters or alterations of the structure, function or architecture of the basal ganglia or midbrain have been postulated.[1] Additionally, recent research has uncovered a potential neurochemical connection.[9] Altered kynurenine metabolism, a neuroactive metabolite that plays a role in the normal physiology of the brain, has been identified as a contributor in neurodegenerative disorders such as Parkinson's disease, Huntington's disease and now the pathogenesis of focal dystonia.[9]

### Management

The treatment of choice for benign essential blepharospasm is chemodenervation via direct subcutaneous injection.[1,8,10] Botox (onabotulinumtoxin A, Allergan) is generally accepted as a first-line treatment for patients suffering from spasms secondary to facial dystonias of all kinds.[11] This medication works by blocking neuromuscular transmissions via the inhibition of acetylcholine release into the synaptic cleft.[10,12] These treatments are extremely effective and well tolerated.[11] The onset of effect typically occurs within one to three days and can last up to four months for cases of BEB.[11] Treatment failures due to antibody production are possible, so injections should be given no more frequently than every three months.[1] Adjunctive or alternative therapy with dopamine-depleting agents, neuroleptics, sedatives, centrally acting cholinergic medications and gamma-aminobutyric acid agonists have all had variable documented success; the drugs with the highest percentages of favorable patient response include Ativan (lorazepam, Valeant), Klonopin (clonazepam, Roche) and Artane (trihexyphenidyl HCl, Lederle Laboratories).[1]

While most patients will achieve successful amelioration of symptoms related to BEB with periodic Botox injections, some may not achieve adequate control with pharmaceutical therapy alone. In some instances, the medication may become less effective after prolonged use.[13] In such cases, surgical myectomy of the upper eyelid may be an effective additive treatment. Myectomy must also be considered for patients who demonstrate apraxia of eyelid opening, a complication associated with BEB and those who acquire blepharospasm-associated deformities. Myectomy is also an option for those who cannot afford or who refuse Botox injections.[13,14]

In all cases of blepharospasm, an easy-to-use disability scale has been developed

to quantify the contractures along with the changes that occur when treatment is instituted.[15] This allows both the patient and the treating physician to understand the overall inconvenience and functioning of the patient as well as the effectiveness of the mode of intervention.[15]

### Clinical Pearls

• BEB is often initially misdiagnosed as a psychiatric condition rather than a true neurological phenomenon. This can unfortunately delay appropriate management.[1]

• Physical and emotional stress can aggravate the symptoms of BEB. Even something as simple as participation in a social gathering can cause an exaggeration of the symptoms.

• Both Parkinson's disease and Huntington's chorea (ceaseless jerky movements with mental status changes) are worthy of being placed into the differential diagnosis of BEB.

• BEB must also be differentiated from secondary blepharospasm, a normal phenomenon that can occur following exposure to direct or indirect, painful ocular stimuli. Secondary blepharospasm presents as reflexive wincing and squeezing of the lids, as the patient attempts to find relief from intense ocular discomfort. Unlike BEB, secondary blepharospasm is transient and resolves when the root cause is eliminated.

• Patients with complete eyelid closure, having lost the ability to open their eyes voluntarily, are said to have apraxia of eyelid opening.[8] This finding may be seen in advanced cases of BEB. More commonly, however, apraxia of eyelid opening is related to a supranuclear disorder, presenting without forceful orbicularis contraction.[8]

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## EYELID LACERATION

### Signs and Symptoms

Patients with eyelid lacerations will present with varying degrees of eyelid swelling, edema, ecchymosis and bleeding.[1] Eyelid lacerations can result from blunt force, cutting injury, extreme irritation secondary to dryness, constant epiphora (from surface or allergic disease) or from blepharitis infection resulting in a fissure at the juncture of the lateral eyelid corners.[2-4] In traumatic cases, blow-out fracture and canalicular laceration can occur simultaneously as a result of the same trauma.[1] Lower lid canalicular lacerations are common in cases involving concomitant blow-out fractures, particularly those involving the medial wall.[1] Similar to most traumatic injury data, ocular eyelid injuries occur with greater frequency in young males.[2,3] The mode of injury is also variable, with numerous documented causes.[5-7] Since the forces necessary to disrupt the anatomy of the eyelid are significant, simultaneous globe injury is possible and must be considered.[6-8] Depending on the etiology, eyelid lacerations should be probed or imaged to rule out the presence of retained foreign matter.[5-8]

### Pathophysiology

The eyelid and ocular adnexa is well vascularized, containing multiple tissue types and sensory nerves. These elements are housed between the palpebral conjunctiva and the dermis.[9-14] The external epidermis consists of multiple layers and lies over the elastin-rich dermis and subcutaneous layer, which contains adipose tissue, connective tissue, vessels and nerves.[9,10] The striated muscle bundles of the orbicularis oculi lie deep to this, expanding throughout the eyelid.[8,10] The submuscular areolar layer lies posterior to the orbicularis, becoming a boundary separating the orbicularis muscle from the tarsal plate.[8,9] Tendonous fibers of the levator aponeurosis (LA, anterior and posterior portion) arise from the levator palpebrae superioris muscle (LPS) of the upper eyelid to course anteriorly, running between the orbicularis muscles. The anterior LA inserts superoanteriorly into the subcutaneous tissue, while the posterior LA inserts anteriorly into the eyelid skin itself and posteriorly over the entire width of the tarsal plate.[10]

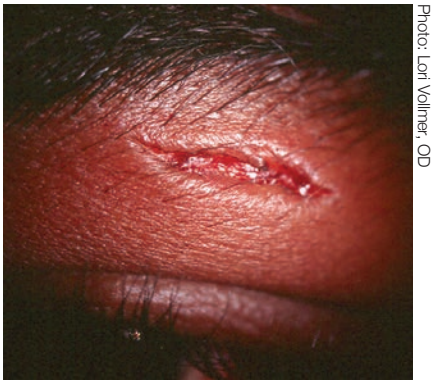

Photo: Lori Vollmer, OD

A superficial lid laceration.

Whitnall's ligament and the intermuscular transverse ligament (ITL) originate from the trochlear portion of the medial wall of the orbit and insert into the lateral orbital wall.[10] This ligament complex is thought to increase leverage by translating horizontal action into a vertical lifting action.[10] The muscle of Müller (responsible for eyelid opening, under sympathetic innervation) rides underneath the LA.[10]

The protective tarsal plate is composed of dense connective tissue designed to provide the lid with rigidity and shape.[9-14] This also allows the lid to maintain a posture aligned with the curvature of the globe.[9] Sebaceous meibomian glands, which produce tear evaporation-reducing oil, are embedded in the tarsus.[9] Zeis and Moll glands, also contributory to ocular surface support, are associated with eyelash follicles.

The nasolacrimal drainage system is contained in the medial-most portions of each eyelid, and the puncta define the outer most boundary.[15,16] Tear flow is contained and maintained secondary to the tonicity of the lower lid via the muscle of Riolan (pars ciliaris portion of the orbicularis oculi).[17] The tears flow into the puncta and into the superior and inferior canaliculi, which extends and expands 2mm in the vertical direction, then medially to the anatomic reservoir at the base of each canalicular arm, known as the ampula.[15,16]

Disruption of the external skin (abrasion, laceration or incision) can allow external pathogens access to the body. This creates the potential for infection (preseptal and orbital cellulitis). Lacerations that extend deeper or laterally have the potential to traverse the nasolacrimal apparatus, eyelid glands, extraocular muscles and tendons.[17] Extensive lacerations have the capability of extruding fat, producing functional and cosmetic consequences.[17,18] Life-threatening intracranial complications such as brain swelling can develop from blunt injuries that produce epidural hemorrhage.[19]

During the proliferative stage of wound healing, fibroblasts fill in the wound with collagen in a process termed granulation.[20] New blood vessels replace vasculature that was lost to trauma. Epithelial cells from the wound margins migrate across the laceration toward the center of the wound. Myofibroblasts then cause contraction of the wound, resulting in shrinkage and apposition of the edges. The wound gradually contracts and is covered by a layer of skin.[20] In the maturation and remodeling stage, collagen formation and remodeling strengthens the scar.[20] Scar tissue is never as strong as original tissue, but it increases over time from 5% tensile strength to nearly 80%.[20]

## Management

Patients presenting with eyelid lacerations require first aid. The first step is controlling bleeding or stabilizing impaling material. Impaling material should never be extracted, instead it should be stabilized. Once hemostasis has been achieved, attention can be directed to the globe and internal tissues. History is critical in determining the likelihood of retained particulate foreign matter. The area of injury should be inspected to rule out the presence of air (crepitus/orbital emphysema), which would increase the suspicion of bone fracture. Acuity measurement, slit lamp evaluation and tonometry will assist in fully assessing the possibility of globe damage. Dilated ophthalmoscopy should be completed unless a contraindication such as lens subluxation or globe rupture is suspected.

Lacerations created via bite, scratch or lesions with an accompanying bone fracture demand oral antibiotic prophylaxis, usually with a penicillin derivative such as phenoxymethylpenicillin 250mg BID PO. Amoxicillin, dicloxacillin and erythromycin 500mg BID PO are suitable as well.[17,21] While infection is a risk with sutures, one study found primary suturing of wounds caused by animal bites resulted in infection rates similar to non-suturing, with better cosmetic results on head and facial wounds.[22]

Small abrasions or cuts without evidence of fat or orbicularis evulsion and lateral fissures not caused by trauma can be repaired using topical ophthalmic antibiotic ointment BID-TID with closure enhanced via the application of Steri-strips (3M) or skin tape where necessary.[17,20] Pain management for cases that are not referred for repair can be accomplished by cold compresses and over-the-counter analgesics such as acetaminophen or ibuprofen. If severe ecchymosis or poorly controlled bleeding is present, avoid the use of aspirin or NSAIDs for pain control. Occasionally, narcotic analgesics may be needed for adequate pain management.

Tissue adhesive (cyanoacrylate glue) is not recommended, as it has the potential to produce unwanted adhesions. Uncomplicated wounds can be healed using light-activated sutureless substances in a process known as photochemical technique.[23] Complicated lacerations or those involving the nasolacrimal apparatus require the skill of an oculoplastic surgeon.[24-27] In these circumstances, after hemostasis and first aid has stabilized the injury, the eye should be lightly covered with a dressing and protected with a Fox (JedMed) or similar aluminum or plastic eye shield and promptly referred to an expert who has the skill to complete the restoration.

## Clinical Pearls

- The forces necessary to disrupt the anatomy of the eyelid skin and adnexa are significant; simultaneous injury to the globe and internal ocular contents is possible and must be ruled out.
- Injuries with proximity to muscles can result in alterations in eyelid function and mobility.

• Any laceration produced by a bite or scratch should include treatment with an oral prophylactic broad-spectrum antibiotic.


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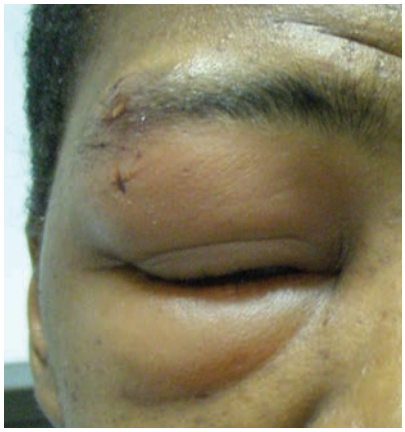
## ECCHYMOSIS and BLUNT ORBITAL TRAUMA

### Signs and Symptoms

The word *ecchymosis* takes its origin from the Greek words *ek* (to extravasate blood from) and *chymos* (juice) to mean "a spilling out of blood from the juice."[1] Patients with eyelid and periorbital injuries will present with varying degrees of eyelid swelling, eyelid edema, bruising and bleeding.[2,3] Eyelid hematomas and periorbital tissue swelling results from blunt force injuries ranging from falls and fists to missile impacts (balls, bats, clubs, tools, air bags, etc.) and skull base fractures (raccoon eyes or panda sign).[2-16] Non-traumatic ecchymosis has been documented after severe vomiting, violent coughing and sneezing.[15-17]

Ecchymosis may be shallow with fluid and blood only layering under the skin, or may be more substantial, seeping into muscle or subcutaneous dermal tissues. The characteristics and coloration of the bruise at the site of the injury will range from red to purple and is subject to: the severity of the impact; amount of bleeding that has occurred; depth of the injury; color, complexion, tone and condition



Ocular contusion injury associated with blunt force trauma.

of the skin; coagulative state of the patient; and the age of the injury.[18] Yellowing can be noted as the injury heals. Accompanying injuries in traumatic cases which produce ecchymosis may include blow-out orbital fracture, canalicular laceration, subconjunctival hemorrhage, eyelid laceration, globe rupture, corneal or conjunctival laceration, corneal abrasion, iritis, iridodialysis, hyphema, lens luxation, levator disinsertion, commotio retinae, posterior vitreous and retinal detachment, vitreous hemorrhage and optic nerve contusion and evulsion.[2-10]

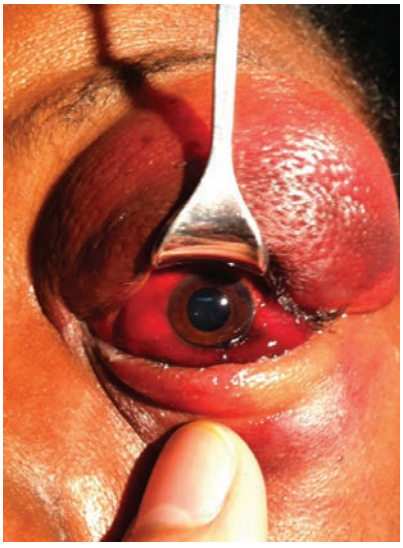
Depending upon the cause, symptoms may include pain, photophobia, lacrimation and crepitus (the crackling sound of air escaping from soft tissues following bony fractures) if bones have been broken and air has invaded the tissue (pneumatic or orbital emphysema).[17] If blow-out fracture has occurred, diplopia may be present from extraocular muscle entrapment. As the lid swells, vision will be compromised secondary to obstruction of the visual axis. If concomitant internal injuries have occurred, vision may remain reduced despite opening of the eyelid. If retinal detachment has ensued, tractional photopsias (flashes and floaters) may be present. If there is a significant iritis, the patient may be photophobic.

Intraocular pressure may be high or low depending upon the status of the ciliary body with respect to aqueous humor production, the amount of anterior chamber inflammation, the presence of hyphema or concurrent damage to the drainage angle.[2-5,14]

The epidemiology of blunt ocular injury is heavily skewed toward young males, often during the warmer months, and there are more incidences of blunt ocular injury related to work and sports.[2-10] Accidental injuries occurring in or around home show a more balanced gender distribution.[14]

## Pathophysiology

The eyelid and ocular adnexa are well vascularized, containing multiple tissue types (supportive and muscular) and sensory nerves (V1, ophthalmic division of the trigeminal nerve). The intricate architecture permits the formation of a thin but formidable cohesive barrier anchoring the skin, levator aponeurosis (LA), orbicularis oculi and tarsal plate into the mainframe of the upper eyelid.[19] As the frontalis muscle does not have a bony insertion point on the skull superiorly, there is no limit to the travel of a bruise in that direction. Gravity, however, encourages the extravasated fluids to seep inferiorly into the lid and upper cheek. The anterior portion of LA interdigitates with the orbital septum superiorly, creating an additional barrier keeping released fluid from accessing the orbit.[18] The barrier is completed by tarsal plate as its orbital border attaches to the orbital septum, while the marginal border attaches to the lid margin.[10] These barriers limit extravasation of blood into the periorbital skin and the subcutaneous tissues around the eyes. Raccoon eyes or panda sign are distinctive types of periorbital ecchymosis where the bruising is mitigated by the orbital septum, limiting the spread of the discoloration beyond the tarsal plate.[15,16]



**Ocular contusion with subconjunctival hemorrhage.**

Completing the layers of the eyelid, the muscle of Müller rides underneath the anterior and posterior layers of the LA. It extends superiorly to connect to the inferior branch of the levator palpebrae superioris, which is contiguous with the LA and frontalis.[19] The subcutaneous connective tissue under the eye, referred to as the nasojugal fold, is the bony fascial attachment of the skin and connective tissue limiting the inferior movement of ecchymotic swelling.

Ecchymosis results from capillary leakage secondary to traumatic insult.[15-19] The etiology can be traced to a combination of two mechanisms: shear stress (push-pull) or hydraulic-induced (pressure-related) tensile stress.[20] Results from experiments testing both models of disruption have demonstrated that the predominant mechanism of failure is hydraulic-induced tensile stress.[19] This was concluded via observations made directly under impact zones where capillaries bifurcate.[20] These results are supported by the concept that bruising can occur via blunt trauma in which no shearing incisions or lacerations occur.[15-19] As blood and its constituents are liberated from the capillaries, it flows with the assistance of gravity into the tissues until it reaches a barrier or until hemostasis begins the process of clotting and repair.[15,16,21] Patients who are on anticoagulation therapy or have primary hemostatic clotting disorders demonstrate a propensity for easy and more extensive bruising.[21] Patients with secondary hemostatic disorders typically manifest with delayed, deep bleeding into muscles and joints.[21]

Immediately following an insult, blood-laden dermal layers take on a darkened red-blue-purple appearance. The amount of pain and discomfort is proportionate to the sensitivity of the affected nerves and the total area of damage. Damaged capillary endothelial cells release endothelin, a hormone that causes a narrowing of blood vessels, which begins hemostasis.[22-25] Secondarily, von Willebrand factor is released, initiating comprehensive coagulation.[21-24] Bruises change color (black-brown-green-yellow) due to the breakdown of red blood cell hemoglobin.[22-25] The colors of a bruise are caused by the phagocytosis and sequential degradation of hemoglobin into biliverdin (green), bilirubin (yellow) and hemosiderin (red/brown/blue). As the products are reabsorbed in demolition and repair, the bruise disappears.[22-25]

Any disruption of the external skin will enable pathogens access to the internal anatomy and communicative vasculature. This creates the potential for infection and preseptal cellulitis. Impacts that are significant enough to create eyelid hematomas are also capable of fracturing and bruising bones of the orbit or initiating intraorbital bleeding, resulting in sight-threatening retrobulbar hemorrhage.[25,26] Life-threatening intracranial complications such as epidural hematoma and subarachnoid hemorrhage from transmitted forces are possible as well.[27]

## Management

If any bleeding is present, it must be arrested and the patient's overall systemic health must be evaluated. History is critical in assessing the nature and extent of the injury. The area of injury must be inspected for breaks in the skin or irregularities at the lid margin or nasolacrimal apparatus. The globe and ocular tissues must be examined completely; a dilated ophthalmoscopic examination should be completed unless a contraindication such as lens subluxation or globe rupture is uncovered. The area of injury should be palpated to rule out the presence of crepitus and orbital emphysema.[11-17]

In cases where the eyelid is tight and full and cannot be elevated manually, it can be lifted with a lid retractor. This is necessary for obtaining initial visual acuity, ocular tissue inspection, intraocular pressure and fundus examination. If crepitus or orbital emphysema is detected—indicating an orbital wall fracture—oral antibiotic prophylaxis with a broad-spectrum antibiotic such as cephalexin, amoxicillin, dicloxacillin and erythromycin may be necessary.[17,25-28]

Small abrasions or cuts without evidence of laceration can be prophylactically protected by topical ophthalmic antibiotic ointment BID-TID. In most cases, periorbital swelling will subside naturally over two to four weeks. It can be hastened with cold compresses, upright sitting and head elevation during sleep. This encourages the blood to settle and enhances the environment for reabsorption. In the event that pain and edema are severe, a short course of oral steroids can help. Pain management can be accomplished by over-the-counter analgesics such as acetaminophen or ibuprofen.

A novel consideration to hasten the resolution of ecchymosis is hydrogen peroxide 15% carbamide gel under occlusion.[22] Hydrogen peroxide in water is sold over the counter as a topical antiseptic. Carbamide peroxides are used as over-the-counter teeth whiteners, earwax softeners and hair bleachers.[22] Hydrogen peroxide causes hemolysis. Since a bruise is made up of red blood cells extravasated into the dermis and subcutaneous tissue, the hydrogen peroxide mixture theoretically causes localized lysis and breaks the double bonds in erythrocyte pigments, hastening bruise resolution.[22] Because of its corneal toxicity, this mixture should be used with extreme caution around the eye and likely used only in extreme situations where cosmesis is crucial; the study used to document the effect reported concerned a bruise on the thigh.[22] Overall, it is better to let ecchymosis resolve on its own.

## Clinical Pearls

- Ecchymosis is not a diagnosis, but rather a finding associated with blunt force injury. The description of raccoon eyes or panda sign should be limited to the specific circumstance of periorbital ecchymosis from skull base trauma.
- Substantial ecchymosis can inhibit the levator from opening the lid and limit the extraocular muscles from moving the globe, altering function and mobility.
- Oral antibiotics are necessary for protecting against infection in confirmed or suspected cases of fracture.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# PINGUECULA and PINGUECULITIS

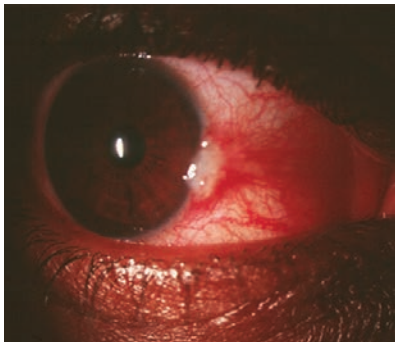
## Signs and Symptoms

Pingueculae are characterized by yellowish, slightly raised, interpalpebral exacerbations of tissue in the nasal and temporal bulbar conjunctiva.[1-14] In most cases, pingueculae are an ancillary finding, causing little, if any, ocular symptoms. Research has linked the severity of pingueculae with exposure to ultraviolet light (chronic sunlight exposure, welding), contact lens wear (more so with rigid lenses) as well as natural conjunctivochalasis of the individual.[11-14]

Pterygia are wedge-shaped fibrovascular growths that evolve by progressing over top of pingueculae to extend onto the cornea. They are frequently, but not always, the byproduct of the chronic pathophysiological sequelae introduced by pingueculae.[5] Both lesions possess vasculature and the potential to become inflamed. Both can disrupt tear flow, producing incomplete corneal wetting and resulting in corneal punctate epitheliopathy and adjacent areas of focal corneal dehydration with dellen formation.[1-6] Despite these relationships and a high degree of coexistence and comorbidities, the literature continues to consider the two lesions as separate entities.[14] When a pinguecula becomes acutely inflamed, producing focal conjunctival redness with accompanying ocular irritation, the condition is referred to as pingueculitis.[4-8]

## Pathophysiology

Pingueculae are considered to be a conjunctival degenerative process initiated by exposure to noxious environmental stimuli and ultraviolet radiation.[3-6,11,14] The initial lesion is thought to result from chronic exposure to solar radiation, which induces an alteration of the collagen and elastic tissues of the conjunctival stroma, leading to elastotic degeneration and deposition of abnormal elastic fibers in the conjunctival substantia propria.[2,3,6]



**Pingueculitis presents with an acutely red eye and mild to moderate discomfort.**

Histologically, the lesions contain deposits of degenerating collagen fibers, granular deposits, elastoid fibers and an increased population of metabolically active stromal fibrocytes.[11] Once a pinguecula develops, depending on its size the tear film may become thin and discontinuous in that zone, producing a bed of dryness.[1,2,11-14] When the tissue itself and neighboring cornea are sufficiently affected, inflammation ensues; vascular dilation allows histamine, seratonin, bradykinin and prostaglandins to be released, producing the acute irritative symptoms that characterize pingueculitis.[11,14]

In severe cases, the conjunctival surface becomes sufficiently dry to cause microulceration of the surface epithelium, damage to limbal stem cells with the release of matrix metalloproteinases and vascular endothelial growth factor-C (VEGF-C).[14,15] These changes promote an increase in lymphatic microvessel density, which is the impetus for pterygium formation.[1-3,8,14,15] Research has also suggested that, on the continuum of the same process, inflammatory cell infiltration may contribute to the formation of conjunctival inclusion cysts seen within pterygia, pingueculae, vernal conjunctivitis and pyogenic granuloma.[8]

## Management

Management of pingueculae is predicated mostly on the nature and extent of symptoms. Patients who have occupations or hobbies that increase the risk of pinguecula formation should be counseled on the preventative benefits of protective sun wear such as UV-blocking coatings and goggles that limit dust exposure.[4] In cases of mild pingueculitis, where symptoms are subtle, ocular lubricating drops are indicated. Nonsteroidal anti-inflammatory medications may also suppress discomfort until ocular surface homeostasis can be restored.[14] When symptoms and inflammation become more significant, topical steroids such as 1% prednisolone acetate suspension, 0.5% loteprednol etabonate or 0.25% fluorometholone, Q2H–QID are acceptable.[1,3,4,6,14]

A recent report studying symptomatic pinguecula found that intralesional betamethasone injection in depot form provided a significant clinical improvement.[16] Argon laser photocoagulation has also been documented as an effective and safe method for removing a pinguecula for cosmetic purposes.[17] The method permits good control of the extent and depth of removal, minimizing conjunctival defects and other complications.[17] The method is reserved for severe cases where the tissue interferes with vision, contact lens wear or corneal wetting. In this study, it was preferred over standard surgical resection.[1-4,17]

## Clinical Pearls

- Differential diagnoses must be considered when intrapalpebral conjunctival masses and elevations are discovered. Such lesions are not always benign and may include conjunctival dermoids, intraepithelial neoplasia (squamous cell carcinoma), phlyctenulosis, pannus, conjunctival retention cysts and limbal follicles.

• While pingueculitis is typically self-limiting and rarely constitutes a sight threatening event, prompt treatment with topical lubrication and anti-inflammatory therapy hastens recovery and greatly helps to diminish symptoms.

• Appropriate forms of UV-blocking eye wear can minimize the risk of pinguecula formation for those persons at elevated risk (e.g., people who fish, boaters, skiers, outdoor painters, roofers, etc.).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## SCLERAL MELT

### Signs and Symptoms

Scleral melt—also known as *scleral ischemia* or *scleral necrosis*—is an uncommon condition that typically presents in older adults. In most cases, scleral melt represents a late complication of ophthalmic surgery and in such instances is more appropriately referred to as *surgically induced scleral necrosis* (SINS).[1] It may also occur as a sequela of chemical or thermal trauma to the eye, or rarely as an isolated complication of systemic autoimmune disease.[2] Clinically, the condition may be seen as a focal area of scleral thinning between the corneal limbus and the insertion of the extraocular muscles, with the dark blue/black coloration of the underlying uvea visible beneath the lesion. A variable degree of adjacent conjunctival inflammation may accompany scleral melt, depending upon the etiology and associated pathology.

Individuals presenting with scleral melt generally report symptoms of mild to moderate discomfort. Foreign body sensation, stinging and blurred vision are common, as are excessive lacrimation and possibly photophobia. Rarely do patients complain of intense ocular pain. No racial predilection has been identified. Women do appear to be affected more often than men.[3] A history of systemic autoimmune disease is another common finding; some of the associated conditions may include rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, inflammatory bowel disease, Wegener's granulomatosis, relapsing polychondritis, diabetes mellitus and thyroid disorders.[1-4]

### Pathophysiology

The most common predisposing factor in cases of scleral melt is prior ocular surgery. There is a particularly high association with pterygium excision, especially in those cases where either adjunctive radiation or chemotherapy was used.[1,5,6]

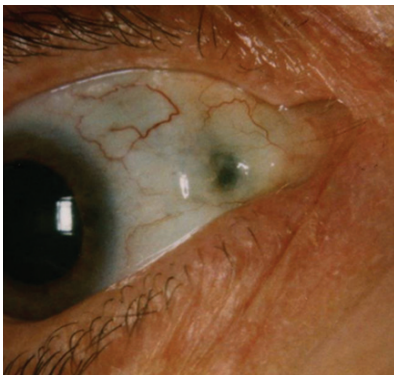

Photo: Wayne Bizer, DO

**Scleral melts can be seen following ocular surgery, as noted in this patient.**

Scleral melt has also been described after cataract extraction, trabeculectomy, strabismus surgery, vitrectomy, retinal detachment repair, intravitreal implant surgery, orbital/ocular radiation and "eye-whitening" procedures.[2,3,7-12] Alternatively, the patient may report a prior incident involving a severe chemical or thermal burn to the ocular surface. Scleral melt may occur as soon as one day or as late as 50 years after the antecedent trauma.[13-15] Less commonly, scleral melt is encountered as a sequela of severe ocular surface disease (e.g., keratoconjunctivitis sicca), ocular infection, systemic vasculitis or connective tissue disorders.[16-20]

Scleral melt is presumed to represent a delayed-onset hypersensitivity response to localized ischemia involving the episcleral blood vessels.[6] Such ischemia can be precipitated by surgical trauma (especially when accompanied by beta irradiation or mitomycin C therapy), chemical or thermal injury or less commonly, by severe autoimmune disease or vasculitis.[2] The exact mechanism of damage is poorly understood, but enzymes produced by polymorphonuclear cells and stimulated by surgical manipulation are likely implicated, leading to destruction of collagen and proteoglycans that comprise the scleral stroma.[1,10,18] Evidence to support these hypotheses include the success of systemic immunosuppression

in the treatment of scleral melts, as well as the presence of immune complexes in the episcleral vessel walls among such patients.[16,21] Research has identified elevated levels of both tumor necrosis factor alpha (TNF-α) and MMP-9 in patients with surgically-induced scleral necrosis.[22]

## Management

Therapeutic intervention in cases of scleral melt depends on a number of factors, most notably the disposition of the patient and the risk of global perforation. For those cases that are relatively asymptomatic and not in danger of rupture, periodic observation (e.g., every four to six months) along with liberal use of ophthalmic lubricants may be all that is required.[2] However, patients in the postoperative period, such as pterygium resection with adjunctive antimetabolite, who present with a mild scleral melt should be evaluated sooner, preferably at one week. More severe cases may require the application of surgical patch grafts to maintain tectonic support of the globe.[2]

Tenonplasty, a surgical procedure involving excision of necrotic superficial tissue along with dissection and advancement of viable underlying Tenon's capsule, is performed initially to reestablish the blood supply to the ischemic sclera. Then, donor sclera tissue or a lamellar corneal graft is typically transplanted to the wound and covered with either an amniotic membrane or a conjunctival flap.[2,23,24] Postoperatively, treatment with topical corticosteroids (e.g., 1% prednisolone acetate QID) and prophylactic antibiotics (e.g., 0.5% moxifloxacin TID) helps control subsequent inflammation and infection.[2] There has been some conjecture regarding the appropriatness of corticosteroids due to the belief that they may potentiate collagenases. Additionally, corticosteroids and NSAIDs have also been noted to cause scleral melt.

A variety of other surgical techniques have also been piloted, with varying success.[24,25] The concurrent use of immunosuppressive agents such as oral cyclophosphamide, azithioprine, cyclosporin A and tacrolimus may be helpful to prevent graft rejection in difficult cases.[26] Hyperbaric and normobaric oxygen therapy have also been used in patients who failed to respond as desired to medical or surgical intervention.[27,28]

In cases of scleral melt that do not have an obvious traumatic or iatrogenic etiology, and especially in those cases that involve the limbal and peripheral corneal regions, a medical workup to rule out associated systemic disease is essential. According to a landmark study, as many as 63% of scleral melt cases are associated with an underlying medical disorder, of which the most common group is connective tissue diseases such as rheumatoid arthritis, Wegener's granulomatosis, or polyarteritis.[29-31]

## Clinical Pearls

- Scleral melt is a serious and challenging clinical problem, as it threatens the integrity of the eye. Even asymptomatic cases likely warrant a surgical consultation to assess the potential for perforation.
- Numerous conditions can masquerade as scleral melt. These include benign entities such as senile scleral plaques and dellen, as well as more serious conditions including ciliary body melanoma and scleromalacia perforans.
- Scleromalacia perforans can be differentiated from scleral melt in that patients with the former are generally asymptomatic and present with bilateral involvement. In addition, the eyes are usually otherwise quiet in patients with a chronic history of rheumatoid arthritis.


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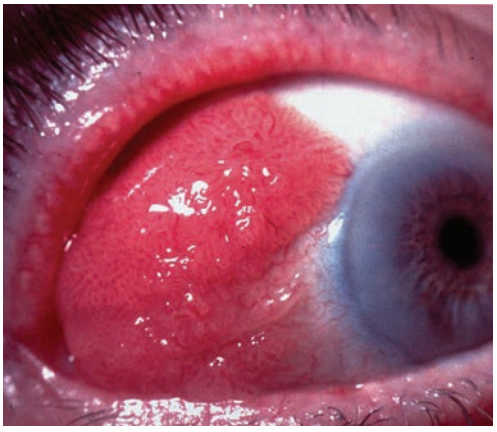

MALT lymphoma of the conjunctiva.

