Special Issue

The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Management and Treatment of Meibomian Gland Dysfunction

Gerd Geerling,[1] *Joseph Tauber,*[2] *Christophe Baudouin,*[3] *Eiki Goto,*[4] *Yukihiro Matsumoto,*[5] *Terrence O'Brien,*[6] *Maurizio Rolando,*[7] *Kazuo Tsubota,*[5] *and Kelly K. Nichols*[8]

The goals of the subcommittee were to review the current practice and published evidence of medical and surgical treatment options for meibomian gland dysfunction (MGD) and to identify areas with conflicting, or lack of, evidence, observations, concepts, or even mechanisms where further research is required. To achieve these goals, a comprehensive review of clinical textbooks and the scientific literature was performed and the quality of published evidence graded according to an agreed on standard, using objective criteria for clinical and basic research studies adapted from the American Academy of Ophthalmology Practice Guidelines[1] (Table 1). It should be noted that, in many of the clinical textbooks and previous reports, terminology is often interchanged and the management of anterior and posterior blepharitis and/or meibomitis is often considered concurrently. Thus, a broad scope of documents was reviewed in this process. Consistency in terminology and global adoption of the term "meibomian gland dysfunction" would significantly aid clinical research and clinical care in MGD going forward.

Current Practice Patterns

Although there is general agreement among the recommendations of major clinical handbooks concerning the management of MGD, there are significant differences in practice patterns across the world, in part because of the availability of therapeutics as well as the clinical manuals that are commonly used. Specifically, *The Moorfields Manual of Ophthalmology*[2] and *The Wills Eye Manual*[3] (Table 2) recommend:

- warm compresses and lid massage up to four times per day for 15 minutes,
- adjunctive use of lubricants in cases of additional dry eye disease,
- topical antibiotic ointments for moderate to severe cases, and
- systemic tetracycline derivatives (e.g., tetracycline 250 mg four times per day or doxycycline 100 mg two times per day) for 6 weeks to several months in recurrent cases, and/or
- to consider topical steroids in severe cases for a short term and incision and curettage with optional steroid injection in chalazion.

Both manuals in reference to the management of blepharitis and meibomitis also recommend cleansing the lid margins with mild (baby) shampoo and cotton buds and suggest to advise patients about the chronic nature of the condition with no known cure.

Recently Lemp and Nichols[4] published a perspective on the management of blepharitis that was based on a survey of 120 ophthalmologists and 84 optometrists attending an informational seminar sponsored by an ophthalmic pharmaceutical manufacturer. Respondents reported their clinical perception that 69% of blepharitis patient visits result in some form of treatment, with approximately half of this group receiving prescription-based therapy. Treatment goals for anterior and posterior blepharitis varied slightly between ophthalmologists and optometrists with the latter stressing the importance of reducing symptoms and a high safety profile of the prescribed medication, whereas ophthalmologists emphasized the importance of reducing the bacterial load in anterior blepharitis and improving meibomian gland function in posterior blepharitis. These goals are, of course, not incompatible.

Current MGD Treatment Practice Patterns

Overall, treatment of MGD varies greatly among eye care providers on different continents. Underreporting makes it difficult to assess practice patterns accurately, but most practitioners agree that underdiagnosis is common and clinical follow-up irregular. Recommendations for the performance of lid warming and lid hygiene are commonly made, but the precise technique varies greatly, both in duration and frequency of lid warming and cleansing.[2,3] Practitioners have noted widespread deficiencies in both the patient education provided to differentiate aqueous-deficient dry eye and evaporative dry eye, and perhaps more important, MGD; patients' comprehension of these nuances, even when provided, are varied. Likewise, practitioners on all continents note that patients commonly develop their own methods of performing lid hygiene, regardless of instruction. As a result, suboptimal and

From the [1]Department of Ophthalmology, Heinrich-Heine University, Düsseldorf, Germany; the [2]Tauber Eye Center, Kansas City, Missouri; the [3]Department of Ophthalmology, Quinze-Vingts Hospital, Department of Ophthalmology, University of Paris, Paris, France; the [4]Department of Ophthalmology, School of Dental Medicine, Tsurumi University, Yokohama, Japan; the [5]Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan; [6]Bascom Palmer Eye Institute, Palm Beach Gardens, Florida; [7]The Eye Institute, University of Genoa, Genoa, Italy; and the [8]College of Optometry, Ohio State University, Columbus, Ohio.

Supported by the Tear Film and Ocular Surface Society (TFOS; http://www.tearfilm.org); individual author support is listed in the Appendix of the Introduction.

Submitted for publication December 6, 2010; accepted March 23, 2011.

Disclosure: Each Workshop Participant's disclosure data can be found in the Appendix of the Introduction.

Corresponding author: Kelly K. Nichols, College of Optometry, 338 W. 10th Avenue, Ohio State University, Columbus, OH 43210-1280; knichols@optometry.osu.edu.

DOI:10.1167/iovs.10-6997g
Investigative Ophthalmology & Visual Science, Special Issue 2011, Vol. 52, No. 4

TABLE 1. Grading Level of Evidence of Clinical and Basic Research Studies[1]

Clinical Studies*	
Level I	Evidence obtained from at least one properly conducted, well-designed randomized controlled trial or evidence from studies applying rigorous statistical approaches
Level II	Evidence obtained from one of the following: Well-designed controlled trial without randomization Well-designed cohort or case-control analytic study from one (preferably more) center(s) Well-designed study accessible to more rigorous statistical analysis.
Level III	Evidence obtained from one of the following: Descriptive studies Case reports Reports of expert committees Expert opinion Meeting abstracts, unpublished proceedings
Basic Science	
Level I	Well-performed studies confirming a hypothesis with adequate controls published in peer-reviewed journal
Level II	Preliminary or limited published study
Level III	Meeting abstracts or unpublished presentations

* Studies specific to MGD/management of MGD discussed in the text are identified by the level of evidence.

ineffective lid hygiene is commonly practiced and abandoned prematurely as ineffective. Many patients use artificial lubricants, but often because of misdiagnosis and/or concurrent diagnosis of dry eye. Many forms of lubricants, some with lipid components, are available across the world. Systemic tetracycline is the most common prescription given for the treatment of posterior blepharitis in the United States,[4] but is less frequently used in Europe or Japan. The second most common prescription medication is for a topical antibiotic and/or an antibiotic–steroid combination. It should be noted that antibiotic–steroid combinations are used clinically for acute exacerbated cases or for anterior blepharitis, although, because of confusion in clinical differentiation of anterior and posterior blepharitis, use patterns are difficult to assess. Topical azithromycin, a macrolide antibiotic with presumed anti-inflammatory effects, is available in some but not all countries. Further, studies of its efficacy in treatment of MGD or blepharitis have been few outside the United States. There have been studies reporting the use of topical cyclosporine in patient groups with MGD combined with aqueous-deficient dry eye, although cyclosporine itself is also not widely available commercially outside of North America.

Evidence Supporting Available Treatment Options

Artificial Lubricants in the Treatment of MGD

Understanding the role of artificial lubricants, popularly called artificial tears (AT), in the treatment of MGD requires a brief discussion of the pathophysiologic mechanisms at work in both MGD and aqueous-deficient dry eye. Although aqueous tear deficiency is not a central pathophysiologic mechanism in MGD, it is a concomitant disease in many patients with MGD. Although published estimates vary between 50% and 75% according to the type of clinical practice surveyed, it is likely that the coincidence of aqueous tear underproduction and MGD is even higher.[4] As suggested by the mentioned practice patterns, MGD is perhaps the most underdiagnosed, undertreated, and underappreciated disease in eye care worldwide.

Many patients in whom dry eye has been diagnosed by symptoms and/or routine clinical tests may instead have—according to clinical experience—MGD alone or MGD in combination with dry eye. Because the symptoms of aqueous-deficient dry eye are so difficult to differentiate from those of MGD-related, evaporative dry eye, it may be impossible to truly separate patients into distinct groups. In fact, it may be that these two forms of dry eye disease are spread across a spectrum, with patients only rarely experiencing symptoms and exhibiting signs of one type exclusively. This notion makes pathophysiologic sense, as both increased evaporation of tears and reduced production (volume) of tears increase the osmolarity of tears, believed to be a central mechanism of pathophysiology in dry eye.[5]

This co-mingling of aqueous-deficient dry eye and MGD is very important in crafting the approach to treating patients with various degrees of both of these diseases. Supplementation of the tear film can address the "final common pathway" that mediates the range of ocular surface disease, including evaporative dry eye (with or without MGD) and aqueous-deficient dry eye. Increasing tear volume reduces hyperosmolarity[6] and also reduces friction between the tarsal conjunctiva and more specifically the epithelium of the lid wiper,[7–9] corneal epithelium, and palpebral conjunctiva. It also improves

TABLE 2. Recommendations in Clinical Handbooks for Treatment of Posterior Blepharitis and Meibomitis

	Moorfields Manual[2]	Wills Eye Manual[3]
Lid-heating, massage, and cleaning	Warm wet face cloth for 5 minutes once or twice a day; massage upper and lower lid	Warm compresses for 15 minutes four times per day; clean with wet cotton bud and mild (baby) shampoo
Topical medication	Antibiotic ointment twice a day for 3 weeks; short term topical steroids in severe cases	Antibiotics at night in severe cases
Systemic medication	With corneal involvement: doxycycline 100 mg once a day or erythromycin 250 mg four times a day for 8 weeks	Tetracycline 250 mg four times a day or doxycycline 100 mg twice a day for 6 weeks
Adjunctive treatment	Lubricants if dry; management of skin disease	Lubricants four to eight times a day

spreading of the tear film lipid layer[10] (clinical studies level II). In addition, the use of AT rinses the ocular surface of toxins and debris and may dilute the concentration of inflammatory cytokines and other proinflammatory molecules that have been found in the tears[11–16] (clinical studies level II/III). Via all these mechanisms, the frequent use of AT serves to reduce proinflammatory stimuli[17] (clinical studies level II).

This proposed explanation of a positive role in the use of AT must be regarded as speculative and unproven, as neither basic science nor clinical studies of the use of AT in MGD have been published to substantiate the hypothesis. Even in the absence of the evidence from a randomized controlled study, most practitioners rely on AT as a mainstay of treatment for aqueous-deficient dry eye and for most varieties of ocular surface disease across disease severity. Under the broad umbrella of ocular surface disease, the efficacy of AT in the management of ocular allergy perhaps relates to the rinsing and lubricating effects achieved from regular and repeated doses. Many clinicians apply the same reasoning to the treatment of MGD in recommending the chronic use of AT.

Evidence from studies of aqueous-deficient dry eye provides a basis for rational selection of artificial lubricants in MGD.[1] Key concerns in the selection of an AT include the role of preservatives, the role of viscosity, and more recently, the supplementation of oil (lipid) to the tear film. The role of preservatives in ocular surface toxicity has received increasing attention over the past decade.[18–28] Even with indisputable evidence of preservative-induced toxicity in epithelial cells in vitro, clinical studies do not provide data that determine how frequently a preserved AT can be safely used in MGD. Conventional wisdom has been that bottled (preserved) AT can be used from four to six times daily without significant clinically evident toxicity (uptake of fluorescein stain by the corneal epithelium). Most studies of preservative-induced epithelial toxicity have studied detergent-type preservatives, such as benzalkonium chloride (BAK). Whether this recommendation should be modified because of increased incorporation of oxidative or so-called vanishing preservatives, such as sodium chlorite or perborate and sodium perborate 1.5% (Purite 0.15%; Allergan, Irvine, CA) cannot be determined on the basis of studies published to date in MGD and MGD-related dry eye disease.

