Lid margin disease: Incidence, etiology, and diagnosis

by Henry D. Perry, M.D.

There are very few papers that even suggest the incidence of blepharitis. The best I've found was from Walter Reed: a study showing that 3.1% of recruits between 18 and 22 years old had blepharitis versus 71.1% of the pensioners. So obviously this is a condition that increases with age. Lemp's dry eye study showed that in patients with dry eye disease, virtually 70% of them have an associated blepharitis.

What about the etiology? Lid margin cultures are positive in virtually 100% of these patients. Pathogenic strains can occur between 35 and 95%. It's important to remember that bacteria have lipolytic exoenzymes and collagenases that degrade the lipid, forming an inflammatory soup that is dumped on the corneal surface and leads to the problems we see in our patients. We also have Demodex folliculorum, a mite that lives at the base of the lashes and is present in 5% of normals and 35% of patients with blepharitis.

Diagnosis and classifying
How do we make a blepharitis diagnosis? Symptoms wax and wane. Patients complain of burning, irritation, and foreign body sensation; it especially seems prominent in the morning. Patients say their lids stick, here is a patient with several signs of blepharitis: severe neovascularization of the lid margin, the inspissation of some of the glands, and complete obstruction of some of the other glands and changes associated with the eyelashes themselves.

Educational Objectives
Ophthalmologists who take part in this educational activity will:

- Discuss the etiology, diagnosis, and incidence of ocular surface disease and blepharitis
- Demonstrate an understanding of the impact of ocular surface conditions on cataract and refractive surgery outcomes
- Discuss therapeutic options for the treatment of the ocular surface
- Integrate appropriate pre- and postoperative treatment regimens to improve surgical outcomes and patient satisfaction

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| Bausch & Lomb A                   |          | Ocularis Pharma. A |
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| InSite A                          |          | Terrence P. O’Brien, M.D. |
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and they have crusting. We are all familiar with the numerous signs such as collarette, scurf, lash changes, inspissation in meibomian glands, and neovascularization of lid margins, characteristic inferior superficial punctate keratopathy, chalazia, and not infrequently, marginal ulceration.

Classifying blepharitis is quite difficult, but I think McCulley developed the best classification scheme to date. Basically, he divided it up into Staphylococcal, seborrheic, occurring alone or in combination with staph disease, and occurring in combination with primary meibomitis.

We see patients with primary meibomitis most frequently.

If we culture our patients, even normal patients will tend to have involvement with several bacteria. The most common ones that are seen are coagulase-negative staphylococi, S. aureus, P. acne, and Corynebacterium species. It’s interesting to note that in the patients with the various forms of blepharitis, these bacteria are present in very high amounts.

Last year, Shaeffer Tseng showed a group of patients in a retrospective study, six in all, who had severe blepharitis that was unresponsive to steroids and systemic tetracyclines (various manufacturers). In this group he epilated their lashes, studied the base, and found heavy Demodex infestations. He treated these with tea tree oil and found a very good response within a six-week period. These were severe patients who had significant corneal findings; three were thought to have limbal stem cell deficiency and they all responded to this therapy.

Chronic blepharitis

In cases of chronic blepharitis, the pathophysiology leads us to believe there is no single bacteria that’s responsible. Rather it’s a production of the bacteria in terms of their lipolytic effect on the meibum that is present and the changes that occur in the lipid at the base of the lashes. Staph aureus, Corynebacterium species, and P. acne all have effects on these lipolytic enzymes. These all act together in concert to create an increase in free fatty acids. This increase is central to the theme of the pathology that occurs in this disease. What we’re having is saponification. The problem that occurs in our patients is that there’s a detergent action to the tear film which leads to a recalcitrant superficial punctate keratopathy.

Therapy is directed at control, not cure. I tell my patients that the difference between blepharitis and true love is that one is forever.

In the acute phase, we try to bring the disease under control. We then have the chronic phase of therapy where we want to maintain control. The key factor is lid hygiene. This is the basic therapy that we should impress on all of our patients. We also encourage warm salt water soaks four times daily, and in this process there is a change in the ownership of treatment from the physician to the patient. This helps the patient realize that it is not only the physician who is responsible for improvement.