## CONJUNCTIVAL LYMPHOMA

### Signs and Symptoms

While basal cell carcinoma, sebaceous cell carcinoma and malignant melanoma are the most common malignancies of the periocular skin, lymphoma represents the most common malignant neoplasm of the ocular adnexa, and the conjunctiva is the site of involvement in about 35% to 40% of cases.[1] This condition can be seen as an isolated entity (primary lymphoma), or it may arise as a localized manifestation of systemic disease (secondary lymphoma).[2] Conjunctival lymphomas most often present as rapidly-growing mass lesions of the superficial ocular surface. The typical appearance is that of one or more pink, "fleshy" masses arising from within the fornix and extending toward the cornea. Alternatively, they may present as smaller, solitary lesions of the bulbar conjunctiva.[3] Classically, lymphomas of the conjunctiva are described, based on their color, as "salmon-patch lesions."[1,3] They may present bilaterally in 7% to 24% of patients.[1,4] Affected individuals are usually in the fifth to seventh decade of life, with a median age of 65 at the time of diagnosis.[1-4] Patients are also predominantly female.[1,2,4] Individuals with conjunctival lymphoma often have cosmetic concerns regarding chronic redness and occasionally report dryness, irritation, or both, but rarely experience substantial ocular pain.[5] Vision may be variably impacted, depending upon the location and extent of the lesion.

### Pathophysiology

Lymphoid tissue is present in most organs throughout the body. The lymph tissues are producers of immune cells. They are connected by channels and conduits to regional lymph nodes, located primarily in the neck, axillae, groin and abdomen. The primary function of the lymphatic system is to serve as a collection reservoir for interstitial fluid and to provide a conduit for the return of this fluid back to the vascular system. Lymphoma represents an abnormal, malignant growth of lymphoid tissue. It is classified as a cancer of the various elements of the lymphatic system. From an ocular point of view, primary lymphoma can manifest as a mass lesion of the external eye, localizing to the conjunctiva, the orbit, lacrimal gland or eyelid.[6] Alternatively, patients may present with primary intraocular lymphoma, demonstrating choroidal infiltration with secondary vitritis, infiltrative optic neuropathy, or both.[6,7] Secondary lymphoma can likewise be extraocular or intraocular, but these lesions are far less common than primary lymphomas of the eye.[2]

Throughout the years, a number of classification systems have been developed to describe lymphoid tumors, including the Rappaport classification, Kiel classification, Lukes-Collins classification, Working Formulation, British National Lymphoma Investigation classification and Revised European-American Lymphoma (REAL) classification.[8] These systems were based on either the histological appearance of tumor growth (nodular or diffuse), size of cells (small, medium or large) or cell immunophenotype (B, T, natural killer [NK] or null).[8] Today, the accepted standard is the World Health Organization (WHO) classification, established in 2001 and revised in 2008.[9,10] The WHO classification is based on morphology, immunophenotype and genetic, molecular and clinical features.[11] This system recognizes five broad categories: precursor B- and T-cell neoplasms, mature B-cell neoplasms, mature T/NK-cell neoplasms, Hodgkin's lymphoma and immunodeficiency-associated lymphoproliferative disorders.[10] It then further subdivides these into numerous specific entities based on the aforementioned criteria, ultimately yielding nearly 60 unique clinical diagnoses.[11]

Most conjunctival lymphomas fall into the category of B-cell neoplasms of the non-Hodgkin's variety.[12] These are frequently broken down further into mucosa-associated-lymphoid-tissue (MALT) lymphomas and non-MALT lymphomas. MALT lymphomas a more prevalent and generally follow a more indolent course, while non-MALT lesions are considered highly malignant and invasive.[3,13]

### Management

Although conjunctival lymphomas often have a characteristic appearance, it is important to differentiate them from

other benign tumors of the ocular surface such as squamous papilloma, pyogenic granuloma and lymphangiectasis. Additional differential considerations should include benign reactive lymphoid hyperplasia, episcleritis, scleritis, ectopic lacrimal gland, chronic follicular conjunctivitis, ocular surface squamous neoplasia and amelanotic melanoma.[14] It is not possible to differentiate between benign and malignant lymphoid tumors (or MALT vs. non-MALT lymphomas) simply on the basis of clinical presentation. Hence, tissue biopsy is crucial to establish a definitive diagnosis via flow cytometry and formalin-fixed tissue analysis.[14] In addition, any patient with biopsy-proven lymphoma warrants a complete medical evaluation to determine if systemic lymphoma is present. Ideally, this should be done upon referral to or in coordination with a board-certified oncologist. Testing should include careful palpation of peripheral lymph nodes, complete blood count with differential, liver function tests, bone marrow biopsy and CT scans of the orbit, chest, abdomen and pelvis.[15]

Therapy for conjunctival lymphoma depends on the disposition of the tumor and whether there is disseminated lymphoma elsewhere in the body. Isolated conjunctival lymphoma (i.e., involving the conjunctiva but no other ocular or systemic structures) is most often treated with external beam radiation therapy (EBRT), on the order of 25 to 30 Gy (gray units).[1,16,17] Dosage and exposure tends to be higher for more aggressive non-MALT lymphomas, though care must be taken to minimize long-term complications of ocular radiation such as xerophthalmia, cataract formation, ischemic retinopathy, optic atrophy and neovascular glaucoma.[15-18] Alternative or adjunctive therapeutic options may include intralesional injection of interferon-α, intralesional injection of Rituxan (rituximab, Genentech) (anti-CD20 antibody), oral doxycycline (as an association with infection by *Chlamydia psittaci* has been noted for ocular lymphoma), or simple observation following excisional biopsy.[18-22] Those patients with invasive or disseminated lymphoma may require systemic chemotherapy in addition to local treatment. The standard regimen for non-Hodgkin's lymphoma is a combination of Rituxan, cyclophosphamide, doxorubicin, vincristine and prednisone, referred to in oncologic circles as R-CHOP.[23-27]

## Clinical Pearls

- Conjunctival lymphoma should be part of the differential in all cases of sudden onset, rapidly growing lesions of the fornix, particularly those that are highly vascularized and fleshy in nature. Never assume these lesions to be benign; the most prudent course of action is to obtain a prompt biopsy.
- Staging and histologic subtyping are essential in the design of a therapeutic regimen and determination of prognosis, since about 15% of cases present with disseminated disease.
- Though conjunctival lymphoma may be associated with systemic lymphoma, the ocular lesions have not been shown to metastasize to any significant degree. The five-year survival rate for primary MALT lymphomas is excellent.
- Localized therapy for conjunctival lymphoma may not be required in those individuals with secondary, disseminated lymphoma who are already undergoing systemic chemotherapy.


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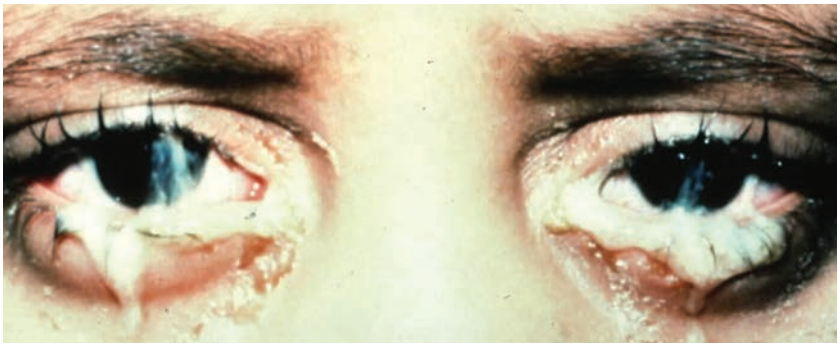

Hyperacute keratoconjunctivitis in gonococcal infection.

## CHLAMYDIAL and GONOCOCCAL CONJUNCTIVITIS

### Signs and Symptoms

Chlamydial infection is recognized as the world's most common sexually transmitted disease.[1-8] The spectrum of ocular sequelae includes trachoma, adult inclusion conjunctivitis and neonatal conjunctivitis.[1-10]

*Chlamydia trachomatis* (CT) is the most prevalent sexually transmitted bacterial infection in the world, with more than 100 million cases reported annually.[1-6] The disease is transmitted by the *C. traucomatis* organism serotypes A-C via close human contact and is endemic to countries with water purity issues (Middle East, parts of Africa, India and Southeast Asia).[2-8] Trachoma is often transmitted either via sexually active young adults or through contaminated water secondary to poor hygiene or faulty purification.[2,4,7] It remains among the leading causes of worldwide blindness, progressing from a painful suppurative follicular conjunctivitis with ocular injection and limbal follicles to florid follicular palpebral conjunctival scarring (Herbert's pits) and fibroproliferative scarring on the superior palpebral conjunctiva, which produces horizontal linear cicatrization (Arlt's lines) capable of inducing corneal panus, ulceration and ultimately sight-threatening keratopathy.[1-10] Permanent eyelid deformities, trichiasis, entropion and ectropion result and contribute to catastrophic corneal compromise.[1-8]

Adult inclusion conjunctivitis is caused by the *C. trachomatis* organism serotypes D-K.[1,2] It also presents in sexually active teens and young adults.[1-4] The classic ocular sign of adult chlamydial conjunctivitis includes a suppurative eye infection that persists despite treatment with topical antibiotics.[1-12] The symptoms include global conjunctival injection, variable mucopurulent discharge, matting of the eyelashes, variable ocular irritation, punctate epithelial keratitis, corneal pannus, peripheral corneal subepithelial infiltrates and, in severe cases, iritis.[2,12-18] A palpable preauricular node is almost always present.[14,15] Affected female carriers may show genitourinary symptoms such as chronic vaginitis or cervicitis, while affected males may remain relatively asymptomatic.[2,7,8]

Neonatal chlamydial conjunctivitis (ophthalmia neonatorum) has been reported to have an overall incidence of 0.65 of 1,000 live births with numbers remaining consistent over the years.[5] Along with gonococcal infection, it is a frequent infectious cause of neonatal conjunctivitis in the United States.[2,4,5] Risk factors for ocular infection in the newborn include a history of active vaginitis, pelvic inflammatory disease or urethritis in the mother at the time of delivery.[1-3,10] Neonatal chlamydial or gonococcal conjunctivitis typically presents within four weeks of birth.[2] Hemorrhagic eye discharge is a highly specific sign of neonatal chlamydial conjunctivitis.[11] Unlike the other forms, follicles or similar responses are not expected here since they are not developed that early.

An estimated 498 million new cases of curable sexually transmitted infections occur worldwide annually.[19] Of these, 106 million are gonococcal infections, caused by *Neisseria gonorrhoeae*, rendering gonorrhea the second most prevalent sexually transmitted infection after chlamydia.[19] Gonococcal conjunctivitis (or keratoconjunctivitis, should the cornea also be involved), is sometimes referred to as hyperacute conjunctivitis.[20-23] While most cases are the result of sexually transmitted vectors, infected individuals have been detected without evidence of genital signs or symptoms.[21]

Although sensitive to heat and drying, *N. gonorrhoeae* may remain viable in discharge on a cloth for several days.[22] As such, communal baths, towels or fabrics, rectal thermometers and poorly sanitized caregiver hands are alternate means of transmission.[20,22] The infection is prevalent worldwide with more than 60 million new cases documented.[23] Immunity from prior infection does not protect against reinfection even with the same strain, and a viable vaccine remains elusive.[20,22] Gonococcal ophthalmia neonatorum is the most common manifestation in infants born to mothers with gonococcal genital tract infections.[5,13,23]

Systemically, gonococcal infections are associated with organism colonization of the urethra, cervix and rectum.[18,24,25] The unusually contagious ocular disease typically presents as an acute, red eye with severe mucopurulent discharge of less than four weeks duration.[17] The conjunctivitis has an incubation period of two to seven days.[20,24] Matting of the eyelashes, conjunctival papillae, superficial punctate keratitis and marked chemosis are almost always present.[20-25] Subconjunctival

hemorrhage, hemorrhagic conjunctivitis, pseudo- or true membrane formation and preauricular adenopathy are usually present. In chronic, recalcitrant or severe cases, peripheral subepithelial corneal infiltration may occur, leading to corneal ulceration with iritis.[25] Sight-threatening consequences are possible.[26]

## Pathophysiology

*Chlamydia trachomatis* is an intracellular parasite that contains its own DNA and RNA.[7,8,27] The subgroup A causes chlamydial infections, while the serotypes A, B, Ba and C cause trachoma. Serotypes D through K produce adult inclusion conjunctivitis.[4,7,8,27] The mode of ocular transmission may be by hand contact from a genital site of infection to the eye, laboratory accidents, mother infecting the newborn, shared cosmetics and occasionally an improperly chlorinated hot tub.[1-5,22] In 1911, Lindner and colleagues identified the microscopic finding of intracytoplasmic inclusions in the cells of infants with conjunctivitis. They called the disease "inclusion conjunctivitis of the newborn."[1] In their report, they were able to demonstrate that mothers of affected infants had these "inclusions" within their cervical epithelial cells, along with the fact that the fathers also had "inclusions" in their urethral cells.[1] This confirmed their suspicion that the disease was caused by sexually transmitted chlamydial infection.[1]

*C. trachomatis* is protected from the humoral immune response by residing within remodeled intracellular vacuoles.[8] The vacuole-bound pathogen manipulates host-cellular functions, invading host cells and establishing a replicative niche.[8] The first immune response to the infection is a local one, whereby immune cells such as leukocytes are recruited to the site of infection and subsequently secrete proinflammatory cytokines and chemokines, which initiate and potentiate chronic inflammation through the production of reactive oxygen species

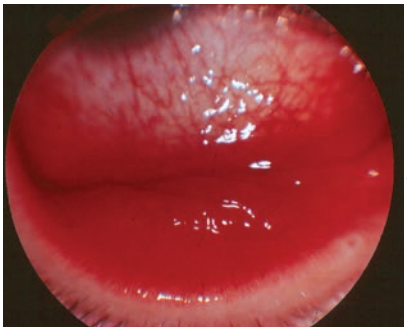

Photo: Diana Shechtman, OD

**A 25-year-old woman with chlamydial infection (adult inclusion conjunctivitis).**

and the release of molecules with degradative properties, including defensins, elastase, collagenase, cathepsins and lysozyme.[4] Long-term inflammation leads to cell proliferation (a possible precursor to cancer), tissue remodeling and scarring.[4]

While the neonatal and adult variations of the disease are considered acute, trachoma is a chronic process with distinct stages.[2,28] The Maccallan classification system, first described in 1908, stages the progress based on conjunctival findings: (I) Lymphoid hyperplasia; (IIa) Mature follicles on the superior tarsus; (IIb) Mature follicles with florid inflammation; (III) Early cicatrization; and (IV) Follicles replaced by papillae as scarring.[2,28] Today, The World Health Organization uses a simplified derivative of that system to include all phases of the disease: (I) Follicular conjunctivitis; (II) Diffuse inflammation; (III) Tarsal scarring; (IV) Trichiasis; and (V) Corneal opacification.[2,29]

The causative organism in gonococcal infection is *Neisseria gonorrhoeae*.[20-23] *N. gonorrhoeae* is a gram-negative, intracellular diplococcus that possesses the capability of invading an intact mucosal membrane.[20] Additionally, via its natural mechanisms or via chemokines released at the limbus secondary to resultant scleral inflammation, this organism can penetrate an intact corneal epithelium.[23] Transmission to the eye is generally by direct or indirect sexual contact or contact with an infected individual.[20-23]

## Management

Clinicians diagnose sexually transmitted conjunctivitis empirically by the history, indicative signs and symptoms, along with a suggestive history.[29-31] The Centers for Disease Control and Prevention (CDC) mandates that a doctor suspecting a sexually transmitted disease complete confirmation with appropriate laboratory studies and proper reporting.[31] While the standard method of clinical testing has been a combination of local, urethral, rectal and pharyngeal culturing, the use of nucleic acid amplification tests (NAAT) associated with serology testing has gained momentum for diagnosis.[9,31,32] *C. trachomatis* and *N. gonorrhoeae* infections can be diagnosed by cell culture, direct immunofluorescence, enzyme immunoassay, direct DNA hybridization and more recently by NAAT.[32,33] The development of NAAT has been a major advance in the diagnosis of chlamydia and gonorrhea.[32,33] The introduction of assays based on amplification of genetic material has subsequently increased the sensitivity of detecting both organisms and offers the opportunity to use noninvasive sampling techniques.[32,33]

A number of prophylactic antibiotic or antiseptic agents have been used to prevent newborn chlamydial and gonococcal conjunctivitis.[1-5,11,12-14,17-24] Prophylaxis with 1% silver nitrate ophthalmic drops, 0.5% erythromycin ophthalmic ointment or 1% tetracycline ointment has demonstrated comparable efficacy for the prevention of chlamydial infection.[3] Topical erythromycin or tetracycline have been used as prophylactic agents with the advantage of reducing secondary chemical conjunctivitis as compared to silver nitrate (the traditional Crede's prophylaxis).[3] Povidone-iodine ophthalmic solution 2.5% also showed success for preventing ophthalmia neonatorum at a reduced cost.[3]

In cases of sexually transmitted chlamydial conjunctivitis, options include oral

tetracycline 250mg to 500mg QID PO for three weeks or its alternatives (doxycycline, minocycline or azithromycin) along with a topical antibiotic (fourth generation fluoroquinolone), QID-Q2H, topical corticosteroids QID-Q2H and cycloplegia as necessary.[2,4,26] Since tetracycline requires administration one hour before or after meals to avoid gastrointestinal side effects, is less effective with interference by dairy products and can deform bones and teeth in the young (less than 10 years old), its alternatives may present a better option. Amoxicillin and erythromycin, 250mg to 500mg QID PO for three weeks or doxycycline 100mg BID PO for one week are acceptable alternatives.[1-5,12,13,15,16,20,21,26] Ceftriaxone, cefixime, spectinomycin and azithromycin are all acceptable alternatives that have shown effectiveness against resistant strains of gonorrhea and chlamydia.[26.32,33] The CDC recommends oral doxycycline (100mg BID x 7 days) or oral azithromycin (1g in a single bolus dose) as first-choice antibiotic options for the treatment of chlamydial infection.

Topical azithromycin has been evaluated in clinical studies for use in the treatment of trachomatous conjunctivitis.[34] Azithromycin 1.5% ophthalmic solution has been shown to have excellent in vitro activity against *C. trachomatis*.[34] In children, three-day treatment with azithromycin 1.5% solution was noninferior to a single dose of azithromycin oral suspension. The azithromycin ophthalmic solution was well tolerated in all patients.[34] It should be noted that topical azithromycin 1.5% ophthalmic solution is not commercially available in the United States at the present time. AzaSite (1% azithromycin ophthalmic solution, Akorn) is indicated only for the treatment of bacterial conjunctivitis caused by susceptible isolates.

Medical management of gonococcal conjunctivitis begins with an intramuscular 1g loading dose of ceftriaxone.[15] Ideally, therapy should continue with hospital admission and intravenous administration of ceftriaxone 1g Q 12 to 24 hours.[35-37] Continuing treatment is completed via oral antibiotics that are added following discharge.[35,36]

Mechanical removal of all discharge and debris is a critical element to both the success of infection resolution and improving patient functioning. The eyelids should be everted to rule out the presence of large follicles and pseudomembranes. Follicles will self-resolve as the treatment takes effect. In the event that a shield ulcer develops, topical anti-inflammatory therapy should be added. If present, pseudomembranes can be removed via topical anesthesia and a cotton-tipped applicator. Over-the-counter oral analgesics can be used to increase patient comfort along with palliative measures such as cold compresses and ocular lubricants.

The high rates of reinfection with sexually transmitted diseases suggest a need for retesting patients with confirmed cases at an interval of three to six months after symptom resolution.[38] It is also important to treat sexual partners to avoid reinfection.

## Clinical Pearls

- Inclusion conjunctivitis should be one of the differential diagnoses any time a patient presents with a chief complaint of chronically red eyes or when any conjunctivitis is recalcitrant to topical antibiotic therapies.
- Patients with hyperacute conjunctivitis should be examined frequently until consistent improvement is noted; they should also be educated that they are contagious until they are symptom free for three days.
- Patients should be educated that partners need to be informed and systemic genitourinary examination is in order.
- If a sexually transmitted disease is confirmed, the CDC should be contacted for instructions and recommendations. Lab testing should be considered to rule out the presence of other sexually transmitted diseases such as syphilis and human immunodeficiency virus.
- Unfortunately, genital and pharyngeal gonococcal infections in young children are almost always acquired via a sexual encounter with an infected adult and may be a sign of sexual abuse. In cases where these signs or symptoms accompany an ocular condition, authorities or the patient's pediatrician should be notified.
- While hyperacute conjunctivitis has been widely thought to be gonococcal in origin, remember that other virulent organisms can cause an equally severe conjunctivitis and not all hyperacute presentations are necessarily an STD.


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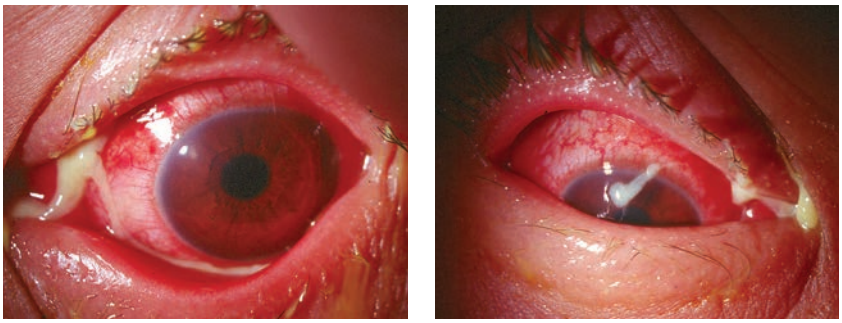
# ACUTE BACTERIAL CONJUNCTIVITIS

## Signs and Symptoms

Patients with acute bacterial conjunctivitis present with injection of the bulbar conjunctival and episcleral vessels. In some cases, the palpebral conjunctiva is also affected. Infection typically begins in one eye and subsequently spreads to the other eye within 24 to 48 hours.[1] There may be mild photophobia and discomfort, but pain is not typical unless there is concurrent corneal epitheliopathy. There will be mucopurulent discharge, and the patient usually reports that the eyelids and eyelashes are matted shut upon waking.[1,2] In fact, a history of the eyelids being "glued shut" in the morning is highly predictive of bacterial infection.[2] There frequently is spillover of the discharge onto the patient's adnexa due to rapid bacterial reproduction with a concomitant, mucopurulent response from the host. While patients of any age can be afflicted with acute bacterial conjunctivitis, it is especially common in children.[3-8] Wearing soft contact lenses presents an additional risk factor.[9]

Visual function typically is normal. However, in that the discharge is often corneotoxic, a coarse punctate epitheliopathy may be present. When this occurs, the condition is better termed acute bacterial *kerato*conjunctivitis. Significant epitheliopathy may cause vision reduction and discomfort in some cases. Due to drainage of the infection through the nasolacrimal system, there typically is no preauricular node involvement, though some aggressive bacterial strains such as *gonococcus* can cause lymphadenopathy. A conjunctival papillary or pseudomembranous (composed of coagulated fibrins, bacteria, and leukocytes) response may also be present.[2]



Abundant mucupurulent discharge is suggestive of bacterial conjunctivitis.

## Pathophysiology

The eye has a series of defense mechanisms to prevent non-native bacterial invasion. These include bacteriostatic factors within the tears, nutrient-poor tears that don't support bacterial growth, the shearing force of the blink, an intact immune system and a population of normal colonizing non-pathogenic bacteria that competitively prevent invasion by abnormal organisms. When these defenses break down or are overwhelmed by a pathogen that is not sensitive to their mechanisms of action, an infection can occur.

Invading bacteria, along with secreted exotoxins, are foreign antigens that induce an antigen-antibody immune reaction and subsequent inflammation. In a normal, healthy eye, invading pathogenic bacteria will eventually be eradicated as the eye strives to return to homeostasis.[5,10-13] However, the external load of organisms can potentiate corneal infection or involvement of other adnexal structures.

The most commonly encountered organisms are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[3,4,6,8,9] Several studies have identified *H. influenzae* and *S. pneumoniae* as the most prevalent infective bacteria, ranging from 29% to 45% and 20% to 31% of isolates, repectively.[4,6] *S. viridans*, *Moraxella catarrhalis*, *Enterobacteriaceae* and *Neisseria meningitides* are also encountered.[6,14]

Occasionally, there will be more than one organism in an acute bacterial conjunctivitis.[6] Also, otitis media may present concurrent with acute bacterial conjunctivitis, especially in children. This syndrome is highly indicative of *H. influenzae* infection.[4,15] In these cases, the infection often originates in the nasopharynx.[15]

## Management

In the majority of cases, acute bacterial conjunctivitis is a self-limiting disease requiring no treatment. However, most reports indicate that, despite the benign, self-resolving nature, bacterial conjunctivitis should be treated with topical antimicrobial therapy in order to shorten the disease course and improve the rate of clinical and microbiologic remission.[5,10,11,13,16,17] This is especially true early in the clinical course, if sexually transmitted diseases are the suspected etiology, and in contact lens wearing patients.[18] However, if the patient presents having had the infection for several days, and is already improving, topical antimicrobial treatment likely will provide only marginal, if any, benefit.[11]

As in any bacterial infection, a microbiologic study with culturing and sensitivity testing is the optimum means to reach a conclusive diagnosis and treatment plan. However, due to the expense of microbiologic studies and the relatively benign, self-limiting nature of the condition, most clinicians advocate the use of broad-spectrum, empirical topical antibacterial therapy, reserving culturing for hyperacute conditions, concurrent severe nasolacrimal infections, or those that fail to respond to initial therapy.

There are many options for empirical therapy. Excellent initial broad-spectrum topical antibiotics include ciprofloxacin, ofloxacin, levofloxacin, polymyxin B sulfate–trimethoprim, gentamicin and tobramycin.[6-8,10,13-19] These will provide good coverage against gram-positive and gram-negative organisms, though the aminoglycosides (gentamicin and tobramycin), through increased resistance, may have weak activity against some *Staphylococcal* species and some strains of *Pseudomonas*. Additonally, the generic versions may cause ocular toxicity. A formulation of tobramycin ophthalmic solution with enhanced viscosity showed excellent cure rates, even against tobramycin-resistant pathogens.[19] Polyantimicrobial therapy may be necessary to cover all possible organisms in the worst presentations.

Newer-generation topical fluoroquinolones—moxifloxacin (Moxeza, Alcon) and gatifloxacin (Zymaxid, Allergan)—have gram-negative coverage similar to the existing fluoroquinolones but with enhanced coverage of gram-positive species, with lower incidence of bacterial resistance.[20] Research shows they are well tolerated ocularly, with little induced damage to the cornea.[21-25] Gatifloxacin administered twice daily for five days is proven effective in treating patients aged one year and older.[26] There is some evidence that indicates that moxifloxacin may have a lesser corneotoxic effect due to the lack of the preservative benzalkonium chloride.[21]

These agents are also more effective than previous fluoroquinolones in resistant bacterial infections.[20,27] Moxifloxacin has been shown to be effective at eradicating superficial bacterial infections with excellent tolerability.[28] Both moxifloxacin and gatifloxacin have been shown to be clinically equivalent to a fortified cefazolin-tobramycin combination in managing bacterial keratitis.[29] For these reasons, newer-generation fluoroquinolones are extremely popular in managing ocular bacterial infection and surgical prophylaxis.[17]

Newer medications have been shown to be effective in managing patients with acute bacterial conjunctivitis. Besifloxacin ophthalmic suspension 0.6% (Besivance, Bausch + Lomb) has been demonstrated to be effective against susceptible bacteria with an efficacy and tolerability similar to that seen in topical moxifloxacin.[30-33] Recently, it has been shown that dosing with besifloxacin as low as twice daily for three days was effective in eradicating bacterial conjunctivitis in adults and children.[34,35] Additionally, topical azithromycin 1% (AzaSite, Akorn) has been seen as effective in managing patients with bacterial conjunctivitis.[36] Polymyxin B sulfate/trimethoprim solution has been seen as a cost-effective alternative to moxifloxacin with comparable efficacy in children.[37]

Resistance has become an issue with many antibiotics, even including the newer-generation fluoroquinolones.[3,4,7,20,27] Resistance has been noted with all major classes of topical antibiotics including aminoglycosides, polymyxin B combination therapies, macrolides and fluoroquinolones.[38] Even so, it appears that the later generation fluoroquinolones still retain excellent efficacy against even methicillin-resistant *S. aureus* (MRSA).[39] There appears to be an increased risk of MRSA infections in patients with giant fornix syndrome (a condition similar to floppy eyelid syndrome) where a capacious upper conjunctival fornix leads to a purulent conjunctivitis and toxic keratopathy. MRSA infection should be considered in patients with this clinical profile.[40,41]

Although antibiotics will eradicate the antigenic bacteria, they will do little to suppress the concurrent inflammation. If there is no significant corneal disruption, then corticosteroids such as prednisolone acetate 1%, difluprednate 0.05% emulsion (Durezol, Alcon) or loteprednol etabonate 0.5% (Lotemax, Bausch + Lomb) concomitantly with the antibiotics can be used to speed resolution of the inflammation. Steroid-antibiotic combinations such as neomycin-polymixin B sulfate-dexamethasone, (Maxitrol, Alcon), tobramycin-loteprednol (Zylet, Bausch + Lomb), and both tobramycin-dexamethasone and

tobramycin-dexamethasone suspension (Tobradex ST, Alcon) are also possible choices for therapy when the cornea is intact.[42] In cases where inflammation is problematic, topical steroids can be used, even in the face of a compromised cornea, so long as the topical antibiotic has been adequately loaded and it is clear that the therapy is working. Here, the addition of topical steroids can safely be initiated while the anti-infective coverage is maintained.

## Clinical Pearls

- While patients with bacterial conjunctivitis will report that their lids are matted shut in the morning with mucopurulent material, patients suffering from viral and allergic conjunctivitis will sometimes report similar experiences.
- Patients with viral and allergic conjunctivitis have crusting of the lashes due to drying tears and serous secretions; those with bacterial conjunctivitis will manifest wet, sticky, mucopurulent matting of the lashes. Too often, clinicians consider the dry crusting of the lashes to be the same as the mucopurulent matting and misdiagnose the condition.
- Due to the excellent defense systems of the external eye, acute bacterial conjunctivitis is an uncommon condition. Viral and allergic conjunctivitis is more common.
- Tapering antibiotics can lead to resistance. Never prescribe below the recommended dosing. Once a condition resolves, discontinue antibiotic therapy abruptly.
- Because mucopurulent discharge is corneotoxic, with significant discharge there is often concurrent epitheliopathy. Removal of the discharge with warm saline lavage will benefit patients; they should be instructed to do so frequently.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# Besivance®

**besifloxacin ophthalmic suspension, 0.6%**

## *POWERFULLY*

### *BREAKS THE CHAIN IN PATHOGENS OF GREATER CONCERN*[1-4]

## Indication

BESIVANCE® is a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: *Aerococcus viridans*,* CDC coryneform group G, *Corynebacterium pseudodiphtheriticum*,* *Corynebacterium striatum*,* *Haemophilus influenzae*, *Moraxella catarrhalis*,* *Moraxella lacunata*,* *Pseudomonas aeruginosa*,* *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis*,* *Staphylococcus lugdunensis*,* *Staphylococcus warneri*,* *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae*, *Streptococcus salivarius**

*Efficacy for this organism was studied in fewer than 10 infections.

## Important Risk Information about BESIVANCE®

- BESIVANCE® is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.
- As with other anti-infectives, prolonged use of BESIVANCE® may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE®.
- The most common adverse event reported in 2% of patients treated with BESIVANCE® was conjunctival redness. Other adverse events reported in patients receiving BESIVANCE® occurring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.
- BESIVANCE® is not intended to be administered systemically. Quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.
- Safety and effectiveness in infants below one year of age have not been established.

**Please see the Brief Summary of the BESIVANCE® full prescribing information on the adjacent page.**

**References: 1.** BESIVANCE® Prescribing Information, September 2012. **2.** Tepedino ME, Heller WH, Usner DW, et al. Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. *Curr Med Res Opin*. 2009;25(5):1159-1169. **3.** DeCory HH, Comstock TL, Gearinger LS, Morris TW. Clinical efficacy of besifloxacin ophthalmic suspension, 0.6% against MRSA and MRSE. Poster presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology; May 6-10, 2012; Fort Lauderdale, FL. **4.** Data on file, Bausch & Lomb Incorporated.

For product-related questions and concerns, call **1-800-323-0000** or visit **www.bausch.com**.