Several published studies support the superiority of the higher viscosity artificial lubricants in the treatment of dry eye.[29–32] Most clinicians choose from the dozens of available AT preparations, assuming that the ocular surface residence time of a more viscous product will be longer. Ointments last longest, gel drops last next longest, and thin lubricants remain on the surface of the eye for the shortest time. Surface residence time must be balanced with undesired blurring of vision, which tends to correlate directly with viscosity.

Topical Lipid Supplements in the Treatment of MGD

Supplementation of tear film lipids has been attempted by the use of lipid-containing eye drops and sprays, emulsion-type eye drops, and ointments. Historically, lipid-containing lubricant eyedrops have not been used widely because of the induced blurring of vision after their use. In recent years, newer formulations have been better accepted, although the number of published studies is small.[16,33–36]

In patients with noninflamed, obstructive MGD, with and without aqueous-deficient dry eye, Goto et al.[37] reported a small randomized controlled clinical trial (clinical studies levels I and II) in which a self-formulated low-concentration preparation of homogenized 2% castor oil eye drops was used six times daily. Subjective symptom scores ($P = 0.004$), tear interference image grades ($P < 0.0001$), tear evaporation rates ($P = 0.01$), rose bengal staining scores ($P = 0.007$), tear film breakup time (TBUT; $P < 0.0001$), and meibomian gland expressibility grades ($P = 0.002$) after the oil eye drop period showed significant improvement compared with the results after the placebo period.

An emulsion-based lubricant eye drop has been studied in normal subjects and patients with aqueous-deficient dry eye, with or without MGD (clinical studies level II).[38,39] Compared with the control eyes, emulsion-treated eyes showed rapid restructuring of the preexisting tear lipid film in tear-interference image examination.

Lipid-containing eye drops are difficult to obtain in many countries. Thus, the use of conventional eye ointment as topical lipid supplements in evaporative dry eye or MGD treatment has been tested. As bulk application of eye ointment causes long-lasting visual blur, Goto et al.[40] (clinical studies level II) used a low-dose, 0.05-g lipid-containing ointment applied across the full length of the eyelid margin in patients with dry eye and meibomian gland obstruction and in a second study of patients with severe MGD[41] (clinical studies level III). Ofloxacin eye ointment was chosen, as it contains both polar and nonpolar lipids. This method of application was used three times daily in addition to the preexisting ongoing treatment. After the additional lipid treatment, the symptom scores of ocular dryness ($P < 0.0001$), lipid layer thickness measured with a tear-interference camera ($P < 0.0001$), TBUT ($P = 0.01$), and meibum expressibility grades ($P = 0.0005$) improved significantly. Tear film interferometry indicated a more uniform thickness of the tear lipid layer after application of the ointment. Such an improvement was also observed in the treatment of meibomian absence in EEC (ectrodactyly-ectodermal dysplasia-clefting) syndrome with meibomian gland dysplasia.[41]

The presence of the antibiotic together with lipid ointment in these supplementation studies introduces some uncertainty about whether the lipid or the antibiotic is responsible for the observed improvements. Confirmation of the efficacy of the lipid formulation alone would require a suitably designed, randomized controlled trial comparing the ointment base alone with an ofloxacin preparation.

A lipid-containing liposomal spray has been studied in two prospective randomized multicenter trials (clinical studies level II) in patients who have evaporative dry eye, as defined by low TBUT and inflammatory lid margin changes. Patients received hyaluronate AT, triglyceride gel, or a phospholipid-liposome eye spray, each for a minimum of 6 weeks. Phospholipid liposomal spray achieved a significantly greater reduction of the lid-parallel conjunctival folds, lid margin inflammation, and improvement in the break-up time than did hyaluronate eye drops or triglyceride gel.[42,43]

Comments. The use of lipid supplements in clinical studies has been demonstrated to improve some signs and symptoms of MGD, perhaps by improving tear film stability. Further randomized controlled masked clinical trials of patients with well-defined MGD are needed to determine efficacy across disease severity.

Lid Hygiene and Warm Compress or Heat Application

Lid hygiene is regarded as the mainstay of the clinical treatment of MGD. It usually consists of two components: application of heat and mechanical massage of the eyelids.

Eyelid Warming. The application of warmth, either with moisture or without has received frequent study in MGD.[37,44–49] Obstructive MGD has previously been defined as being associated with decreased meibum secretion. Yokoi et

al.,[50] using meibometry, reported that MG function in patients with MGD was significantly reduced compared with that in healthy subjects (basic science level II). McCulley and Shine[51] suggested that meibomian secretions with ester fractions of different composition can have different melting points and that MGD can cause a shift toward lipids with higher melting points, producing a stagnant and less dynamic tear film (basic science level II). Indeed, meibomian secretions from normal subjects have been shown to begin to melt at 32°C and 35°C in patients with obstructive MGD.[51] Eyelid-warming therapies can be expected to improve MG secretion by melting the pathologically altered meibomian lipids. The warming can be achieved by many diverse means, including simple warm compresses (e.g., hot wet towel, heated rice bag) or devices such as infrared or hot air sources[37,44–49] (clinical studies level II/III).

Warm compress therapy is a commonly recommended but poorly standardized treatment for MGD that is performed by patients for variable durations of heat application and with varying compliance. Nagymihalyi et al.[52] reported that eyelid temperature significantly influenced the delivery of the meibomian gland secretions in healthy human volunteers (clinical studies level III). The application of a 250-W infrared lamp from a distance of 50 cm increased the eyelid surface temperature and increased the meibomian oil delivery on the eyelid margin. Olson et al.[49] reported that 5 minutes of treatment with warm towel compresses (40°C) applied to the skin of closed eyelids increased the tear film lipid layer thickness by more than 80% in patients with obstructive MGD, with an additional 20% increase after 15 minutes of treatment. There was no increase in tear film lipid layer thickness with 5 minutes of treatment with towel compress at room temperature (24°C) applied to the contralateral control eyes[49] (clinical studies level II). The increase in tear film lipid layer thickness in that study was found to be significantly related to the reduction of symptom scores. A protocol to optimize warm compress treatment has been published by Blackie et al.[44] and recommends the continuous application of 45°C hot compresses for at least 4 minutes with optimal contact between compress and eyelid, replacing the compress every 2 minutes with a new compress preheated to 45°C to achieve adequate warming to alter secretions (clinical studies level II).

Alternative sources of heat for warm compress therapy include eye warmer devices, delivering infrared irradiation or moist air or eye warmer masks. Goto et al.[53] reported increased tear stability and decreased dry eye symptoms after 2 weeks of treatment with an infrared eyelid-warming device applied to the eyelids for 5 minutes twice daily in patients with obstructive MGD (clinical studies level III). The application also improved tear evaporation, ocular surface epithelial damage, and meibomian gland orifice obstruction. Mori et al.[48] reported warming of the eyelids with a disposable (noninfrared) eyelid-warming device for 5 minutes once a day for 2 weeks, which improved dry eye symptoms, tear stability, and uniformity of the tear lipid layer in MGD patients (clinical studies level II–III).

Matsumoto et al.[47] reported that warm moist air device use for 10 minutes twice daily for a period of 2 weeks provided symptomatic relief of ocular fatigue, improvement of tear stability and ocular surface epithelial damage in patients with MGD (clinical studies level II). The thickening of the tear film lipid layer after 10 minutes of device application was confirmed in both patients and controls in that study. Mitra et al.[54] reported that treatment of MGD with a moist air device increased the lipid layer thickness in normal individuals, helped achieving a more stable tear film, and provided subjective improvement in ocular comfort (clinical studies level II).

Ishida and Matsumoto also reported that eye warmer masks (Orgahexa; Therath Medico Inc., Tokyo, Japan) applied for 10 minutes for 2 weeks improved both tear functions and ocular surface status, and decreased symptoms significantly in MGD patients[46] (clinical studies level III). The application of these masks were found to be more effective in MGD patients, but not in normal controls, compared to the conventional eye masks applied for the same period.

Eyelid warming with warm compresses has also been reported to induce transient visual degradation due to corneal distortion, apparently resulting from the application of light pressure with warm compresses, as evidenced by the polygonal reflex of Fischer-Schweitzer[44,55] (basic science level II). Further larger-scale prospective randomized comparative studies investigating the alterations of subjective and objective findings in healthy controls and MGD patients with such devices have not been performed and should be conducted.

Mechanical Lid Hygiene. Lid hygiene (i.e., scrubs, mechanical expression and cleansing with various solutions of the eyelashes and lid margins) is frequently recommended, together with lid warming in the treatment of MGD. Romero et al.[56] reported in a nonrandomized, uncontrolled, prospective study that lid hygiene with a combination of heated saline solution and preservative-free AT significantly improved tear break-up time and relieved symptoms in patients with MGD (clinical studies level II). The MGD patients in this study were treated with the aforementioned regimen for 6 weeks but were not compared to normal subjects. In an additional study of lid hygiene, Key reported that the use of hypoallergenic bar soap, dilute infant shampoo, or commercial lid scrubs is useful in the treatment of anterior blepharitis[57] (clinical studies level III). The biomicroscopic features of the blepharitis improved after treatment, but this study also lacked a comparative control group. Paugh et al.[58] also reported that lid scrub and massage increased the TBUT in patients with MGD (clinical studies level II).In this study, 2 weeks of treatment was found to be effective in the resolution of clinical signs with no significant changes observed in the controls. Matsumoto et al. evaluated the response to treatment including hygiene, topical steroid, and topical antibiotic in obstructive MGD using confocal microscopy, although hygiene alone was not assessed[59] (clinical studies level II). Current literature seems to have no studies on the above topics with clinical studies level I of scientific evidence, and such studies are needed, to confirm the efficacy of this frequent clinical treatment option in the future.

Properly performing lid massage may help the patient's therapy; proper instruction to the patient is therefore necessary. For example, patients may be told that after application of a hot compress to the eyelids, they should apply traction on the lateral canthus to immobilize the upper and lower eyelids; that should be followed by down- or upward mild compression of the eyelids with the finger of the opposite hand beginning at the nasal canthus and moving laterally toward the lateral canthus.

Physical expression of meibomian glands for therapeutic purposes is an in-office procedure with at least an 80-year history.[60–63] It can be supplemented by the patient's performing self-expression and massage at home. The reported techniques vary from gentle massage of the lids against the eyeball[61] to forceful squeezing of the lids either against each other[63] or between a rigid object on the inner lid surface and a finger, thumb, or rigid object (e.g., glass rod, Q-tip, or metal paddle) on the outer lid surface.[62,63–66] The rigid object on the inner lid surface is used to protect the eyeball from forces transferred through the eyelid during expression and also to offer a stable resistance, to increase the amount of force that can be applied to the glands. The amount of force needed to express obstructed glands can be significant and is usually limited by the pain induced by the expression and not by the amount of force that can be applied. The amount of pain

increases rapidly as the force of expression exceeds 15 g/mm^2 (~5 PSI) with forces of 80 g/mm^2 (~25 PSI) and greater, frequently producing excruciating pain, thus considerably limiting clinical application.[67,68] Regardless of the method of meibomian gland physical expression, the goal is to express the meibomian gland obstruction and other material from the gland, thereby facilitating normal gland function. Clinically it is recommended that treatment with physical expression should be continued until the dysfunction is resolved.

Comments. Lid hygiene is widely considered an effective mainstream therapy for MGD and blepharitis, despite the lack of standardization of the technique and the uncertainty about patient compliance. Studies comparing specific techniques of lid hygiene would allow evidence-based recommendations regarding this simple and presumably effective therapy. Studies comparing the efficacy of the many available methods for eyelid warming are also lacking. Nonetheless, given the near unanimity of support for this therapy among international experts and clinicians alike, patients should be instructed in lid-warming and hygiene and urged to remain compliant, to maintain long-term control of symptoms. Follow-up examinations are to be recommended as a means of ensuring the patient's compliance, as many patients are unlikely to remain compliant with these methods from one annual examination to the next.