The patients who require topical antibiotics are those with staph, coagulase-negative staphylococi, and patients with mixed Staphylococcal and seborrheic disease. Virtually all patients with chronic blepharitis need antibiotics at least intermittently in some form.
Identifying risk factors can help clinicians treat and prevent lid margin disease

Clinicians have to manage dry eye concurrently with lid margin disease. Angular blepharitis is most frequently associated with gram-positive organisms. Proteolytic enzymes can cause lid margin maceration. Bacterial conjunctivitis is frequently associated with blepharitis. It can be cyclical and lead us to believe there’s a viral component. You may see corneal changes associated with blepharitis: marginal corneal infiltrates which are type 4 hypersensitivity reaction to the Staphylococcal species. These typically present with a clear space between the infiltrate and the limbus and may or may not have an overlying epithelial defect. You frequently see superficial punctate keratopathy, especially inferiorly. In rare circumstances, we see infectious keratitis.

The diagnosis of infectious keratitis is made by culture and sensitivity. We choose our therapy based on the results of these cultures.

Post-surgical infections

Infections can be associated with refractive or cataract surgery.

The incidence of infections after LASIK ranges from 0.2% to 1.2%, and 5% of these can be bilateral. Several large case series report absolutely no infections, however. The symptoms, just as with standard bacterial keratitis, include redness, blurry vision, and photophobia, but the most common presenting symptom is pain.

In a pseudomonas infection, the corneal infiltrate is typically present. An anterior chamber reaction or epithelial defect may be present. There may be separation of the flap, epithelial ingrowth, or melting of the flap overlying the infiltrate. Gram-positive organisms are more likely to present with pain, discharge, and an epithelial defect.

The onset of infection after LASIK helps us determine what etiology it may be. Early onset infections (in the first week) are more often gram-positive. Gram-negative infections are rarely found.

Normal eyes don’t develop ulcerative keratitis because they have an innate natural host defense mechanism. After LASIK, some of that is broken down partly due to a relative neurotrophic keratopathy with dry eye syndrome, an epithelial irregularity at the flap edge, and a true potential space or pocket created, which allows for a stromal abscess in the cornea.

The risk factors for the patient include blepharitis and meibomian gland dysfunction, a dysfunctional tear state or dry eye, Herpes simplex keratitis, and collagen vascular disease in those rare individuals.

The procedure itself can provide risk factors: the bandage lens, the epithelial defect, topical anesthetic abuse afterwards, chronic use of topical steroids, and other factors such as not using post-op antibiotics or irregular flap or instrument contamination.

The overwhelming cause of most LASIK keratitis is gram-positive organisms.
Long term, we can still see infections after LASIK due to trauma or epithelial instability.

**Prevention of infection**

A few years ago more than 50% of the organisms that were associated with LASIK keratitis included atypical Mycobacteria. Now, 90% of these are gram-positive organisms. The source of these organisms, the bacterial, fungal and parasitic source, is likely the surface flora.

What do we do to minimize this? We can use pre-op measures, as well as local intra-op control and post-op prophylaxis.

Instruct your staff in the principles of sterile operative techniques.

It’s very important that patients not wear eye makeup. Makeup can harbor very dangerous bacteria. We use povidone-iodine 5 to 10% on the lids or lashes to help with that.

Perhaps not as frequent is treating the pre-existing blepharitis using eye scrubs, warm compresses, and omega-3 supplements. We treat blepharitis patients with AzaSite (azithromycin, Inspire Pharmaceuticals, Durham, N.C.), which is good against gram-positive organisms. It’s very important to remind patients that they shouldn’t wear contact lenses for at least 2 to 3 days prior to surgery to minimize the bacterial load on the surface.

**Endophthalmitis**

There are two types of endophthalmitis: endogenous from hematogenous spread and exogenous from surgery, foreign bodies, or trauma. Endogenous endophthalmitis is the smaller category of the two, only 2 to 15% of all cases of endophthalmitis. The rest are exogenous. Sixty percent of these cases occur after surgery; the incidence after cataract surgery is 0.06% to 0.3%.