BAUSCH + LOMB



Besivance®
besifloxacin ophthalmic suspension, 0.6%

BAUSCH + LOMB

# Besivance®

**besifloxacin ophthalmic suspension, 0.6%**

***Brief Summary:*** Based on full prescribing information revised September 2012.

**To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

## INDICATIONS AND USAGE

Besivance® (besifloxacin ophthalmic suspension) 0.6%, is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:

- *Aerococcus viridans**
- CDC coryneform group G
- *Corynebacterium pseudodiphtheriticum**
- *Corynebacterium striatum**
- *Haemophilus influenzae*
- *Moraxella catarrhalis**
- *Moraxella lacunata**
- *Pseudomonas aeruginosa**
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Staphylococcus hominis**
- *Staphylococcus lugdunensis**
- *Staphylococcus warneri**
- *Streptococcus mitis* group
- *Streptococcus oralis*
- *Streptococcus pneumoniae*
- *Streptococcus salivarius**

*Efficacy for this organism was studied in fewer than 10 infections.

## DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once before use.
Instill one drop in the affected eye(s) 3 times a day, four to twelve hours apart for 7 days.

## CONTRAINDICATIONS

None

## WARNINGS AND PRECAUTIONS

### Topical Ophthalmic Use Only

NOT FOR INJECTION INTO THE EYE.
Besivance® is for topical ophthalmic use only, and should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

### Growth of Resistant Organisms with Prolonged Use

As with other anti-infectives, prolonged use of Besivance® (besifloxacin ophthalmic suspension) 0.6% may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

### Avoidance of Contact Lenses

Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance®.

## ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with the rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.
The data described below reflect exposure to Besivance® in approximately 1,000 patients between 1 and 98 years old with clinical signs and symptoms of bacterial conjunctivitis.
The most frequently reported ocular adverse event was conjunctival redness, reported in approximately 2% of patients.
Other adverse events reported in patients receiving Besivance® occurring in approximately 1-2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

**Pregnancy Category C.** Oral doses of besifloxacin up to 1000 mg/kg/day were not associated with visceral or skeletal malformations in rat pups in a study of embryo-fetal development, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased fetal body weights, and decreased fetal ossification were also observed. At this dose, the mean $C_{max}$ in the rat dams was approximately 20 mcg/mL, >45,000 times the mean plasma concentrations measured in humans. The No Observed Adverse Effect Level (NOAEL) for this embryo-fetal development study was 100 mg/kg/day ($C_{max}$, 5 mcg/mL, >11,000 times the mean plasma concentrations measured in humans).
In a prenatal and postnatal development study in rats, the NOAELs for both fetal and maternal toxicity were also 100 mg/kg/day. At 1000 mg/kg/day, the pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation were delayed, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behavior, including activity, learning and memory, and their reproductive capacity appeared normal.
Since there are no adequate and well-controlled studies in pregnant women, Besivance® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Nursing Mothers

Besifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when Besivance® is administered to a nursing mother.

### Pediatric Use

The safety and effectiveness of Besivance® in infants below one year of age have not been established. The efficacy of Besivance® in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials *[see Clinical Studies (14) in the full Prescribing information].*
There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

### Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed.
No *in vitro* mutagenic activity of besifloxacin was observed in an Ames test (up to 3.33 mcg/plate) on bacterial tester strains *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA. However, it was mutagenic in *S. typhimurium* strain TA102 and *E. coli* strain WP2(pKM101). Positive responses in these strains have been observed with other quinolones and are likely related to topoisomerase inhibition.
Besifloxacin induced chromosomal aberrations in CHO cells *in vitro* and it was positive in an *in vivo* mouse micronucleus assay at oral doses $\geq$ 1500 mg/kg.
Besifloxacin did not induce unscheduled DNA synthesis in hepatocytes cultured from rats given the test compound up to 2,000 mg/kg by the oral route. In a fertility and early embryonic development study in rats, besifloxacin did not impair the fertility of male or female rats at oral doses of up to 500 mg/kg/day. This is over 10,000 times higher than the recommended total daily human ophthalmic dose.

## PATIENT COUNSELING INFORMATION

Patients should be advised to avoid contaminating the applicator tip with material from the eye, fingers or other source.
Although Besivance® is not intended to be administered systemically, quinolones administered systemically have been associated with hypersensitivity reactions, even following a single dose. Patients should be advised to discontinue use immediately and contact their physician at the first sign of a rash or allergic reaction.
Patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Besivance® or other antibacterial drugs in the future.
Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with Besivance®.
Patients should be advised to thoroughly wash hands prior to using Besivance®.
Patients should be instructed to invert closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, and with bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).

Manufactured by: Bausch & Lomb Incorporated
Tampa, Florida 33637


U.S. Patent No. 6,685,958
U.S. Patent No. 6,699,492
U.S. Patent No. 5,447,926



September 2012

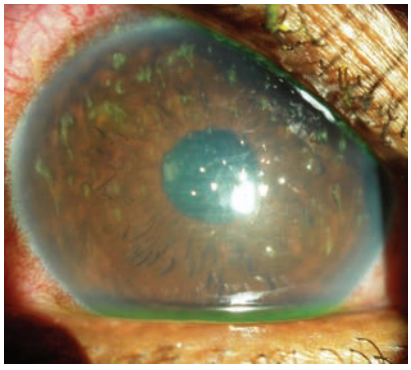
9159601

## FILAMENTARY KERATITIS

### Signs and Symptoms

Patients with filamentary keratitis typically present with variable reports of ocular discomfort, ranging from grittiness and mild foreign body sensation to pronounced pain. Tearing, photophobia and blepharospasm may accompany these symptoms in more severe cases.[1] The condition may be unilateral or bilateral, depending upon the underlying etiology. Associated signs include ocular hyperemia, particularly in the limbal area, as well as a pseudoptosis. The hallmark finding is the presence of corneo-mucus filaments. These often consist of a focal "head," which may be firmly adherent to compromised areas of the corneal epithelium, and a strand-like "tail" of varying length that extends inferiorly across the ocular surface. Filaments can be seen more readily on biomicroscopy with the application of vitals dyes such as lissamine green, rose bengal and sodium fluorescein.[1] Other ocular findings that may accompany filamentary keratitis include a reduced tear break-up time (TBUT) and punctate epithelial keratopathy.

While the exact prevalence of filamentary keratitis is unknown, evidence suggests that this condition is more common in elderly patients, women, those with connective tissue disorders and those with immune deficiency.[1,2]



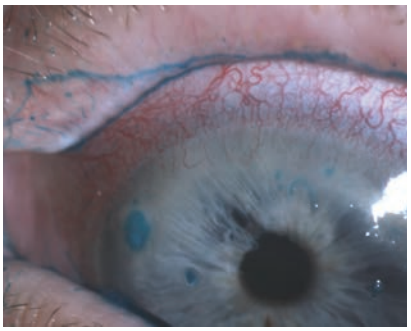
Filamentary keratitis in a patient that had previously been treated for herpetic keratitis.

Coincidentally, these same populations tend to demonstrate a greater incidence of keratoconjunctivitis sicca and other ocular surface disorders. The condition also may develop in those taking systemic medications that have the capacity to diminish aqueous tear production, such as antihistamines, diuretics, mood stabilizing agents and certain antineoplastic agents.[1,4]

### Pathophysiology

Filamentary keratitis is seen most commonly in association with advanced dry eye disease, though a variety of other ocular surface disorders can induce this condition.[2] Among the various etiologies are superior limbic keratoconjunctivitis (SLK) of Theodore, herpetic keratitis, recurrent corneal erosion, vernal keratoconjunctivitis, neurotrophic keratitis, epitheliopathy due to aerosol exposure, radiation keratitis, bullous keratopathy, a recent history of cataract or other ocular surgery, prolonged eye patching, blepharospasm and even large-angle strabismus.[1-3,5,6]

Research suggests that individual filaments consist of desquamated corneal epithelial cells at their core, surrounded primarily by degenerating conjunctival epithelial cells entwined in a thick layer of membrane-associated mucins, including MUC5AC and MUC16.[4,7] Subjects with filamentary keratitis appear to suffer progressive dysfunction within the basal epithelial and Bowman's layers of the cornea, leading to focal detachments at the level of the basement membrane. Under constant shear pressure from the eyelids, these corneal foci become inflamed, and sloughing of epithelial cells may ensue. At the same time, frictional stress from blinking and eye movement, combined with diminished tear volume and ocular surface inflammation, results in abnormal tear mucin production and degeneration of conjunctival epithelial cells.[6] These combined elements form filaments that



Filamentary keratitis in a patient with Sjögren's syndrome. The mucus filaments are stained with lissamine green dye.

may be seen clinically as long strands, large clumps or irregular dendriform deposits, depending upon whether they are stretched, twisted or tightly coiled.[7,8] The filaments are motile in the tear film but have an affinity for compromised areas of the corneal surface, where they form strong adhesions. Lid movement across these bound filaments induces vertical traction and further shearing of the corneal epithelium with each blink, resulting in microtrauma and stimulation of the pain-sensitive corneal nerves. Thus, a vicious cycle of epithelial damage, inflammation and filament formation ensues.

### Management

The management of filamentary keratitis is aimed at alleviating the stressors that cause ocular surface inflammation and epithelial degradation. Elimination of the filaments is the initial step. Identifying and treating the underlying pathology is also vital to break the disease cycle. Removal of large filaments can be performed mechanically using fine-tipped forceps at the slit lamp under topical anesthesia; however, it is important to realize that this process can further contribute to epithelial damage and should be undertaken only by skilled and experienced clinicians. Bandage soft contact lenses can be used in cases where the clinician wishes to avoid manually debriding the tissue tags.

Ocular lubricants are helpful in addressing discomfort and also stabilizing the tear film in mild to moderate cases. While some have advocated hypertonic saline, other practitioners (including these authors) prefer lipid-based artificial tears as first-line therapy.[9,10] In more recalcitrant cases, topical N-acetylcysteine can help to dissolve cornea-bound mucus plaques.[2] This mucolytic agent is typically employed as an oral inhalant for patients with bronchial disease (e.g., emphysema, cystic fibrosis), in accordance with its FDA approval. Acetylcysteine solution must be prepared by a compounding pharmacist when prescribed for off-label topical ophthalmic use. In those with filamentary keratitis secondary to chronic dry eye disease, 5% to 10% acetylcysteine eye drops used at least four times daily may be very effective in reducing or eliminating the mucus strands and plaques. Other treatments for refractory cases of filamentary keratitis may include the use of bandage soft contact lenses, amniotic membrane therapy or Botox (onabotulinumtoxin A, Allergan) injection to the pretarsal orbicularis muscle.[1,3,11]

Addressing the underlying ocular surface disease may ultimately prove more challenging than temporary elimination of corneal filaments. Because an inflammatory etiology is often assumed, the use of anti-inflammatory pharmaceuticals such as corticosteroids and non-steroidal agents has been widely advocated, often with clinical success.[5,9,12] In those cases where dry eye disease is determined to be the primary etiology of filamentary keratitis, short-term use of topical corticosteroids QID combined with long-term use of topical cyclosporin A BID has been shown to be helpful.[13] Punctal plugs may also be employed for those with true aqueous deficiency.[1] More severe cases may require treatment with autologous serum eye drops, which, as the name implies, are derived from the patient's own blood serum.[14,15]

## Clinical Pearls

- Despite the fact that the condition has a unique ICD-9 code (370.23), filamentary keratitis is not a disease entity in and of itself. Rather, it should be considered a sign of severe ocular surface disease, the etiology of which must ultimately be determined and addressed for successful long-term management of the patient.
- Topical 10% acetylcysteine QID is often a helpful adjunct in managing filamentary keratitis. Patients should be advised that this solution may have an unusual color, a peculiar odor and a tendency to sting unless it is kept refrigerated. Also, because it is formulated without preservatives, topical ophthalmic acetylcysteine must be discarded after approximately 60 days. The recommendation to employ acetylcysteine drops is based upon clinical experience of several noted experts and the underlying pathophysiology of filament formation. There are currently no prospective, controlled clinical studies to substantiate this practice, however.
- While not commercially available in the United States, a 5% acetylcysteine solution is currently being manufactured by the French company Laboratories Pharmaster, and marketed by Moorfields Pharmaceuticals in the United Kingdom, under the trade name Ilube. In addition to acetylcysteine, this product contains purified water, hypromellose, sodium hydroxide, disodium edetate and benzalkonium chloride as a preservative.[16]
- Therapy for filamentary keratitis may take weeks or even months before adequate resolution is realized; the time depends greatly upon the etiology, the severity of the presentation and the aggressiveness of care. Affected patients should understand that the underlying condition is often chronic and filaments may recur, requiring ongoing therapy.
- Patients found to have aqueous-deficient dry eye disease in association with filamentary keratitis may benefit from investigation for rheumatologic involvement, such as the Sjö test. Eye care providers can use this point-of-care diagnostic test to help to identify Sjögren's syndrome in patients who might otherwise go undiagnosed for months or years.[17]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# SALZMANN'S NODULAR DEGENERATION

## Signs and Symptoms

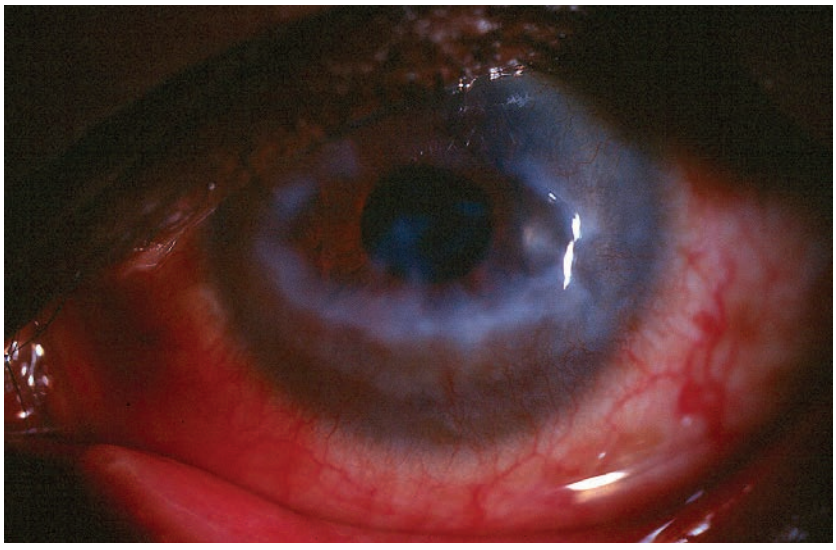
Patients with Salzmann's nodular degeneration are often asymptomatic, particularly in the early stages of the disease. Some may present with subjective glare, photophobia or diminished visual acuity if the nodules are situated on or near the visual axis.[1,2] Nonspecific dry eye complaints such as burning, grittiness and foreign body sensation may also be reported.[2,3] Eyes with more advanced disease are prone to intermittent bouts of recurrent corneal erosion. During these episodes, patients may experience pronounced discomfort, photophobia, blepharospasm and excessive tearing.[1]

Clinically, Salzmann's degeneration appears as an accumulation of round to oval, bluish-white (and sometimes creamy, yellowish-white) subepithelial corneal nodules, often arranged in an annular fashion.[1,2] Most commonly, the nodules are situated in the mid-peripheral cornea, but central and peripheral lesions have also been noted.[2] Vascularization of Salzmann's nodules is likewise variable. The condition is non-inflammatory in nature; hence, the involved eye is typically white and quiet, unless there is associated corneal erosion. In that event, there will be limbal injection, corneal edema and an anterior chamber reaction. Most patients with Salzmann's degeneration appear to have bilateral involvement, with two large retrospective series reporting bilateral disease in approximately 66% and 63% of cases, respectively.[2,3] The condition affects various ages and races, but usually presents in the sixth decade of life, and appears to be encountered more frequently in women than in men.[1-3]

## Pathophysiology

Although the precise etiology of Salzmann's degeneration has not been clearly determined, the prevailing theory is that chronic irritation to the ocular surface or a history of corneal trauma is involved in the pathogenesis.[2] Most patients can relate a history of prior trauma, surgery or other ocular inflammation, which may predate the corneal manifestations by a number of years.[1,3] Associated disorders include phlyctenular disease, meibomian gland dysfunction (including ocular rosacea), vernal keratoconjunctivitis, trachoma or interstitial keratitis.[1-7] Additionally, patients with a history of epithelial basement membrane dystrophy, rigid contact lens wear, keratoconus, filamentary keratitis, chemical (or thermal) trauma, LASIK and incisional corneal surgery are all regarded as having increased risk.[1-7] The inflammation associated with these disorders appears to provoke histopathologic and functional changes at the level of the superficial stroma, particularly Bowman's layer. This initiates a cascade of changes that produces the disease's signs and symptoms.[1,3,8-10]

At the cellular level, the nodules seen in Salzmann's degeneration consist of collagen fibers and extracellular material at the anterior stroma.[2] They display reduced cell density and a hyaline-like appearance.[11] Oxytalan fibers, which are present in other degenerative corneal disorders such as keratoconus and Fuchs' endothelial dystrophy, have also been identified in Salzmann's nodular degeneration.[9] As the condition progresses, there is subsequent degradation of Bowman's layer in the areas that overlie the nodules. The normal architecture is replaced by an accumulation of a basement membrane-like substance. The corneal epithelium associated with these areas thins accordingly. In some specimens, only a single layer of flattened squamous cells remains.[2] Descemet's membrane and the corneal endothelium characteristically remain intact. With proliferation of the nodules, there is widespread disorganization of the cornea's epithelial basement membrane. This predisposes these patients to painful epithelial erosions.[3]



Focal, whitish lesions are characteristic of Salzmann's nodular degeneration.

## Management

It has been suggested that asymptomatic patients with Salzmann's degeneration require no therapy.[1,12] However, since chronic low-grade irritation of the ocular surface has been proposed as a driving force in the disease's development and progression, it seems reasonable and appropriate to employ topical lubricants

as first-line therapy.[2] In two large series examining patients with Salzmann's nodular degeneration, a favorable response to conservative medical therapy (i.e., artificial tears, lid hygiene and oral doxycycline for associated meibomian gland dysfunction) was noted in 72% and 68% of cases, respectively.[2,3] These individuals did not require further surgical intervention.

Patients with associated corneal erosions require specific treatment aimed at diminishing pain and promoting re-epithelialization. This is best accomplished with cycloplegia (e.g., 5% homatropine BID) and topical nonsteroidal anti-inflammatory agents (e.g., 0.45% ketorolac tromethamine BID), as well as prophylactic, broad-spectrum antibiotics and copious lubrication. Additionally, some sources recommend therapeutic bandage contact lenses in cases of recurrent corneal erosion.[13-15] Human amniotic membrane may also be beneficial in the rehabilitation of such cases.[16]

Corneal surgery may be warranted for more severe, recalcitrant or symptomatic disease. The most common indication for surgical intervention is visual disturbance, followed by subjective discomfort associated with recurrent corneal erosions.[2,3] Superficial keratectomy is beneficial in cases of subepithelial lesions on or near the visual axis, or for midperipheral lesions inducing irregular astigmatism.[1] Phototherapeutic keratectomy (PTK) performed with an excimer laser is another option. PTK has been shown to enhance visual function by improving contrast sensitivity while decreasing higher-order aberrations.[13] Because these procedures have the potential for scar formation, incomplete resolutions or both, most surgeons today employ an antimetabolite agent, which has been shown to greatly improve outcomes.[17-19]

Alternatively, individuals who are unwilling or unable to endure surgery may derive some benefit from the use of custom fitted corneal, hybrid or scleral contact lenses. A recent study evaluated the use of the PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem, BostonSight) system on a small group of patients with Salzmann's nodular degeneration who were unsuccessful with conventional therapy and who also elected not to undergo traditional surgical offerings. The results were encouraging, demonstrating a statistically significant improvement in visual acuity and ocular surface symptomology.[20]

In advanced cases of Salzmann's degeneration where central or deep stromal scarring is present, or if chronic epithelial breakdown makes the condition otherwise unmanageable, lamellar or penetrating keratoplasty may be the only recourse for restoration of vision.[1] Still, recurrence is possible; though exceedingly rare, several publications have described the regeneration of Salzmann's nodules in donor corneas several years after penetrating keratoplasty.[12,21,22]

## Clinical Pearls

- The critical issue in managing Salzmann's degeneration is proper diagnosis. Conditions such as band keratopathy, spheroid degeneration (i.e., climatic droplet keratopathy) and corneal keloids may all present with a similar clinical appearance. Consultation with a corneal specialist is advisable in those cases where the diagnosis is equivocal.
- Refractive changes may precede or complicate visual compromise associated with Salzmann's nodular degeneration. The peripheral location of the nodules can induce flattening of the central cornea, resulting in a hyperopic shift.[16,19] Irregular corneal astigmatism has also been noted on topographic analysis.[16,20]
- It may be tempting to use topical corticosteroids in Salzmann's degeneration, particularly if the patient is symptomatic. However, since this condition is noninflammatory in nature, steroids are merely palliative and do not alter the progression of the disease; additionally, their use introduces unnecessary risks such as elevation of intraocular pressure, cataracts and secondary infection.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## BACTERIAL KERATITIS

### Signs and Symptoms

A patient with bacterial keratitis will present with a typically unilateral, painful, photophobic, injected eye. Visual acuity may be reduced, and profuse tearing is common. There will be a focal stromal infiltrate with an overlying area of epithelial excavation. Often, there will be a history of contact lens wear, corneal trauma, or other corneal defects as common precipitating conditions.[1-3]

Mucopurulent discharge may emanate from the eye. The cornea is often edematous. The conjunctival and episcleral vessels will be deeply engorged and inflamed, often greatly out of proportion to the size of the corneal defect. In bacterial keratitis, bulbar conjunctival injection is typically 360 degrees rather than sectoral as seen in noninfectious corneal infiltrates. A pronounced anterior chamber reaction, occasionally with hypopyon, is present in severe cases. IOP may be either reduced due to secretory hypotony of the ciliary body, or elevated due to blockage of the trabecular meshwork by the inflammatory cells. Often, the eyelids may also be edematous.[1,4]

### Pathophysiology

Once defenses are breached, the cornea is prone to colonization by pathogenic bacteria, either a virulent invading organism or part of the normal ocular flora. Factors known to compromise defenses include direct corneal trauma, chronic lid disease (including poor lid congruity and misdirected lashes), systemic immune disease, tear film abnormalities affecting the ocular surface and hypoxic trauma from contact lens wear.[1-4]

Presentations of acute bacterial keratitis. *Top Left:* Note the large, ulcerated lesion just temporal to the visual axis. *Top right:* Bacterial keratitis in a 15-year-old contact lens wearer. *Bottom right:* Smaller, more peripheral lesions are usually associated with Staphylococcal bacterial keratitis.

Bacteria colonizing the corneal stroma immediately become antigenic, both directly and indirectly, by releasing enzymes and toxins. An antigen-antibody immune reaction with chemotactic factors induces an inflammatory reaction where polymorphonuclear leukocytes (PMNs) mobilize and aggregate at the area of infection, creating an infiltrate. The PMNs phagocytize and digest the bacteria, but also damage stromal tissue by releasing numerous collagenolytic enzymes that directly degrade stromal tissue.[1,4] The collagen of the corneal stroma is poorly tolerant of the bacterial and leukocytic enzymes and undergoes degradation, necrosis and thinning, leading to scarring of the cornea. As thinning advances, the cornea may perforate, thus introducing bacteria into the eye with ensuing endophthalmitis.

The most commonly occurring organisms in bacterial keratitis vary depending on the precipitating factors of the ulcer and the geographic location of the patient. In cases involving contact lens wear, the most common infective organism is *Pseudomonas aeruginosa*.[1,5] Throughout North America, the most common infective organism in bacterial keratitis is *Staphylococcus aureus*. It appears that there is an increased incidence of gram-positive colonizaton in infectious keratitis.[1,5]

### Management

Proper diagnosis and prompt therapy are essential to preserve vision in bacterial keratitis. Microbial identification, as well as antibiotic sensitivity studies, will aid in management. The first step should be to obtain samples from the corneal lesion for microbiologic studies. Traditional culturing involves scraping the cornea with a platinum spatula and plating directly onto blood or chocolate agar medium. An alternative for culturing of less threatening keratitis involves a mini-tip calcium alginate culturette and transport-media-containing carrier. However, the effectiveness of the fluoroquinolone antibiotics has led many practitioners away from routine microbiologic culturing. Microbiologic identification is most crucial for central lesions that threaten vision, for ulcerations presenting a risk of perforation, in cases also involving scleral tissue, injury with vegetative matter, and in institutionalized patients in nursing homes and hospitals where methicillin-resistant *S. aureus* infections are possible.[6]

Empirical broad-spectrum antibiotic therapy must be initiated prior to obtaining culture results. Monotherapy with fluoroquinolone eye drops has been shown to result in shorter duration of

intensive therapy and shorter hospital stay when compared to combined fortified therapy (tobramycin-cefazolin). This finding may have resulted from quicker clinical response of healing as a result of less toxicity found in the patients treated with fluoroquinolones. In large, deep ulcers seen in the elderly, some poor outcomes due to resistance were encountered. Here, caution should be exercised regarding empirical use of single-agent topical fluoroquinolones.[7,8]

Despite the clear efficacy of fluoroquinolones in the management of bacterial keratitis, consideration must be given to increasing resistance.[4,9-11] There has been a rise in the incidence of bacterial isolates in keratitis that exhibit resistance to the early generation fluoroquinolones, especially among the gram-positive organisms.[4,5,12-15] Even cephazolin has seen increasing bacterial resistance.[14]

One method of combating the increasing problem of fluoroquinolone resistance and rising level of gram-positive infections is use of the later generation fluoroquinolones. Two fourth-generation formulations—moxifloxacin (Vigamox, Moxeza, Alcon) and gatifloxacin (Zymar, Zymaxid, Allergan)—have a greatly lowered resistance rate while providing much greater gram-positive activity than previous generation fluoroquinolones.[15-21] Gatifloxacin has a significantly better action against gram-positive cocci both in vitro and in vivo when compared with ciprofloxacin.[22] Gatifloxacin 0.3% ophthalmic solution, due to its strong activity against various gram-positive and gram-negative microbes, is strongly effective in the treatment of acute bacterial keratitis.[23] Monotherapy with later generation fluoroquinolones such as moxifloxacin have seen equivalent efficacy to fortified therapy with aminoglycosides and cephalosporins with much better tolerability.[24,25]

Levofloxacin 1.5% (Iquix, Santen) offers the highest concentration available for any ocular antibiotic for the treatment of bacterial keratitis.[26] Manufacture of this product in the United States has recently been discontinued. Additionally, Besivance (besifloxacin, Bausch + Lomb) is an effective and well tolerated option for the management of bacterial keratitis. Besivance has no oral formulation, so development of resistance is theoretically lower.[27]

Strong cycloplegia is also recommended adjunctively in the form of homatropine 5%. If this is insufficient, then atropine 1% is indicated. Adjunctive use of cold compresses will also help to reduce inflammation.

The patient should be followed daily until the infection shows improved status. If the results of cultures and sensitivities show that the initially-prescribed antibiotic is appropriate for the infective organism, or if the patient shows signs of clinical improvement (the ulcer does not worsen and pain and photophobia are reduced) at the 24 to 48 hour follow-up visit, a topical corticosteroid such as prednisolone acetate 1%, difluprednate 0.05% or loteprednol etabonate 0.5% can be added to speed resolution and decrease corneal scarring. While steroids have historically been avoided in the management of infectious keratitis, judicious use can be beneficial. Antibiotics will suppress the infective organism while corticosteroids can inhibit the corneotoxic inflammatory response. It has been feared that the immunosuppressive effects of steroids could enhance bacterial replication and worsen infection. However, if the chosen antibiotic is effective against the organism, the concurrent use of steroids will not inhibit the bactericidal effect.[28-34]

Steroids should not be employed until the antibiotic has been given enough time to kill bacteria. A minimum 24-hour antibiotic-only loading period is recommended. Be sure that the infection is not of herpetic, fungal or protozoan origin prior to initiating topical steroids. Steroids should only be used with true bactericidal antibiotics such as fluoroquinolones or fortified antibiotics.

More recently, controlled clinical trials have given mixed results on the adjunctive use of corticosteroids along with topical antibiotics in the management of bacterial keratitis. The most notable research comes from the Steroids for Corneal Ulcer Trial (SCUT) study, which examined the adjunctive use of prednisolone phosphate 1% to eyes treated with moxifloxacin 0.3%. The results showed no detrimental effects of adjunctive steroid use, but also failed to show an improvement in vision at three months; thus, the study did not advocate for the addition of topical steroids.[35] However, later analyses indicated that there was a potential benefit and that adjunctive topical corticosteroid therapy may be associated with improved long-term clinical outcomes in bacterial corneal ulcers not caused by *Nocardia* species.[36] Additionally, sub-analyses of the original data showed that larger, more central ulcers with very poor initial visual acuity may benefit from adjunctive steroid use.[37] It was noted that eyes treated adjunctively with topical steroids within two to three days of antibiotic therapy fared better visually than those treated after four days or more with antibiotics alone, thus advocating for early use.[38]

Newer treatments for resistant or non-resolving cases of bacterial keratitis include laser thermal ablation, corneal crosslinking and amniotic membrane therapy. Argon laser phototherapy may be useful, though not universally accepted at this point, as an adjunctive treatment for resistant infected corneal ulcers.[39] In one report, during the first four weeks after laser treatment, all patients showed complete healing of the epithelial defect and resolution of stromal infiltration with no adverse effects.[39] Corneal crosslinking has been seen as an adjunctive therapy for both early and severe non-healing bacterial keratitis.[40,41]

## Clinical Pearls

• If a patient presents with a corneal infiltrate without overlying epithelial staining, it is likely not infectious bacterial keratitis.

• The use of strong bactericidal antibiotics will eliminate the infective organisms and sterilize the infectious keratitis, but will do nothing to quell the inflammatory reaction. In this instance, the inflammatory reaction is as damaging to the cornea as is the infective organism. If there is evidence that the antibiotic is suppressing the infective organism, then corticosteroid use will inhibit the inflammatory reaction and speed healing and reduce the potential for corneal scarring.

• For steroids to be most beneficial, prescribe them while the ulcer bed is still open, usually within the first 24 to 48 hours after you initiate antibiotic therapy. If you wait until the ulcer re-epithelializes before adding a steroid, its beneficial effects will be reduced. A cautionary note: Be comfortable that the antibiotic has had time to sterilize the lesion before instituting the steroid.

• Oral doxycycline and high-dose vitamin C have some potential to reduce stromal damage in bacterial keratitis.

• Despite recent research showing possibly only marginal benefits from the adjunctive use of topical steroids, we have practiced in times where only antibiotics were used and other times when steroids were added adjunctively. We can clearly state that patients treated with both antibiotics and adjunctive steroids had faster recovery and better quality of life compared to antibiotic therapy alone.


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# CORNEAL ABRASION and RECURRENT CORNEAL EROSION

## Signs and Symptoms

Corneal abrasion is one of the most common urgent clinical entities in practice.[1-11] Patients present with some or all of the following: acute pain, photophobia, pain upon blinking and upon eye movement, lacrimation, blepharospasm,

foreign body sensation, blurry vision and a history of contact lens wear or ocular trauma.[2-11] Biomicroscopy of the injured area often reveals diffuse corneal edema and epithelial disruption. In severe cases, when edema is excessive, folds in Descemet's membrane may be visible. Cobalt blue light inspection with the instillation of sodium fluorescein dye will illuminate the damaged segment in bright green.[4] In more severe cases, the trauma that caused the corneal damage may have the potential to create an anterior chamber reaction.[4,11]

## Pathophysiology

The cornea has distinct layers; epithelium, Bowman's membrane, stroma, Dua's layer, Descemet's membrane and endothelium.[12-14] The corneal epithelium is actually composed of three tissues: the stratified surface epithelium, whose microvilli increase surface area and permit adherence of the tear film by interacting with its mucous layer; the wing cell layer (containing the corneal nerves); and the mitotically active basement membrane. Bowman's membrane is a structure that prevents penetrating injuries. The stroma is composed of 250 well organized lamellar sheets of collagen. It helps create the cornea's optical power and contributes to its transparency. Dua's layer, sometimes referred to as pre-Descemet's layer (PDL), is a histologically confirmed row of acellular keratocytes composed of five to eight lamellae of predominantly type-1 collagen bundles arranged in transverse, longitudinal and oblique directions.[13,14] Identification of this layer of the cornea has explained the corneal biomechanics of posterior corneal pathologies such as acute hydrops seen in keratoconus, descemetocele and pre-Descemet's membrane dystrophies.[13] It is connected to beams of collagen emerging from the anterior surface of its periphery, which continue as the beams of the trabecular meshwork (TM).[14] The new data provides an insight into the origins of the collagen core of the TM and may impact future research into the TM and glaucoma.[13,14] Descemet's membrane and the endothelium constitute the innermost layers of the cornea, and are necessary to maintain the health, metabolism and hydration of the entire tissue.[12]

There are two categories of corneal abrasion: superficial (not involving Bowman's membrane) and deep (penetrating Bowman's membrane, but not rupturing Descemet's membrane). Abrasions may result from foreign bodies, contact lenses, chemicals, fingernails, hair brushes, tree branches, dust and numerous other etiologies.[1-13]

The cornea has remarkable resilience as a result of complex healing properties.[15-18] The epithelium adjacent to any insult expands in size to fill in the defect, usually within 24 to 48 hours.[12,15-17] Damaged cells release protein kinase C delta, stimulating CAP37, an innate immune system molecule that modulates corneal epithelial cell migration, adhesion, and proliferation.[15-17] This explains the rapid healing of superficial injuries and relatively rare rates of infection. Lesions that are purely epithelial often heal quickly and completely without intervention and without subsequent scarring. Lesions that extend below Bowman's membrane produce scar formation.[12,15-17] The creation of post injury corneal opacity is mediated by the complex actions of many cytokines, growth factors and chemokines.[17] These substances are produced by epithelial cells, stromal cells, bone marrow-derived cells, lacrimal tissues and nerves.[17] Stromal opacity after corneal injury is specifically related to the presence of myofibroblasts with decreased corneal crystallins, along with the disorganized extracellular matrix produced by these cells and their chemokines.[17] Regeneration of a fully functional epithelial basement membrane also appears to play a critical role in the maintenance of corneal epithelial and stromal transparency after corneal injuries.[17,18]

The corneal epithelial basement membrane is positioned between basal epithelial cells and the stroma.[18] This highly specialized extracellular matrix functions to anchor epithelial cells to the stroma and provide scaffolding during embryonic development.[18] Basement membranes are composed of a diverse assemblage of extracellular molecules composed of four primary components: collagens, laminins, heparan sulfate proteoglycans and nidogens.[18] The basement membrane zone (BMZ) is located in the uppermost region of the stroma. When collagen VII, a constituent of the region, is destabilized by the process of injury, the BMZ undergoes pathological changes that affect the function of the epidermal junction, creating an environment conducive to recurrent erosion.[18]

## Management

Treatment for corneal abrasion begins with the patient's history. The time, place and activity surrounding the injury should be recorded. Visual acuity should be recorded before any procedures or drops are given, if possible. If the blepharospasm is sufficiently intense to preclude an acuity measurement, one drop of topical anesthetic can be administered with the VA measured immediately thereafter (pinhole, if necessary). If the possibility exists for an open globe, an unopened bottle of anesthetic should be used.