Topical Antibiotic Agents in the Treatment of MGD

The uncertain role of bacteria in the pathophysiology of MGD and the incompletely understood optimal balance of normal lid microbiota make the role of topical antibiotics in therapy indeterminate. No evidence suggests that bacterial infection is the primary pathophysiologic process in MGD, but numerous clinical findings often seen in MGD may be related to the effects of the bacteria that colonize the eyelids. Bacteria may have both direct and indirect effects on the ocular surface and on meibomian gland function. These include direct effects on the production of toxic bacterial products (including lipases) and indirect effects on ocular surface homeostatic mechanisms, including matrix metalloproteinases (MMPs),[69] macrophage function, and cytokine balance (Jacot JL, et al. *IOVS* 2008;49:ARVO E-Abstract 1985). The complexity and uncertainty of the role of bacteria in the MGD process, characterized by both infectious and inflammatory processes, has implications for appropriate recommendations for therapy. In the absence of peer-reviewed studies, recommendations for the use of this class of therapeutic agent in MGD must be regarded as speculative, and readers should individually evaluate the applicability of the data reviewed.

The mere demonstration of the presence of bacteria on the lid margin of patients with MGD does not imply causality. It may be that the excessive colonization of the lids, demonstrated in patients with blepharitis,[70,71] with coagulase-negative staphylococcus (*Staphylococcus epidermidis*), *Staphylococcus aureus*, *Propionibacterium acnes* or other microbes is an epiphenomenon, indicating the possibility that microbes find the altered eyelid environment in MGD more hospitable than that of the normal eyelid. Keratinization of the lid margin epithelium, the accumulation of keratinized cell debris, within and/or around the meibomian orifice, and the presence of abnormal lipids all provide a rich substrate for the resident bacterial microbiota. Thus, it is also possible that the subsequent release of toxic bacterial products such as lipases or the secondary production and release of proinflammatory cytokines is pathogenic. Excessive bacterial colonization may be pathogenic via preferential selection of certain microbial species. Quorum sensing has been proposed as a mechanism to explain how excessive colonization can trigger certain species of bacteria to release potentially toxic bacterial products.[72,73] Normally, as a kind of feedback mechanism, signaling molecules called autoinducers, allows bacteria to monitor the relative number of their own and other species in the same environment, facilitating coexistence. Malfunctions in this system may be triggered by the appearance of new bacterial species in the environment and may result in the release of potentially toxic bacterial products.[74,75]

In theory, for an antibiotic agent to be beneficial in MGD, it must be effective against the pathogens most likely to be present in this condition. A complete review of antibiotics and their properties is beyond the scope of this report, but commonly used topical antibiotics, their dosages, and their advantages and disadvantages will be briefly reviewed.

Bacitracin. Bacitracin is a protein disulfide isomerase inhibitor that interferes with bacterial cell wall synthesis. It has been used primarily as a topically applied agent, since it can be highly nephrotoxic in systemic use. Poor aqueous solubility limits its use primarily to ointment formulations. Bacitracin has a spectrum of activity similar to that of penicillin and has also been used to treat anterior blepharitis.[76]

Fusidic Acid. Fusidic acid, a topical antibiotic with efficacy against Gram-positive organisms, has been in clinical use since 1962. It inhibits protein synthesis by blocking aminoacyl-sRNA transfer to protein in susceptible bacteria. Although not widely used to treat blepharitis, research indicates that this drug may be effective for patients with blepharitis and associated rosacea. Seal et al. [77] (clinical studies level II) used a treatment of 1% fusidic acid and noted improvement in the symptoms in 75% of patients with concurrent blepharitis and rosacea. In comparison, oral oxytetracycline yielded improvement in just 50% of these patients. Treatment was much less successful in patients who had blepharitis without rosacea. These patients had no response to fusidic acid alone, although 25% did respond to oxytetracycline.

Metronidazole. Metronidazole, FDA-approved as a 1% dermatologic preparation for the treatment of rosacea,[78,79] is bactericidal against susceptible bacteria. Its exact mechanism of action is not completely understood, but an unidentified polar compound breakdown product is believed to be responsible for metronidazole's antimicrobial activity, by disrupting DNA and nucleic acid synthesis in anaerobic bacteria. Barnhorst et al.[78] (clinical studies level II), in a study of 10 patients, found ocular rosacea lid hygiene combined with topical metronidazole gel applied to the lid margin for 12 weeks to be more effective than lid hygiene alone in the fellow eye in improving eyelid and ocular surface scores. No adverse effects of the metronidazole treatment were encountered in this study. Saccà et al.[80] reported a 50% positive response to metronidazole therapy in patients with *Helicobacter pylori* culture-positive blepharitis, although the authors conclude that the causative nature of *H. pylori* in chronic blepharitis warrants further evaluation.

Fluoroquinolones. The availability of topical fluoroquinolone antibiotics has influenced prescribing habits in a wide range of ocular infectious diseases.[81] These drugs have minimal ocular surface toxicity, provide excellent coverage of both Gram-positive and -negative organisms, and have become the treatment of choice in treating even serious corneal infections. Concerns about emerging bacterial resistance have, in part, limited widespread use of this highly effective class of antibiotics in patients with blepharitis.[82,83]

Macrolides. Macrolide antibiotics are products of actinomycetes (soil bacteria) or semisynthetic derivatives of them. Erythromycin, the first macrolide antibiotic, has been widely available since its discovery in the soil in the early 1950s. Erythromycin and other macrolide antibiotics inhibit protein

synthesis by binding to the 23S rRNA molecule (in the 50S subunit) of the bacterial ribosome blocking the exit of the growing peptide chain. Because of frequent use and high selection pressure, the extensive use of erythromycin may provoke resistance among Gram-positive organisms, and its overall efficacy for ophthalmic applications for ocular infection is now questioned. Ophthalmic use of erythromycin is also limited by its low aqueous solubility; therefore, it is most often compounded as an ointment for ocular use. An eye drop formulation is available in some European countries. Newer topical macrolides, such as azithromycin, clarithromycin, and roxithromycin, have become available and offer an expanded spectrum of coverage and better penetration than older macrolide antibiotics.[84,85]

Antibiotic Anti-inflammatory Efficacy. Macrolide antibiotics exert immunomodulatory and anti-inflammatory effects that are separate from direct antibacterial actions. Many studies have been conducted in the past decade in an attempt to understand the various cellular and molecular processes involved in the inflammatory response affected by macrolide compounds. Most in vivo studies have involved patients with chronic inflammatory respiratory diseases (asthma and diffuse panbronchiolitis). These studies have documented clinical and functional improvement after treatment with subtherapeutic levels of macrolides in respiratory disease patients, sometimes within weeks of therapy.[86–88] There are similarities in the nature of these respiratory diseases and MGD. Both involve elements of infectious and inflammatory pathophysiology on a mucosal surface with complex biofilm. Whether drugs found to be useful in treating respiratory disease could prove useful in treating MGD is worthy of investigation.

Although the specific molecular mechanisms which give rise to the above-mentioned benefits are not clear, several areas have been investigated. Macrolides' effects on proinflammatory mediators have been studied in clinical settings and in vitro. In both cases, a significant reduction of cytokine release (particularly IL-8, IL-6, and TNF-α) has been observed.[89,90] Although the role of these cytokines in MGD is not well understood, their role in dry eye has been better studied.

In addition, macrolides have potent effects on neutrophil functions, including chemotaxis and phagocytosis.[91,92] Macrolides' effects on neutrophils may be mediated by downregulation of adhesion protein expression.[93,94] Macrolides also have potent effects on the functions of phagocytic cells, including macrophages.[11,15,95–97] Finally, macrolides have been reported to downregulate genes coding for MUC5AC production.[88,98] The mechanisms at work in respiratory diseases such as asthma, cystic fibrosis, and autoimmune bronchiolitis have much in common with MGD.

Macrolides have the ability to break down and prevent further development of the biofilms protecting the mucoid *Pseudomonas aeruginosa* strains, relevant in pulmonary diseases. Of the 14- and 15-membered macrolides, azithromycin has been demonstrated to have the highest potency for these activities, further supporting its immunomodulatory potential in respiratory diseases[99] and potentially, in MGD. Extensive research in these areas remains ongoing.

The large body of data briefly summarized herein has generated substantial interest in studying the role of macrolide antibiotics such as azithromycin in the treatment of MGD. After oral administration, macrolides show a low serum concentration, along with a high tissue concentration and, in the case of azithromycin, an extended tissue elimination half-life. In a rabbit model following the FDA-approved regimen of 1 drop twice daily for 2 days then 1 drop once a day for 5 days, topical azithromycin (AzaSite; Inspire Pharmaceuticals, Durham, NC) produced a maximum azithromycin concentration in eyelids of 180 μg/g and a half-life of 125 hours (data on file from the manufacturer).[100]

Review of Published Studies of Antibiotics in the Treatment of MGD. In a study (clinical study level II) in which topical metronidazole plus lid hygiene was compared to lid hygiene alone, the researchers observed a significant improvement in the combined eyelid and ocular surface scores in treated eyes, but not in control eyes.[78]

Another single-center, open-label clinical trial demonstrated significant improvement in signs and symptoms of MGD after 2 and 4 weeks of treatment with topical 1% azithromycin solution. Resolution of in signs and symptoms correlated with spectroscopic analysis of expressed meibum demonstrating improvement in ordering of lipids and phase transition temperature of lipids in the meibomian gland secretion[101] (clinical studies level III).

An open-label multicenter study (clinical studies level III) demonstrated effectiveness of topical 1% azithromycin in treatment of subjects with blepharitis. Four-week azithromycin treatment demonstrated significant decreases from baseline in investigator-rated signs of meibomian gland plugging, eyelid margin redness, palpebral conjunctival redness, and ocular discharge at day 29 ($P \leq 0.002$), which persisted 4 weeks after treatment ($P \leq 0.006$).[102] In an additional recent open-label study (clinical study level III), patients with MGD blepharitis were treated with azithromycin plus warm compresses or warm compresses alone.[103] After using azithromycin twice daily for the first 2 days followed by once daily for the next 12 days of treatment, the azithromycin-treated patients showed significant improvements in meibomian gland plugging, quality of meibomian gland secretions, and eyelid redness. Also, a higher percentage of patients in the azithromycin group rated their symptomatic relief as good or excellent. Data from spectroscopic analysis of pre- and posttreatment meibomian gland secretions demonstrates a restoration of order pattern of the lipids and a correlative reduction in lipid phase transition temperature, which suggests that azithromycin alters the lipases acting on the meibomian gland lipids in MGD.[101]

The efficacy of azithromycin may be attributable to several factors mentioned previously. Animal studies of systemic azithromycin have shown it to have anti-inflammatory as well as antimicrobial effects.[87,104] Pharmacokinetic studies also have shown that topical ocular azithromycin was detectable in all tissues and fluids for 6 days after the dose of a single drop, suggesting that topical azithromycin is likely to have a sustained duration of effect.[100]

Comments. Topical antibiotics offer both opportunities and challenges in management of MGD and are not yet completely understood as a treatment regimen for MGD. Several topical and systemic antibiotics with activity against lid-related bacteria are available, but solid evidence from randomized controlled clinical trials is lacking to conclusively guide antimicrobial management of MGD. Although a handful of comparative studies have been performed, additional research is needed to better define the role of topical antibiotics, including macrolides, thought to have anti-inflammatory effects in a chronic management scheme for MGD.

Treatment of *Demodex* Mite Infestation in Blepharitis

Demodex mites are elongated mites with clear head–neck and body–tail segments, of which the former has four pairs of legs. There are more than 100 species of *Demodex* mites, many of which are obligatory commensals of the pilosebaceous unit of several mammals. *Demodex folliculorum* and *Demodex brevis* have been confirmed to be the most common ectoparasites in humans. In the eye, *D. folliculorum* is found preferentially in

the lash follicles and *D. brevis* in lash sebaceous glands. A role for *Demodex* mites in the pathogenesis of MGD has not yet been convincingly established[105,106] (clinical studies level III).