Frequently, you see pain out of proportion to the clinical signs. There is typically a little lid edema, corneal edema, fibrinous membrane in the anterior chamber, and progressive loss of the red reflex. *P. acnes*, however, can present in a more indolent fashion.

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**Causative Organisms in Postoperative Endophthalmitis**

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<tr>
<td><em>S. epidermidis</em></td>
<td>41%</td>
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<tr>
<td><em>S. aureus</em></td>
<td>19%</td>
</tr>
<tr>
<td>Gram negatives</td>
<td>16%</td>
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<tr>
<td><em>Streptococcus spp.</em></td>
<td>6%</td>
</tr>
<tr>
<td>Fungi</td>
<td>5%</td>
</tr>
<tr>
<td>Other gram positives</td>
<td>9%</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>2%</td>
</tr>
<tr>
<td>Mixed flora</td>
<td>2%</td>
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<tr>
<td><em>Bacillus spp.</em></td>
<td>0%</td>
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(Continued from page 3)

The causative organisms in post-op endophthalmitis are overwhelmingly gram-positive. Prevention is similar to LASIK associated keratitis with povidone-iodine 5% prep for the skin and the conjunctival fornices, sterile draping techniques, and very meticulous treatment of the pre-existing blepharitis and external disease.

We like fourth generation fluoroquinolones for our prophylaxis. We generally do not favor intracameral antibiotics as do most surgeons until they become more standard.

In conclusion, lid margin disease can be associated with significant patient discomfort as well as a spectrum of clinical findings, which can range from mild redness and crusting to significant infections in the lids and surrounding ocular structures. Blepharitis is a significant risk factor for infection after both refractive and intraocular surgery. Appropriate measures should be taken pre-op, intra-op, and post-op to minimize the risk of infection after surgery.

Helen K. Wu, M.D., is assistant professor of ophthalmology, Tufts University School of Medicine, and director of the Refractive Surgery Service, New England Eye Center, Boston, Mass.

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**REFERENCES**


Henry D. Perry, M.D., is senior founding partner, Ophthalmic Consultants of Long Island; medical director, Lions Eye Bank; and chief, Cornea Service, Nassau University Medical Center, East Meadow, N.Y.
Creating the healthiest ocular surface possible pre-op will help improve outcomes post-op

Ocular surface disease is incredibly underdiagnosed. There are approximately 55 million Americans with dry eye disease, and an estimated 39 million dry eye sufferers have not yet been diagnosed.

We all know the symptoms of dry eye disease: discomfort, dryness, burning, and stinging. Dry eyes have a huge impact on anterior segment surgery. Every patient experiences dry eye post-op but not all patients develop symptoms. The quality of vision starts with a healthy ocular surface. The tear film is by far the most important refracting surface of the eye. Dry eye and the co-morbidities of blepharitis and allergic conjunctivitis are the most common and potentially most devastating complications of anterior segment surgery.

Disruption of the ocular surface induces distortion that’s magnified by a multifocal IOL. Disruption of the tear film magnifies the glare and halo inherent in all multifocal IOLs. Patients with multifocal IOLs and ocular surface disease have a huge difference in the point spread functions and the way they view the world.

Contributing factors

There are contributing factors that can add to ocular surface abnormalities. Among these is a lack of lubrication during the surgery or epithelial defects. For instance, if we’ve stretched the lid of an older patient, that may lead to a flaccid lid for several weeks or months, which then leads to lagophthalmos and exposure keratitis.

Dry eye disease overlaps with meibomian gland disease. More than a third of the dry eye patients have meibomian gland disease and 13% also have allergies.