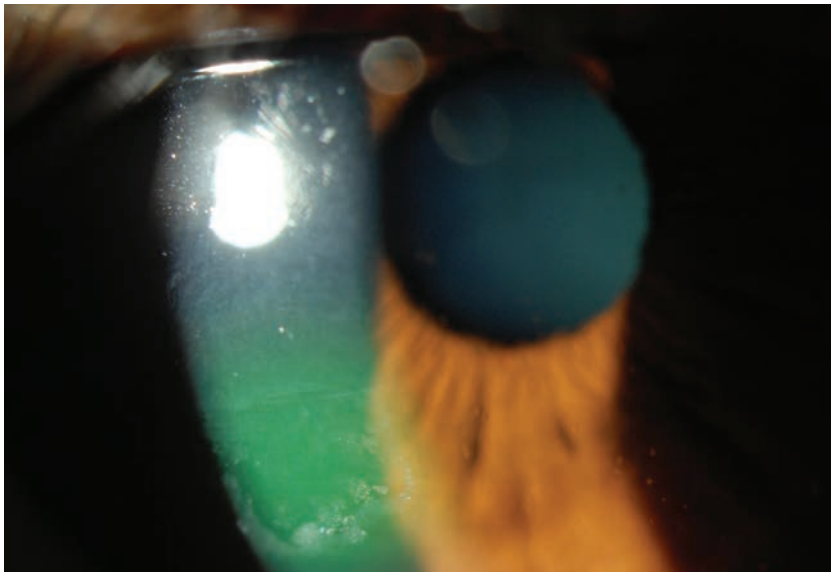
The eye exam should proceed in a logical fashion from external adenexa to funduscopic examination. The eyelids should be everted and fornicies scrutinized to rule out the presence of foreign material. Fluorescein dye (without anesthetic) should be instilled to identify the corneal defects. The Seidel test is used to rule out full thickness injuries. The abrasion should be documented for size, shape, location and depth. It should be cleaned and scrutinized for foreign

matter. The anterior chamber should be observed for any evidence of inflammation. A dilated examination should be completed to rule out any posterior effects from the trauma, if indicated.

Ophthalmic treatment is initiated by using adequate cycloplegia if the patient is sufficiently symptomatic. Topical fluoroquinolone antibiotics QID or another suitable broad spectrum agent can be used to protect against infection.[3,11,19,20] Cold compresses, artificial tears and over-the-counter analgesics can be used to relieve acute pain. In cases where pain is severe, topical nonsteroidal anti-inflammatory medications or a thin, low-water-content bandage contact lens can be prescribed.[2-7,10,19] A pressure patch, while not commonly used, is not contraindicated and is still considered useful for larger abrasions unless the injury is contact lens-related.[19] Patients should be re-evaluated every 24 to 48 hours until the abrasion is re-epithelialized.[2–8]

Riboflavin-ultraviolet A (UVA) treatment is a procedure that induces collagen crosslinking to stiffen the corneal stroma.[23-25] Like the use of vitamin C drops (which must be compounded), the procedure induces a reduction in stromal swelling while increasing resistance to microbial and enzymatic degradation. While studies have centered on corneal ectatic diseases, the procedure demonstrates promise for corneal injuries of all types that demonstrate delayed healing times.[23-25] Standard protocol for this procedure requires the eyes have a minimum corneal thickness of 400µm after epithelial debridement.[25] This prerequisite has been stipulated to protect the corneal endothelium and intraocular tissues from the deleterious effect of ultraviolet-A (UVA) radiation.[25] Studies with contact lens-assisted corneal crosslinking has shown promise for patients with thin corneas.[24]

Reports have recognized tetracyclines and their derivatives for their ability to protect the cornea, inhibiting matrix metalloproteinases (MMP) independent of antimicrobial properties.[26-28] These compounds—primarily through restriction of gene expression of neutrophil collagenase, epithelial gelatinase suppression of alpha1-antitrypsin degradation and scavenging of reactive oxygen species—are able to limit production of the inflammatory mediator MMP.[27,28] Oral tetracyclines can be used along with other topical therapeutic agents to inhibit collagenolytic degradation of the cornea.[26-28] Topical steroids can also be employed following early-stage repair of superficial ocular injuries to increase the efficiency of corneal wound healing by suppressing inflammatory enzymes.[27,28]



Recurrent corneal erosion in a patient with anterior basement membrane dystrophy.

Using 50mg to 100mg of doxycycline BID PO for four to 12 weeks in addition to the other topical medications has demonstrated efficacy in patients with recurrent corneal erosion syndrome who have failed other forms of treatment.[26-28] This noninvasive treatment modality is also effective with ocular lubricant management.[26-28] However, these studies admit the need for randomized controlled trials using standardized methods to establish the benefits of many of these newer treatments.

Patients with a history of corneal abrasions are prone to recurrent corneal erosions secondary to altered formation of the hemidesmosomes of the epithelial basal cell layer.[9-26] When the hemidesmosomal anchoring fibers are not established properly, a peeling off of the epithelium can result. This most frequently occurs upon awakening (morning syndrome).[9-22,28-30] Patients who suffer from corneal dystrophies (epithelial basement membrane dystrophy, Meesmann's corneal dystrophy, Reis–Bucklers dystrophy, honeycomb dystrophy and granular and lattice dystrophies) are also more susceptible to recurrent corneal erosions.[9,31,32] In cases such as these, palliative treatment should include hyperosmotic solutions and lubricants. When recurrent erosion does occur, patching and bandage lenses may be employed.[2,4,5,10,31,33]

When these modalities fail to promote adequate corneal healing, manual debridement or superficial PTK may assist.[26,34] Oral tetracycline, topical steroids and collagen crosslinking can also be employed following debridement.[23-30] Anterior stromal puncture is yet another option.[30] The procedure

involves repeated puncturing of the Bowman's layer, penetrating into the anterior one-third of the corneal stroma with either a Nd:YAG laser or a short (5/8in) 25-gauge bent needle on a tuberculin syringe.[30,35] Both options serve to produce purposeful scarring, which strengthens the adherence of the overlying superficial epithelium to the Bowman's layer.[30,35] While the complications of the needle-based procedure include pain, potential for infection, reduced acuity secondary to excessive scarring and accidental penetration, a new laser-based practice has been evaluated in small studies to reduce the frequency of attacks while only producing mild post procedural discomfort.[35]

Tarsorrhaphy is used primarily for recalcitrant epithelial defects.[36] Here the eyelids are temporarily sutured together, providing a complete form of patching and complete immobilization of the eyelid, which yields more efficient healing.[36]

## THERAPEUTIC USES OF AMNIOTIC MEMBRANES

While the use of preserved human amniotic membrane is a relatively new addition to the optometric armamentarium, the tissue itself has been employed by Western ophthalmologists for nearly 20 years, and even longer in other countries.[1,2] The amnion represents a thin but tough avascular layer of human placental tissue that encapsulates the infant in utero and serves to provide protection from immunologic insult.[3,4] It is composed primarily of collagens, proteoglycans, fibronectin, laminin and hyaluronic acid (HA).[5] The latter appears to be the most critical component of amniotic membrane as it has unique properties; it has been shown to suppress T-cell activation, inhibit giant cell formation and promote regenerative healing of damaged tissues.[6,7] Transplanted preserved amniotic membrane can serve to diminish inflammation, neovascularization and fibrosis of human ocular tissue, allowing for more efficient and complete healing.[3,8]

In the United States, the first commercially available amniotic membrane product, Amniograft (Bio-Tissue), was introduced in 1997. It is still widely employed today in surgical settings. In 2005, a self-retaining version was introduced under the trade name Prokera (Bio-Tissue). This device was designed to impart the beneficial aspects of Amniograft for treating ocular surface inflammation without the necessity of surgical attachment via sutures or fibrin glue. Prokera's design incorporates a dual polycarbonate ring system to suspend the membrane and ensure its retention within the ocular fornices, while holding it firmly against the ocular surface. The introduction of Prokera helped to extend the utility of amniotic membrane therapy from the limited realm of corneal surgery into general ophthalmic practice.

### Clinical Uses

A substantial number of publications over the last 10 years have demonstrated the wide clinical utility of preserved amniotic membranes for an array of ophthalmic disorders.[9-19] Broadly, the indications include: corneal surface disorders, with or without limbal stem cell deficiency; conjunctival surface reconstruction such as after pterygium removal; as a carrier for ex vivo expansion of corneal epithelial cells; in conjunction with surgical treatment of glaucoma; treatment of scleral melts and support for repaired corneal perforations; and other miscellaneous indications. Sutureless amniotic membranes are generally restricted to the management of corneal disorders, although placement of the tissue supports the overall health of the ocular surface. Two independent, retrospective analyses assessed

***Left:*** **A Prokera (original) to treat severe OSD.** ***Right:*** **A Prokera Slim on a patient who had severe filamentary keratitis associated with Sjögren's syndrome.**

the indications for use of this technology at eye care clinics associated with large teaching hospitals.[12,15] These demonstrated that the most common reason for using sutureless amniotic membrane was neurotrophic keratopathy, followed closely by non-healing infectious keratitis and limbal stem cell deficiency. It was also used frequently in cases of chemical injury, corneal scarring with neovascularization, epithelial basement membrane disorder and persistent corneal epithelial defects. Additional indications included band keratopathy, failed corneal graft, exposure keratopathy, bullous keratopathy, adenoviral membranous keratoconjunctivitis, chronic keratoconjunctivitis, recurrent pterygium, contracted anophthalmic socket and acute toxic epidermal necrolysis involving the eye and adnexa.[12,15]

There are essentially two types of sutureless amniotic membrane devices available today: cryopreserved or dehydrated. Prokera and its related products (Prokera Slim and Prokera Plus) are cryopreserved; no other cryopreserved, sutureless human amniotic membranes are available for ophthalmic use in the United States. Prokera products must be maintained at reduced temperatures prior to use; their shelf life is three months if stored in a standard refrigerator (1°C → 10°C), one year if stored in a standard freezer (-49°C → 0°C) or two years if stored in an ultralow temperature freezer (-85°C → -50°C). The alternative method of dehydration is employed by two commercially available products in the United States, AmbioDisk (IOP Ophthalmics) and BioDOptix (BioD). Both can be shipped and stored at ambient temperatures prior to use. AmbioDisk has a shelf life of five years from the date of manufacture; BioDOptix can be stored for a maximum of two years.

### Clinical Procedure

Prior to application, the Prokera is removed from storage and allowed to come to room temperature for approximately 10 minutes. Insertion is relatively straightforward, and retention of the membrane is accomplished by virtue of its inherent polymeric ring

Often, the sutures are left tied but not knotted and then taped to the forehead so they can be tightened and loosened for the purpose of opening the lids to instill medications. Partial tarsorrhaphy can be accomplished when complete closure is not required. While a tarsorrhaphy is simple, safe and effective, it can be somewhat unsightly and create cosmetic concern for the patient. This is typically only done in extreme cases such as neurotrophic keratitis.

Amniotic membrane transplantation (AMT) is a surgical modality used to create a temporary "tissue" patch for non-healing corneal lesions secondary to limbal stem cell deficiency.[37,38] While traditional AMT is surgical in nature, newer options such as AmbioDry (IOP Ophthalmics) only require a bandage lens over the transplant. The membrane can serve as a reconstructive graft for both cornea and conjunctiva.[37,38] AMT is primarily used to treat conditions

structure. AmbioDisk and BioDOptix, because of their dehydrated nature, must be applied to a dry cornea, requiring a lid speculum and appropriate tools to ensure relative epithelial desiccation. Once the membrane has been placed, it must be smoothed into position and covered with a bandage contact lens to ensure retention on the ocular surface.

Practitioners who perform amniotic membrane therapy in-office should employ CPT code 65778, "Placement of amniotic membrane on the ocular surface; without sutures." For some commercial carriers, code V2790, "Amniotic membrane for surgical reconstruction, per procedure" may also be submitted; this allows for additional reimbursement of materials. Realize too that code 65788 carries a 10-day global period, and office visits during this follow-up time will not be reimbursed by insurance.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**INDICATIONS FOR SUTURELESS AMNIOTIC MEMBRANES FROM MANUFACTURERS' PROMOTIONAL MATERIALS**

| Prokera (Prokera Slim and Prokera Plus) | AmbioDisk | BioDOptix |
|---|---|---|
| • Dry Eye<br>• Corneal Abrasions<br>• Recurrent Corneal Erosions<br>• Corneal Wounds<br>• Infectious Keratitis<br>• Corneal Ulcers<br>• Neurotrophic Persistent Epithelial Defects<br>• Chemical Burns<br>• Salzmann's Nodular Degeneration<br>• Stevens-Johnson Syndrome<br>• Post PRK Haze<br>• Post DSEK for Bullous Keratopathy | • Post-Infectious Keratitis (herpetic, vernal and bacterial)<br>• Corneal Erosions<br>• Non-Healing Epithelial Defects<br>• Neurotrophic Ulcerations<br>• Acute Chemical/Thermal Burns | • Ocular Surface Disorders<br>• Corneal Epithelial Defects<br>• Corneal Ulcer<br>• Pterygium<br>• Band Keratopathy<br>• Bullous Keratopathy<br><br>*As an adjunct to:*<br>• PRK<br>• PK Cornea Transplant |
| Source: www.biotissue.com/products/prokera/prokera-indications.aspx | Source: www.iopinc.com/store/ambiodisk | Source: http://ojomed.com/wp-content/uploads/2013/05/Optix_SaleSheet.pdf |

where the normal corneal reparative process is either faulty or cannot gain momentum.[35,37,38] AMT can be sutured onto a viable corneal limbus, attached via fibrin glue or applied via the novel approach of Prokera (Bio-Tissue).[38] Prokera supports a bioactive amniotic membrane within a rigid ring with an inner opening of 15.5mm to 17.9mm and an outer diameter of 21.6mm. This large diameter biological bandage has been used in a variety of non-healing corneal disorders with great success.[38]

A dendritic polymer known as a dendrimer seems to have applications as a nano-adhesive to improve corneal wound repair.[39-42] The agent is composed entirely of the biocompatible products glycerol and succinic acid.[39] The adhesive has advantages over sutures in the repair of corneal lacerations, securing unstable LASIK flaps and RK incisions, and closing leaky cataract surgical incisions.[39-42] Other applications for potential usage of the adhesive includes ocular emergencies involving perforation of tissues due to trauma or infections. It may also be applied to strengthen or build up weak tissues that have been compromised by the destructive processes associated with inflammation.[39-42]

## Clinical Pearls

- To promote healing, prevent recurrent erosion and reduce corneal edema, a hypertonic solution or ointment may be prescribed. The minimum period of recommended application for this type of therapy is one month; however, unusual cases may require permanent use.
- In cases where excess epithelium impairs regrowth, a cotton-tipped applicator saturated with anesthetic may be used to debride the loose tissue.
- When significant inflammation is present, topical steroids may be required. They must be used judiciously as they can retard corneal healing, raise IOP and increase risk for infection.
- Worsening subepithelial infiltration, increased pain and injection in the setting of an epithelial break may be a sign of secondary bacterial infection, especially in patients who are imunocompromised.


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RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

### Important Safety Information

### Contraindications

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

### Warnings and Precautions

**Potential for Eye Injury and Contamination:** To avoid the potential for eye injury and contamination, individuals prescribed RESTASIS® should not touch the vial tip to their eye or other surfaces.

**Use With Contact Lenses:** RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion.

### Adverse Reactions

In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

**Please see Brief Summary of the full Prescribing Information on adjacent page.**

**Reference: 1.** RESTASIS® Prescribing Information.

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**RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%**

**BRIEF SUMMARY—PLEASE SEE THE RESTASIS® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.**

**INDICATION AND USAGE**

**RESTASIS®** ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

**CONTRAINDICATIONS**

**RESTASIS®** is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

**WARNINGS AND PRECAUTIONS**

**Potential for Eye Injury and Contamination**

To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces.

**Use with Contact Lenses**

**RESTASIS®** should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

**ADVERSE REACTIONS**

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, the most common adverse reaction following the use of **RESTASIS®** was ocular burning (17%).

Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

**Post-marketing Experience**

The following adverse reactions have been identified during post approval use of **RESTASIS®**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Teratogenic Effects: Pregnancy Category C**

Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 5,000 and 32,000 times greater (normalized to body surface area), respectively, than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater (normalized to body surface area), respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 7,000 times greater than the daily human topical dose (0.001 mg/kg/day) normalized to body surface area assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of **RESTASIS®** in pregnant women. **RESTASIS®** should be administered to a pregnant woman only if clearly needed.

**Nursing Mothers**

Cyclosporine is known to be excreted in human milk following systemic administration, but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of **RESTASIS®** ophthalmic emulsion, caution should be exercised when **RESTASIS®** is administered to a nursing woman.

**Pediatric Use**

The safety and efficacy of **RESTASIS®** ophthalmic emulsion have not been established in pediatric patients below the age of 16.

**Geriatric Use**

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

*Carcinogenesis:* Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

*Mutagenesis:* Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

*Impairment of Fertility:* No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

**PATIENT COUNSELING INFORMATION**

**Handling the Container**

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. To avoid the potential for injury to the eye, advise patients to not touch the vial tip to their eye.

**Use with Contact Lenses**

**RESTASIS®** should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

**Administration**

Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

**Rx Only**

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## EXFOLIATIVE GLAUCOMA

### Signs and Symptoms

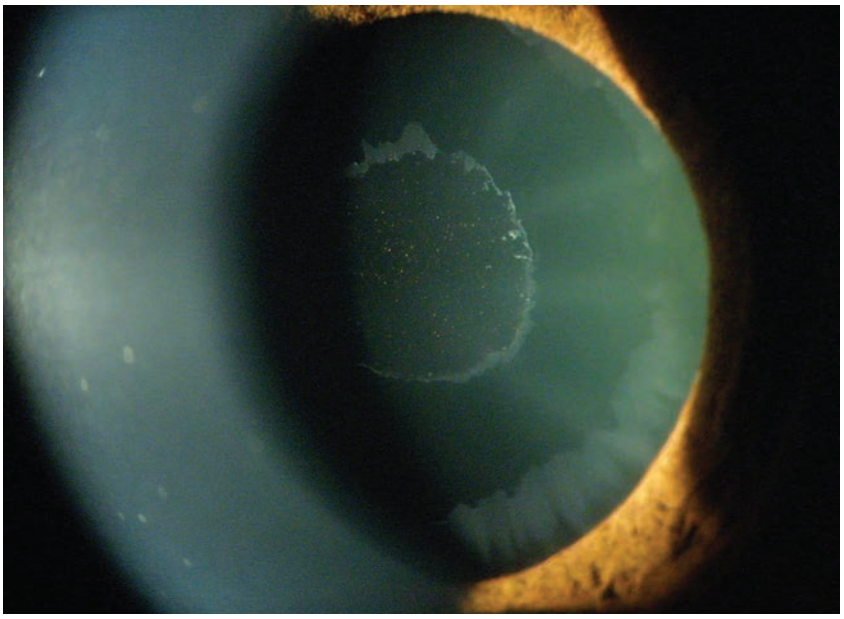
Exfoliation syndrome and exfoliative glaucoma occur in high rates throughout northern Finland, Iceland, Saudi Arabia, Great Britain and Greece. The condition has a predilection for northern climates.[1-4] Exfoliation occurs in 5% of older Americans.[5] This condition is considered uncommon in patients of African descent, though it does occur.[6,7] The true overall prevalence of exfoliation may be underestimated, as 15% of cases may be missed clinically.[8]

Exfoliative glaucoma is predominately a disease of the elderly and is rarely found in patients younger than 50.[4,9] The lowest age of onset reported thus far occurred in a 17-year-old girl.[10] The highest prevalence rates have been found in patients over the age of 70.[11-15]

Patients present with a fine, flaky material on the anterior lens capsule at the pupillary margin. Over time, this will coalesce into the characteristic "bull's-eye" pattern typically seen in exfoliation syndrome. On the lens capsule, there will be a central area of exfoliative material, surrounded by a clear area where the material has been eroded by the iris contracture, which itself is surrounded by a peripheral area of exfoliative material. This classic pattern is usually only observable when the patient's pupil is dilated. Beyond the anterior lens surface, exfoliative material is most commonly seen accumulating at the pupillary margin. This may be visible in an undilated state. Pigment loss from the pupil margin with subsequent pigment granular deposition on anterior chamber structures is a hallmark of the condition.[9] This leads to increased transillumination of the iris at the pupillary margin, termed peripupillary transillumination defects. There may be pigment granules on the corneal endothelium and iris surface. Within the angle there may be observable pigment, clear flaky material, or both.[16-18] Gonioscopically, the trabecular meshwork pigmentation is often not as solid as seen in pigment dispersion syndrome, as there is more than just pigment in the exfoliative angle.

Initially, intraocular pressure is unaffected in exfoliation syndrome; however, elevated intraocular pressure can develop, and characteristic glaucomatous cupping and visual field loss may ensue. In one report, 16% of patients with clinically apparent exfoliative material required treatment upon presentation, with 44% developing a need for therapy over the next 15 years.[13] Roughly a 32% conversion rate from exfoliation syndrome to exfoliative glaucoma occurred over a 10-year period in another study.[14] One report noted a 45% conversion rate from exfoliation syndrome to exfoliative glaucoma over a mean time frame of five years.[19] Clinically, exfoliative glaucoma is markedly asymmetric with biomicroscopically unilateral involvement in many cases.[4,5,13,14,20]

Patients with exfoliation are more prone to developing cataracts as well as surgical complications during extraction.[21-25] Complications include poor pupillary mydriasis, poor zonular integrity and intraoperative zonular dialysis, spontaneous lens dislocations and vitreous loss during surgery. Occasionally lens displacement with pupil block and angle closure may occur.[26,27]



This classic "bull's eye" pattern is seen in exfoliation and exfoliative glaucoma.

### Pathophysiology

Exfoliation involves the production and accumulation of an abnormal fibrillar extracellular material within the anterior chamber of the eye.[28,29] The accumulated material consists of a fibrillar component and an amorphous component, though the exact chemical composition remains unclear.[30-34] It appears that the material represents abnormal basement membrane secreted by all structures within the anterior chamber and deposited on the anterior lens capsule, iris surface and trabecular meshwork.[30-34] Due to accumulation of material at the pupillary margin, there is increased lenticular apposition with the iris and subsequent erosion of iris pigment as the pupil dilates and constricts. This leads to increased iris transillumination and deposition of pigment granules on the endothelium, iris surface and trabecular

meshwork similar to PDS. The iris will also rub this material off the lens surface, with a mid-peripheral clear zone. As this is a condition that involves deposition of material on the anterior lens capsule, and not flaking off of the lens capsule, lensectomy is not curative.

There has been conjecture as to whether this condition should be called exfoliative glaucoma or pseudoexfoliative glaucoma, and both terms are often used interchangeably. True exfoliation of the lens capsule is a rare disorder in which the lens capsule is thickened and the superficial portion of the lens capsule splits from the deeper layer, often due to exposure to intense heat or infrared radiation. Because material is laid down upon the surface of the lens, and the lens capsule is not being rubbed off, many prefer to use the term pseudoexfoliation. However, iris contracture is rubbing the material off the lens, so exfoliative glaucoma seems a more appropriate term.

The development of glaucoma typically occurs due to a buildup within the trabecular meshwork of pigment granules and exfoliative material. The primary cause of IOP elevation appears to be phagocytosis of accumulated pigment and material by the trabecular cells and Schlemm's canal cells with subsequent degenerative changes of Schlemm's canal and trabecular meshwork tissues. Thus, this is a secondary open angle glaucoma mechanism.[26,27] However, due to zonular dehiscence from accumulations of exfoliative material, there can be lens displacement with secondary pupil block and angle closure mechanisms.[26,27]

Patients with exfoliation have demonstrated aggregates of similar material in the fibrovascular connective tissue septa of the skin as well as in some internal organs (e.g., heart, lung, liver and kidney). Some evidence suggests an association with transient ischemic attacks, aortic aneurysm formation and systemic cardiovascular diseases.[27,33] Thus, exfoliation syndrome is considered to be a generalized systemic disorder rather than solely an ocular condition.[33]

Genetic studies have identified a highly significant association between several polymorphisms in the lysyl oxidase-like 1 (LOXL1) gene in both exfoliation syndrome and exfoliative glaucoma, occurring in almost 100% of exfoliative patients worldwide. LOXL1 is a pivotal crosslinking enzyme in extracellular matrix metabolism and seems to be specifically required for elastic fiber formation and stabilization. This suggests that LOXL1 enzyme function and expression are abnormal and thereby play a role in glaucoma development, possibly due to abnormalities in the lamina cribrosa.[35] There is evidence for an exfoliation-specific elastinopathy of the lamina cribrosa resulting from a primary disturbance in LOXL1 regulation, possibly making exfoliative eyes more vulnerable to pressure-induced optic nerve damage and glaucoma development and progression.[35,36]

There also appear to be significant differences in corneal biomechanical properties in eyes with exfoliation syndrome and glaucoma compared to normal eyes and those with primary open angle glaucoma (POAG). Exfoliative eyes have been measured with the Ocular Response Analyzer (Reichert) to have a lower corneal hysteresis (CH) and corneal resistance factor (CRF) than nonexfoliative eyes.[37-39] While this information may not be clinically necessary to make a diagnosis of exfoliative glaucoma, it can help to partially explain the reason for this condition being a more aggressive form of open angle glaucoma.

## Management

Exfoliation syndrome without intraocular pressure rise requires periodic monitoring of the IOP, discs, nerve fiber layer and visual fields due to possible later development of IOP elevation.[13,14,19] Establishing a diurnal pressure curve with multiple IOP readings is especially important, as patients with exfoliation syndrome and exfoliative glaucoma demonstrate great variations in IOP.[40,41] Patients with exfoliative glaucoma, more than POAG, exhibit a diurnal range greater than 15mm Hg. Forty-five percent of exfoliative glaucoma patients demonstrate a peak IOP, at times, outside normal office hours.[42]

Exfoliative glaucoma is medically treated in the same manner as POAG. It can be a particularly aggressive form of open angle glaucoma, possibly due to an abnormal elastinopathy of the lamina cribrosa, lowered CH and CRF, or both. It appears that exfoliative eyes are more likely to show progressive disease than eyes with POAG, even at similarly treated IOP levels.

If not systemically contraindicated, the clinician may use topical beta-blockers, topical carbonic anhydrase inhibitors, prostaglandin analogs and alpha adrenergic agonists. However, the IOP in exfoliative glaucoma is typically higher than in POAG and is more difficult to temporize. Typically, a greater amount of medical therapy is needed to control patients with exfoliative glaucoma compared to POAG patients.[43-45] Selective laser trabeculoplasty is a viable treatment option for exfoliative glaucoma, often showing a greater effect than in eyes with POAG.[46,47] It was shown that both forms of laser trabeculoplasty (selective and argon) had equal IOP reduction through six months.[48] Invasive procedures such as trabeculectomy, drainage implant surgery, cataract surgery and ab interno trabeculectomy are viable management options.[49]

## Clinical Pearls

- Peripupillary iris transillumination defects are a common and important finding in patients with exfoliation. In fact, they may precede the development of clinically observable exfoliative material on the lens surface. This finding mandates a careful inspection of the

anterior lens surface following dilation.

- A pigment shower in the anterior chamber can occur following diagnostic dilation.
- Eyes with exfoliation typically do not dilate well due to subclinical posterior synechiae. Radial streaks of pigment on the surface of the lens seen after dilation are a strong indicator of exfoliation.
- Exfoliative glaucoma can be especially difficult to control. Give special care to earlier, aggressive pressure reduction when exfoliation is present.
- While exfoliation can appear unilateral, it is likely bilateral and asymmetric.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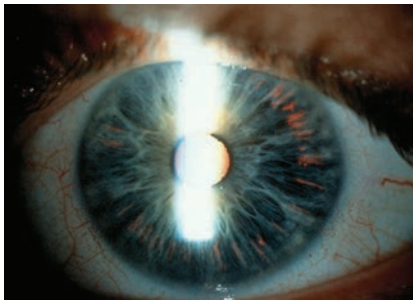
## PIGMENT DISPERSION SYNDROME and PIGMENTARY GLAUCOMA

### Signs and Symptoms

Pigment dispersion syndrome (PDS) is an asymptomatic disorder typically discovered upon routine evaluation.[1] Pigmentary glaucoma (PG), a sequela of pigment dispersion syndrome, is also asymptomatic. Patients rarely present



Iris transillumination defects in PDS.

with complaints related to episodic rises in intraocular pressure secondary to exercise, such as colored haloes around lights, blurred vision or subtle ocular pain.[2,3] Both conditions are typically encountered in young, typically myopic, Caucasian males between the ages of 20 and 40.[4] One population-based study observed pigment dispersion syndrome in 2.45% of Caucasians undergoing glaucoma screening.[4] Pigment dispersion syndrome and pigmentary glaucoma also occur in African American patients, though less commonly than in Caucasians.[5-7] The majority of patients in this category are older, female and hyperopic.[5-7]

Patients with pigment dispersion syndrome and pigmentary glaucoma demonstrate liberation of iris pigment within the anterior chamber. Often, this is seen as diffuse accumulation or possibly a granular brown vertical band along the corneal endothelium known as a Krukenberg's spindle.[8-10] Pigment accumulation may also be evident on the lens and the surface of the iris.

Dense pigmentation is seen gonioscopically, often covering the trabecular meshwork for 360 degrees; it is most prominent in the inferior quadrant due to gravity.[8,11] When pigment accumulates on Schwalbe's line, it is referred to as Sampaolesi's line.[5] The angle recess remains unchanged and open. Radial, spoke-like transillumination defects of the mid-peripheral iris are common.[5,7,8]

There seem to be some differences in the appearance of pigment dispersion syndrome and pigmentary glaucoma in African American patients. Here, the degree of corneal endothelial pigmentation is quite mild, and Krukenberg's spindles are not usually present. The degree of corneal endothelial pigmentation is not predictive of the amount of trabecular meshwork pigment that may have accumulated. Iris transillumination defects are rarely present, possibly due to a thicker iris stroma.[5,6,9]

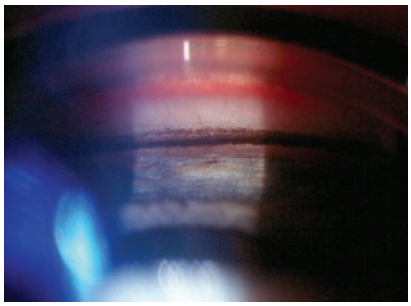
While the intraocular pressure (IOP) is not altered in pigment dispersion syndrome, it may rise sharply in cases of pigmentary glaucoma. Likewise, pigment dispersion syndrome presents with a normal optic nerve appearance, while patients with pigmentary glaucoma manifest evidence of glaucomatous optic atrophy and associated field loss.