Demodex infestation is thought to be nonexistent in healthy children under the age of 10 years, increases in an age-dependent manner, and is very likely present in the skin of 100% of the elderly.[10,107] Although *Demodex* mites have been implicated as a cause of many human skin disorders, their pathogenic role has long been debated,[10,108,109] in part because some *Demodex* mites can be found in the skin of asymptomatic individuals.

There is evidence that Demodex infestation of the lash follicles contributes to the occurrence of anterior blepharitis and that cylindrical dandruff is a pathognomonic clinical sign.[110,111] Gao et al.[110] and Keirkhah et al.[111] reported that weekly lid scrubs with 50% tea tree oil (TTO) and daily lid scrubs with tea tree shampoo are effective in eradicating ocular *Demodex* infestation in vivo, as evidenced by the reduction of the *Demodex* count to 0 in 4 weeks in most patients. This was associated with improvement in previously refractory ocular surface inflammation. Because TTO also may exert antibacterial, antifungal, and anti-inflammatory actions, its therapeutic benefit may be independent of its effect of killing mites. It has been postulated that the mites act as vectors to bring in common skin bacterial microbiota[106,112,113] and that symbiosis or commensalism between mites and microbes could be part of the pathogenesis of MGD. The positive correlation between facial rosacea and serum immunoreactivity to two proteins derived from *Bacillus oleronius*, a bacterium that lives symbiotically within the mites, has led to suggestions that rosaceal manifestations, including lid margin inflammation, could be due to a strong host immune response to this organism.[105,106]

Comments. It appears that *Demodex* mites have an etiologic role in some forms of anterior blepharitis and that treatment with TTO is merited in these cases. There is no evidence yet that these mites can cause MGD, and therefore the role of pharmaceutical eradication of mites in the treatment of MGD is uncertain.

Tetracycline and Derivatives (Systemic)

The tetracyclines are bacteriostatic antibiotics, developed in 1948 and first proposed for the treatment of the cutaneous manifestations of acne rosacea in 1966.[114] In the management of rosacea and MGD, they are mainly used for their anti-inflammatory and lipid-regulating properties, rather than for their antimicrobial effects[79,115–119] (clinical studies level I–III).

Mechanisms of Action. At the systemic doses currently used in the treatment of MGD and rosacea, the antimicrobial effects of tetracycline derivatives in the lids are probably limited. The exception is minocycline, which has been shown to reduce the population of lid flora in rosacea patients, at a dose of 100 mg.[120,121] This finding may reflect differences in the lipophilicity and hence pharmacokinetics of these drugs. Oxytetracycline and tetracycline are poorly lipophilic, whereas doxycycline, and to a greater extent, minocycline, are lipophilic.[122] In this study, the concentration of oxytetracycline, tetracycline, minocycline, and doxycycline was measured in tears after 5 days of daily treatment by mouth. Although oxytetracycline and tetracycline do not achieve antimicrobial levels in the tears at standard doses, minocycline does so in normal subjects at a dose of 100 mg, and doxycycline reaches near inhibitory concentrations.[122] The authors conclude that doxycycline and minocycline are clinically effective at lower doses than tetracycline or oxytetracycline. It is hypothesized that the lipophilicity facilitates the entry of doxycycline and minocycline into the central nervous system and presumably influences its delivery to ocular structures and lid tissues presumably including the meibomian glands[122] (basic science level I).

However, there is good evidence that the efficacy of tetracyclines in the management of MGD depends on the suppression of microbial lipase production and hence the release of proinflammatory free fatty acids and diglycerides at the lid margin and ocular surface[123–126] (basic science level I and II). Thus, the production of lipases and esterases by lid commensals such as *S. epidermidis* and *P. acnes*, is highly responsive to low doses of tetracyclines. To a lesser extent, this applies to both sensitive and resistant strains of *S. aureus*. Minocycline therapy has the particular attraction of both reducing the resident lid flora and inhibiting their production of lipases.

Effects on Lipids and Meibomian Gland Secretions. Tetracyclines inhibit lipase activity and therefore decrease deleterious free fatty acids[125,126] (clinical studies level II). Free fatty acids destabilize the preocular tear film and promote inflammation (chemotaxis to neutrophils and reactive oxygen species [ROS] production, among others). Excessive lipase activity and alterations of lipid composition thus directly influence tear stability and cause inflammation, inside meibomian glands, in tears and most likely throughout the ocular surface. High oleic acid may also play a role in keratinization of the lid margin and plugging of meibomian gland orifices. Minocycline at 100 mg per day for 3 months showed marked decrease of diglycerides and free fatty acids[125] (clinical studies level III).

Inhibition of Inflammation. Tetracyclines may have anti-inflammatory properties through multiple mechanisms and events demonstrated in ocular tissues or nonocular systems. Target cells may be neutrophils (migration and chemotaxis), lymphocytes (proliferation, transmigration, and activation), and, most likely, epithelial cells (corneal, conjunctival, and others). Antioxidative effects have also been found (anti-ROS inhibition and accelerated degradation of NO synthase), as well as inhibition of phospholipase A2 and metalloproteinases (MMPs)[12,127] (basic science level I).

Inhibition of MMPs. The gelatinases MMP2 and -9, stromelysin MMP3, and the cytokines as IL-1α and IL-1β have been found at elevated levels in tears of patients with MGD[14,128,129] (basic science level I and II). Moreover, there is a strong interaction between MMPs and inflammatory cytokines, each one activating the other type of mediator from its respective inactive precursor. Collagenase-2 (MMP8) has also been found in elevated levels in the tears of rosacea patients and decreases with doxycycline treatment[130] (clinical/basic science level II).

Antiangiogenesis and Antiapoptotic Properties. Antiangiogenesis and antiapoptotic properties have also been reported,[14] through direct (inhibition of caspase-1 IL-1β) or indirect (collagenases and other MMPs for angiogenesis; MMP- or ROS-mediated apoptosis) effects.

Clinical Effects. The use of tetracycline derivatives has been reported to be efficacious in many clinical studies. Rosacea, with cutaneous and/or ocular manifestations, is the most studied application. Although most studies were not placebo controlled, significant effects on symptoms, lid margin, ocular surface inflammation, and tear film stability have been described, although the effects seem less prominent on keratitis and conjunctival staining[115–118] (clinical studies level I,[100] clinical studies level II[98,99,101]). Overall tolerance is mostly good, with minor concerns, such as diarrhea, nausea, headache, photosensitization, and vaginal or oral candidosis, which are reported to a lesser degree at lower doses. In most cases, these side effects do not result in discontinuation of treatment.

Dosages and Routes of Administration. Most studies have addressed tetracyclines given orally at doses considered subantimicrobial, ranging between 250 mg once to four times a day (tetracycline and oxytetracycline) and 50 to 100 mg once or twice a day (doxycycline and minocycline). It should be

noted that a subantimicrobial dose of doxycycline of 40 mg a day, chosen for its anti-inflammatory properties, is used for rosacea[79,119] (clinical studies level I).

Topical administration has also been proposed with doxycycline and tested in experimental models with promising results, in terms of MMP activation, corneal barrier function and surface keratinization[12,129] (basic science level I, clinical studies level III).

Clinical Trials and Methodological Issues. Tetracycline derivatives are widely used in rosacea and various cutaneous diseases. In MGD, the use of these compounds has been described in level II or III clinical trials,[115,116,118] showing a significant improvement in symptoms and signs. However, fewer placebo-controlled studies (clinical studies level I) have been published, and they showed milder effects than did open trials comparing effects before and after treatment.[79,119] In one interesting level I trial, lid hygiene alone was compared to lid hygiene plus minocycline and showed significant changes in fatty acid composition, together with improvement in some, although not all, clinical signs.[126] Nevertheless, many clinical studies even when not placebo-controlled, reported objective biological criteria that were strongly supportive of a significant role of tetracyclines, such as decreased lipase activity,[126] improved meibomian lipids,[125] or decreased MMP-8.[130] Moreover, proof of concept was often addressed in experimental models, mainly of dry eye, showing a decrease or normalization of MMPs, inflammatory cytokines, corneal barrier dysfunction, or keratinization.

Comments. Tetracyclines are widely used in a variety of ocular surface diseases, including ocular rosacea, blepharitis, recurrent erosions, corneal angiogenesis, and dry eye. These compounds may act through several modes of action, mostly related to inflammation control and lipase inhibition. Although the individual response of patients is variable and the protocols more empiric than evidence-based, tetracycline derivatives may be helpful for blocking the vicious-circle characteristics of dry eye disease and severe MGD, through anti-inflammatory and antiapoptotic properties, and by counteracting the free fatty acid accumulation responsible for MGD development. Oral tetracyclines are perhaps one of the most studied therapies in rosacea-related ocular conditions and MGD, although additional comparative studies against other therapies are needed.

Steroids

As is true in other conditions characterized by both inflammatory and infectious processes, there is controversy regarding the role of topical corticosteroids in the treatment of MGD, since inflammation may be present or absent in this entity. The clinical value of controlling inflammation in chronic inflammatory disease is obvious, but so are the potential complications of long-term treatment with corticosteroids. It is difficult to justify potential cataractogenesis, elevation of intraocular pressure, and the other well-known potential complications of steroids as acceptable risks to control a condition (MGD) that is generally not vision threatening. It is much easier to define a role for topical corticosteroids for acute flares of inflammation or to manage inflammatory complications of MGD. Examples of such situations may include intralesional injection of corticosteroids for chalazia or topical corticosteroids for the treatment of marginal hypersensitivity keratitis associated with MGD. Clinical level II evidence supports the use of intralesional corticosteroids for chalazia.[131–134] No published study supports long-term maintenance therapy with corticosteroid, combination corticosteroid–antibiotic ointments, or eyedrops for MGD, although studies of combination therapy including hygiene, warm compresses, topical antibiotics, and steroids have been performed short-term.[59,135] Although no study has been published quantifying the risks of such therapy in patients with MGD, conclusions may be drawn from published studies of the risks of chronic corticosteroid therapy in other conditions. The risk of steroid-induced ocular hypertension may be as high as 50% to 60%.[136] In 2006, a panel found that available evidence supported the practice of careful lid hygiene, possibly combined with the use of topical antibiotics, with or without topical steroids for blepharitis[137] (clinical studies level III).