The prevalence of post-op dry eye has been exhaustively studied. Most of the peer-reviewed literature concerns LASIK and PRK, but there are articles about post-cataract dry eye. The incidence of dry eye is much higher in post-cataract patients than in post-LVC patients. Roberts’ found the incidence to be as high as 87%. Li looked at 37 patients/50 eyes. They found post-op dry eye in cataract patients peaked at one month and persisted for at least three months. Visual function may be negatively impacted if the dry eye symptoms persist. Li and his co-authors concluded that symptoms of
Dry eye will inevitably emerge in most patients, and misuse of eye drops was a major pathogenic factor.

**Corneal epithelial integrity**

Corneal sensation is vital for maintaining corneal epithelial integrity. With cataract surgery, the incision and limbal relaxing incisions (LRIs) transect the nerves responsible for corneal innervation. With LASIK, we’re creating a 270-degree flap that cuts nerves, and the ablation amputates a few more. We should also remember 10% of refractive IOL patients will have both cataract surgery and laser vision correction.

LASIK pre-op risk factors are the degree of myopia, the depth of the laser treatment, female sex, dry eyes, previous contact lens use, eyelid disorders and anomalies, and diabetes. Pre-op, it’s important to recognize and treat these conditions so our patients will sail through the post-op period and have better outcomes.

Lid anatomy and function should be assessed, as well as the blink rate, the tear film volume and quality, the tear breakup time and ocular surface staining with lissamine green or rose bengal.

**Candidate choice**

If dry eye symptoms have no effect on vision, the patient is a good candidate for LASIK. If there is concomitant dry eye and fluctuating vision, the patient is a moderate to poor candidate. If the dry eye symptoms and decreased vision are due to ocular surface disease, the patient should be a non-candidate until the surface can be improved with treatment.

Look for supravital conjunctival staining. If none exists, the patient is probably a good candidate. Supravital conjunctival staining with no corneal staining is a moderate candidate. If the patient presents with supravital conjunctival staining with central fluorescein corneal staining, he is probably not a candidate at all.

Topical corticosteroids, when used appropriately with and without cyclosporine, can be helpful in both the treatment of dry eye and blepharitis.

We need to use everything we have in our bag of tricks to optimize the ocular surface pre-op because that will improve the outcomes. There will be decreased post-op dry eye and faster visual recovery. With IOLs you get a more reliable keratometry and improved IOL power accuracy. If the patient needs LASIK in a bioptics procedure, you’ll get improved wavefront evaluation.

In summary, recent advances in technology and the evolution of cataract and refractive surgery really raise the bar for successful outcomes. As clinicians, we need to treat aggressively. Presume visual fluctuation is dry eye until proven otherwise. This all requires a coordinated, premeditated, perioperative regimen.

**REFERENCES**


Marguerite B. McDonald, M.D., is cornea, refractive, anterior segment specialist, Ophthalmic Consultants of Long Island, N.Y.; adjunct clinical professor of ophthalmology, Tulane University School of Medicine, New Orleans, La.; and clinical professor of ophthalmology, New York University, N.Y.
Conventional therapeutic approach to lid margin diseases

by Edward J. Holland, M.D.

**Lid scrubs, warm compresses, and corticosteroids should be considered as the primary treatment options**

Ten years ago, not many clinicians were interested in dry eye or blepharitis. Dry eye really came to the forefront with refractive surgery patients. We began talking about how to properly diagnose and treat it. In the next 3 to 4 years, these discussions will become even more prevalent as cataract and refractive surgeons realize that one of the leading causes of decreased vision in our patients is the health of the ocular surface. This is extremely important for our multifocal IOL patients. Posterior lid margin disease is probably the most common misdiagnosed and prevalent condition that affects our patients’ visual acuity.

It is critical to differentiate the findings of the ocular surface, whether it’s aqueous tear deficiency, blepharitis, or both. The majority of the patients with blepharitis will have anterior or posterior meibomian gland disease. Patients with posterior lid margin disease have chronic complaints. We look for inspissation of glands, erythema and telangiectasia around the glands, the pouting of oil, and the rapid tear break up time. That really identifies the unstable tear film and why these patients have fluctuation in vision.

Corneal specialists see complications of chronic blepharoconjunctivitis. These patients are in chronic discomfort. We do see corneal involvement with scarring and neovascularization and significant loss of vision in some patients.