## Pathophysiology

The pathophysiology of pigmentary glaucoma must be considered in two parts: mechanism of pigment release and mechanism of pressure elevation. Pigment dispersion occurs as a result of the proximity between the posterior iris pigment epithelium and the zonular fibers of the lens. The abrasive nature of this physical contact leads to mechanical disruption of the iris surface and release of pigment granules into the posterior chamber, which follows the flow of the aqueous convection currents into the anterior chamber angle.[13-15]

Many patients with pigment dispersion syndrome and pigmentary glaucoma demonstrate a concave approach of the iris as it inserts into the anterior chamber angle, giving the iris a "backward bowed" appearance on gonioscopy.[15] This posterior bowing of the iris places the posterior iris into apposition with the lens zonules. As the iris responds to light, iridozonular friction results in pigment liberation from the posterior iris. Sometimes the degree of pigment loss in the mid-peripheral areas produces visible transillumination defects corresponding to packets of iris zonular fibers.[14] While the majority of these patients have a concave iris approach, others may have a flat or planar approach.[15]

It has been theorized that in cases with a markedly concave iris insertion, the iris functions as a flap valve lying against the anterior lens surface. When a pressure gradient develops that is greater in the anterior chamber, the iris is forced backwards, closing the valve and stopping the aqueous from moving into the anterior chamber. This increased anterior chamber pressure subsequently forces the iris into the concave approach of the iris and has been termed "reverse pupillary block." The blocked flow increases IOP and over time produces the expected neural damage.[16,17] This phenomenon has been found to increase with patient blinking.[14,18,19]



PDS showing pigment accumulation in the inferior angle on gonioscopy.

When excessively released pigment accumulates in the trabecular meshwork, there are two possible consequences. First, pigment may reside benignly in the trabecular meshwork. Here, IOP is unaffected and the condition remains pigment dispersion syndrome. Alternatively, when the pigment causes a rise in IOP and the nerve and function suffer, the patient develops pigmentary glaucoma.[14]

Interestingly, physical blockage of the trabecular meshwork by pigment granules is not the likely cause of the pressure rise.[20] Endothelial cells lining the trabecular beams of the trabecular meshwork quickly phagocytize small amounts of accumulated pigment, preserving the normal architecture of the trabecular meshwork.[21-23] However, in chronic cases of pigment dispersion, greater amounts of pigment are more difficult for the cells to phagocytize. When this occurs, the endothelial cells that line the trabecular meshwork beams disintegrate. The resultant degeneration of the trabecular meshwork with the accumulation of debris, collapsed beams

and loss of intratrabecular spaces is what produces the rise in IOP.[23] The IOP rise in pigmentary glaucoma mostly occurs due to a breakdown of normal phagocytic activity of the endothelial cells and subsequent loss of normal trabecular architecture and function.[23]

## Management

As pigment dispersion syndrome has no direct ramifications on ocular health or vision, other than potential future development of pigmentary glaucoma, these patients should be treated as glaucoma suspects. Patients should be monitored for IOP spikes and optic nerve changes three to four times a year, with threshold visual fields, diagnostic imaging and gonioscopy performed annually. One study noted the conversion rate from pigment dispersion syndrome to pigmentary glaucoma to be 20%, with the vast majority converting within 10 years from the diagnosis of pigment dispersion syndrome.[24] However, patients with pigment dispersion syndrome who were followed for greater than 10 years without developing pigmentary glaucoma had a low risk of developing pigmentary glaucoma subsequently.[24] Another study noted the risk of developing pigmentary glaucoma from pigment dispersion syndrome was 10% at five years and 15% at 15 years. Young, myopic men were more likely to convert to pigmentary glaucoma, and an IOP greater than 21mm Hg at initial examination was associated with an increased risk of conversion.[25]

Medical treatment of pigmentary glaucoma involves reduction of IOP with aqueous suppressants.[8] There has been conjecture that prostaglandin medications should be avoided in glaucoma patients where pigment liberation is involved in the etiology, as these medications increase the amount of melanin in stromal melanocytes and could potentially impair drainage further. However, this fear is unfounded as the melanocyte size has only been confirmed to increase within the iris stroma. Prostaglandin medications have been seen to successfully lower IOP in eyes with pigment dispersion from pseudoexfoliative glaucoma. Thus, prostaglandin medications are a good therapeutic option for pigmentary glaucoma.[26-28]

Laser peripheral iridotomy (LPI) has intermittently been performed for patients with pigment dispersion syndrome and pigmentary glaucoma where there is significant iris concavity.[14-16] It has been well reported that the iris can convert from a concave to a planar approach following LPI.[14-16] However, there is very little information available regarding the effect of LPI on IOP in pigmentary glaucoma. In a retrospective study, data was analyzed on patients with bilateral pigmentary glaucoma who received uniocular LPI.[29] The main outcome measure was the post-laser intraocular pressure course of the treated eyes, compared with the fellow, untreated eyes. The conclusion of this study did not show a benefit in long-term IOP control in eyes with pigmentary glaucoma undergoing LPI.[29]

A prospective, controlled, randomized study looked at 166 eyes with pigment dispersion syndrome and elevated IOP, but no glaucomatous damage, and randomized eyes to either LPI or no LPI with a primary outcome of conversion to pigmentary glaucoma at three years. Analyses showed no evidence of any difference in time to visual field progression or commencement of topical therapy between the two groups. This study concluded that there was no benefit of LPI in preventing progression from PDS with associated ocular hypertension to pigmentary glaucoma within three years of follow up.[30]

Patients with pigmentary glaucoma tend to respond well to argon laser trabeculoplasty, presumably due to the improved thermal effects on trabecular tightening, secondary to the increased meshwork pigmentation.[31-35] There appears to be little published data regarding the efficacy of selective laser trabeculoplasty (SLT) in pigmentary glaucoma. However, because SLT works by creating inflammation where the immune system effectively cleans the spaces between the trabecular beams and the mechanism of pigmentary glaucoma is secondary to beam damage, it would seem logical that SLT would not be effective. In one series involving four patients, researchers found that post-SLT IOP elevation was a serious adverse event.[36] Trabeculectomy remains an option for patients with recalcitrant pigmentary glaucoma.

## Clinical Pearls

- Pigmentary glaucoma should be strongly considered when encountering glaucoma in younger patients.
- Pigmentary glaucoma is often under-diagnosed in African American patients due to the lack of corneal endothelial pigment and iris transillumination defects. Often, the trabecular hyperpigmentation is incorrectly attributed to overall racial pigmentation.
- Diurnal IOP variations can be quite extreme in pigmentary glaucoma.
- There appears to be no role for LPI in the management of PG.
- The issue of exercise-induced liberation of pigment with resultant IOP spike arises from a single published case. Attempts at experimental induction of this phenomenon have met with little success. There is no reason to discourage young patients with pigment dispersion syndrome from exercise.

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## ANTERIOR UVEITIS

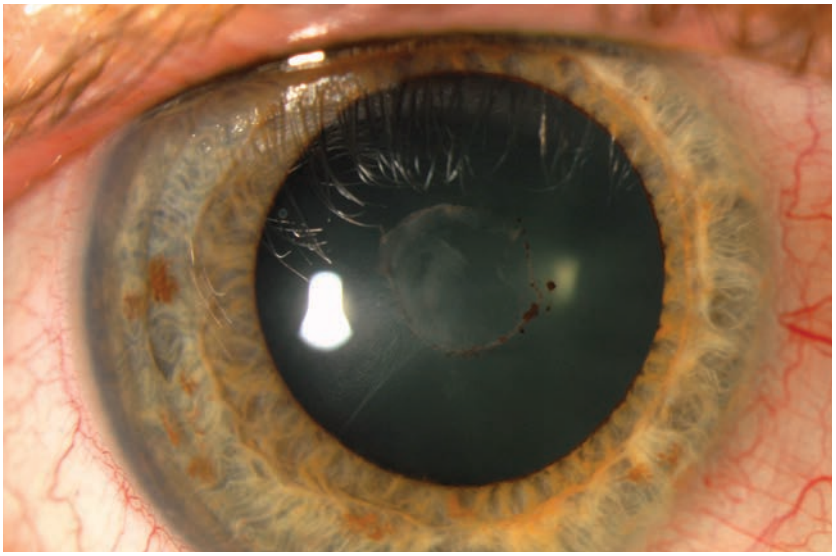
### Signs and Symptoms

Uveitis may be noted in individuals of any age, but is most commonly encountered in those between 20 and 60 years of age.[1,2] Anterior uveitis does not tend to favor either gender, nor is there any particular racial predilection.[2,3] Patients with anterior uveitis typically present with complaints of pain, photophobia and hyperlacrimation. The pain is characteristically described as a deep, dull ache, which may extend to the surrounding orbit. Associated sensitivity to lights may be severe, and, often, these patients will present wearing dark sunglasses. Excessive tearing results secondary to increased neural stimulation of the lacrimal gland.

Visual acuity is variably affected. In the earliest stages of anterior uveitis, visual acuity is minimally compromised; however, as the condition persists over days to weeks, accumulation of cellular debris in the anterior chamber and along the corneal and lenticular surfaces may result in subjectively blurred vision.[4,5] Accommodative tasks may be difficult or painful due to ciliary spasm. The patient with anterior uveitis may display a sluggish, fixed and/or irregular pupil on the involved side. Ocular motility is generally intact. Gross observation may reveal a pseudoptosis secondary to photophobia. There typically no notable lid edema.[5]

Clinical inspection of patients with uveitis typically reveals a deep perilimbal injection of the conjunctiva and episclera, although the palpebral conjunctiva remains unaffected. The cornea displays mild stromal edema upon biomicroscopy, and in more severe or protracted reactions, keratic precipitates may be noted on the endothelium. In nongranulomatous cases, these small, irregular gray to brown deposits with a predilection for the central or inferior cornea can be observed without large depositions ("mutton fat" keratic precipitate).[5]

The hallmark signs of nongranulomatous anterior uveitis are "cells and flare." Cells represent leukocytes liberated from the iris vasculature in response to inflammation and are observable and freely floating in the convection currents of the aqueous. Flare is the term used to describe proteins liberated from the inflamed iris or ciliary body. When present, flare gives the aqueous a particulate, or smoky, appearance. When the inflammation is profound and the anterior chamber seems to be smothered in a cellular slurry, the condition is referred to as plasmoid aqueous. In the worst cases, such as those seen in endophthalmitis, the white blood cells will settle, creating what is known as hypopyon uveitis. Whenever there are sufficient cells in the anterior chamber, convection currents have the ability to carry some cells behind the iris into the anterior vitreous. This is termed spillover and must be differentiated from an intermediate or posterior uveitis.



Anterior uveitis. Note the fibrin plug on the anterior lens capsule along with areas of broken synechiae.

Iris findings may include adhesions to the lens capsule (posterior synechia) or, less commonly, to the peripheral cornea (peripheral anterior synechia, PAS). Synechiae are the cause of irregular or fixed pupils in cases of uveitis. Additionally, granulomatous nodules are sometimes seen at the pupillary border (Koeppe nodules) and within the iris stroma (Bussaca nodules) in cases of uveitis associated with systemic disease.[5,6]

IOP is often impacted; it may be depressed, normal or elevated depending on the stage of presentation and the duration of the disease process. In early stages, IOP is characteristically reduced due to secretory hypotony of the inflamed ciliary body.[5] However, as the reaction persists, inflammatory by-products may accumulate in the trabeculum, which can cause normalization at first, and elevation of IOP later. In severe cases, sustained IOP elevation signals the presence of uveitic glaucoma with increased potential for PAS and secondary angle closure.[5,7] Elevated IOP may also occur as a consequence of prolonged topical corticosteroid therapy for anterior uveitis, but this is encountered only in a small percentage of patients.[8-10]

## Pathophysiology

Uveitis should be thought of not as a singular ocular disorder, but rather as a diverse collection of pathological conditions with similar, clinically observable signs. A vast multitude of etiologies may induce uveitis, ranging from blunt trauma to widespread systemic infection (e.g., tuberculosis) to generalized ischemic disorders (e.g., giant cell arteritis).[11-16] Some other well-known systemic etiologies include ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, sarcoidosis, systemic lupus, Behçet's disease, inflammatory bowel disease, multiple sclerosis, syphilis, Lyme disease, histoplasmosis and herpetic diseases.[15,16] Of course, not all forms of uveitis are associated with identified systemic illness. Localized inflammations may occur as well, either by iatrogenic or idiopathic means. Some primary uveitic syndromes include Fuch's heterochromic iridocyclitis and Posner-Schlossman syndrome (technically a trabeculitis).[5,16]

While the precise pathophysiology of anterior uveitis is not entirely clear, the cascade of events during this inflammatory state can be reasonably explained. In the normal human eye, the anterior chamber remains free of cells and plasma proteins by virtue of the blood/aqueous barrier. The blood/aqueous barrier is comprised of tight junctions between the endothelial cells of the iris vasculature and between the apico-lateral surfaces of the nonpigmented epithelium of the ciliary body.[17] In an inflamed ocular state, cytokines mediate numerous tissue changes, among them vasodilation and increased vascular permeability.[18,19] When the uveal vessels dilate, plasma, white blood cells and proteins exude into the extravascular spaces (e.g., the anterior chamber). Small molecular weight proteins may cloud the ocular media, but have little impact otherwise; however, as larger molecular weight proteins, such as fibrinogen, accumulate in the aqueous or vitreous, pathological sequelae follow. Fibrinogen is ultimately converted into fibrin, an insoluble protein involved in the blood-clotting process. In the anterior chamber, fibrin acts like glue, binding with cellular debris to form keratic precipitates. More importantly, fibrin facilitates the adhesion of adjacent ocular structures, forming synechiae.[7] With synechiae comes the risk of secondary glaucomas, particularly angle closure with or without pupillary block.[7] Additionally, chronic uveal inflammation results in an increased concentration of vasoproliferative mediators, promoting angiogenesis or neovascularization.[18-20] Neovascular changes in the iris and angle can further predispose the uveitic eye to secondary glaucoma.

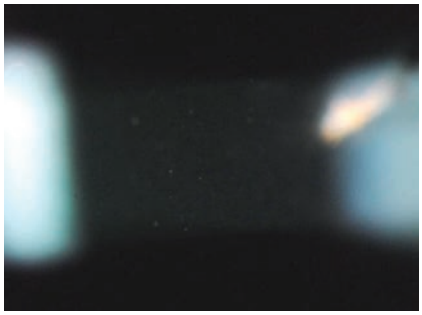
## Management

The primary goals in managing anterior uveitis are threefold: (1) immobilize the iris and ciliary body to decrease pain and prevent exacerbation of the condition; (2) quell the inflammatory response to avert detrimental sequelae; and (3) identify the underlying cause. Cycloplegia is a crucial step in achieving the first goal. This may be accomplished using a variety of

topical medications. Depending on the severity of the reaction, practitioners may employ 5% homatropine BID-QID or 1% atropine QD-TID. Cyclopentolate is typically not potent enough to achieve adequate cycloplegia in the inflamed eye, and hence should be avoided.

Topical corticosteroids are used to address the ocular inflammatory response. For many years, the "gold standard" for uveitis management was 1% prednisolone acetate, ideally obtained in its branded form, PredForte (Allergan). In recent years however, many clinicians have recognized the utility of Durezol (0.05% difluprednate, Alcon) in controlling anterior uveitis.[21-23] Clinical trials have demonstrated that Durezol can be dosed at roughly half the frequency as 1% prednisolone acetate while achieving the same clinical efficacy.[22,23] Topical corticosteroids should be administered in a commensurate fashion with the severity of the inflammatory response. In pronounced cases, dosing every 15 to 30 minutes may be appropriate; however, at minimum, steroids should be instilled every three to four hours initially.

In cases where there are associated posterior synechiae, attempts can be made to break the adhesions in-office using 1% atropine in conjunction with 10% phenylephrine.[24] Secondary elevations in IOP may be addressed by using aqueous suppressant anti-glaucoma agents such as beta blockers, carbonic anhydrase inhibitors and alpha adrenergic agonists. Miotics are contraindicated in the treatment of uveitic glaucoma, as they can worsen the inflammatory response by mobilizing the uveal tissues and disrupting the blood-aqueous barrier.[7] Likewise, many physicians tend to avoid topical prostaglandin analogs after early reports that these IOP-lowering agents showed limited efficacy in the face of inflammation, and perhaps even exacerbated the uveitic response.[25] However, other studies suggest that prostaglandin analogs are indeed both safe and effective in cases of uveitic glaucoma, with their principle disadvantage being length of time to adequate pharmacologic effect.[26-28]



Anterior chamber cells and flare, seen on high magnification, in this patient with anterior uveitis.

After treatment is initiated, patients should be re-evaluated every one to seven days, depending on the severity of the reaction. As resolution becomes evident, cycloplegics may be discontinued and topical steroids may be tapered to QID or TID. It is generally advisable to taper slowly rather than abruptly, and patients may need to remain on steroid drops daily or every other day for weeks or months to ensure treatment success. Recalcitrant cases of anterior uveitis that are unresponsive to conventional therapy may necessitate the use of injectable periocular or intraocular depot steroids, oral corticosteroids (e.g., prednisone 60mg to 80mg daily in divided doses), oral nonsteroidal anti-inflammatory preparations or systemic immunosuppressants such as cyclophosphamide, Trexall (methotrexate, Rheumatrex), azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, interferon or Remicade (infliximab, Janssen).[29-34] As a cautionary note, oral corticosteroids and systemic immunomodulatory agents have significant potential for adverse and unforeseen effects. These agents should only be prescribed when the etiology is recognized by clinicians who are well-trained in their use and able to manage their complications. Otherwise, comanagement with a rheumatologist or internist is recommended.

Medical testing is indicated in cases of simultaneous bilateral uveitis (unrelated to trauma), granulomatous uveitis or recurrent unilateral or bilateral uveitis—defined as two or more unexplained incidents.[5] A medical workup is particularly relevant when the history or associated symptoms are suggestive of a particular etiology.[35] Laboratory testing is not always productive, though the results may be helpful as part of the complete clinical picture. Some of the more common and important tests to consider include: complete blood count with differential and platelets; erythrocyte sedimentation rate; antinuclear antibody; human leukocyte antigen typing; rheumatoid factor; angiotensin-converting enzyme; purified protein derivative with anergy panel; fluorescent treponemal antibody absorption and rapid plasma reagin; and lyme immunoassay.[36] Imaging is also part of the medical workup, particularly when the clinical picture is suggestive of ankylosing spondylitis, tuberculosis or sarcoidosis. X-rays of the sacroiliac joint are useful in the diagnosis of ankylosing spondylitis, while a chest radiograph helps to identify tuberculosis or sarcoidosis infiltration into the pulmonary system.[36]

## Clinical Pearls

- Cases of acute anterior uveitis as a result of blunt ocular trauma generally resolve without incident and do not recur when properly managed.
- A comprehensive, dilated fundus evaluation is mandatory in all cases of uveitis. This is particularly important when visual acuity is significantly diminished. However, this may not be possible on the initial presentation as uveitic eyes are often slow to dilate. A detailed fundus evaluation may have to wait until the first follow-up when the eye is fully cyclopleged.
- Many cases of suspected anterior uveitis actually constitute collateral damage from intermediate or posterior

uveitis. Such is the case with toxoplasmosis, for example, where the cells observed in the anterior chamber actually represent "spillover" from posterior segment inflammation.

- When in doubt regarding the potency or frequency of topical corticosteroid therapy, it is usually better to overtreat than to undertreat. The potential negative effects associated with corticosteroids (e.g., IOP elevation, cataract formation) often take weeks or months to become apparent, but sight-threatening sequelae of unchecked intraocular inflammation can escalate within hours or days.
- Patients with endogenous uveitis (i.e., those cases secondary to infectious or autoimmune disease) often require months of therapy, and some individuals may need to use topical corticosteroids indefinitely to control the inflammation. Physicians who are uncomfortable with such long-term management are advised to refer patients to a specialist with experience in treating uveitis.
- While most eye care practitioners are capable of ordering laboratory tests for uveitis directly, it is often more productive to communicate with the patient's primary care physician before proceeding, so all aspects of the systemic history can be taken into account. Should the patient be diagnosed with a contributory systemic disease, comanagement with the primary care physician, internist or rheumatologist becomes paramount.
- Take care to rule out masquerading syndromes such as neoplastic disease in patients presumed to have chronic idiopathic uveitis, especially if recalcitrant.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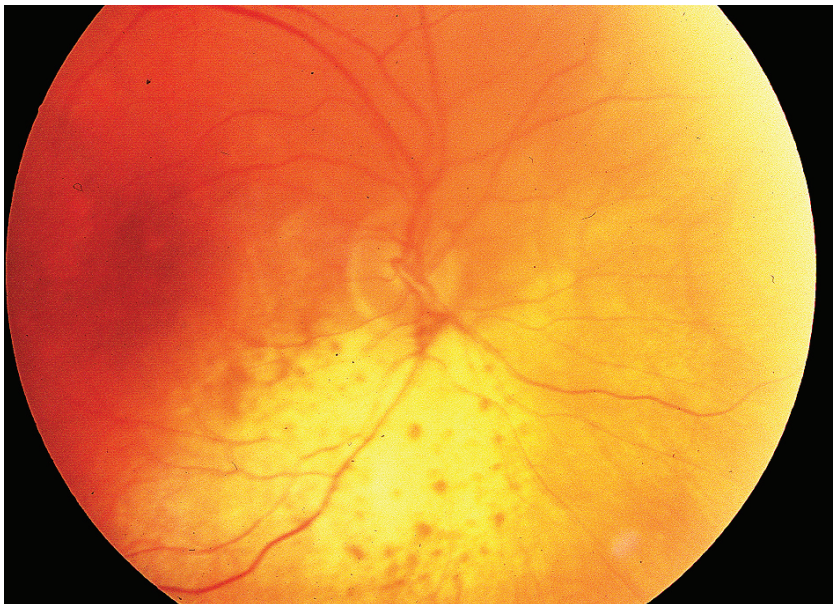
## METASTATIC CHOROIDAL TUMORS

### Signs and Symptoms

Metastatic tumors of the choroid may present with an assortment of signs and symptoms. Commonly, patients complain of visual symptoms such as blurred vision, scotoma or metamorphopsia.[1] Patients may also report photopsia, floaters, visual field defects, red eye and even pain in some cases.[1,2] Less commonly, patients may be entirely asymptomatic.[1]

Ophthalmoscopically, choroidal metastases appear as mild to moderately elevated placoid or oval lesions. They are typically creamy yellow in appearance with variable mottling, although the color may vary from white to orange depending upon the tumor's origin.[1,2] These lesions characteristically display irregular brown pigment deposits overlying the mass, which gives them a unique leopard skin appearance; the pigment spots have been shown histologically to represent macrophages containing lipofuscin.[3] Choroidal metastases are often multilobular, multifocal and



Metastatic carcinoma of the choroid. This patient had a history of bilateral breast cancer, and was also found to have metastatic bone disease.

bilateral.[1,2,4,5] These characteristics are in contradistinction to primary choroidal melanomas, which are almost invariably isolated and unilateral in presentation. Choroidal metastases have a predilection for the posterior pole, and frequently present with associated subretinal fluid and serous retinal detachment.[1,4]

Choroidal metastases may be encountered at virtually any age, although the mean age at the time of diagnosis is 55.[1] Patients with breast cancer tend to be diagnosed earlier (mean age of 48), while those with lung cancer are somewhat older (mean age of 61).[1] There is no known racial predilection. The literature recognizes women to be more commonly affected than men.[6] Patients typically have a concurrent history of cancer, although on occasion the diagnosis of ocular metastasis actually precedes the discovery of a systemic malignancy.[4,7,8]

## Pathophysiology

Metastasis is the process by which malignant cells disseminate throughout the body from one organ system to another. It is a complex mechanism that occurs via vascular and lymphatic channels throughout the body. The choroid, which is particularly well vascularized, is the most common site of ocular metastasis.[1,2,4] Embolic tumor cells reach the uvea by traveling through the internal carotid artery, the ophthalmic artery and the posterior ciliary arteries until they arrive at the choriocapillaris. The process of metastasis is not random; chemokines guide the tumor cells, targeting certain organ systems and tissues over others.[9]

A number of specific tumor types have been associated with choroidal spread. The most common of these by far is breast carcinoma, accounting for 40% to 47% of all uveal metastases.[1,2,4,10] The second most common primary tumor site is the lung (21% to 29%), followed by the gastrointestinal tract (4%), kidney (2% to 4%), prostate (2%) and skin (2%).[10] Metastasis to the eye has been reported for carcinomas of the pancreas, thyroid, testes, ovaries and urothelial tract, as well as carcinoid tumors.[2,6,10,11] In roughly 17% of intraocular metastases, the primary tumor site remains unknown.[6,10]

## Management

Differentiating choroidal metastases from other malignant and nonmalignant conditions is the first step of proper management. The most common differential diagnoses when considering metastasis include amelanotic choroidal melanoma or nevus, choroidal hemangioma, lymphoma, choroidal osteoma, disciform macular scarring, posterior scleritis, congenital hypertrophy of the retinal pigment epithelium (CHRPE) and rhegmatogenous retinal detachment.

While the majority of diagnoses are made by direct clinical inspection, ancillary testing is often helpful for confirmation. Historically, the most frequently used modalities have included fluorescein angiography and ultrasonography. Angiography of choroidal metastases characteristically demonstrates hypofluorescence during the arterial and early venous phases, with hyperfluorescence in the late venous phase, associated with persistent pinpoint leakage.[1] This fluorescein pattern is not entirely diagnostic however, as other entities (e.g., choroidal hemangioma or melanoma) may demonstrate similar features.[2,6] On ultrasound evaluation, choroidal metastases show medium to high internal reflectivity with A-scan and appear echo-dense on B-scan, with a significantly lower height-to-base ratio compared to melanomas.[10] Ultrasonography can also help demonstrate shallow serous detachments which may not be discernable with ophthalmoscopy alone.

Newer methods of differentiating choroidal metastases include fundus autofluorescence (FAF) and optical coherence tomography (OCT). FAF shows hypoautofluorescence of the tumor, with overlying areas of bright hyperautofluorescence correlating to the deposits of lipofuscin; hyperautofluorescence of subretinal fluid can also be seen.[10,12] OCT often demonstrates an "undulating" retinal surface overlying

the mass, with areas of hyperintense irregularities in the photoreceptor layer.[10] The RPE displays thickening, and overlying subretinal fluid may be evident.[13] Additional diagnostic modalities may include indocyanine green angiography, magnetic resonance imaging and fine needle aspiration biopsy.[2,10]

Treatment for choroidal metastases depends on the degree of tumor activity, location and laterality of the tumor, extent of ocular or visual symptoms and the patient's overall health status. For patients who are terminally ill with disseminated metastases and poor constitutional health, palliative therapy with observation is usually preferred.[7,10] More aggressive treatment is indicated if the metastasis is threatening to vision or the overall health of the globe, or if the tumor continues to grow despite concomitant systemic chemotherapy.[2,7]

Therapeutic options for choroidal metastases are diverse; for multifocal or bilateral lesions, systemic chemotherapy, immunotherapy, hormone therapy or whole eye radiotherapy are recommended.[10] For solitary lesions, external beam radiotherapy, proton beam radiotherapy and plaque brachytherapy are the most common first-line options.[1,10,14,15]

A variety of other treatments have been used and continue to be explored in the management of choroidal metastasis, including laser photocoagulation, transpupillary thermotherapy, gamma knife radiosurgery, photodynamic therapy and anti-VEGF injections.[1,2,5-7,10,14-22] Enucleation, which is employed much more readily for a variety of other ocular malignancies, is generally reserved for those cases of choroidal metastasis associated with severe vision loss and intractable pain associated with secondary glaucoma.[2,6,10,14]

Despite numerous treatment options, ocular metastasis carries an exceedingly poor systemic prognosis. Life expectancy for these patients is generally less than five years; the mean survival time after diagnosis of metastatic breast carcinoma to the choroid is 21 months, while for lung carcinoma the mean survival time after diagnosis is 12 months.[4,23,24] In general, patients with breast, lung, thyroid or carcinoid tumors seem to have a longer survival rate than those with metastases from the pancreas, kidney, gastrointestinal tract or cutaneous melanoma.[6] However, survival times are quite variable. Given the unfortunate outlook, quality of life should be a key consideration when advising patients who are considering any invasive therapeutic options.

## Clinical Pearls

- Metastatic lesions are considered to be the most common type of intraocular malignant tumor in adults. Since these patients are frequently terminally ill and usually have concurrent metastases to other organ systems, the diagnosis is often made in an alternate setting, such as tertiary care centers, hospitals, nursing homes or even on autopsy studies.
- While the choroid is the most common site of ocular metastasis, numerous other tissues can be involved, including the eyelids, iris, ciliary body, retina, optic nerve and even the vitreous. Anterior segment metastases account for less than 15% of reported cases.
- Perhaps more important than treating the choroidal lesions associated with ocular metastasis is ensuring that the primary neoplasm is properly addressed, especially if the patient presents without a prior diagnosis of cancer.
- An immediate referral to an ocular oncologist in all suspicious cases is warranted. Unfortunately, ocular oncologists are relatively few in number. The Eye Cancer Network (www.eyecancer.com) can assist in searching over 200 specialists in more than 50 countries around the world.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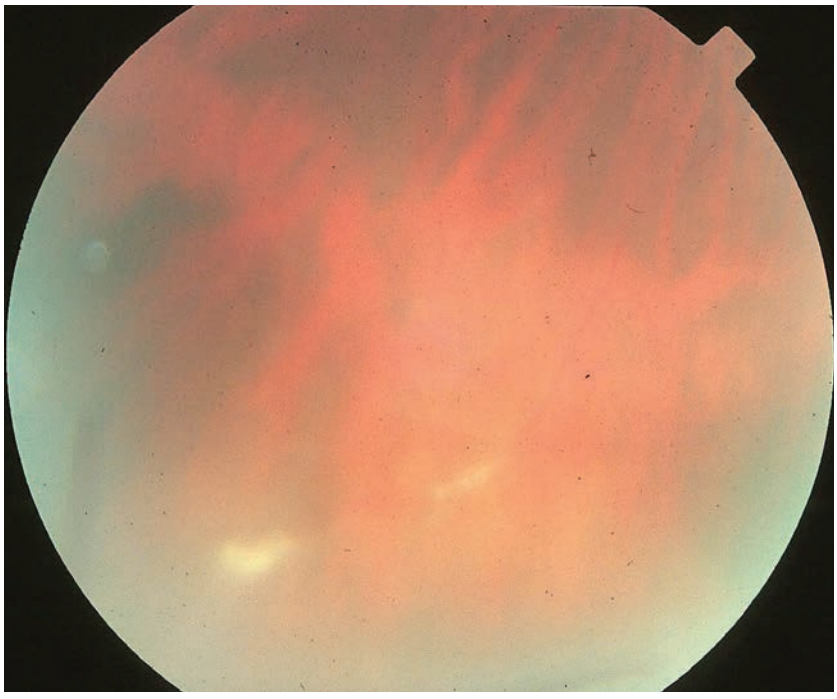
## POSTERIOR UVEITIS

### Signs and Symptoms

Posterior uveitis is an encompassing term indicating inflammation of the posterior segment. The inflammation may be posterior, intermediate or panocular. As the causes of posterior uveitis are numerous, so are the signs and symptoms. Patients with posterior uveitis typically complain of vision reduction, floaters and possibly visual field loss. Pain, photophobia and lacrimation, typical of anterior uveitis, are usually absent in cases of posterior uveitis. Due to the myriad potential causes, there is no identifiable age, sex or racial predilection. However, for each cause of posterior uveitis, there may be a racial, gender or age predominance.

Posterior uveitis is a set of conditions that can be broadly ascribed to either an infectious or noninfectious inflammatory cause. As such, patients may have a preexisting diagnosis of an infectious disease such as histoplasmosis, toxoplasmosis, toxocariasis, syphilis, tuberculosis, herpes simplex, herpes zoster, cytomegalovirus, West Nile virus, Dengue fever, Chikungunya, Rift Valley fever, rickettsioses or bacterial or fungal septicemia. Alternately, patients may suffer from a diagnosed inflammatory condition such as Behçet syndrome or sarcoidosis. Patients with no known medical conditions may manifest posterior uveitis as the initial marker of an infectious or inflammatory condition.[1-8]

Clinical findings vary depending upon the cause of posterior uveitis and may include vitritis, posterior vitreous detachment (PVD), cystoid macular edema (CME), retinal and anterior segment neovascularization, cataract, serous retinal detachment, retinal hemorrhage, vitreous hemorrhage, chorioretinitis, vasculitis, solitary tumor-like masses, retinochoroidal punctate or plaque-like lesions, retinitis and neuroretinitis, granulomas, occlusive retinal vasculitis, optic neuritis, choroidal and retinal infiltration, inflammatory exudates ("snowballs" and "snow banks"), and "candle-wax drippings" adjacent to retinal vessels, to name a few.[1-8]



Inflammatory exudate in posterior uveitis.