Calcineurin Inhibitors and Cyclosporine

Steroid-sparing strategies are commonly used to control chronic inflammatory ocular conditions. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are generally not included in a long-term treatment strategy because of the frequency of development of corneal epitheliopathy.[138] Calcineurin inhibitors such as cyclosporine are used in the treatment of many inflammatory ocular conditions, such as uveitis, atopic keratoconjunctivitis, and vernal keratoconjunctivitis. Topical cyclosporine was approved by the U.S. Food and Drug Administration for increasing tear production in patients with inflammatory dry eye disease. Several published studies conducted in small groups of patients provide support for the treatment of MGD in conjunction with rosacea and/or aqueous-deficient dry eye with cyclosporine.[139–141] Perry et al.[140] (clinical studies level 1) demonstrated a significant improvement at 3 months in lid margin redness, meibomian gland inclusions, telangiectasia, and corneal staining in MGD patients, defined by symptoms, lid margin irregularity, blocked meibomian glands, lid margin redness, and telangiectatic vessels. Subjects using topical cyclosporine versus AT did not demonstrate significant improvement in Schirmer scores, although the scores were moderate (~12 mm wetting at baseline). The effect on blocked glands was not significant until the 2-month visit, and the results were maintained at 3 months. Limitations of the study include the relatively small size and considerable dropout rate (26/33 completed the study).[122] An additional study of topical cyclosporine was completed by Rubin and Rao[141] (clinical studies level I–II). In this study, topical cyclosporine was compared to topical tobramycin and dexamethasone in 30 patients with posterior blepharitis (15 per group). Blepharitis was defined by posterior lid margin redness and telangiectasia, as well as failure on previous warm compress and hygiene, doxycycline, drops, or ointment therapy. The Schirmer scores at baseline were lower than those in the study by Perry et al. (~8 mm wetting at baseline), statistically significant improvements in wetting were demonstrated in both groups from baseline at 3 months, and the cyclosporine group was significantly better than the tobramycin/dexamethasone group (2.33 mm wetting). The quality of meibomian gland secretions improved over the course of the study, with the cyclosporine group demonstrating better results, although the difference of less than one grade may not be clinically meaningful.[123]

Schechter et al.[139] (clinical studies level I) evaluated rosacea-related eyelid and corneal changes. Topical cyclosporine was shown to significantly improve Schirmer test–measured aqueous production (~10 mm wetting in 5 minutes at baseline) by approximately 3 mm in the cyclosporine group, whereas Schirmer scores worsened in the AT group. After 3 months of treatment, the mean number of expressible meibomian glands also improved significantly in the cyclosporine group.

Tacrolimus ointment has been evaluated in an exploratory study in comparison to corticosteroid ointment, with reference to the intraocular pressure in the treatment of eyelid eczema in patients with atopic keratoconjunctivitis (AKC), but not MGD

specifically.[142] The authors report that both treatments were effective in reducing signs and symptoms of eyelid eczema, with a near superior benefit for tacrolimus in terms of eczema (total skin score) signs ($P = 0.05$). The effect of tacrolimus on specific signs of MGD has yet to be evaluated.

Comments. The studies of topical cyclosporine are somewhat challenging to interpret, as the influence of a reduced Schirmer score or the presence of ocular rosacea complicates the interpretation. All three studies, although small in sample size, were designed in a randomized, controlled manner with attempts at reducing examiner bias with some form of masking. Participant dropout, always a challenge, is a critical element in smaller studies. In addition, although these studies examined some component of the lids, a uniform criterion to classify the patient's MGD was not used between the studies, making comparison difficult. In addition, the presence of moderate aqueous deficiency, which is improved in two of the three studies, creates a conundrum of whether the treatment improved the lacrimal gland status and thus the lid margin as an indirect result, or the other way around. In each case, the effect was not demonstrated until the 2-month visit, and should be considered in making management decisions in patients with combined (or mixed) aqueous deficient dry eye and MGD. Further studies in this area are needed, and the results of these studies are worth consideration. Additional studies of tacrolimus may be warranted.

Sex Hormones

Extensive basic science research has probed the relationship between androgen sex hormones and the meibomian gland. Androgens have been shown to influence gene expression in mouse meibomian glands, especially to suppress genes associated with keratinization and stimulate genes related to lipogenesis.[143,144] Androgen receptor dysfunction has been associated with marked clinical abnormalities in meibomian gland function,[145] and the use of systemic antiandrogen medications has been associated with clinical MGD.[146] Despite these clues from basic science investigations, there is no level I or II published study showing a beneficial effect in humans for a topical androgen preparation. One case report (clinical studies level III) was published describing successful treatment of dry eye by means of an androgen containing eye drop in a 54-year-old male resulting in a restored lipid phase of the tear film.[147]

Essential Fatty Acids

Dietary supplements of ω-3 fatty acids have gained in popularity over recent years because of the beneficial effects on anti-inflammatory by-products of prostaglandin metabolism. Clinical studies level II epidemiologic[148] and clinical trials[149] have demonstrated an association between the use of oral supplements of ω-3 and symptoms of dry eye.

Few studies have been published on the efficacy of dietary ω-3 supplements for MGD. Pinna et al.[150] (clinical studies level II) reported the superiority of ω-3 supplementation over lid hygiene or placebo treatment in patients with MGD. A recently published study included a randomized controlled trial (clinical studies level I) of the use of dietary supplementation with ω-3 fatty acids in patients with MGD. In this prospective masked randomized placebo-controlled trial, patients with simple obstructive MGD and blepharitis who had discontinued all topical medications and tetracyclines received oral ω-3 dietary supplementation consisting of 2000 mg three times a day for 1 year. Outcomes included symptom severity assessed according to the Ocular Surface Disease Index (OSDI)[151] and objective clinical measures, including tear production and stability, ocular surface staining, meibomian gland assessment, and meibum evaluation. The study reported efficacy in improving both symptoms and objective findings between baseline measurements and 1-year measurements in both the treatment group and the placebo group (to a lesser degree). For the key outcome measures of TBUT, meibum score, and OSDI, no statistically significant differences between groups were found (both groups improved).[152]

Comments. Published data provide some evidence to recommend dietary modification or the inclusion of dietary ω-3 supplements in a treatment plan for patients with MGD. Further large-scale clinical trials with more subjects are needed to determine whether ω-3 supplements are beneficial when patients are classified as MGD, MGD with aqueous-deficient dry eye, or aqueous-deficient dry eye alone as part of the study design.

Surgical Options

Surgical options in the treatment of MGD are generally limited to treatment of the complications of the disease, rather than the primary disease. MGD can be associated with pathologic conditions, such as conjunctivochalasis, entropion, ectropion, or horizontal eyelid laxity, which may be treated surgically, and treatment of these conditions can improve control of MGD. Meibomian gland secretion may be facilitated by the mechanical pumping effect of lid movements. This method requires a certain amount of tension in the medial or lateral canthal tendon. Increasing horizontal lid tension may increase excretion of meibum. One published case report (clinical studies level III) described a 41-year-old man with bilateral ocular irritation and floppy eyelid syndrome. Histology of the tarsus removed at surgical correction revealed cystic degeneration and squamous metaplasia of the meibomian glands, abnormal keratinization, and granuloma formation. These findings suggest that MGD may be associated with keratoconjunctivitis in floppy eyelid syndrome.[153]

Other pathologic eyelid conditions, such as chalazion, trichiasis, and keratinization of the lid margin may be associated with MGD. The incidence of trichiasis, keratinization, and cicatricial entropion secondary to MGD remains unknown. Treatment of these conditions with appropriate surgical procedures may improve patient symptoms, but the effect on MGD specifically cannot be determined. Discussion of the surgical management of these co-morbid conditions is beyond the scope of this article, and the treatment of such conditions should occur independently but concurrent with the management of existing MGD.

Intraductal probing has recently been introduced as a treatment for MGD. One report (clinical studies level III) on this management approach for MGD describes a modified surgical procedure as a primary treatment non–end stage MGD. This study of 25 patients demonstrated a high frequency of short-term symptomatic relief (Maskin S, et al. *IOVS* 2009;50:ARVO E-Abstract 4636).[154] Further study of this technique is in progress.

Treatment Recommendations

Staged Treatment Algorithm

Without generally accepted definitions for a staging system of clinical severity of MGD, it is problematic to propose a treatment plan based on disease stage. Nonetheless, in the hope of assisting eye care providers who are attempting to fashion a logical, evidence-based treatment approach, the following disease-staging summary (Table 3) and staged treatment algorithm[155–160] (Table 4) are proposed.

In the staging of disease, it is recognized that it is difficult clinically to separate the effects of MGD and the effects of aqueous-deficient dry eye on the ocular surface. In addition,

co-morbid diseases are often present. Thus, Table 3 represents a clinical picture of staged disease. Co-morbid conditions, defined as "plus" disease may require concurrent management per standard-of-care protocols.

Table 4 reflects an evidence-based approach to the management of MGD. The staged diagnosis algorithm is similar, yet not exactly identical to the severity grading found in the Diagnosis Report. This algorithm represents a consensus of recommendations from the panel of experts participating in the preparation of this report, having considered the evidence-based review of published studies of treatments, with consideration of the clinician who encounters a hybrid of MGD and other co-morbid conditions on a daily basis. Detailed grading of individual parameters of the eyelid may be more appropriate for clinical trials; however, details of the grading are incorporated into the table to provide additional points of reference.

With every systemic medication, systemic side effects have to be considered. With the above treatment algorithm in mind, phototoxicity for systemic tetracycline derivative use and anticoagulant effects of essential fatty acids (EFAs) may be of specific concern. EFAs are nutritional supplements that have received much attention, but only one published clinical study to date supports their efficacy in MGD. This lack of evidence is also true of the use of sex hormones. There is no clinical support of the efficacy of hormones in treating MGD, and no licensed product is available. Hence, although it is discussed in this article, the panel agreed not to assign this potential treatment modality to a grade of disease. The risks of prolonged topical corticosteroid therapy (e.g., induction of cataract and elevated intraocular pressure) are well known. Hence, the use of such medications should be reserved for the treatment of acute exacerbations in MGD and should not be used in long-term therapy. Regular monitoring of intraocular pressure is mandatory with the use of topical corticosteroids.

Additional Therapies for MGD and Co-morbid "Plus" Conditions

The 2007 DEWS report recommended moisture chamber goggles, autologous serum, and large-diameter scleral contact lenses for the more severe levels of dry eye disease.[1] Although some of these therapies may be beneficial for patients with aqueous-deficient dry eye in combination with MGD, studies of these therapies for MGD alone have not been performed. It can be hypothesized that a reduction in airflow across the corneal surface in a patient with lipid abnormalities or aqueous-deficient dry eye (related to MGD) could reduce tear evaporation. Kimball et al.[161] have demonstrated that goggle wear in normal subjects decreases the rate at which the tear film thins between blinks. Similar studies in MGD subjects could provide additional insight to the etiology behind tear film stability.

In theory, large-diameter sclera contact lenses and autologous serum augment corneal health, with the serum providing nutrients in the form of growth factors and other factors, while the contact lens protects the ocular surface from further damage. It is unclear what the benefit would be for patients with MGD.

"Plus" disease therapies should follow standard of care guidelines and should be considered independent of MGD.

Future Developments

Since the precise mechanism of MGD remains uncertain, it is unclear whether any of the current treatments reviewed are palliative, provide indirect effect, or address underlying disease pathophysiology. The development of new examination devices such as noninvasive meibography and confocal microscopy provide new hope for better understanding of the pathophysiology of the gland and ocular surface dysfunction. Several clinical observations provide clues for future investigations of risk factors, pathophysiology, and novel treatment approaches. The prevalence of MGD in contact lens wearers is higher than expected, suggesting a role for the interplay between the tear film and meibomian gland function. A recent study of topical ω-3 fatty acid supplementation demonstrated preliminary therapeutic potential,[16] and along with other therapies, raises hope for an approach to management and prevention of MGD in the future. Since aging is a recognized risk factor for MGD and dry eye syndrome, it is possible that antiaging therapies, such as antioxidants, will be developed in the future.[162,163]

Surgical, Mechanical, or Physical Treatment

Because compliance with prolonged, time-consuming therapies is traditionally poor, there is interest in treatment approaches that could provide long-lasting improvement with minimal application. Such new approaches, including surgical probing of the duct, were recently reported as a treatment for symptomatic MGD.[154] The insertion of small stainless-steel probes (2, 4, or 6 mm in length) into the meibomian gland orifices and ducts was reported to relieve lid tenderness, improve vision, and reduce other symptoms of posterior blepharitis. In addition, several in-office eye-warming devices, thought to assist in improving meibomian gland secretions, have been tested or are in development. Long-term efficacy and safety are yet to be demonstrated with these techniques.