**Treatment options**

Anterior blepharitis, while not very common in my practice, is certainly due to Staph disease. Treatment options are lid hygiene with hot compresses and commercial lid scrubs. We do use antibiotic ointments; corticosteroids are rarely indicated. Sometimes in anterior lid margin disease we’ll have an associated conjunctivitis and discomfort.

For those who present with posterior lid margin disease, patient education is vitally important. These patients have chronic discomfort, chronic red eyes, and waxing/waning vision. They are looking for a cure and there isn’t any. But we do have ways to make these patients more comfortable and improve their visual acuity. Again, lid hygiene and warm compresses are the cornerstone for treatment. Patients prefer commercial lid scrubs to trying to mix up some kind of solution on their own. I often tell them to use hot compresses in the shower and make it simple, typically twice a day. Patients are just not compliant beyond twice daily.

We used to recommend rotating an antibiotic to reduce the colony counts of bacteria on lid surfaces, but I have not been that impressed.

An example of meibomian gland disease. Note the intense eyelid involvement (left)

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Anti-infective and anti-inflammatory effects of azithromycin

by Terrence P. O’Brien, M.D.

Pharmacodynamics make azithromycin particularly suitable for ocular infections

The first principle in treating ocular infectious diseases is to know the enemy before engaging in battle. That implies an understanding of the epidemiology of the patterns of ocular infectious disease as well as the susceptibility patterns of the agents that cause the disease.

The second principle is to respect the enemy because we are clearly outnumbered. Ocular pathogens will change course to adapt quickly to our efforts at eliminating them. They represent the ultimate opportunists and survivalists.

We know there is an emergence and spread of antimicrobial resistance. It’s an increasing global concern. Mutations happen, leading to new resistant bacteria. We always felt immune to the problem of resistance in ophthalmology because we can apply our agents topically. Yet data from the Campbell lab and others have shown recently that there is an alarming increased resistance among isolates causing ocular infections, including keratitis, endophthalmitis, conjunctivitis, and blepharitis. 1-3

The next principle is to know the agents. If we could pick the ideal agent, it would be broad spectrum, bactericidal in action, biocompatible, meaning non-cytotoxic, and bioavailable, having favorable pharmacodynamics.

Antibiotic parameters

Bacitracin (various manufacturers) has been around for awhile and is used frequently to treat blepharitis. But it’s insoluble and only available in ointment form, having a negative effect on vision. Erythromycin (various manufacturers) is used widely, but it, too, is insoluble and is only available as an ointment.

The real problem with these, though, is a considerable resistance, especially among Staphylococci.

Aminoglycosides are mainly gram-negative acting agents. They are very toxic and rapidly create keratopathy, and they inhibit wound healing. Interestingly, chloramphenicol (various manufacturers) is the most widely used anti-infective globally because of its relative inexpensiveness. However, it can cause a rare but devastating bone marrow idiosyncratic toxicity that could be fatal.

Sulfacetamide (various manufacturers), our old friend from the 1940s, is still used occasionally. It has reasonable effect but can cause a hypersensitivity.

We now have some very potent 8-methoxy fluoroquinolones that have improved spectrum of activity against Streptococci and other gram

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“Azithromycin gives us a high therapeutic index by achieving very high concentrations in the ocular surface tissues.”

Terrence P. O’Brien, M.D
Novel Therapeutic Regimens in Treating Ocular Surface Disease and Blepharitis

by Kerry D. Solomon, M.D.

Advanced treatment of blepharitis and expert panel recommendations

Quality of vision is going to be most important for all your cataract patients, especially your refractive cataract patients, premium IOL patients, LASIK and PRK patients. We need to remember the refractive surface of the eye is the tear film, not the cornea or lens. Dry eye syndrome and blepharitis are two of the most common diseases we deal with. Blepharitis really is a type of dry eye, an evaporative dry eye. We’ve been trained for years that when we evaluate cataracts, we put the slit lamp right back to the lens and we bypass the lid.