### Pathophysiology

Like virtually all inflammations within the body, posterior uveitis in its most basic form represents an antigen-antibody response. Infectious agents such as tuberculosis, syphilis and herpes viruses are the antigenic stimuli. In noninfectious posterior uveitis, various conditions can initiate an autoimmune response where the body reacts to its own tissues. There has been research and speculation regarding the underlying pathophysiology of posterior uveitis with regard to the mechanisms producing inflammatory cell damage to the retina. Inflammatory CD4 T-cells, effector macrophages and proinflammatory cytokines have been implicated, disrupting immune privilege in the posterior segment of the eye.[9]

### Management

A thorough history may identify a potential etiology of posterior uveitis or, at minimum, direct a tailored medical evaluation. A crucial initial part of managing patients with posterior uveitis is determining if the cause is infectious or inflammatory. Infectious causes of posterior uveitis respond well to disease-specific oral or intravenous antimicrobial therapy. Once an infectious cause has been eliminated, inflammatory posterior uveitis can be treated with oral, intravenous or intraocular immunosuppressive anti-inflammatories.[10] However, if systemic or intraocular steroids are employed in cases of infectious posterior uveitis without concurrent antimicrobial therapy, the immunosuppression can significantly worsen the condition.

Many cases of posterior and intermediate uveitis—such as toxoplasmosis, pars planitis, histoplasmosis and retinal white dot syndromes (acute posterior multifocal placoid pigmentary epitheliopathy or birdshot choroidopathy)—can

be diagnosed ophthalmoscopically. However, conditions such as syphilis and sarcoidosis may present with nonspecific findings of posterior inflammation; the definitive diagnosis must be made through laboratory investigations.

Whenever possible, a medical evaluation tailored towards the most likely causes based upon the clinical examination, the patient's systemic signs and symptoms and epidemiology should be undertaken. Depending on the suspected etiologies, medical evaluation may include venereal disease research labs, rapid plasma reagin, fluorescent antibody absorption testing, anti-toxoplasma enzyme linked immunoassay titers, tuberculin skin test, chest X-ray and angiotensin converting enzyme.[1,8]

Should an infectious cause of posterior uveitis be discovered, appropriate systemic antimicrobial therapy can be employed as follows:

For toxoplasmosis, recommended treatments include Daraprim (pyrimethamine, GlaxoSmithKline) and sulfadiazine or Bactrim (trimethprim/sulfamethoxazole (Hoffmann-LaRoche) for four to six weeks. For cases of posterior uveitis caused by syphilis, IV aqueous penicillin G is recommended. Should tuberculosis be identified, possible treatments include isoniazid, Rifadin (rifampin, Aventis), pyrazinamide and Myambutol (ethambutol, X-GEN Pharmaceuticals) for up to seven months. Some, including the military, recommend or require nine-month treatment courses. Care must be taken when using these agents as toxic optic neuropathy may ensure. Viral causes are treated with oral Zovirax (acyclovir, Delcor Asset), Valtrex (valacyclovir, GlaxoSmithKline) or IV ganciclovir. There is no well identified treatment for toxocariasis.[1,8]

Should infectious causes be ruled out and the condition is considered strictly inflammatory, then systemic anti-inflammatory therapy is employed. Sustained-release intraocular corticosteroid treatment has shown to be an effective strategy for the treatment of noninfectious posterior uveitis. Currently, there are three approved sustained-release intraocular corticosteroid implants: Ozurdex (dexamethasone, Allergan), Retisert (fluocinolone acetonide, Bausch + Lomb) and Iluvien (fluocinolone acetonide, Alimera Sciences).[11-17] These sustained-release intraocular implants have been shown to be very effective in controlling inflammation and improving visual acuity in eyes with noninfectious posterior uveitis.[11-17]

An alternative to sustained-release corticosteroids has always been systemic steroids and other immunosuppressants. The drawback to systemic therapy is that it is nonspecific; long-term use of some of these agents may induce significant adverse effects.[18] However, it has been shown that systemic corticosteroids plus immunosuppression for noninfectious intermediate, posterior and panuveitis is effective and well tolerated.[19] While sustained-release corticosteroid implants largely avoid systemic adverse effects, they do carry the risk of cataract and elevated intraocular pressure with subsequent glaucoma.[20] However, the intensive, site-specific anti-inflammatory action of sustained-release implants may have better ability to control inflammation in posterior uveitis.[21]

## Clinical Pearls

- Many conditions that cause posterior uveitis, including toxoplasmosis and the white dot syndromes, can be diagnosed ophthalmoscopically. However, many patients present with nonspecific findings such as vitritis and vasculitis where the diagnosis is not evident. In all cases, medical evaluation is necessary.
- Infectious etiologies of posterior uveitis must be eliminated before systemic or intraocular steroid therapy is used.
- There is no evidence that topical corticosteroid therapy is effective for posterior uveitis.
- Vitritis from posterior uveitis commonly causes PVD. Consider vitritis and posterior uveitis in young PVD patients.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## CYSTOID MACULAR EDEMA

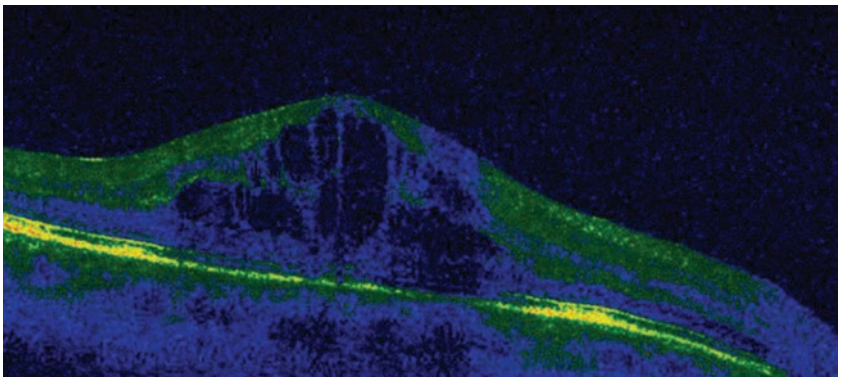
### Signs and Symptoms

Cystoid macular edema (CME), not a true diagnosis but a finding arising from numerous causes, is named for its intraretinal polycystic histopathologic appearance.[1-6] The term is overly used by many to indicate Irvine-Gass syndrome, which is characterized by intraretinal swelling with a petaloid (like the petals of a flower) fluorescein angiographic appearance that results when fluid fills into intraretinal cystic spaces surrounding the macula postoperatively following complicated intracapsular cataract extraction with vitreous loss.[2-5] Today, the term CME is used to describe this type of macular edema (easily confirmed with OCT) whenever it is discovered.[6,7]

Causative factors include ocular eye drop preservatives, topical prostaglandin analogs (rarely, and if there is an open posterior capsule), topical beta-blockers, retinal vein occlusion, diabetes mellitus, central serous chorioretinopathy, anterior or posterior uveitis, pars planitis, retinitis pigmentosa, radiation retinopathy, posterior vitreous detachment, epiretinal membrane formation, macular retinal telangiectasia, post Nd:YAG laser procedure and blunt trauma, to name a few.[2-18] Given the broad base of potential causative pathologies, with the exception of cataract surgery where some hard predictive data exists, the epidemiology for the formation CME rests with the particulars of the inciting disease.[2-18] After cataract surgery, the second most common cause of CME is diabetes.[2]

Historically speaking, pseudophakic cystoid macular edema (PCME) was first described in 1953 by A. Ray Irvine, Jr., who observed that some patients had unexplained visual loss following intracapsular cataract extraction.[4,5] The underlying cause of the visual loss was later identified by Gass and Norton.[2,4,5] They added to the work of Irvine, documenting a phenomenon exhibiting a perifoveal petaloid pattern of staining along with late leakage from the optic nerve upon intravenous fluorescein angiography (IVFA).[4,5] The condition came to be known as Irvine-Gass syndrome.[2] Today, the incidence of PCME has decreased significantly for several reasons: the transition from intracapsular to extracapsular cataract surgery; development of small-incision phacoemulsification; deployment of small incision foldable lenses; improved technology enabling less intraoperative energy use; faster surgical times with better intraoperative cushioning agents; initiation of preoperative anti-infective/anti-inflammatory agents, and the development and use of better topical anti-inflammatory agents. While the modern incidence of PCME-related symptoms (defined as symptomatic vision loss 20/40 or worse) is only approximately 0.1% to 2.35% of all cases, an estimated 20% to 30% of patients undergoing phacoemulsification will demonstrate some form of mild PCME on IVFA.[4] The rate has been estimated to be as high as 41% using OCT.[3] Fortunately, most patients who have PCME detected with IVFA or OCT imaging have no visual disturbances and require no intervention.[4]

The predominant symptoms caused by CME of any etiology is visual distortion (metamorphopsia) and acuity reduction.[2-18] Visual acuity may be minimally reduced or can decrease to 20/400.[3-18]



OCT imaging of prostaglandin-induced cystoid macular edema.

The ophthalmoscopic appearance of perifoveal retinal thickening is difficult to observe. The normal appearance of retinal tissue should be transparent and flat. Edematous retinal tissue can be stereoscopically appreciated using indirect biomicroscopic technique as being raised, having depth and with an opalescence contributing to both the tissue's cloudiness and an inability to discern underlying choroidal detail.[2] In most cases, however, a frank petalloid appearance is not appreciable. In severe cases, intraretinal cysts and the gathering of luteal pigment can create a radiating or oval yellow nodule in the region of the macula.[2] With indirect lighting, a honeycombed appearance may be discernable, corresponding to the delineation of the individual fluid-filled cysts.[2] The compromise to the precise foveomacular retinal architecture often causes a loss of the foveal light reflex. The true petaloid appearance of CME is best appreciated with fluorescein angiography.[2-4] OCT testing is preferred when possible, as it permits non-invasive observation of the cystic, fluid-filled spaces.[6]

### Pathophysiology

Cystoid macular edema is not a specific disease, but rather a clinical feature occurring in a number of conditions. Intracellular fluid and Müller cell swelling produce the condition's distinctive hexagonal appearance.[2] When the fluid

remains intracellular, the effects of the disruption remain reversible.[2] Once the cellular membranes rupture, giving rise to extracellular leakage, the damage is both irreversible and more significant.[2] Leaking perifoveal capillaries, subject to the pathophysiology of the underlying cause, go on to create the formation of intraretinal polycystic fluid-filled spaces which disrupt light from reaching the photoreceptors and retard efficient dialogue to the visual pathway.[2-4] Exudative or transudative fluid collects in the loosely arranged outer plexiform layer of Henle (where the axons of the photoreceptors synapse with the dendrites of the horizontal, bipolar and amacrine cells). The fibers in Henle's layer are horizontally arranged, allowing maximum light transmission. This is what creates the fovea's parabolic shape with the thinnest region being the foveola. This anatomy, along with the sequential filling of cysts, fosters the petaloid appearance seen during fluorescein angiography.[3,4]

Various factors and mechanisms are involved in the pathogenesis of CME, including the release of endogenous inflammatory mediators such as prostaglandins.[2-4] Light toxicity from the operating microscope and mechanical irritation of the internal ocular tissues are also provocative.[2-4] Inflammatory mediators disrupt the blood/aqueous barrier (and blood/retinal barrier), leading to increased vascular permeability.[2-4] Any disease process that can break down these barriers can induce CME.[2-21] Surgical manipulation may lead to the excessive release of arachidonic acid from cell membranes with production of either leukotrienes via the lipooxygenase pathway or prostaglandins via the cyclooxygenase pathway.[2-4] These inflammatory biomarkers can result in increased retinal vessel permeability and the development of CME.[2-21] Light toxicity from the operating microscope may contribute to free radical release with subsequent prostaglandin synthesis.[2-5] Prostaglandins contribute to tissue inflammation, increasing vasodilation and vasopermeability.[2] Any contraction of the posterior hyaloid membrane as a result of epiretinal membrane formation secondary to surgical procedures, inflammation from disease processes, anomalous posterior vitreous detachment, or vitreomacular adhesions may lead to traction onto the perifoveal retinal capillaries and the vasogenic and cytotoxic factors that produce CME.[2,21]

In cases of CME occurring from any form of uveitis, it can logically be assumed that the inflammatory process initiated by released prostaglandins contributes to perifoveal capillary dilation with increased permeability with fluid exudation.[2,7,20] The same reasoning can be extended to CME occurring secondary to prostaglandin analog use in the management of glaucoma. This is more prevalent in patients that have undergone incisional ocular surgery with an opened posterior capsule, which, theoretically, allows easier access deep into the eye.[2,9,10] Chronic CME can permanently alter the macular architecture via rupture of the inner wall of the foveal cystoid spaces.[24] This transformation is accompanied by a substantial reduction in macular thickness known as a lamellar macular hole (LH).[2,21-24] LH typically does not lead to changes in visual function.[24] There have been cases of full-thickness holes resulting from CME treatments with injectable steroids such as triamcinolone.[25]

## Management

When CME is caused by conditions such as diabetes, retinal vein occlusion, retinitis pigmentosa or uveitis, the treatment is dictated by standards of care for the causative condition.[2-34] Cases of CME arising from diabetic retinopathy or retinal vein occlusion would warrant consideration of focal/laser photocoagulation of the leaking perifoveal capillaries, alone or in combination with injections of anti-VEGF such as Avastin (bevacizumab, Genentech), Lucentis (ranibizumab, Genentech) or Eylea (aflibercept, Regeneron), intravitreal steroid injections or intravitreal steroid implants. In inflammatory diseases such as uveitis, pars planitis, scleritis and retinitis, topical cycloplegics such as atropine 1% BID-TID, along with topical and oral nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressants, laser photocoagulation and anti-VEGF agents are often considered.[31-33]

Medications for CME include the oral nonsteroidal medicines ibuprofen and indomethacin and the corticosteroid prednisone. Topical nonsteroidal medications such as ketorolac, nepafenac and bromfenac have also been successful. Topical corticosteroid drops such as prednisolone acetate, loteprednol etabonate and difluprednate can be added for unresponsive or more severe cases.[2-5,34,35] Common dosing ranges from QID to Q2H. Often a loading dose of Q2H is initiated and then rapidly dropped to QID after several days. Duration of therapy may be several days to months, depending upon the severity of the CME.[2-18,34,35]

Oral carbonic anhydrase inhibitors (CAIs) like acetazolamide and methazolamide have been documented as helpful in recalcitrant cases of CME.[36] These agents increase active transport by the retinal pigment epithelium to facilitate fluid movement from the retina through the choroid.[36] They work best in cases caused by diffuse retinal pigment epithelial failure (retinal dystrophies).[36] The use of these agents is limited to the patient's ability to tolerate the medication's side effects.[36] Topical CAI agents have been tested, yielding reduction in retinal thickening without significant gains in visual acuity.[36]

The majority of cases of symptomatic CME following cataract surgery resolve spontaneously without intervention within eight months, and many cases

resolve faster.[2-6,34] In rare instances, CME can remain angiographically or tomographically detectable in excess of five years, though patients may not be visually disturbed.[2]

In cases where vitreous traction has induced or contributed to the formation of CME, surgical vitrectomy has demonstrated success.[37] New endoscopic laser delivery systems allow surgeons the option of shaving the vitreous without having to complete removal.[37] The effectiveness of vitreous surgery with internal limiting membrane (ILM) peeling stems from relief of posterior hyaloid membrane traction, removal of inflammatory cytokines and increasing preretinal oxygen pressure.[37] It is hypothesized that the ILM is the basement membrane of the Müller cells and may act as a diffusion barrier decreasing transretinal fluid movement.[37] New investigations seek to duplicate the results seen in vitrectomy using intravitreal pharmacologic agents.[37] Vitreosolve (Innovations in Sight), a carbamide derivative, is currently being evaluated in Phase III randomized controlled trials in patients with nonproliferative diabetic retinopathy (NPDR).[37] Jetrea (ocriplasmin, Thrombogenics), an intravitreally injected fragment of plasmin currently being used to treat vitreomacular traction syndrome, is also being studied as a treatment for DME in a sham-controlled trial.[37] Surgeons have found synergistic effects by mixing radial sheath optic neurotomy, pars plana vitrectomy with ILM peeling and postoperative intravitreal triamcinolone injection for the treatment of continuing retinal vein occlusion-induced CME.[37]

## Clinical Pearls

- CME remains a potential complication of cataract extraction even in uncomplicated cases.
- CME following a cataract procedure is more likely in cases when the capsule has been ruptured or the vitreous incarcerated.
- Clinically significant macular edema (CSME) refers to the location of the perifoveal swelling as defined by the Early Treatment of Diabetic Retinopathy Study (ETDRS). The histopathology of the intraretinal fluid accumulation is polycystic.
- When oral or topical steroids are used, intraocular pressure must be monitored. If the pressure rises, it must be treated with an ocular hypotensive that has a low risk for aggravating the condition. As such, avoid prostaglandin analogs.
- Amsler grid home monitoring can be used to track the progress of recovery and ensure condition stability. OCT testing can be used in office.
- Prostaglandin analogs should be used with caution in patients with a history of incisional ocular surgery, especially if there is also a broken posterior capsule.
- A prime cause of vision reduction in posterior uveitis is CME.
- If left untreated, CME may predispose the eye to form a macular cyst or lamellar hole.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## RETINAL EMBOLI

### Signs and Symptoms

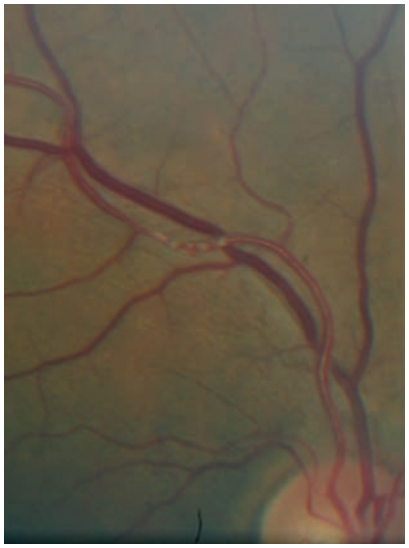
The word *embolus* comes from the Greek word *emballein*, meaning "wedge-shaped stopper." Today, the term is used to describe an abnormal particle within the circulatory system.[1-10] Patients observed to have retinal emboli are typically elderly and often have a concurrent history of hypertension, diabetes, carotid artery disease, peripheral vascular disease, blood dyscrasia, hypercholesterolemia, hyperlipidemia, smoking and atherosclerosis.[2-20] The three most common retinal emboli are cholesterol (Hollenhorst plaque), fibrinogen platelet aggregate (fibroemboli, or Fisher plug) and calcium (calcific valvular debris).[11-13] Other exogenous and endogenous sources of embolic material include air, infectious/inflammatory debris, talc and amniotic fluid.[14-20]

Emboli are markers of local or systemic processes, not a disease per se.[2-17] Patients with retinal emboli are often asymptomatic, with plaque found during routine dilated eye examination. Since they represent intravascular matter capable of interrupting blood flow, similar to the way corrosive material can block the flow of fluid thorough a pipe, patients who form emboli often present having experienced transient episodes of interrupted function.[5,8,12,20] This might manifest as tingling or weakness of limbs or a momentary loss of dexterity or altered mentation.[18,19] In the eye, these particles can produce varying degrees of monocular vision loss and visual field disturbance.[7,8,20-27]

Today, these episodes of transient monocular vision loss (TMVL), historically termed *amaurosis fugax* (from the Latin and Greek meaning "fleeting darkness"), constitute a transient ischemic attack (TIA). TIAs are focal ischemic events lasting less than 24 hours (most resolving within minutes) with no subsequent neuroimaging abnormalities.[20,21] Symptoms that arise are consistent with the extent and portions of the affected vascular stream.[20] Patients experiencing TVML/TIA secondary to retinal embolization have described episodes of visual blur, visual fuzziness (sometimes referred to as transient visual obscurations or TVO), altitudinal and sector field loss, "blotchy/patchy" field loss, visual dimming and the experience of "a curtain coming down over their eyes."[20]

Embolic TIA may often include more complicated and integrated presentations with additional neuro-systemic findings such as hemiparesis, paraesthesia, dysphagia and/or altered mentation.[18,19,21] In the absence of complete retinal artery occlusion, emboli-associated TIA/TMVL, whether lasting seconds or hours, permits full restoration of function as the plaque dissipates, flows downstream, or shifts position.[20,21,27] TIA/TMVL may be non-embolic and can also serve as a clue for hemodynamic (blood dyscrasias), vascular (giant cell arteritis), cardiac (myopathy), vasospastic (migraine) and inflammatory (optic neuropathy) events.[2,13-21] This is another reason why no retinal emboli are seen upon examination in patients with TIA/TMVL.[7,20] Ophthalmoscopic clues persist, allowing the clinician to observe related clinical manifestations, including Roth spots, cotton wool spots, flame-shaped hemorrhages, arteriolar narrowing, venous nicking, increased arterial light reflex or venous sheathing.[7,13-21]

Ophthalmoscopically, intra-arteriolar or intracapillary plaques are seen as one or more small, round to oval, white/yellow masses.[20-25] Emboli trapped in capillaries may appear suspended as the vessel walls are too small to be appreciated. Larger obstructions typically lodge in retinal vessels near the optic disc or at a vessel bifurcation.[7,9] Simultaneous bilateral involvement is possible but uncommon. There may be multiple emboli within the same eye.



Multiple retinal emboli within the superior temporal branch of the central retinal artery.

The incidence and epidemiology of retinal emboli depend on the disease influencing their production.[9-23] Incidence is approximately 1.5% in the general population with an increasing prevalence associated with Caucasian race, increased age (>70 years) and male gender.[3,9,10,22,23] There is increased risk of stroke, with decreased survivorship with the appearance of retinal emboli.[9,26]

### Pathophysiology

The mechanism by which an embolus creates compromise—whether in the eye, an organ or the central nervous system—is through mechanical obstruction of blood flow.[13-28] The formation of cholesterol and fibrinogen platelet emboli is related to progressing arteriolar and atherosclerotic disease.[5,12,13,20,26,28] Here, the end process creates an atheroma, which leads to atheromatous

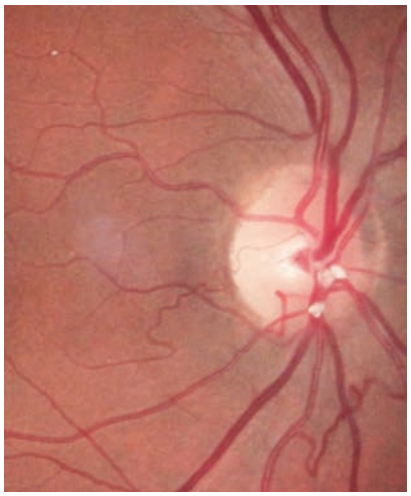
plaques that cause vascular endothelial rupture, casting participating cholesterol crystals, clotting elements and immune system cells into the lumen.[12,13,20,28] Lipid retention, inflammation, phosphate signaling and osteogenic transition play roles in the development of cardiovascular calcific valve disease.[29,30] When the friction of cardiac output pries them loose, they become calcific emboli.[20,29-31]

Once an embolus has entered the circulatory system, it will travel until it lodges in a vessel whose caliber will impede further flow. If blood flow is significantly impaired distal to the blockage, ischemia to that tissue will ensue. In the eye, if the embolus completely obstructs blood flow, retinal ischemia with corresponding vision loss occurs secondary to retinal artery occlusion. In the case of cholesterol emboli, most blockages quickly dislodge without permanent vision impairment, and the patient may experience TMVL.[7,20,27] Multiple bouts of TMVL may indicate multiple emboli or secondary partial interruptions outside the boundaries of the eye.

The physical appearance of the embolus is determined by its makeup. Hollenhorst plaques are composed mainly of cholesterol. They present with a reflective or retractile appearance.[24,25] Calcific plaques such as those generated by the dislodged debris from the valves of the heart have a white, dull and bulky presentation.[10] Fibrinogen-platelet plaques have an elongated, white, chalky presentation, resembling caulking within the vessel.[1,4,7,9,10,22-25] Cholesterol emboli are the most commonly encountered, representing 80% of emboli.[10] Fibrin-platelet emboli represent 14% of emboli and calcific emboli account for just 6% of visible retinal emboli.[10]

## Management

There is no direct treatment for asymptomatic visible retinal emboli. In fact, when blood flow is uninterrupted, ocular intervention is contraindicated.[20,27] The proper approach to patients manifesting TIA/TMVL or visible asymptomatic retinal emboli is to find the underlying cause. Patients should be referred to their internist with appropriate correspondence explaining the findings and recommending a course of action.[20] Reasonable first round testing should rule out hypertension, atherosclerosis, diabetes, coagulopathy, hyperviscosity, carotid artery disease and cardiac sources. The first wave of laboratory testing should include a complete blood count with differential and platelets (CBC c Diff and PL), a lipid panel, an echocardiogram with ultrasound of the heart valves (ECG c 2D echo), sphygmomanometry, fasting blood sugar (FBS), prothrombin time (PT), and partial thromboplastin time (PTT).[3-27]



**Large emboli near the origin of the retinal vasculature.**

The key to visual recovery in any persisting embolic retinal arterial occlusion is timely intervention. The potential for recovering any vision is greatest when the blockage is dislodged within 100 minutes of the onset of the first symptoms.[32,33-37] While frequently unsuccessful, all treatments are designed to increase retinal perfusion by re-establishing retinal blood flow.[33-37] The traditional acute intervention for new onset artery occlusion is intraocular pressure lowering and digital ocular massage. Fast-acting topical pharmaceuticals such as timolol 0.5%, apraclonidine 1% or brimonidine 0.1% and oral carbonic anhydrase inhibitors (such as two acetazolamide 250mg tablets PO or neptazane 50mg PO) lower intraocular pressure for the purpose of lowering the resistance to ocular perfusion. Simultaneously, aggressive digital palpation with sudden release will stimulate retinal autoregulatory mechanisms so that arterioles and capillaries vasodilate, allowing the embolus pass downstream. This also creates vascular back-pressure, which when released might force embolus dislodgement.[32-34] If these actions fail, emergent paracentesis will rapidly drop the IOP to zero, fostering minimal resistance to in-flow.[36] An alternate strategy involves stimulating retinal vascular dilation by increasing blood carbon dioxide levels, either by breathing into a paper bag or by inhaling a carbogen mixture (95% oxygen, 5% carbon dioxide), or with sublingual nitroglycerine.[32,36]

The oral agent pentoxifylline has been used to increase red blood cell (RBC) deformability, with the hope of allowing easier RBC passage through the capillaries. New strategies include attempting to vaporize retinal emboli via Nd:YAG laser; however, this procedure is still being refined.[24,31] Selective intra-arterial ophthalmic or meningo-ophthalmic artery thrombolysis using thrombolytic agents such as urokinase or tissue plasminogen activating factor (tPA) has also been attempted with mixed success.[35] Hyperbaric oxygen ($HBO_2$) has demonstrated promise for incomplete central artery occlusions when instituted within eight to 24 hours of the onset of the event.[37] If the patient responds to $HBO_2$, follow-up treatment with supplemental oxygen can be customized to maintain retinal viability until the obstructed retinal artery recanalizes, typically within 72 hours.[37] Unfortunately, even given these innovations, heroic

measures rarely impact the final outcome.[32-37]

For all cases of retinal embolization, the concern must be subsequent occurrences with permanent retinal infarct, cerebrovascular accident or myocardial infarction. A preventative approach dictates that all modifiable risk factors, such as diet, obesity, sedentary lifestyle and smoking, be altered. Magnetic resonance angiography, transthoracic and transesophageal echocardiography may be indicated.[7] There is poor consensus on the need for carotid ultrasonography in patients with asymptomatic retinal emboli, as the majority of these patients do not have high grade carotid stenosis.[5,9,24,25,38] Thus, carotid imaging is not necessarily mandated in patients with visible retinal emboli.