Pharmacologic Treatments

The treatment options for dry eye have been greatly expanded in the past 10 years, in large part due to improved understanding of the inflammatory process within the ocular surface functional unit. This understanding contributed to the development of treatment options such as cyclosporine, cevimeline, and pilocarpine, and additional options for the treatment of dry eye continue to be investigated. In contrast, the limited understanding of the pathophysiology of MGD has hampered the development of pharmacologic treatment of MGD. Inflammation, hormonal effects, oxidative stress, lipid production, postsecretion lipid changes, and aging are all important therapeutic considerations for the development of pharmacologic treatments for MGD. It is likely that the current enthusiasm of researchers regarding the study of the pathophysiology of MGD and the unmet needs of patients who have symptoms of this disease will drive development of new therapies.

Existing therapies, either alone or in conjunction with one another, require further evaluation in well-controlled masked

Table 3. Clinical Summary of the MGD Staging Used to Guide Treatment

Stage	MGD Grade	Symptoms	Corneal Staining
1	+ (minimally altered expressibility and secretion quality)	None	None
2	++ (mildly altered expressibility and secretion quality)	Minimal to Mild	None to limited
3	+++ (moderately altered expressibility and secretion quality)	Moderate	Mild to moderate; mainly peripheral
4	++++ (severely altered expressibility and secretion quality)	Marked	Marked; central in addition
"Plus" disease	Co-existing or accompanying disorders of the ocular surface and/or eyelids		

TABLE 4. Treatment Algorithm for MGD

Stage	Clinical Description	Treatment
1	No ***symptoms*** of ocular discomfort, itching, or photophobia	*Inform* patient about MGD, the potential impact of diet, and the effect of work/home environments on tear evaporation, and the possible drying effect of certain systemic medications
	Clinical signs of MGD based on gland expression Minimally altered secretions: grade ≥2–4 Expressibility: 1	*Consider* eyelid hygiene including warming/expression as described below (±)
	No ocular surface ***staining***	
2	Minimal to mild ***symptoms*** of ocular discomfort, itching, or photophobia	*Advise* patient on improving ambient humidity; optimizing workstations and increasing dietary omega-3 fatty acid intake (±)
	Minimal to mild MGD ***clinical signs*** Scattered lid margin features Mildly altered secretions: grade ≥4-<8 Expressibility: 1	*Institute* eyelid hygiene with eyelid warming (a minimum of four minutes, once or twice daily) followed by moderate to firm massage and expression of MG secretions (+)
	None to limited ocular surface ***staining***: DEWS grade 0–7; Oxford grade 0–3	*All the above, plus* (±) Artificial lubricants (for frequent use, non-preserved preferred) Topical azithromycin Topical emollient lubricant or liposomal spray Consider oral tetracycline derivatives
3	Moderate ***symptoms*** of ocular discomfort, itching, or photophobia with limitations of activities	*All the above, plus* Oral tetracycline derivatives (+)
	Moderate MGD ***clinical signs*** ↑ lid margin features: plugging, vascularity Moderately altered secretions: grade ≥8 to <13 Expressibility: 2	Lubricant ointment at bedtime (±) Anti-inflammatory therapy for dry eye as indicated (±)
	Mild to moderate conjunctival and peripheral corneal ***staining***, often inferior: DEWS grade 8–23; Oxford grade 4–10	
4	Marked ***symptoms*** of ocular discomfort, itching or photophobia with definite limitation of activities	*All the above, plus* Anti-inflammatory therapy for dry eye (+)
	Severe MGD ***clinical signs*** ↑ lid margin features: dropout, displacement Severely altered secretions: grade ≥13 Expressibility: 3	
	Increased conjunctival and corneal ***staining***, including central staining: DEWS grade 24–33; Oxford grade 11–15	
	↑ signs of inflammation: ≥moderate conjunctival hyperemia, phlyctenules	
"Plus" disease	Specific conditions occurring at any stage and requiring treatment. May be causal of, or secondary to, MGD or may occur incidentally	
	1. Exacerbated inflammatory ocular surface disease	1. Pulsed soft steroid as indicated
	2. Mucosal keratinization	2. Bandage contact lens/scleral contact lens
	3. Phlyctenular keratitis	3. Steroid therapy
	4. Trichiasis (e.g. in cicatricial conjunctivitis, ocular cicatricial pemphigoid)	4. Epilation, cryotherapy
	5. Chalazion	5. Intralesional steroid or excision
	6. Anterior blepharitis	6. Topical antibiotic or antibiotic/steroid
	7. Demodex-related anterior blepharitis, with cylindrical dandruff	7. Tea tree oil scrubs

Meibum quality is assessed in each of eight glands of the central third of the lower lid on a scale of 0 to 3 for each gland: 0, clear; 1, cloudy; 2, cloudy with debris (granular); and 3, thick, like toothpaste (total score range, 0–24). *Expressibility* is assessed on a scale of 0 to 3 in five glands in the lower or upper lid, according to the number of glands expressible: 0, all glands; 1, three to four glands; 2, one to two glands; and 3, no glands. *Staining scores* are obtained by summing the scores of the exposed cornea and conjunctiva. Oxford staining score range, 1–15; DEWS staining score range, 0–33.

randomized clinical trials of adequate sample size. Several promising pharmacologic therapies are currently being evaluated, and with the renewed interest in MGD, the future is bright for new therapeutic options.

References

1. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop. (2007). *Ocul Surf.* 2007;5:163–178.
2. Smith GT, Dart J. External eye disease. In: Jackson TL, ed. *Moorfields Manual of Ophthalmology.* Philadelphia: Mosby Elsevier; Chap 4:2008.
3. Ehler J, Shah ChP. *Wills Eye Manual*. Philadelphia: Lippincott Williams & Wilkins; 2008.
4. Lemp MA, Nichols KK. Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment. *Ocul Surf.* 2009;7:S1–S14.
5. The Dry Eye WorkShop Group. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop. *Ocul Surf.* 2007;5:75–92.
6. Gilbard JP, Carter JB, Sang DN, Refojo MF, Hanninen LA, Kenyon KR. Morphologic effect of hyperosmolarity on rabbit corneal epithelium. *Ophthalmology.* 1984;91:1205–1212.
7. Korb DR, Herman JP, Blackie CA, et al. Prevalence of lid wiper epitheliopathy in subjects with dry eye signs and symptoms. *Cornea.* 2010;29:377–383.
8. Korb DR, Herman JP, Greiner JV, et al. Lid wiper epitheliopathy and dry eye symptoms. *Eye Contact Lens.* 2005;31:2–8.
9. Korb DR, Greiner JV, Herman JP, et al. Lid-wiper epitheliopathy and dry-eye symptoms in contact lens wearers. *CLAO J.* 2002;28:211–216.
10. Yokoi N, Yamada H, Mizukusa Y, et al. Rheology of tear film lipid layer spread in normal and aqueous tear-deficient dry eyes. *Invest Ophthalmol Vis Sci.* 2008;49:5319–5324.
11. Aubert JD, Juillerat-Jeanneret L, Fioroni P, Dayer P, Plan PA, Leuenberger P. Function of human alveolar macrophages after a 3-day course of azithromycin in healthy volunteers. *Pulm Pharmacol Ther.* 1998;11:263–269.
12. De Paiva CS, Corrales RM, Villarreal AL, et al. Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye. *Exp Eye Res.* 2006;83:526–535.
13. Kamemoto A, Ara T, Hattori T, Fujinami Y, Imamura Y, Wang PL. Macrolide antibiotics like azithromycin increase lipopolysaccharide-induced IL-8 production by human gingival fibroblasts. *Eur J Med Res.* 2009;14:309–314.
14. Li DQ, Lokeshwar BL, Solomon A, Monroy D, Ji Z, Pflugfelder SC. Regulation of MMP-9 production by human corneal epithelial cells. *Exp Eye Res.* 2001;73:449–459.
15. Murphy BS, Sundareshan V, Cory TJ, Hayes D Jr, Anstead MI, Feola DJ. Azithromycin alters macrophage phenotype. *J Antimicrob Chemother.* 2008;61:554–560.
16. Rashid S, Jin Y, Ecoiffier T, Barabino S, Schaumberg DA, Dana MR. Topical omega-3 and omega-6 fatty acids for treatment of dry eye. *Arch Ophthalmol.* 2008;126:219–225.
17. Sanchez MA, Torralbo-Jimenez P, Giron N, et al. Comparative analysis of carmellose 0.5% versus hyaluronate 0.15% in dry eye: a flow cytometric study. *Cornea.* 2010;29:167–171.
18. Fraunfelder FW. Corneal toxicity from topical ocular and systemic medications. *Cornea.* 2006;25:1133–1138.
19. Labbe A, Pauly A, Liang H, et al. Comparison of toxicological profiles of benzalkonium chloride and polyquaternium-1: an experimental study. *J Ocul Pharmacol Ther.* 2006;22:267–278.
20. Guenoun JM, Baudouin C, Rat P, Pauly A, Warnet JM, Brignole-Baudouin F. In vitro study of inflammatory potential and toxicity profile of latanoprost, travoprost, and bimatoprost in conjunctiva-derived epithelial cells. *Invest Ophthalmol Vis Sci.* 2005;46:2444–2450.
21. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol.* 2002;86:418–423.
22. Debbasch C, Brignole F, Pisella PJ, Warnet JM, Rat P, Baudouin C. Quaternary ammoniums and other preservatives' contribution in oxidative stress and apoptosis on Chang conjunctival cells. *Invest Ophthalmol Vis Sci.* 2001;42:642–652.
23. Furrer P, Mayer JM, Plazonnet B, Gurny R. Ocular tolerance of preservatives on the murine cornea. *Eur J Pharm Biopharm.* 1999;47:105–112.
24. Palmer RM, Kaufman HE. Tear film, pharmacology of eye drops, and toxicity. *Curr Opin Ophthalmol.* 1995;6:11–16.
25. Lapalus P, Ettaiche M, Fredj-Reygrobellet D, Jambou D, Elena PP. Cytotoxicity studies in ophthalmology. *Lens Eye Toxic Res.* 1990;7:231–242.
26. Burstein NL. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. *Surv Ophthalmol.* 1980;25:15–30.
27. Baudouin C. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. *Acta Ophthalmol.* 2008;86:716–726.
28. Furrer P, Mayer JM, Gurny R. Ocular tolerance of preservatives and alternatives. *Eur J Pharm Biopharm.* 2002;53:263–280.
29. Khanal S, Simmons PA, Pearce EI, Day M, Tomlinson A. Effect of artificial tears on tear stress test. *Optom Vis Sci.* 2008;85:732–739.
30. Khanal S, Tomlinson A, Pearce EI, Simmons PA. Effect of an oil-in-water emulsion on the tear physiology of patients with mild to moderate dry eye. *Cornea.* 2007;26:175–181.
31. Simmons PA, Vehige JG. Clinical performance of a mid-viscosity artificial tear for dry eye treatment. *Cornea.* 2007;26:294–302.
32. Wang J, Simmons P, Aquavella J, et al. Dynamic distribution of artificial tears on the ocular surface. *Arch Ophthalmol.* 2008;126:619–625.
33. Rieger G. Lipid-containing eye drops: a step closer to natural tears. *Ophthalmologica.* 1990;201:206–212.
34. Tiffany JM. Lipid-containing eye drops. *Ophthalmologica.* 1991;203:47–49.
35. Korb DR, Scaffidi RC, Greiner JV, et al. The effect of two novel lubricant eye drops on tear film lipid layer thickness in subjects with dry eye symptoms. *Optom Vis Sci.* 2005;82:594–601.
36. Craig JP, Purslow C, Murphy PJ, Wolffsohn JS. Effect of a liposomal spray on the pre-ocular tear film. *Cont Lens Anterior Eye.* 2010;33:83–87.
37. Goto E, Shimazaki J, Monden Y, et al. Low-concentration homogenized castor oil eye drops for noninflamed obstructive meibomian gland dysfunction. *Ophthalmology.* 2002;109:2030–2035.
38. Di Pascuale MA, Goto E, Tseng SC. Sequential changes of lipid tear film after the instillation of a single drop of a new emulsion eye drop in dry eye patients. *Ophthalmology.* 2004;111:783–791.
39. Solomon R, Perry HD, Donnenfeld ED, Greenman HE. Slitlamp biomicroscopy of the tear film of patients using topical Restasis and Refresh Endura. *J Cataract Refract Surg.* 2005;31:661–663.
40. Goto E, Dogru M, Fukagawa K, et al. Successful tear lipid layer treatment for refractory dry eye in office workers by low-dose lipid application on the full-length eyelid margin. *Am J Ophthalmol.* 2006;142:264–270.
41. Ota Y, Matsumoto Y, Dogru M, et al. Management of evaporative dry eye in ectrodactyly-ectodermal dysplasia-clefting syndrome. *Optom Vis Sci.* 2008;85:E795–E801.
42. Khaireddin R, Schmidt KG. Comparative investigation of treatments for evaporative dry eye (in German). *Klin Monatsbl Augenheilkd.* 2010;227:128–134.
43. Dausch D, Lee S, Dausch S, Kim JC, Schwert G, Michelson W. Comparative study of treatment of the dry eye syndrome due to disturbances of the tear film lipid layer with lipid-containing tear substitutes (in German). *Klin Monatsbl Augenheilkd.* 2006;223:974–983.
44. Blackie CA, Solomon JD, Greiner JV, Holmes M, Korb DR. Inner eyelid surface temperature as a function of warm compress methodology. *Optom Vis Sci.* 2008;85:675–683.
45. Goto E, Endo K, Suzuki A, Fujikura Y, Tsubota K. Improvement of tear stability following warm compression in patients with meibomian gland dysfunction. *Adv Exp Med Biol.* 2002;506:1149–1152.