If the ocular surface is not healthy, visual distortions will follow LASIK, PRK, and multifocal IOL surgeries.

Dry eye, as we typically think about it, is auto-immune related. Most clinicians use corticosteroids, like Lotemax (loteprednol etabonate 0.5%, Bausch & Lomb, Rochester, N.Y.), or Restasis (cyclosporine ophthalmic emulsion, Allergan, Irvine, Calif.). Clinicians should apply the same methods used to treat aqueous insufficiency to lid margin disease and blepharitis.

Dry eye and surgery

Dry eye is the most common complication we see — one in four patients will have dry eye symptoms or complaints. We’ve learned that the quality of the tear film and health of the corneal epithelium are extremely important in obtaining good outcomes.

To do this, clinicians must treat the underlying problem pre-op, protect during surgery, and manage appropriately after surgery. Cataract surgery is likely to induce dry eye or exacerbate pre-existing dry eye in a significant portion of patients.

We are familiar with the signs and symptoms of blepharitis, as well as the sequelae, both anterior and posterior lid margin disease. Much of the dry eye we see is related to blepharitis by itself or in combination with aqueous insufficiency.

Conventional management includes warm compresses and lid scrubs. The ideal mechanism in my opinion for AzaSite (azithromycin, Inspire Pharmaceuticals, Durham, N.C.) is not bacterial conjunctivitis but blepharitis. One drop gives 100-fold concentration that will last for a very long time on the eyelid.

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Potential Severe Consequences of Untreated Dry Eye Disease

 Sterile Melting  Bacterial Keratitis

Left uncontrolled, dry eye disease can lead to sterile melting (on left) or bacterial keratitis (on right)
with the results. Patients don’t like antibiotic ointments, as they don’t really penetrate the lid very well. A similar problem occurs with the current fluoroquinolones. I’ve given this step up altogether in my practice. Tetracyclines (various manufacturers) are very effective, but make sure you’re prescribing a sub-antibiotic dose. In my practice, I’ve found doxycycline (various manufacturers) 20 mg/b.i.d. is very effective. You almost eliminate the GI upset and the photosensitivity, and you retain the efficacy at that dosing. Doxycycline and minocycline (various manufacturers) should be used but in a low dose and you’ll have the same effect.

About 20% of the patients with posterior lid margin disease will have facial rosacea, which impacts significantly on the quality of life. Recommendations here are for tetracycline and metronidazole, or a dermatological referral. MetroGel (metronidazole, Galderma Laboratories, Fort Worth, Texas) to the face is effective twice a day. Patients started applying it to their lid margins and it’s very well tolerated.

**Steroids and supplements**

Topical steroids are very important in the management of posterior lid margin disease. Any patient with corneal involvement, from an inflammatory aspect, should be placed on a course of corticosteroids. In patients with chronic neovascularization scarring, Lotemax (loteprednol etabonate 0.5%, Bausch & Lomb, Rochester, N.Y.) should be used because it’s effective and has a very good safety profile. It’s also one of the most effective treatments for the chronic discomfort of posterior lid margin disease. Patients may have conjunctivitis associated with chronic pain, and corticosteroids are very effective for that.

The omega-3 nutritional supplements are very effective in the management of posterior lid margin disease and dry eye. The combination of flaxseed oil and fish oil together are synergistic and I do recommend that. In my practice, we are putting this in front of tetracycline.

**Summary**

I recommend lid hygiene in all patients, nutritional substitutes as a second choice, and tetracycline use as the third option. If there’s conjunctival and corneal involvement, consider corticosteroids. No one treatment is effective for all patients. You have to find out what works for the patient. Continued patient education will get him or her to buy into the treatment. Although we have some good standard treatments, we have patients that don’t respond to everything that I’ve mentioned here.

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**REFERENCES**

In summary, we need to know the enemy and the possible agents that are available. Be aware of susceptibility data and the patterns of resistance. Try to integrate the pharmacokinetics with the microbiology. Analyze data carefully and objectively. I think we’re meeting our needs better with azithromycin to treat these challenging conditions.

REFERENCES

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