A large population study, collecting data over a 10- to 12-year period, found a 30% rate of mortality for those who presented with retinal emboli, with 4% dying from stroke-related complications and 16% from cardiovascular causes.[26] These death rates were greater than those for age-matched people not having retinal emboli. There is no clear indication for carotid endarterectomy in patients with asymptomatic retinal emboli, even in the setting of concurrent high grade carotid stenosis.[5,9,38-40] There does seem to be a benefit to carotid endarterectomy in patients with TIA/TMVL and high-grade carotid stenosis.[41]

## Clinical Pearls

- Retinal emboli can be difficult to detect ophthalmoscopically.
- Older males with a history of hypertension and smoking are at greatest risk for retinal emboli. The retinal arterial tree should be examined most closely in these patients.
- Asymptomatic retinal emboli are not highly associated with severe carotid stenosis. Carotid ultrasonography may be suggested, but is not required.
- Retinal artery occlusion is rarely reversible; however, treatment should be attempted out of compassion and the possibility, however slight, of a positive outcome.
- Patients with asymptomatic retinal emboli are typically not endarterectomy surgical candidates, especially if they are older than age 70.
- The most significant modifiable risk factor for retinal emboli is smoking. Smoking cessation is crucial in reducing the risk of future embolic phenomenon in patients with asymptomatic retinal emboli.
- Rather than automatically ordering carotid studies, it may be preferable to refer the patient to a primary care physician and recommend an atherosclerotic evaluation.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# RETINAL ARTERIAL MACROANEURYSM

## Signs and Symptoms

Retinal arterial macroaneurysms (RAM) are acquired saccular or fusiform dilatations of the large arterioles of the retina.[1-7] They are usually observed within the first three orders of bifurcation and can occur at arteriovenous crossings as well.[4,7] Patients who develop RAM are typically between the ages of 50 and 80.[1-7] They rarely occur in younger patients, but when they do the most consistently associated systemic disease is hypertension.[7] There appears to be a female preponderance.[4-6] The most common comorbidity is systemic arterial hypertension, occurring in approximately 80% of patients.[1-7] There is also an increased incidence of cardiovascular disease and arteriosclerosis.[5,6]

Ophthalmoscopically, RAM appear as an exudative, dilated arteriole within a major vascular branch within the first three bifurcations.[1-9] In rare circumstances, they can occur just off of the optic disc.[10] RAM are typically unilateral, but may be bilateral or multifocal.[3,5] In many cases, unruptured lesions remain asymptomatic until discovered during routine dilated exams.[1,2] Even without loss of function, by the time the patient presents to the clinician, there has often been significant leakage into surrounding areas, manifesting as visible exudates with variable presentations of pre-, intra- or subretinal hemorrhage.[1-9] Vitreous hemorrhage may also occur with RAM.[11-18] Occasionally, spontaneous pulsation of an unruptured aneurysm may be noted.[6]

When there is extensive intraretinal or pre-retinal bleeding, it is often difficult to identify RAM as the cause, especially if they are in an unusual position such as closer to the disc.[10] In these cases, neovascularization is often misdiagnosed as the source.[10] If focal dilatation is questionable ophthalmoscopically, OCT and fluorescein angiography can provide diagnostic evidence.[1,6,9] Eyes with RAM imaged with spectral domain-OCT demonstrate a round hyperreflective wall with a hyporeflective lumen.[9] With fluorescein angiography, the aneurysms will hyperfluoresce early in the angiogram, revealing a characteristic balloon appearance that demonstrates leakage in the recirculation phase.[5,7] In cases where OCT or fluorescein imaging is contraindicated secondary to extensive hemorrhage, indocyanine green (ICG) angiography, which images in the infrared spectrum, may support visualization through blood, fluid and lipid, identifying the aneurysmal dilatation.[7,11,12]

Vision and field loss from RAM are directly related to the size and location of leakage (blood and products, lipid and macular edema).[1-21] RAM rupture has a strong association with the development of macular holes and retinal detachment, which can leave patients with profound vision loss despite complete resolution of the leakage from the initial lesion.[19-25] Additionally, RAM have been seen in association with retinal telangiectasias, arterial emboli and vein occlusion.[5,26]

## Pathophysiology

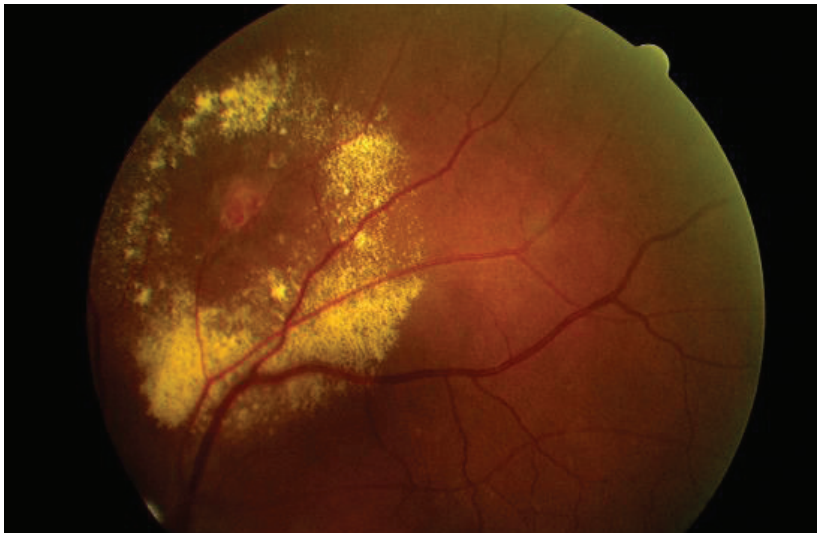
Retinal arterial macroaneurysms are acquired out-pouchings of the retinal arterioles.[1-5] These balloon-like formations are caused by a break in the internal elastic lamina of the arteriole wall, through which serum, lipids and blood exude into the surrounding retina.[27] The lesions seem to have an affinity for the bifurcations of vessels where structural integrity is weakest.[7] Aging arterioles demonstrate an increase in intimal collagen and replacement of medial muscle fibers by collagen, making them less elastic.[5] This loss of elasticity makes arterioles more susceptible to dilatation from elevated hydrostatic pressure occurring in hypertension.[5] The strong association of RAM with hypertension/atherosclerosis supports this process and mechanism. There are two types of RAM: saccular, where the vessel develops one or more prominent out-pouchings; and fusiform, where there is less obvious focal widening and more general widening of the affected artery.[4-7]

## Management

The natural course of RAM typically involves spontaneous sclerosis and thrombosis, particularly after hemorrhaging.[5,6,27-31] For this reason, so long as there is no increased threat of macular hemorrhage, periodic observation is indicated.[27-31] Asymptomatic nonleaking RAM may be monitored at four to six month intervals. If there is leakage in the form of exudation, hemorrhage, or both, that does not threaten the macula, then monitoring at one to three month intervals is indicated.[27-31]

If hemorrhage threatens or involves the macula or if there is persistent macular edema reducing vision or creating visual field loss, then direct photocoagulation of the RAM may speed resolution.[1,4-6,28,30-34] In these cases, moderately intense photocoagulation is applied directly to the RAM so as not to produce complete occlusion of the involved artery, but to induce coagulation and subsequent thrombosis.[23] Alternately, to avoid potential arterial occlusion, perianeurysmal laser application can be performed.[32] In the event a nonhemorrhagic RAM is observed to be spontaneously pulsating, immediate direct photocoagulation is indicated, as ensuing rupture is likely.[23,32]

The tunable dye yellow laser seems to provide the greatest flexibility in these circumstances.[33] Laser therapy works as



A large retinal arterial macroaneurysm displaying a circinate exudative response.

heat conduction extends into overlying nonpigmented and adjacent cells.[34] This approach is laden with complications, including enlarged laser scars, the potential for choroidal neovascularization, branch retinal artery occlusion, increased retinal traction with symptomatic metamorphopsia and subretinal fibrosis.[34] Recent advances in laser application techniques have produced the technique known as subthreshold laser photocoagulation/therapy.[34] Here, retinal hyperthermia is created below the cell death threshold by using a subvisible clinical endpoint.[34] Selective RPE damage is hypothesized to lead to an improved balance in angiogenic factors and cytokine release, improving endpoints and minimizing complications.[34,35] Studies have shown promise in creating similar clinical outcomes without the side effects seen with other lasers.[34,35]

The visual prognosis for eyes with ruptured or leaking RAM depends on the degree and type of macular involvement. In the majority of cases, there is gradual and spontaneous involution concurrent with hemorrhage resorption.[5,6,13,36] Eyes with vitreous hemorrhage or premacular subhyaloid hemorrhage typically recover good vision, while the vision in those with submacular hemorrhage generally remains poor.[13] Early vitrectomy is recommended for RAM-related vitreous hemorrhage to allow for observation of the fundus, particularly the macula.[11,32-40]

In cases where there is significant preretinal hemorrhage, resolution and drainage can be greatly assisted by Nd:YAG laser rupture of the internal limiting membrane in front of the hemorrhage.[13,20,37-39] Laser photodisruption of the posterior hyaloid membrane releases the preretinal hemorrhage into the vitreous space, where it can be more easily resorbed or surgically removed. More concerning and urgent are submacular hemorrhages that develop from RAM rupture, as they have the greatest potential for residual visual morbidity.[32,37-39] Submacular surgery to remove accumulated hematoma should be performed within several days of the development of submacular hemorrhage in order to prevent permanent photoreceptor damage.[11,13,18,38,39] Alternately, pneumatic displacement of the submacular hematoma can help reduce permanent vision loss.[38,39] Researchers are currently investigating anti-VEGF drugs for their ability to decrease the permeability of retinal arteries and normalize vascular walls by localized inhibition of VEGF.[19,41,42] Intravitreal Avastin (bevacizumab, Genentech) has shown promise as an effective therapy for complicated RAM and cases with submacular exudation. Reports have documented improved acuity along with normalized arterial and retinal thickness in treated cases.[19,41,42]

## Clinical Pearls

- In cases of unexplained vitreous, pre-, intra- or subretinal hemorrhage, consider RAM as the cause. RAM is an entity with the potential to produce hemorrhage anywhere from the subretina to the vitreous.
- When the characteristic balloon appearance is not readily observable ophthalmoscopically, then OCT, fluorescein or ICG angiography may aid diagnosis by providing a clearer portrait of the vessel's characteristic dilatation.
- There is a high rate of mortality in patients with RAM due to cardiovascular disease. Patients discovered to have RAM should be referred to a cardiologist for systemic evaluation.
- Laboratory testing, including a fasting blood glucose, complete blood count with differential and platelets, fasting lipid profile, blood pressure evaluation and electrocardiogram, are indicated.
- Macroaneurysms can occur also in a venule, but this is much more rare than occurrence in an arteriole.
- Physical exertion can cause rupturing of RAM.

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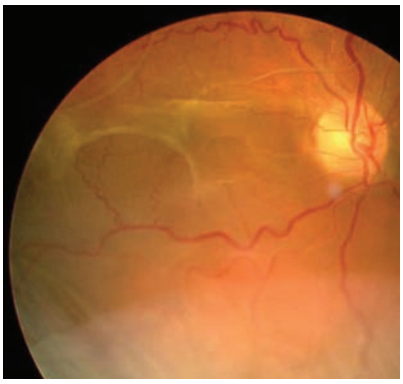
## SICKLE CELL RETINOPATHY

### Signs and Symptoms

The ocular signs of sickle cell anemia are variable and may include: comma-shaped vessels in the bulbar conjunctiva; iris atrophy; iris neovascularization; dull-gray fundus appearance; retinal venous tortuosity; nonproliferative retinal hemorrhages (which may be subretinal, intraretinal or preretinal) and salmon patch hemorrhages (orange-pink-colored intraretinal hemorrhages); black sunbursts (RPE hypertrophy secondary to deep retinal vascular occlusions); glistening retractile deposits in the retinal periphery (hemosiderin-laden macrophages); angioid streaks (breaks in Bruch's membrane radiating from the optic nerve); "macular depression signs" such as a loss of the foveal reflex; venous occlusion or artery occlusion; and peripheral neovascularization (in a "sea fan" appearance) with possible attendant vitreous hemorrhage and tractional retinal detachment.[1-8]

Ocular symptoms are uncommon in the early stages of any form of sickle cell disease (SCD).[9,10] Studies involving SD-OCT of the macular and peripapillary retina have uncovered that a large percentage of sickle cell patients have focal macular thinning with significantly decreased retinal sensitivity compared to those without focal thinning and normal controls.[11-13] This is an important new data point with respect to structural monitoring.[11-13] The discovery is also important as the finding may confound the diagnosis of glaucoma in patients being considered for or treated with concurrent disease.[11-13]

The exact number of people living with SCD in the United States is unknown.[14] The Centers for Disease Control (CDC) in collaboration with the National Institutes of Health and seven states (California, Florida, Georgia, North Carolina, New York, Michigan and Pennsylvania), have coordinated the Registry and Surveillance System for Hemoglobinopathies (RuSH) project to learn about the number of people living with disease and to formulate a better understanding of how the disease impacts the well-being of those affected. The CDC estimates it affects 90,000 to 100,000 Americans and occurs in one out of every 500 African-American births and one out of every 36,000 Hispanic-American births.[14] Sickle cell trait is estimated to occur in one out of every 12 African Americans with an incidence in the general population estimated at 15.5 per 1,000 newborns overall.[14,15] Among African-American newborns, the incidence has been estimated at 73.1 per 1,000 with 6.9 per 1,000 among



Sickle cell retinopathy is prone to proliferative vitreoretinal disease and may result in retinal detachment, as shown here.

Hispanic newborns.[15] Over the last 20 years, the incidence of sickle hemoglobin S in African-American births has been reported as 0.163%.[16]

## Pathophysiology

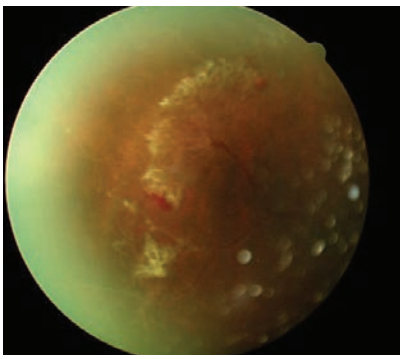
The hemoglobinopathies are a group of inherited disorders characterized by quantitative or qualitative malformations of hemoglobin (Hb).[1-7] Sickle cell disease is a life-threatening genetic disorder associated with acute and chronic complications that require medical attention.[1] From an ophthalmic perspective, the most important representation of this group of diseases is sickle cell retinopathy (SCR).[1-7] This presents with a wide spectrum of fundus manifestations, and it has the potential to lead to irreversible vision loss if not properly diagnosed and treated.[1-8]

Sickle cell disease is the most common genetic disease worldwide.[17,18] SCD can affect virtually every vascular bed in the eye and, if left untreated, can result in severe visual impairment through the development of proliferative retinopathy.[1-7,17] The origin of the genetic abnormality can be traced to Africa where data suggests that the mutation of the hemoglobin chain protected individuals from malaria infection.[9-18] The inheritance mode that induces the formation of the sickle cell hemoglobinopathies is autosomal codominant, with each parent providing one gene for the abnormal hemoglobin.[7] Abnormal hemoglobin S results following a single point mutation substituting valine for glutamic acid at the sixth position.[4,5] Substituting lysine for glutamic acid at this position results in the formation of hemoglobin C. When both parents contribute the S mutation, classic sickle cell anemia or SS disease ensues.[5,17,18] When one parent contributes S mutated hemoglobin and the other contributes C mutated hemoglobin, the SC form of the disease is created.[5,17,18] Inadequate production of either normal or abnormal globin chains creates the S-thalassemia (S-Thal) variant.[5,17,18] Incomplete expression of the disease with some of the genetic mutations produces sickle cell trait (AS).[5,17,18] In all four variations of SCD, systemic and ocular tissues have the potential to become deprived of oxygen secondary to inherited abnormalities of the beta-globin chain.[1,9,10,17,18]

Erythrocytes, having lost their biconcave shape, become rigid, restricting retinal blood flow, inducing thromboses; subsequently, tissues become hypoxic.[1-22] Vascular leakage and liberation of angiogenic cytokines with subsequent retinal neovascularization development (along with all of its attendant complications) dictate the severity of the condition.[1-19,12,23] The pathogenesis of the resultant retinopathy is ultimately a manifestation of arterial and capillary microcirculation obstructive-vasculopathy.[21] Various systemic complications of SCD are known to be more common in patients with the SS genotype, while visual impairment with more severe retinopathy is more common in the SC genotype.[18]

Salmon patch hemorrhages are preretinal or superficial retinal hemorrhages that often dissect into the vitreous humor.[5] They result from disruption of the medium-sized arterioles secondary to chronic ischemic-vascular compromise.[5] Although they are initially bright red, their color evolves. Because they have a tendency to push both forward and backward within the retina, they may leave a retinoschisis remnant when they finally resolve.[5] Since the movement of this blood can disturb the retinal pigment epithelium, irregularly shaped retinal pigment epithelial hyperplastic changes occur, producing the classic black sunbursts.[3-6]

The hallmark proliferative sign of sickle cell disease is the sea fan-shaped frond of neovascularization.[20] A common trait of the SC and S-Thal variations, sea fan neovascularization represents the body's aggressive attempt to supply oxygen to deficient retinal tissue.[5,7-19,22,23] Arteriovenous crossings are the preferential site for sea fan development.[14] Preretinal vascular formations develop from one or more feeder vessels at the border of perfused and nonperfused peripheral retina.[22,23] Since the retinal tissue is not globally ischemic, the abnormal vessels arborize along the border of perfused and starved tissue.[5,22,23] Drained by single or multiple venules, the classic kidney-shaped appearance is driven by environment. Vascular endothelial growth factors are associated with these formations.[20] The neovascularization in sickle cell retinopathy can arise from both the arterial and venous sides of the retinal vasculature.[23] Autoinfarction (complete or partial



Classic sea fan in sickle cell retinopathy.

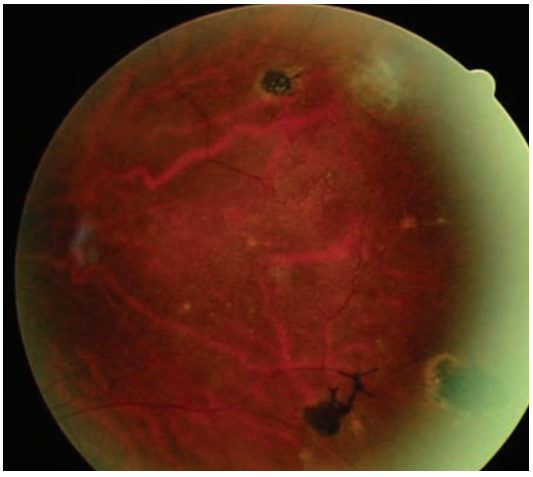
spontaneous involution) appears to occur initially at the preretinal capillary level rather than at the feeding arterioles and has been documented to occur in up to 50% of cases.[23]

Sickle cell retinopathy development is classically broken down into five stages. Stage one is recognized by peripheral retinal arteriolar occlusions. Stage two is marked by the appearance of peripheral arteriovenous anastamoses. Stage three is characterized by the growth of neovascular sea fan fronds. Stage four is marked by vitreous hemorrhage as tractional forces and vitreous collapse tear fragile neovascular membranes. Stage five is the advanced form of the disease, identified by severe vitreous traction and retinal detachment.[1-6, 22,23]

The diagnosis of clearly evident clinical comorbidities such as leg ulcer, osteonecrosis and retinopathy are considered predictors for developing lethal end-organ damage.[21] Fifty-one percent of patients with SCD who go on to have a cerebrovascular accident report a prior chronic collateral condition.[23,24]

## Management

The laboratory testing for SCD in patients with suspicious findings includes the Sickledex (Streck), Sickle Prep and plasma hemoglobin electrophoresis. The treatment for sickle cell retinopathy is aimed at reducing or eliminating retinal neovascularization.[9-20] Patients with asymptomatic SCD, in the absence of ocular manifestations, should be followed biannually with dilated retinal evaluation.[8-19] Referral to a retina specialist is indicated when proliferative retinopathy is seen. Treatment for proliferative disease includes pan or sector retinal photocoagulation. Cryotherapy has not been proven efficacious and is associated with high complication rates.[8] Scleral buckle procedure with or without vitrectomy may be indicated in cases of retinal detachment.[6,25,26] Modern techniques have made presurgical blood transfusions unnecessary.[26] Photodynamic therapy used in the treatment of other diseases known to produce choroidal and retinal neovascularization is not well documented as a therapy for sickle cell retinopathy.[1-6]



Black sunbursts and peripheral arteriovenous anastomoses are characteristic findings in sickle cell retinopathy.

Researchers are investigating antiangiogenic compounds as a potential adjunct for regressing sickle cell neovascularization.[27,28] Reports in the literature indicate there has been some success in individual cases using these formulations to stabilize the membrane's growth.[27,28] The current studies do not present enough numbers or a clear advantage over traditional membrane regression with laser photocoagulation to recommend their use. The compounds must undergo further investigation to determine if there is a beneficial role over traditional approaches.[27,28]

Systemically, genetic risk factors along with other preventative possibilities are also now being explored to extend life and reduce retinopathy progression.[22,24-31] Strong recommendations for prevention include daily oral prophylactic penicillin up to the age of five, annual transcranial Doppler examinations from the ages of two to 16 in those with sickle cell anemia and long-term transfusion therapy to prevent stroke in children with an abnormal transcranial Doppler velocity (≥200cm/s).[2,6] Opioids are recommended for treatment of severe pain associated with a vaso-occlusive crisis, and patients should be instructed to practice incentive spirometry in preparation for events which leave them in a hypoxic state.[2] A combination of non-narcotic analgesics and physical therapy is recommended for treatment of avascular necrosis, and angiotensin-converting enzyme inhibitor therapy for adults demonstrating microalbuminuria.[2]

Hydrea (hydroxyurea/hydroxycarbamide, Bristol-Myers Squibb) is an anticarcinogenic preparation that has significantly reduced the number of deaths and complications from sickle cell disease.[29,30] It increases fetal hemoglobin levels, which seems to prevent red blood cells from sickling.[29,30] The medication has demonstrated an ability to reduce the number of vaso-occlusive crises and acute chest problems, thereby reducing the severity and impact of the disease along with the number of hospitalizations. It also has demonstrated great efficacy and safety in reducing retinopathy in pediatric studies.[21,29-31]

Future therapies for SCD appear varied. Stem cell transplantation has been attempted with limited success, but with some increase in patient longevity, for at least two decades.[29] Niprisan (Nix-0699), an ethanol/water extract derived from four kinds of plants in Africa, has a naturally occurring anti-sickling agent which has demonstrated promise in experiments with mice.[32,33] It may offer the promise of an additional preventative solution in the future.[32,33] New research has led investigators to believe they may be able to stimulate the RPE to initiate production of hemoglobin.[34]

Monomethylfumarate was found to influence RPE cells to express globin genes and synthesize adult and fetal hemoglobin in cultured RPE and erythroid cells in SCD mouse retina.[34] The production also reduced retinal oxidative stress and inflammation.[33] Researchers feel there is future therapeutic potential.[34]

## Clinical Pearls

- With respect to the development of systemic symptoms, the sickle cell anemia variation SS produces the most symptoms. The SC and S-Thal mutations produce the most ocular effects. Overall, the sickle cell trait expression produces the fewest complications.
- The sea fan frond of neovascularization is so characteristic of this disease that, when encountered, must be the prime consideration in undiagnosed patients.
- Systemic symptoms include recurrent, painful vaso-occlusive crises with abdominal and musculoskeletal discomfort. Other systemic manifestations include jaundice, cerebrovascular accidents and infections (particularly by encapsulated bacteria).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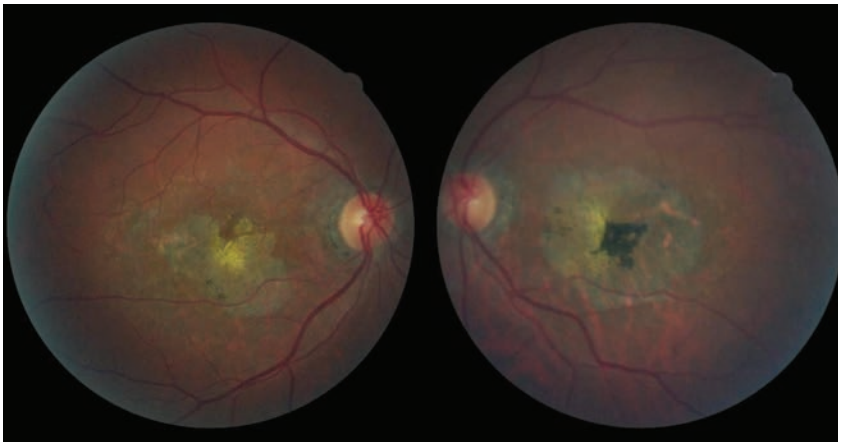
# STARGARDT'S DISEASE (FUNDUS FLAVIMACULATUS)

## Signs and Symptoms

Stargardt's disease is the most common autosomal recessive macular dystrophy, and it is on the continuum of macular degeneration.[1-11] It was first described in 1909 by Carl Stargardt as a flecked retina disease in which patients presented with a chief complaint of decreased visual acuity in the first or second decade of life.[1-4,10,12] Today, many continue to refer to it as juvenile macular degeneration.[1-5] The reported prevalence of the disease is one in 8,000-10,000.[3]

Dysfunction of the ABCA gene causes the pathologic accumulation of lipofuscin, which is toxic to the RPE and photoreceptors.[1-3,12-18] Presenting symptoms, fundus appearance and progression of the disease are variable.[1-7] The disease presents with bilateral atrophic changes in the central retina associated with the degeneration of both photoreceptors and underlying RPE cells.[12] The presence of "fish-shaped" or pisciform yellow flecks extending from the macula is the hallmark characteristic, though not omnipresent.[12] Stargardt's disease has four classic fundus presentation patterns: (1) macular pigmentary changes without flecks; (2) macular pigmentary changes with perifoveal flecks; (3) macular pigmentary changes with diffuse flecks; and (4) diffuse flecks without any macular compromise.[3,4] The most common symptom is diminished

central visual acuity; however, myopic refractive error, mild photophobia, glare disability and color vision defects are also commonly encountered.[5,6] While the onset of symptoms usually occurs in the first or second decade of life, a substantial number of patients remain asymptomatic until the fourth or fifth decade.[1-6] Choroidal neovascularization has been noted as a late complication.[3] The disease has been associated with the broader syndromes of retinitis pigmentosa and Laurence-Moon-Bardet-Biedl disease, as well as obesity, hypogenitalism, retardation, pigmentary retinopathy and polydactyly.[3,17]



A case of advanced Stargardt's disease displaying macular atrophy and pigment clumping, especially in the left eye.

## Pathophysiology

Stargardt's disease has an autosomal recessive transmission pattern, and affected individuals typically exhibit bilateral and symmetrical presentations.[3,5,12] Stargardt's disease is considered to be one of the macular dystrophies.[10-16]

Research has provided a three-step explanation of the pathophysiology of Stargardt's disease. Initially, defective rim protein (a glycoprotein associated with the rim of the photoreceptor outer-segment), encoded by the ABCA4 gene, causes an accumulation of protonated N-retinylidene-PE in the rod outer segments; this ATP binding cassette transmembrane protein is involved in the transport of all-trans-retinal (atRAL) and lipofuscin. Dysfunction in this protein causes accumulation of lipofuscin, which is toxic to the RPE and photoreceptors. It also creates a distinct thickening of the external limiting membrane. A2-E, a byproduct of N-retinylidene-PE and an accumulation of vitamin A-derived lipofuscin fluorophores, then accumulates in the RPE cells and is also toxic. Photoreceptors eventually die secondary to loss of the RPE support function.[1-3,5,10-18] Generically, Stargardt's disease is the result of a faulty lipid transporter that facilitates the removal of potentially toxic retinal compounds from photoreceptors following photoexcitation.[16-18] Many blinding diseases are associated with these same mutations, including cone-rod dystrophy, retinitis pigmentosa and increased susceptibility to age-related macular degeneration.[13,14] Electrophysiologic testing has conclusively confirmed that the defect responsible for the disease's physical and symptomatic expression is in the RPE.[4]

In the milder variant known as late-onset Stargardt's disease, there is increased potential for maintaining visual acuity of 20/40 or better due to the disease's characteristic foveal sparing.[3,20,21] An autosomal dominant form of Stargardt's disease, known in the literature as Stargardt-like dystrophy, has been identified.[12] It is caused by mutations in a gene encoding for ELOVL4, an enzyme that catalyzes the elongation of very long-chain fatty acids in photoreceptors and other tissues.[12]

## Management

Since the destruction of the RPE results in photoreceptor loss, progressively worsening visual consequences are inevitable.[1-7] There exists no effective treatment. Stem cell therapy for ocular disease has made significant progress within the last decade.[14] Stem and progenitor populations for many ocular cell types have been identified. As their behavior becomes understood, it may be possible to conceive potential clinical applications.[14] The application of embryonic stem cell-based therapy is in clinical development for Stargardt's disease and dry age-related macular degeneration.[14] Until these approaches produce clinical results, vision care specialists should advise those at risk of the benefits of genetic counseling in hopes of creating better anticipation and understanding of the disease, its potential prognosis and its risks for inheritance.[1-3,13] Patients should take advantage of programs which provide guidance from subspecialties such as low vision rehabilitation, psychology/psychiatry and work-related therapists.[2,3,6]

Ultra-high frequency and maximum depth OCT is a clinically useful tool for examining intraretinal and subretinal changes—photoreceptor and RPE atrophy in particular—making it a reasonable imaging system for this disease.[10] Short-wavelength fundus autofluorescence (FAF) originates from lipofuscin in the RPE and near-infrared (NIR) autofluorescence originates from RPE melanin. Instruments capable of generating this imaging can gather detailed data in Stargardt's disease patients.[22]

## Clinical Pearls

- Since the disease is capable of producing symptoms without signs in young patients, this entity deserves consideration and testing before a diagnosis of amblyopia is suggested.
- Stargardt's disease generally does not induce the production of choroidal neovascularization.
- A genetic pedigree may be helpful in diagnosis and understanding the mode of transmission of Stargardt's disease, as well as the potential for other associated syndromes.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## NEURORETINITIS

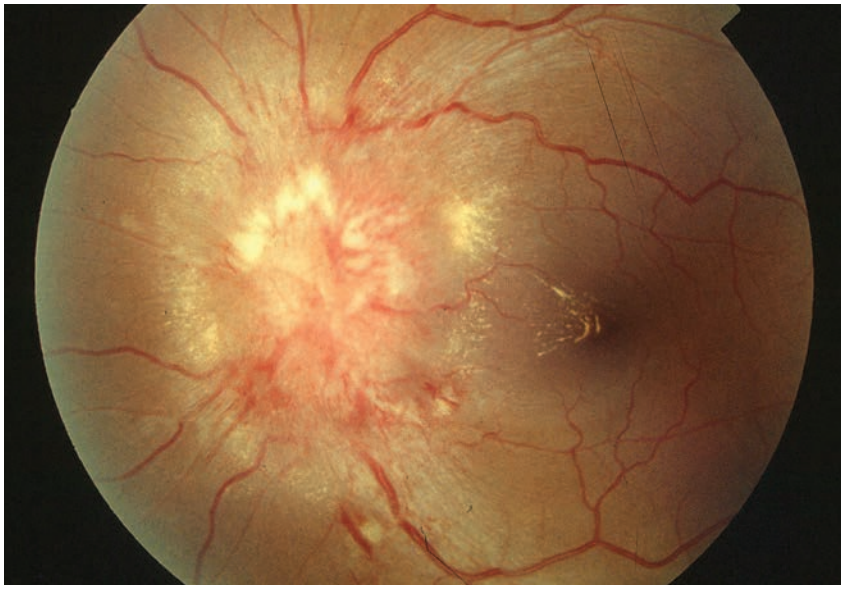
### Signs and Symptoms

While neuroretinitis can present in any age group due to several potential causative etiologies, patients are typically younger, and the condition commonly occurs in children. In fact, the majority of patients are under the age of 20.[1-13] There is no sexual predilection.

Neuroretinitis typically presents as a unilateral, acute, painless loss of vision. Rarely, it presents bilaterally and, just as rarely, without symptoms. Alternatively, vision may decrease as low as finger-counting level.[1-13] The typical visual field loss is a central or cecocentral scotoma.[2,14] A relative afferent pupillary defect (RAPD) will be present if the condition is unilateral or markedly asymmetric. Interestingly, the magnitude of the RAPD will be small relative to what one would expect given the profound degree of vision loss. In fact, in many unilateral cases, there is no detectable RAPD, despite profound vision loss in the affected eye.[2,14]

Ophthalmoscopically, there will be a noticeably edematous disc. There may also be peripapillary hemorrhages due to venous stagnation. Occasionally there will be a mild vitritis overlying the disc. Initially, there will be a serous retinal detachment extending from the disc to the macula. The key diagnostic feature in well-developed neuroretinitis is the presence of macular exudates in the form of a florid macular star.[1-13] However, this finding may not occur for several weeks after onset of visual symptoms, with the diagnosis not apparent early in the course of the disease. It is not uncommon to have a serous retinal detachment within the posterior pole in association with the advent of disc edema. This is highly suspicious for early neuroretinitis with the macular exudates ensuing later.[2,13]

Numerous systemic conditions have been seen in association with neuroretinitis, including toxoplasmosis, toxocariasis, measles, syphilis, Lyme disease, herpes simplex and zoster, mumps, tuberculosis and leptospirosis.[15-25] However, the most common cause by far is *Bartonella henselae*—the organism responsible for cat scratch disease.[26-36] Occasionally, cat scratch disease will be caused by *Bartonella quintana*.[37] In cat scratch disease neuroretinitis, there may be an antecedent history of fever, malaise, and/or lymphadenopathy, occurring several weeks preceding the visual loss. There may also be an antecedent history of a cat scratch or flea bite.[26-37]



Acute neuroretinitis in cat scratch disease.

### Pathophysiology

Neuroretinitis was initially identified by Leber in 1916 as a retinopathy associated with unilateral vision loss and disc edema. Upon discovering that the focus of dysfunction was the optic nerve rather than the retina, the condition was later renamed Leber's idiopathic stellate neuroretinitis.[38] Neuroretinitis, like most optic neuropathies, has many proposed mechanisms, though the exact pathophysiologic pathway has not been identified. Because the majority of cases are due to infectious etiologies, it is plausible that cell invasion with proinflammatory activation occurs.[39]

Visual loss is predominately from the retinal edema rather than optic nerve dysfunction. This is evidenced by the fact that the visual field defects reflect a retinal cause as well as the relative mild degree (or absence) of afferent pupillary defect in the face of profound vision loss.[2,14] While the macular exudates are characteristic of this condition, they may not be evident upon early presentation and it may be several weeks (typically two) before they develop.[2,40] After development of the disc and retinal edema, there will be spontaneous resolution and fluid resorption. The aqueous phase of the edema resolves the fastest, leaving the accumulated lipid exudates within the outer plexiform layer, forming the characteristic macular star.

### Management

When encountering neuroretinitis, it is important to consider and evaluate patients medically for all possible causes. A history should be elicited for exposure to cats, flea and tick bites, travel to lyme endemic areas, exposure to sexually transmitted disease, lymphadenopathy,

skin rashes, malaise, myalgia and fever. Tests that should be ordered (as dictated by the history) include lyme titer, toxoplasmosis titer, toxocariasis titer, purified protein derivative skin testing, fluorescent treponemal antibody absorption test (FTA-ABS), rapid plasma reagin (RPR) and chest X-ray to look for evidence of tuberculosis. However, as the most common cause is infection by *B. henselae* or *B. quintana* from a cat scratch, one must carefully examine for these entities.[41-44] Cat scratch disease can be identified by immunoassay antibody testing for *B. henselae* and *B. quintana*.[5,14,45]

Initially, neuroretinitis may be subtle in regards to macular findings. When the macular edema and star are not present, the patient may seemingly manifest only disc edema, making the actual diagnosis elusive. However, optical coherence tomography (OCT) may be a valuable adjunctive diagnostic test. It has been noted that subretinal fluid not visible on clinical examination or fluorescein angiography may be readily identified with OCT, making it an adjunctive imaging tool in the diagnosis and follow up of patients with cat scratch-related neuroretinitis.[46,47]

The prognosis for visual recovery in neuroretinitis is generally excellent, especially if the cause is cat scratch disease. Most patients will have a return to normal or near normal vision without treatment.[2,14,30] While neuroretinitis from cat scratch disease is typically a self-limiting condition with an excellent prognosis, antimicrobial therapy may be used to hasten recovery. Successful oral agents include Rifadin (rifampin, Aventis), ciprofloxacin, doxycycline, sulfamethoxazole and trimethoprim.[2,3,14,28,29,48-50] A commonly used therapy is doxycycline 100mg PO BID for one month.[2,3,14,28,29] Additionally, oral steroids may be used to mitigate inflammation.[49] Recently, research has shown that intravitreal injection of Avastin (bevacizumab, Genentech) improves visual acuity while also decreasing macular edema.[51,52] However, since neuroretinitis enjoys such a good prognosis for recovery, such invasive therapy may not be justified, especially when one considers that this information comes from case reports rather than controlled clinical trials.