46. Ishida R, Matsumoto Y, Onguchi T, et al. Tear film with "Orgahexa EyeMasks" in patients with meibomian gland dysfunction. *Optom Vis Sci.* 2008;85:684–691.
47. Matsumoto Y, Dogru M, Goto E, et al. Efficacy of a new warm moist air device on tear functions of patients with simple meibomian gland dysfunction. *Cornea.* 2006;25:644–650.
48. Mori A, Shimazaki J, Shimmura S, Fujishima H, Oguchi Y, Tsubota K. Disposable eyelid-warming device for the treatment of meibomian gland dysfunction. *Jpn J Ophthalmol.* 2003;47:578–586.
49. Olson MC, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. *Eye Contact Lens.* 2003;29:96–99.
50. Yokoi N, Mossa F, Tiffany JM, Bron AJ. Assessment of meibomian gland function in dry eye using meibometry. *Arch Ophthalmol.* 1999;117:723–729.
51. McCulley JP, Shine WE. Meibomian secretions in chronic blepharitis. *Adv Exp Med Biol.* 1998;438:319–326.
52. Nagymihalyi A, Dikstein S, Tiffany JM. The influence of eyelid temperature on the delivery of meibomian oil. *Exp Eye Res.* 2004;78:367–370.
53. Goto E, Monden Y, Takano Y, et al. Treatment of non-inflamed obstructive meibomian gland dysfunction by an infrared warm compression device. *Br J Ophthalmol.* 2002;86:1403–1407.
54. Mitra M, Menon GJ, Casini A, et al. Tear film lipid layer thickness and ocular comfort after meibomian therapy via latent heat with a novel device in normal subjects. *Eye.* 2005;19:657–660.
55. Solomon JD, Case CL, Greiner JV, Blackie CA, Herman JP, Korb DR. Warm compress induced visual degradation and Fischer-Schweitzer polygonal reflex. *Optom Vis Sci.* 2007;84:580–587.
56. Romero JM, Biser SA, Perry HD, et al. Conservative treatment of meibomian gland dysfunction. *Eye Contact Lens.* 2004;30:14–19.
57. Key JE. A comparative study of eyelid cleaning regimens in chronic blepharitis. *CLAO J.* 1996;22:209–212.
58. Paugh JR, Knapp LL, Martinson JR, Hom MM. Meibomian therapy in problematic contact lens wear. *Optom Vis Sci.* 1990;67:803–806.
59. Matsumoto Y, Shigeno Y, Sato EA, et al. The evaluation of the treatment response in obstructive meibomian gland disease by in vivo laser confocal microscopy. *Graefes Arch Clin Exp Ophthalmol.* 2009;247:821–829.
60. Keith CG. Seborrhoeic blepharo-kerato-conjunctivitis. *Trans Ophthalmol Soc U K.* 1967;87:85–103.
61. McCulley JP, Sciallis GF. Meibomian keratoconjunctivitis. *Am J Ophthalmol.* 1977;84:788–793.
62. Hom MM, Silverman MW. Displacement technique and meibomian gland expression. *J Am Optom Assoc.* 1987;58:223–226.
63. Duke-Elder WS, McFaul PA. *The Ocular Adnexa*, *Part II*: *Diseases of the Eyelids*. London: H Kimpton; 1974.
64. Korb DR, Henriquez AS. Meibomian gland dysfunction and contact lens intolerance. *J Am Optom Assoc.* 1980;51:243–251.
65. Gifford S. Meibomian glands in chronic blepharoconjunctivitis. *Am J Ophthalmol.* 1921;4:489–494.
66. Mastrota K. The meibomian Mastrota paddle. Rosenberg, TX: Cynacon/Ocusoft, Inc., 2006. Available at http://www.ocusoft.com/for-eye-care-professionals/surgical/misc-surgical-instruments/mastrota-meibomian-paddle.html. Accessed: July 16, 2010.
67. Blackie CA, Korb DR, Knop E, Bedi R, Knop N, Holland EJ. Nonobvious obstructive meibomian gland dysfunction (NOMGD). *Cornea.* 2010;29:1333–1345.
68. Korb D, Blackie C. Diagnostic versus therapeutic meibomian gland expression. Presented at the American Academy of Optometry annual meeting in Orlando, Nov 2009. Available at: http://www.aaopt.org/Submission/Search/SubmissionViewer.asp?SID=25745&BR=SP.
69. Iovieno A, Lambiase A, Micera A, Stampachiacchiere B, Sgrulletta R, Bonini S. In vivo characterization of doxycycline effects on tear metalloproteinases in patients with chronic blepharitis. *Eur J Ophthalmol.* 2009;19:708–716.
70. Dougherty JM, McCulley JP. Comparative bacteriology of chronic blepharitis. *Br J Ophthalmol.* 1984;68:524–528.
71. McCulley JP, Dougherty JM. Bacterial aspects of chronic blepharitis. *Trans Ophthalmol Soc U K.* 1986;105:314–318.
72. Wright JS, 3rd, Jin R, Novick RP. Transient interference with staphylococcal quorum sensing blocks abscess formation. *Proc Natl Acad Sci U S A.* 2005;102:1691–1696.
73. Novick RP. Interrupters on the bacterial party line. *Nat Chem Biol.* 2005;1:321–322.
74. O'Brien TP. The role of bacteria in blepharitis. *Ocul Surf.* 2009;7:S21–22.
75. Groden LR, Murphy B, Rodnite J, Genvert GI. Lid flora in blepharitis. *Cornea.* 1991;10:50–53.
76. McCulley JP, Shine WE. Changing concepts in the diagnosis and management of blepharitis. *Cornea.* 2000;19:650–658.
77. Seal DV, Wright P, Ficker L, Hagan K, Troski M, Menday P. Placebo controlled trial of fusidic acid gel and oxytetracycline for recurrent blepharitis and rosacea. *Br J Ophthalmol.* 1995;79:42–45.
78. Barnhorst DA, Jr, Foster JA, Chern KC, Meisler DM. The efficacy of topical metronidazole in the treatment of ocular rosacea. *Ophthalmology.* 1996;103:1880–1883.
79. Sanchez J, Somolinos AL, Almodovar PI, Webster G, Bradshaw M, Powala C. A randomized, double-blind, placebo-controlled trial of the combined effect of doxycycline hyclate 20-mg tablets and metronidazole 0.75% topical lotion in the treatment of rosacea. *J Am Acad Dermatol.* 2005;53:791–797.
80. Sacca SC, Pascotto A, Venturino GM, et al. Prevalence and treatment of Helicobacter pylori in patients with blepharitis. *Invest Ophthalmol Vis Sci.* 2006;47:501–508.
81. Scoper SV. Review of third-and fourth-generation fluoroquinolones in ophthalmology: in-vitro and in-vivo efficacy. *Adv Ther.* 2008;25:979–994.
82. Bertino JS. Impact of antibiotic resistance in the management of ocular infections: the role of current and future antibiotics. *Clin Ophthalmol.* 2009;3:507–521.
83. Yactayo-Miranda Y, Ta CN, He L, et al. A prospective study determining the efficacy of topical 0.5% levofloxacin on bacterial flora of patients with chronic blepharoconjunctivitis. *Graefes Arch Clin Exp Ophthalmol.* 2009;247:993–998.
84. Amsden GW. Advanced-generation macrolides: tissue-directed antibiotics. *Int J Antimicrob Agents.* 2001;18(suppl 1):S11–S15.
85. Retsema J, Girard A, Schelkly W, et al. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. *Antimicrob Agents Chemother.* 1987;31:1939–1947.
86. Sacre Hazouri JA. Macrolides. Antiinflammatory and immunomodulator effects. Indication in respiratory diseases (in Spanish). *Rev Alerg Mex.* 2006;53:108–122.
87. Beigelman A, Gunsten S, Mikols CL, et al. Azithromycin attenuates airway inflammation in a noninfectious mouse model of allergic asthma. *Chest.* 2009;136:498–506.
88. Shinkai M, Rubin BK. Macrolides and airway inflammation in children. *Paediatr Respir Rev.* 2005;6:227–235.
89. Basyigit I, Yildiz F, Ozkara SK, Yildirim E, Boyaci H, Ilgazli A. The effect of clarithromycin on inflammatory markers in chronic obstructive pulmonary disease: preliminary data. *Ann Pharmacother.* 2004;38:1400–1405.
90. Bouwman JJ, Visseren FL, Bouter PK, Diepersloot RJ. Azithromycin inhibits interleukin-6 but not fibrinogen production in hepatocytes infected with cytomegalovirus and chlamydia pneumoniae. *J Lab Clin Med.* 2004;144:18–26.
91. Yamaryo T, Oishi K, Yoshimine H, Tsuchihashi Y, Matsushima K, Nagatake T. Fourteen-member macrolides promote the phosphatidylserine receptor-dependent phagocytosis of apoptotic neutrophils by alveolar macrophages. *Antimicrob Agents Chemother.* 2003;47:48–53.
92. Bosnar M, Bosnjak B, Cuzic S, et al. Azithromycin and clarithromycin inhibit lipopolysaccharide-induced murine pulmonary neutrophilia mainly through effects on macrophage-derived granulocyte-macrophage colony-stimulating factor and interleukin-1beta. *J Pharmacol Exp Ther.* 2009;331:104–113.
93. Das S, Haddadi A, Veniamin S, Samuel J. Delivery of rapamycin-loaded nanoparticle down regulates ICAM-1 expression and main-