In neuroretinitis, the disc edema will resolve in approximately eight weeks, and the macular exudates will resolve over several months. There may be a residual macular pigmentary atrophy or optic atrophy, which will occasionally lead to a poor visual outcome.[2,3,26]

## Clinical Pearls

- Neuroretinitis should be suspected in cases of disc edema with profuse adjacent retinal edema and painless vision loss with a relatively mild afferent pupillary defect. A confirmatory sign is the appearance of a macular star within 10 to 14 days.
- Very few entities will mimic neuroretinitis, with its characteristic macular star. Mimicking entities include malignant hypertension and anterior ischemic optic neuropathy.
- The afferent pupillary defect will be remarkably mild (or even absent) despite severe vision loss.
- The absence of pain with eye movements greatly helps to differentiate neuroretinitis from demyelinating optic neuritis. Patients with neuroretinitis need not have the same concerns for the development of multiple sclerosis.
- Fleas may be the vectors of the *Bartonella* organisms and hence neuroretinitis. History of an actual cat scratch or bite is not always necessary in order to make this diagnosis.
- While antibiotics are frequently used for cat scratch disease neuroretinitis, there are no controlled clinical trials that indicate a better clinical outcome from this therapy. The same can be said for the use of oral steroids and intravitreal anti-angiogenic medications.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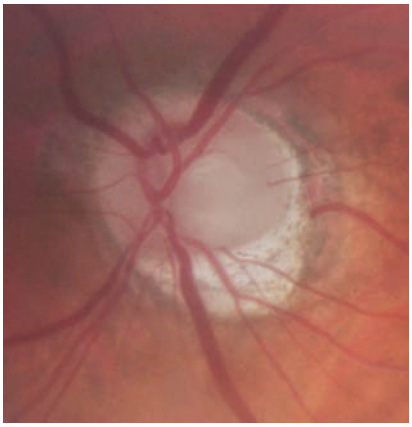
## TILTED DISC SYNDROME

### Signs and Symptoms

Tilted disc syndrome (TDS) is a unilateral or bilateral congenital optic disc anomaly that may be discovered in patients of any age, with an incidence of 2% in the general population.[1] There is neither a sexual predilection nor an identifiable hereditary pattern.[1]

The ophthalmoscopic appearance is variable.[2] In TDS, the disc appears to be rotated about its axis with the long axis of the disc approaching the horizontal meridian in extreme cases. Instead of a vertically oriented disc, the nerve fibers appear shifted so that the superior portion of the disc seems to be positioned in the superior nasal quadrant, giving the disc a D-shaped appearance.[3,4] In many cases, the major retinal vessels emerge from the disc, immediately run nasally, then abruptly turn and course temporally in the traditional vascular branching pattern. This vascular anomaly is termed *situs inversus*.[3,5,6]



**Tilted disc syndrome. Note the characteristic inferior conus adjacent to the nerve head.**

Despite varied appearances, there are some consistent findings in TDS. The most consistently encountered is a conus in the inferior and inferior nasal aspect of the peripapillary retina contiguous with the optic disc. In some cases this anomaly, termed Fuch's coloboma, can involve the inferior aspect of the disc with apparent rim thinning or obliteration with a pseudoglaucomatous appearance. This inferiorly located conus is associated with significant ectasia as well as staphylomatous formation within this localized area.[1,3,7,8] The colobomatous formation may extend inferiorly outward from the disc and manifest as hypoplasia of the retina, retinal pigment epithelium and choroid, appearing as a lightly pigmented fundus.[1-5] Other findings encountered with TDS include myelinated nerve fibers, lacquer cracks, choroidal folds, foveal retinal detachment and retinoschisis and peripapillary choroidal neovascular membranes with subretinal hemorrhages.[1,9,10-13]

Visual acuity is unaffected in TDS; however, visual field loss is common. The most commonly encountered visual field defect is a superior temporal scotoma.[1,14-18] In cases where TDS is bilateral, this can appear as superior bitemporal scotomas suggestive of chiasmal compression.[19] However, in TDS, the visual field defect is unchanging and does not respect the vertical hemianopic line as it would in a chiasmal compressive mass, thus helping to distinguish the two conditions.[14-18] Other potential visual field defects include arcuate scotoma, nasal contraction and an enlarged blind spot.[16]

The most commonly encountered refractive error in patients with TDS is myopic astigmatism at an oblique axis.[1,6,16] There has been conjecture that the refractive error results from fundus alterations seen in TDS.[5] However, it has been seen that clinically significant lenticular astigmatism was present in TDS patients.[20] In another report,

researchers found that in the majority of tilted disc cases, astigmatism was mainly corneal, suggesting that morphogenetic factors in the development of the tilted disc might possibly influence the corneal development in such a way as to result in corneal astigmatism.[21] It has been noted that color vision abnormalities, consisting of red-green, blue and mixed defects were found in eyes with TDS.[22]

## Pathophysiology

Contrary to popular belief, there is no actual tilting or rotation of the disc in TDS, even though the disc may appear to be rotated by as much as 90 degrees about its axis. TDS actually represents a congenital coloboma due to incomplete closure of the embryonic fetal fissure at six weeks gestation.[23] During development, the eye first appears in the form of the optic sulci in the fourth week of gestation. The optic vesicle forms from growth of the optic sulci towards the surface ectoderm. As the optic vesicle reaches the surface ectoderm, it invaginates to form a goblet-shaped optic cup. Incomplete closure upon invagination could result in a coloboma potentially involving the disc, retina and RPE.[2,23]

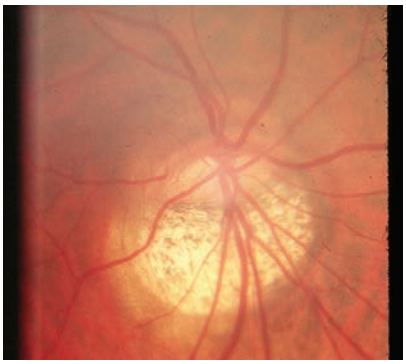
The inferior aspect of the disc (and adjacent fundus) has a congenital absence of tissue.[3,4,8,24] Automated perimetry has disclosed reduced mean deviations in this and other areas of the visual field. Perimetric findings also support the theory that TDS is a variant of optic nerve hypoplasia.[25] The colobomatous formation affects the shape of the chorioscleral canal due to a deficiency in the choroid, neural retina and RPE. As such, the nerve fibers will be concentrated in the superior and superior temporal aspect of the disc, while the inferior and inferior nasal section will be deficient in axons.[3,4,8,24] This gives the nerve a D-shape with the flat edge along the area of the conus. The congenital absence of tissue in the inferior nasal aspect of the nerve may be significant enough that the patient will have a corresponding superior temporal visual field defect that does not respect the vertical hemianopic line.[14-18]

More recently, OCT has revealed that there is a sloping of the lamina cribrosa posteriorly from the upper to the lower part, a protrusion of the upper edge of Bruch's membrane and choroid in eyes with TDS. The abnormalities detected by swept-source OCT and 3D MRI analyses indicate the possibility that the essential pathology of TDS is a deformity of the inferior globe below the optic nerve.[26] OCT images of the optic discs show a protrusion of the upper edge of Bruch's membrane and choroid at the nasal edge of the optic disc, with the retinal nerve fiber tissue herniating into this protrusion and bent superiorly, possibly contributing to visual field defects.[27]

The staphylomatous and ectatic formations caused by the incomplete fetal-fissure closure producing the conus also theoretically stretch the tissues, permitting secondary lacquer crack formation. These breaks in Bruch's membrane may lead to the development of choroidal neovascular membranes with subsequent subretinal hemorrhages.[2,7,9] Additionally, OCT has demonstrated that the subfoveal choroid is relatively thin and the subfoveal sclera thickened in some eyes with TDS.[28] These changes have been associated with choroidal neovascularization and serous retinal detachment.

## Management

As TDS is a congenital anomaly, there is no management for the finding itself. In cases where choroidal neovascular membranes form as a result of TDS, the visual outcomes tend to be quite good, in that the membranes are very responsive to photocoagulation or demonstrate no progression, and may even involute without treatment.[9] One report of a single patient indicated that intravitreal Lucentis (ranibizumab, Genentech) was effective in the management of choroidal neovascularization at the border of an inferior staphyloma associated with tilted disc syndrome.[29] However, another report on three patients with TDS-related choroidal neovascularization showed no visual benefit after intravitreal Avastin (bevacizumab, Genentech) treatment.[30] Serous retinal detachments secondary to TDS respond poorly to intravitreal Avastin treatment.[31,32]



**A pronounced presentation of tilted disc syndrome.**

The most important factor in managing TDS is proper diagnosis. The heaped-up axons in the superior aspect of the nerve in TDS are frequently misdiagnosed as either disc edema or papilledema. Also, the inferior nasal conus and possibly colobomatous extension into the disc is frequently misdiagnosed and treated as normal tension glaucoma. Further, the superior temporal defect in TDS can be confused with chiasmal compressive disease, especially when TDS is bilateral.

## Clinical Pearls

- There is a varied ophthalmoscopic appearance to TDS. However, the most diagnostic feature of TDS is the inferiorly located conus.
- The main differentiating factors between the visual field defect in TDS and chiasmal compressive disease is that the field defects in TDS are nonprogressive and do not respect the vertical

hemianopic midline. However, depending upon the perimetric technology used, the defect may seemingly respect the vertical hemianopic line.

- TDS is often misdiagnosed as disc edema, papilledema, normal tension glaucoma and pituitary tumor.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## LEBER'S HEREDITARY OPTIC NEUROPATHY

### Signs and Symptoms

Most patients affected with Leber's hereditary optic neuropathy (LHON) are males in early adulthood with vision loss occurring typically between the ages of 15 and 35.[1-7] Ninety-five percent of patients will be affected by vision loss before age 50.[3] Rarely, LHON may manifest after age 50.[8] LHON affects approximately one in 14,000 males, and there is approximately a four-fold greater incidence in males than females.[1-6] There is no racial predilection.[1,3]

Patients with LHON will experience a painless, acute or subacute loss of vision in one eye, typically deteriorating below the 20/400 level. Within two to four months, the fellow eye will progress to a similar level. The fellow eye's vision loss often begins within several weeks of the first eye and typically reaches its nadir within six months of the start of visual deterioration in the primary eye. In some cases, vision loss occurs bilaterally at the initial presentation. A small percentage of patients may show spontaneous visual recovery, but most patients will not improve, becoming either visually disabled or legally blind. The loss of visual acuity is accompanied by a dense central or cecocentral scotoma, as well as impaired color vision. Despite an initial asymmetry, a relative afferent pupillary defect is typically not present.[1-6]

Funduscopic evaluation during the acute phase will demonstrate mild edema and hyperemia of the optic disc, teliangiectatic disc capillaries and parapapillary retinal nerve fiber layer (RNFL) swelling. Over time, optic disc pallor will develop initially on the temporal disc, with subsequent progression to diffuse optic atrophy.[1-6]

OCT can show a variable appearance depending upon the stage of the disease. In the disease with a duration of less than six months, there appears to be a thicker parapapillary RNFL in the superior, nasal and inferior quadrants and a higher 360° average RNFL thickness, but a thinner temporal quadrant compared to controls.[9] In later stages, once diffuse optic atrophy occurs, there appears to be a thinner RNFL in all quadrants measured.[10,11] Macular thickness is decreased early in the disease, indicating a specific preference for the small fibers of the papillomacular bundle.[12]

### Pathophysiology

LHON is a maternally transmitted mitochondrial disease. There are three primary mtDNA mutations that account for approximately 95% of all LHON cases: 11778G>A (ND4 subunit), 14484T>C (ND6 subunit)

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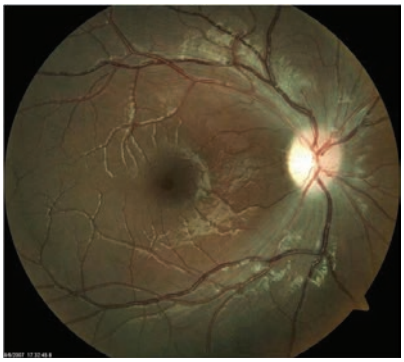

**This patient with LHON displays temporal pallor and profound vision loss.**

and 3460G>A (ND1 subunit).[2,3,13,14] Additionally, research has identified RPE65, 3635G>A and G11778A mtDNA mutations.[15-17] LHON results from a decrease in mitochondrial respiratory chain complex activity, which is associated with a decrease in adenosine triphosphate (ATP) production. These mitochondrial mutations likely lead to a combination of reduced synthesis, increased oxidative stress and induction of cellular apoptosis.[2] Reduced efficiency of ATP synthesis and increased oxidative stress are believed to sensitize the retinal ganglion cells to apoptosis, resulting in significant cell loss.[1-4]

There is a dramatic loss of retinal ganglion cells and their axons in LHON. Small caliber fibers of the papillomacular bundle are most damaged, and the larger peripheral cells are mostly spared. High energy demands of unmyelinated RNFL fibers may explain the reason that LHON targets the optic nerve.[2]

There are several environmental risk factors for the expression of LHON, including smoking, alcohol consumption and the use of certain antibiotics such as macrolides, aminoglycosides, ethambutol, isoniazid, linezolid, chloramphenicol and fluoroquinolones, as well as oral antiviral medications.[18] Research suggests LHON also can be exacerbated by second-hand smoke within the environment.[2]

## Management

LHON can be diagnosed by its characteristic clinical appearance, with OCT and mtDNA mutation testing providing adjunctive evidence.[2] While patients carrying the ND6 subunit may spontaneously improve, most patients with LHON will be permanently visually disabled. Once optic atrophy has ensued, it is highly unlikely that there will be any therapeutic recovery. OCT suggests that a dynamic evolution of the acute stage of LHON continues for three months, which may represent a therapeutic window of opportunity.[19]

Because visual dysfunction in LHON is due to oxidative stress and apoptotic initiation, strategies ranging from neuroprotectants, antioxidants, anti-apoptotic- and anti-inflammatory compounds have been tested with mixed results.[20] Most promising is idebenone, a quinine analog of coenzyme Q10 that was originally developed for the treatment of Alzheimer's disease.[18,20-23] Idebenone appears to have better ability to cross the blood-brain barrier and has higher delivery to mitochondria than coenzyme Q10.

The Rescue of Hereditary Optic Disease Outpatient Study (RHODOS)—a prospective, randomized, placebo-controlled study of 900mg/day of idebenone—showed prevention of further visual loss in patients with discordant visual acuities.[21] Additionally, this dosing was seen to be safe and well tolerated throughout the study. Patients receiving idebenone significantly improved compared to placebo groups, and the therapeutic effect persisted beyond the study completion.[21] Other studies have tested a combination administration of idebenone, vitamin B2 and vitamin C and suggest this approach may better assist recovery of vision in patients with LHON.[22]

Color defects are an early symptom in LHON, and idebenone treatment can protect the patient from loss of color vision, particularly those who are at imminent risk of acuity loss.[23] Idebenone appears to have a particularly protective and restorative activity when administered to patients shortly after the LHON visual dysfunction begins.[20] Since idebenone is safe and well tolerated, its use in early stage disease is recommended.[7] Gene therapy, while promising, has not advanced as a practical solution. Adeno-associated virus-mediated gene therapy of a synthetic wild-type ND4 subunit gene is an area being explored.[17]

Patients diagnosed with LHON should be instructed to avoid environmental smoke, tobacco smoking and alcohol consumption. Patients should be advised to maintain a healthy diet rich in B vitamins, antioxidants and proteins. They should be counseled to avoid any stem cell treatments for optic nerve regeneration, as these therapies are unproven.[2]

## Clinical Pearls

- Patients, especially younger males, who present with evidence of unilateral optic nerve dysfunction without a relative afferent pupillary defect should be considered to have LHON. Subsequent bilateral involvement increases suspicion, and genetic testing confirms the disease.
- The most common condition mimicking LHON is dominant optic atrophy (DOA), which is another mitochondrial dysfunction. In contrast to the acute vision loss in young adults seen in LHON, DOA presents with slowly progressive vision loss beginning in childhood and progressing over years to optic atrophy. DOA is frequently associated with a genetic mutation related to the production of the OPA1 protein.

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## MORNING GLORY SYNDROME

### Signs and Symptoms

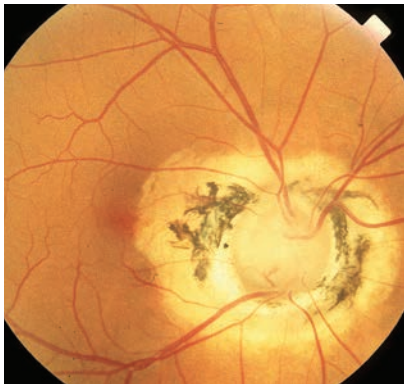
Morning glory syndrome (MGS) is a congenital optic disc anomaly that can be discovered at any age, though most patients are usually made aware of the condition at their first eye examination. The incidence is unknown and the condition is found equally in males and females.[1,2] MGS can be either bilateral or unilateral.[2-8] When the condition is bilateral, visual acuity is typically good.[4,9] However, most patients with unilateral MGS have markedly reduced visual acuity, often to the level of hand motion vision.[4,10] While reports are often contradictory regarding the level of visual function, it can safely be stated that MGS has a spectrum of severity, with most patients retaining useful vision.[11]

There will be a noticeably enlarged anomalous disc and peripapillary retinal changes. The nerve will appear larger than the fellow eye's nerve in unilateral cases. The condition gets its name from its resemblance to a tropical flower of the same name. It is characterized by a funnel-shaped excavated and enlarged dysplasic optic disc, with white tissue surrounded by an elevated pigmented peripapillary annulus. White glial tissue is present at the bottom of the cup and represents an important diagnostic criterion.

The retinal vessels arise from the periphery of the disc anomaly and run an abnormally straight, radial course over the peripapillary retina. The origin of the vessels is obscured by the central tuft of glial tissue. This can give the morning glory disc a pseudoglaucomatous appearance.[1,6,12-14] There will appear to be an excessive number of retinal vessels; however, this is simply due to the fact that glial tissue obscures the branching of the vessels within the optic cup. Retinal detachment may develop during the clinical course.[15-21] Strabismus is frequently encountered in patients with MGS as well.[22]

Many ocular conditions have been found in association with MGS, including microophthalmos, cataracts, myopia, ciliary body cysts, Bergmeister's papilla and hypertelorism.[12,23] Numerous systemic abnormalities have also been identified in association with MGS, including Goldenhar's syndrome; sphenoidal encephalocele; porencephaly and hydronephrosis; renal failure; cerebral malformation; frontonasal dysplasia; endocrine irregularities; neurofibromatosis type 2; midline craniofacial defects such as basal encephalocele, cleft lip and palate; Chiari type I malformation; and agenesis of the corpus callosum.[3,5,6,10,15,24,25] More recently, MGS has been reported in association with Down's syndrome, primary open angle glaucoma and multiple sclerosis.[26-28]

Despite numerous reported associations, these comorbidities seem to be mostly anecdotal cases. Thus, MGS is considered to be an isolated ocular abnormality. Further, in the absence of consistent systemic associations, perhaps the term "syndrome" does not apply to this condition. However, one study reported on 22 eyes with MGS and persistent hyperplastic primary vitreous, giving some credence to a possible association between the two entities.[29]



Morning glory syndrome is a congenital, colobomatous anomaly of the optic disc and surrounding tissue.

## Pathophysiology

Morning glory syndrome is a nonprogressive congenital optic nerve anomaly. The condition has been shown to be limited to the eye with no involvement of the retrobulbar nerve and brain.[2,15,23] MGS has long been considered to be a variant of optic nerve coloboma.[23] However, more recent findings suggest this may not be true. The central glial tissue, vascular anomalies, scleral defects, adipose and smooth muscle tissue within the peripapillary sclera are more consistent with a mesenchymal abnormality.[24,30] An alternate theory suggests that abnormal enlargement of the distal optic stalk during development allows formation of the characteristic excavation seen in MGS.[24] Spectral-domain and swept-source OCT has demonstrated a preretinal tractional membrane and inferiorly decentered excavation in MGS.[31]

Visual dysfunction arises from an undeveloped optic nerve with fibers never reaching the lateral geniculate nucleus. The main associated pathology that occurs in association with MGS is retinal detachment. OCT has demonstrated slit-like retinal breaks within or at the edge of the disc excavation. These slit-like breaks provide a direct communication between the subretinal space and the vitreous cavity, permitting fluid from vitreous syneresis to evolve tissue separation.[16-21,32,33]

## Management

Management of morning glory syndrome typically does not extend beyond proper diagnosis. While the appearance can be quite dramatic, extensive neurological evaluation can be avoided, as this is a non-acquired, nonprogressive disc anomaly. While there have been many associated systemic abnormalities reported, there is not enough consistency to consider these comorbidities anything but coincidental, making extensive evaluation unwarranted. Glaucoma treatment based solely upon the disc appearance should be avoided. Protective eyewear should be recommended in order to safeguard the better-seeing eye in unilateral cases.

The patient must be monitored and educated about the signs and symptoms of retinal detachment. Management of this type of retinal detachment varies, potentially involving pars plana vitrectomy with posterior hyaloid removal, fluid/air exchange, endolaser in the area of the retinal break, and a long-acting gas-bubble injection or silicone oil tamponade.[17,18,34,35]

## Clinical Pearls

- The neuroretinal rim of the morning glory disc is recessed and not readily visible. This has been mistakenly identified as acquired thinning of the rim, as seen in glaucoma. Morning glory syndrome has frequently been misdiagnosed and mistreated as normal tension glaucoma. Always rule out MGS in cases of suspected normal tension glaucoma. Impulsive diagnoses should be avoided.
- In cases where there is reduced visual acuity, MGS may be misdiagnosed as amblyopia.
- While dramatic in appearance, morning glory syndrome does not progress. There is no necessary treatment unless retinal detachment develops.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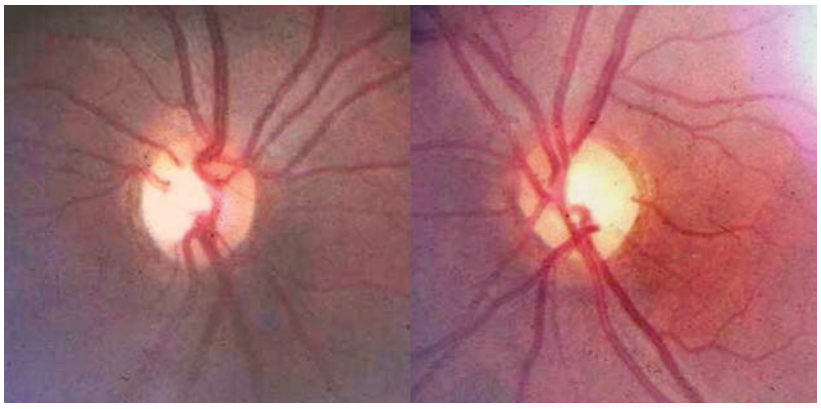

Bilateral temporal pallor in toxic optic neuropathy.

## TOXIC/NUTRITIONAL OPTIC NEUROPATHY

### Signs and Symptoms

Due to myriad potential causes, toxic/nutritional optic neuropathy has no clearly identifiable racial, gender or age-dependent predilection.[1,2] The condition presents as a painless, often progressive, bilateral, symmetric visual disturbance with variable optic nerve pallor. Temporal pallor tends to be the classic rule. This may manifest as a reduction of visual acuity, which may range from minimal to total amaurosis in some cases.[2] There will be attendant loss of central visual field (usually relative cecocentral scotoma) and dyschromatopsia. Relative afferent pupillary defects are not usually present, as the condition is typically bilateral and symmetrical. Initially, most patients will present with visual symptoms in the setting of normal-looking optic discs, which may become edematous before progressing to optic atrophy with temporal disc pallor.[2]

Due to similarities in appearance and pathophysiologic responses, toxic optic neuropathy and nutritional optic neuropathy cannot be distinguished clinically from one another; consequently, both are typically discussed together. The differentiating factors are elicited in patient history. Patients suffering from toxic optic neuropathy will present with a history of exposure to or ingestion of a toxic substance. Well-known toxins causing this neuropathy include ethambutol, linezoilid, isoniazid, dapsone, ciprofloxacin, vigabatrin, disulfifram, methotrexate, cisplatin, cyclosporine, tamoxifen, sildenafil, infliximab, ethanol, ethylene glycol, thallium, lead, mercury, digitalis, chloroquine, streptomycin, carbon monoxide and amiodarone, to name a few of the more common causes.[2-9]

In the absence of toxic exposure, a similar clinical appearance occurs in nutritional optic neuropathy. In this instance, patients will have nutritional deficits of B vitamins such as thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6) or cobalamine (B12), as well as vitamin D, vitamin E, copper and folic acid.[2,10-12] In these patients, there may also be a pronounced history of alcohol ingestion and tobacco use. "Tobacco optic neuropathy" has historically been described as optic nerve dysfunction related to the toxic effects of the constituents in tobacco. It has been considered to be an entity distinct from that often described as "tobacco-alcohol amblyopia," a disorder better described as a nutritional optic neuropathy, as it is not truly amblyopia.[13,14] More recently, nutritional optic neuropathy has been associated with special diets, anorexia, malnutrition and bariatric surgery.[15-17]

### Pathophysiology

Toxic optic neuropathy may result from passive exposures to neuro–poisonous substances in the environment, ingestion of certain foods, intentional or unintentional ingestion of other materials containing toxic substances or from elevated serum therapeutic drug levels occurring in the treatment of other diseases, such as tuberculosis. The origin of toxic neuropathy is not limited to direct toxin exposure and may occur as a result of deficiencies of essential nutrients in the diet or from metabolic disease.[18] In some cases, the substance or agent causing the toxic neuropathy impairs the tissue's vascular supply or metabolism.

The common offender, tobacco, produces metabolic deficiencies as part of the systemic nicotine cascade. The historical term tobacco-alcohol amblyopia is outdated, as tobacco and alcohol abuse—with its attendant nutritional deficiencies—produces organic pathology within the nerve. Today, the condition is more accurately called toxic/nutritional optic neuropathy. Its pathophysiology is poorly understood, but it is generally attributed to toxic effects of cyanide and B12 deficiency.[18] While nicotine has not been indicted to directly cause optic nerve damage, the cyanide in the smoke cannot be detoxified and causes neurotoxicity.[19]

Ethanol (consumable alcohol), like tobacco smoke, produces its toxic effects metabolically. Chronic exposures typically lead to vitamin B12 deficiency, folate deficiency or both. Over time, these deficiencies cause accumulations of formic acid. Both formic acid and cyanide inhibit the electron transport chain and mitochondrial function, resulting in disruption of ATP production and, ultimately, impairment of the ATP–dependent axonal transport system.[2]

The pathophysiologic relationship is unknown for many of the agents identified to date as causes of toxic optic neuropathy. Mitochondria of the retinal ganglion cells and damage to the papillomacular bundle in particular seem to be a common target of toxic optic neuropathy. OCT has identified decreased retinal nerve fiber layer thickness, especially in the temporal papillomacular quadrant, in eyes of patients that have had ethambutol-induced optic neuropathy.[20] Research suggests toxic agents or their metabolic byproducts interfere with the oxidative phosphorylation in mitochondria, causing a buildup of reactive oxygen species, energy depletion, oxidative stress and activation of apoptosis.[21]

## Management

The management for confirmed toxic/nutritional optic neuropathy includes immediate removal of the offending agent. Patients with suspected toxic optic neuropathy require a complete ocular evaluation with formal color vision testing and automated threshold visual field testing. They should also be referred for complete physical and laboratory studies such as a complete blood count with differential, serum B vitamin, copper and folate levels, a heavy metal screening (lead, thallium) and possibly testing for the Leber's mitochondrial DNA mutation.[5] In some cases, the toxic process may be reversible, with both signs and symptoms, demonstrating some progress toward recovery following removal of the offending agent or the addition of nutritional supplementation.[5]

Deficits associated with nutritional optic neuropathy are most commonly seen with deficiencies in vitamins B1, B12, D and E; folate; and copper. It is important that patients with toxic/nutritional optic neuropathy who also have undergone bariatric surgery be evaluated for adequate levels of vitamin B1, copper, vitamin B12, folate, methylmalonic acid and homocystine. Obtaining levels of vitamin A, C, D, K and E, as well as iron, zinc, selenium and magnesium, is advisable. Evaluating total protein, albumin and cholesterol also gives a sense of general nutritional status.[15,17]

Supplements frequently recommended include a multivitamin, iron, vitamin D, folic acid, calcium citrate and vitamin B12. Although vitamin B1 is typically included in a multivitamin, the amount is fairly small. It is recommended to add an additional 100mg daily for at least the first year. In severe vitamin B12 deficiencies, a week of daily intramuscular injections (1,000 units per day) can greatly elevate serum levels of B12.[16]

## Clinical Pearls

- Toxic/nutritional optic neuropathy should be considered in cases of bilateral, progressive vision loss and in patients presenting with bilateral, temporal optic disc pallor.
- An extensive history may be the best method of uncovering circumstances and situations that involve toxic and nutritional optic neuropathy.
- Differential diagnoses in these cases may be challenging. It is essential to exclude other conditions such as Leber's optic neuropathy, dominant optic neuropathy, infiltrative optic neuropathy secondary to sarcoidosis, infectious optic neuropathy and compressive optic neuropathies secondary to space occupying lesion.
- Should prescriptive drugs or workplace exposure result in toxic optic neuropathy, clinicians should remain aware of potential underlying litigation issues such as worker's compensation, product liability, product recall and medical malpractice.


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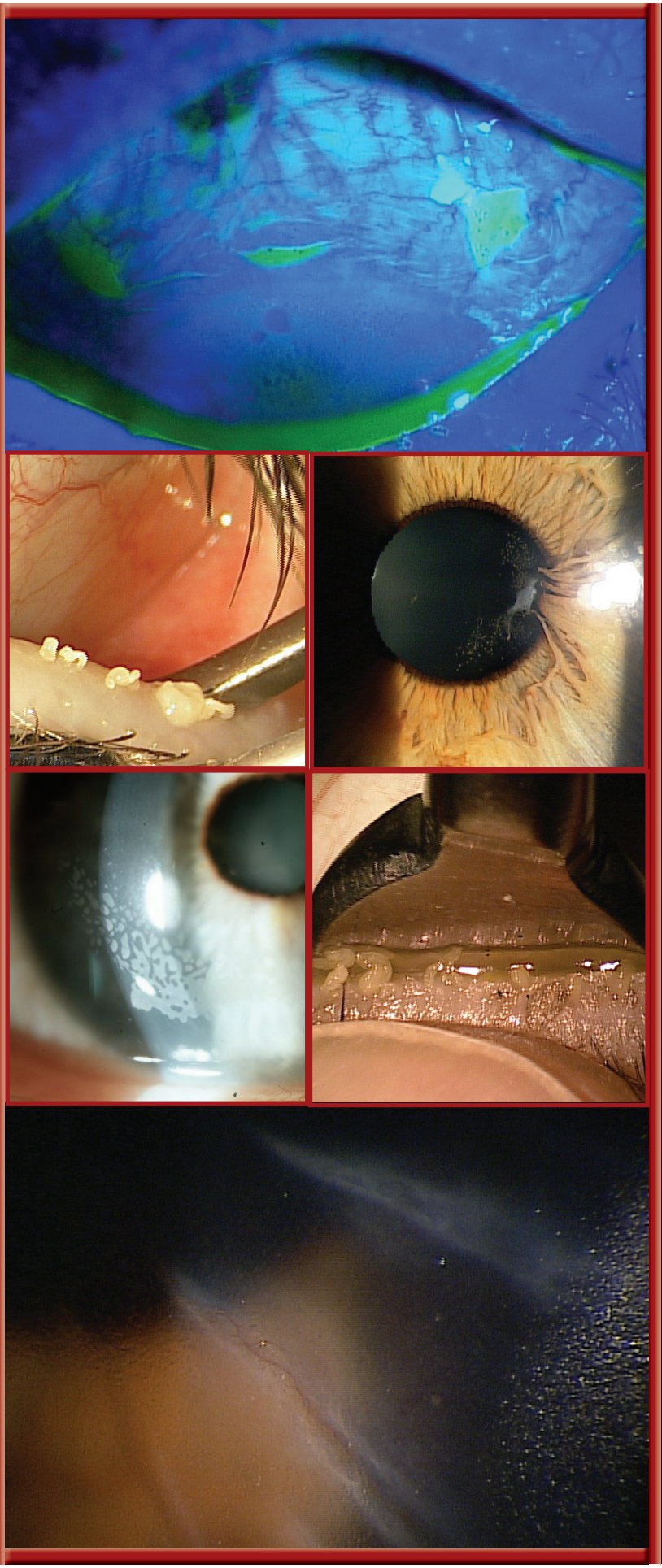

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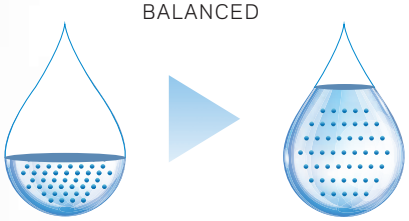

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