tains an immunosuppressive profile in human CD34+ progenitor-derived dendritic cells. *J Biomed Mater Res A.* 2008;85:983–992.
94. Sanz MJ, Nabah YN, Cerda-Nicolas M, et al. Erythromycin exerts in vivo anti-inflammatory activity downregulating cell adhesion molecule expression. *Br J Pharmacol.* 2005;144:190–201.
95. Meyer M, Huaux F, Gavilanes X, et al. Azithromycin reduces exaggerated cytokine production by m1 alveolar macrophages in cystic fibrosis. *Am J Respir Cell Mol Biol.* 2009;41:590–602.
96. Hodge S, Hodge G, Jersmann H, et al. Azithromycin improves macrophage phagocytic function and expression of mannose receptor in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2008;178:139–148.
97. Xu G, Fujita J, Negayama K, et al. Effect of macrolide antibiotics on macrophage functions. *Microbiol Immunol.* 1996;40:473–479.
98. Shimizu T, Shimizu S, Hattori R, Gabazza EC, Majima Y. In vivo and in vitro effects of macrolide antibiotics on mucus secretion in airway epithelial cells. *Am J Respir Crit Care Med.* 2003;168:581–587.
99. Amsden GW. Anti-inflammatory effects of macrolides: an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *J Antimicrob Chemother.* 2005;55:10–21.
100. Akpek EK, Vittitow J, Verhoeven RS, et al. Ocular surface distribution and pharmacokinetics of a novel ophthalmic 1% azithromycin formulation. *J Ocul Pharmacol Ther.* 2009;25:433–439.
101. Foulks GN, Borchman D, Yappert M, Kim SH, McKay JW. Topical azithromycin therapy for meibomian gland dysfunction: clinical response and lipid alterations. *Cornea.* 2010;29:781–788.
102. Haque RM, Torkildsen GL, Brubaker K, et al. Multicenter open-label study evaluating the efficacy of azithromycin ophthalmic solution 1% on the signs and symptoms of subjects with blepharitis. *Cornea.* 2010;29:871–877.
103. Luchs J. Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of posterior blepharitis. *Adv Ther.* 2008;25:858–870.
104. Prescott WA Jr, Johnson CE. Antiinflammatory therapies for cystic fibrosis: past, present, and future. *Pharmacotherapy.* 2005;25:555–573.
105. Lacey N, Kavanagh K, Tseng SC. Under the lash: Demodex mites in human diseases. *Biochem (Lond).* 2009;31:2–6.
106. Li J, O'Reilly N, Sheha H, et al. Correlation between ocular Demodex infestation and serum immunoreactivity to Bacillus proteins in patients with Facial rosacea. *Ophthalmology.* 2010;117:870–877 e871.
107. Forton F, Seys B. Density of Demodex folliculorum in rosacea: a case-control study using standardized skin-surface biopsy. *Br J Dermatol.* 1993;128:650–659.
108. Pena GP, Andrade Filho JS. Is demodex really non-pathogenic? *Rev Inst Med Trop Sao Paulo.* 2000;42:171–173.
109. Baima B, Sticherling M. Demodicidosis revisited. *Acta Derm Venereol.* 2002;82:3–6.
110. Gao YY, Di Pascuale MA, Elizondo A, Tseng SC. Clinical treatment of ocular demodecosis by lid scrub with tea tree oil. *Cornea.* 2007;26:136–143.
111. Kheirkhah A, Casas V, Li W, Raju VK, Tseng SC. Corneal manifestations of ocular demodex infestation. *Am J Ophthalmol.* 2007;143:743–749.
112. Wolf R, Ophir J, Avigad J, Lengy J, Krakowski A. The hair follicle mites (Demodex spp.): could they be vectors of pathogenic microorganisms? *Acta Derm Venereol.* 1988;68:535–537.
113. Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *Br J Dermatol.* 2007;157:474–481.
114. Sneddon IB. A clinical trial of tetracycline in rosacea. *Br J Dermatol.* 1966;78:649–652.
115. Frucht-Pery J, Sagi E, Hemo I, Ever-Hadani P. Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol.* 1993;116:88–92.
116. Quarterman MJ, Johnson DW, Abele DC, Lesher JL Jr, Hull DS, Davis LS. Ocular rosacea. Signs, symptoms, and tear studies before and after treatment with doxycycline. *Arch Dermatol.* 1997;133:49–54.
117. Yoo SE, Lee DC, Chang MH. The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction. *Korean J Ophthalmol.* 2005;19:258–263.
118. Theobald K, Bradshaw M, Leyden J. Anti-inflammatory dose doxycycline (40 mg controlled-release) confers maximum anti-inflammatory efficacy in rosacea. *Skin Med.* 2007;6:221–226.
119. Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol.* 2007;56:791–802.
120. Ta CN, Shine WE, McCulley JP, Pandya A, Trattler W, Norbury JW. Effects of minocycline on the ocular flora of patients with acne rosacea or seborrheic blepharitis. *Cornea.* 2003;22:545–548.
121. Aronowicz JD, Shine WE, Oral D, Vargas JM, McCulley JP. Short term oral minocycline treatment of meibomianitis. *Br J Ophthalmol.* 2006;90:856–860.
122. Hoeprich PD, Warshauer DM. Entry of four tetracyclines into saliva and tears. *Antimicrob Agents Chemother.* 1974;5:330–336.
123. Dougherty JM, McCulley JP, Silvany RE, Meyer DR. The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci. *Invest Ophthalmol Vis Sci.* 1991;32:2970–2975.
124. Duerden JM, Tiffany JM. Lipid synthesis in vitro by rabbit Meibomian gland tissue and its inhibition by tetracycline. *Biochim Biophys Acta.* 1990;1042:13–18.
125. Shine WE, McCulley JP, Pandya AG. Minocycline effect on meibomian gland lipids in meibomianitis patients. *Exp Eye Res.* 2003;76:417–420.
126. Souchier M, Joffre C, Gregoire S, et al. Changes in meibomian fatty acids and clinical signs in patients with meibomian gland dysfunction after minocycline treatment. *Br J Ophthalmol.* 2008;92:819–822.
127. Lekhanont K, Park CY, Smith JA, et al. Effects of topical anti-inflammatory agents in a botulinum toxin B-induced mouse model of keratoconjunctivitis sicca. *J Ocul Pharmacol Ther.* 2007;23:27–34.
128. Sobrin L, Liu Z, Monroy DC, et al. Regulation of MMP-9 activity in human tear fluid and corneal epithelial culture supernatant. *Invest Ophthalmol Vis Sci.* 2000;41:1703–1709.
129. Beardsley RM, De Paiva CS, Power DF, Pflugfelder SC. Desiccating stress decreases apical corneal epithelial cell size–modulation by the metalloproteinase inhibitor doxycycline. *Cornea.* 2008;27:935–940.
130. Maatta M, Kari O, Tervahartiala T, et al. Tear fluid levels of MMP-8 are elevated in ocular rosacea: treatment effect of oral doxycycline. *Graefes Arch Clin Exp Ophthalmol.* 2006;244:957–962.
131. Epstein GA, Putterman AM. Combined excision and drainage with intralesional corticosteroid injection in the treatment of chronic chalazia. *Arch Ophthalmol.* 1988;106:514–516.
132. Meisler DM, Raizman MB, Traboulsi EI. Oral erythromycin treatment for childhood blepharokeratitis. *J AAPOS.* 2000;4:379–380.
133. Palva J, Pohjanpelto PE. Intralesional corticosteroid injection for the treatment of chalazia. *Acta Ophthalmol (Copenh).* 1983;61:933–937.
134. Watson AP, Austin DJ. Treatment of chalazions with injection of a steroid suspension. *Br J Ophthalmol.* 1984;68:833–835.
135. Yalcin E, Altin F, Cinhuseyinoglue F, Arslan MO. N-acetylcysteine in chronic blepharitis. *Cornea.* 2002;21:164–168.
136. Phillips RP, McLean IC, Taylor RJ, Forrester JV. Steroid induced glaucoma: a report of two cases with a review of morbidity and prescribing in general practice. *Scott Med J.* 1990;35:81–84.
137. Jackson WB. Blepharitis: current strategies for diagnosis and management. *Can J Ophthalmol.* 2008;43:170–179.
138. Gaynes BI, Fiscella R. Topical nonsteroidal anti-inflammatory drugs for ophthalmic use: a safety review. *Drug Saf.* 2002;25:233–250.
139. Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. *Adv Ther.* 2009;26:651–659.
140. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Solomon R, Biser SA, Bloom AH. Efficacy of commercially available topical cyclo-

sporine A 0.05% in the treatment of meibomian gland dysfunction. *Cornea.* 2006;25:171–175.
141. Rubin M, Rao SN. Efficacy of topical cyclosporin 0.05% in the treatment of posterior blepharitis. *J Ocul Pharmacol Ther.* 2006; 22:47–53.
142. Nivenius E, van der Ploeg I, Jung K, Chryssanthou E, van Hage M, Montan PG. Tacrolimus ointment vs steroid ointment for eyelid dermatitis in patients with atopic keratoconjunctivitis. *Eye.* 2007; 21:968–975.
143. Sullivan DA, Jensen RV, Suzuki T, Richards SM. Do sex steroids exert sex-specific and/or opposite effects on gene expression in lacrimal and meibomian glands? *Mol Vis.* 2009;15:1553–1572.
144. Schirra F, Richards SM, Liu M, Suzuki T, Yamagami H, Sullivan DA. Androgen regulation of lipogenic pathways in the mouse meibomian gland. *Exp Eye Res.* 2006;83:291–296.
145. Sullivan BD, Evans JE, Cermak JM, Krenzer KL, Dana MR, Sullivan DA. Complete androgen insensitivity syndrome: effect on human meibomian gland secretions. *Arch Ophthalmol.* 2002;120:1689–1699.
146. Krenzer KL, Dana MR, Ullman MD, et al. Effect of androgen deficiency on the human meibomian gland and ocular surface. *J Clin Endocrinol Metab.* 2000;85:4874–4882.
147. Worda C, Nepp J, Huber JC, Sator MO. Treatment of keratoconjunctivitis sicca with topical androgen. *Maturitas.* 2001;37:209–212.
148. Miljanovic B, Trivedi KA, Dana MR, Gilbard JP, Buring JE, Schaumberg DA. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. *Am J Clin Nutr.* 2005;82:887–893.
149. Kokke KH, Morris JA, Lawrenson JG. Oral omega-6 essential fatty acid treatment in contact lens associated dry eye. *Cont Lens Anterior Eye.* 2008;31:141–146; quiz 170.
150. Pinna A, Piccinini P, Carta F. Effect of oral linoleic and gamma-linolenic acid on meibomian gland dysfunction. *Cornea.* 2007; 26:260–264.
151. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615–621.
152. Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). *Trans Am Ophthalmol Soc.* 2008;106:336–356.
153. Gonnering RS, Sonneland PR. Meibomian gland dysfunction in floppy eyelid syndrome. *Ophthal Plast Reconstr Surg.* 1987;3: 99–103.
154. Goldberg L. MG probing: immediate results for a chronic problem. *Ophthalmology Management.* July 2009.
155. Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease: classification and grading of lid changes. *Eye* (*Lond*) 1991;5: 395–411.
156. Pflugfelder SC, Tseng SC, Sanabria O, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. *Cornea* 1998; 17:38–56.
157. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea* 2003;22: 640–650.
158. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* 2007;5:108–152.
159. Dundas M, Walker A, Woods RL. Clinical grading of corneal staining of non-contact lens wearers. *Ophthalmic Physiol Opt* 2001;21:30–35.
160. Caffery BE, Josephson JE. Corneal staining after sequential instillations of fluorescein over 30 days. *Optom Vis Sci* 1991;68:467–469.
161. Kimball SH, King-Smith PE, Nichols JJ. Evidence for the major contribution of evaporation to tear film thinning between blinks. *Invest Ophthalmol Vis Sci.* 2010;51:6294–6297.
162. Den S, Shimizu K, Ikeda T, Tsubota K, Shimmura S, Shimazaki J. Association between meibomian gland changes and aging, sex, or tear function. *Cornea.* 2006;25:651–655.
163. Kawashima M, Kawakita T, Okada N, et al. Calorie restriction: a new therapeutic intervention for age-related dry eye disease in rats. *Biochem Biophys Res Commun.* 2010;397:724–728.