Posterior Blepharitis

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Introduction and Definition

Blepharitis is a chronic inflammatory condition of the eyelids, which can affect ocular surface integrity and lead to ocular irritation and discomfort. Based on anatomical location, blepharitis can be classified as anterior or posterior. Posterior blepharitis is a heterogeneous condition defined as lid margin inflammation posterior to the gray line and may include the following structures: the marginal mucosa, mucocutaneous junction, meibomian glands, and neighboring keratinized skin. Meibomian gland dysfunction (MGD) is one cause of posterior blepharitis and with increasing frequency the two terms are used synonymously [1]. However, there are other etiologies of posterior blepharitis such as infectious or allergic blepharoconjunctivitis, so it is more accurate to consider these conditions as separate entities [1]. MGD will be the focus of this chapter.

Meibomian glands are sebaceous glands and their secretory product, meibum, is the primary source of lipids, which constitute the innermost layer of the tear film. Lipid is a critical component of the tear film because it prevents evaporation and enhances tear film stability by lowering the surface tension of tears. The 2011 International Workshop on Meibomian Gland Dysfunction defined MGD as, "*a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease*" [1]. MGD may be primary or secondary and can be further subdivided in many ways, including on the basis of low-delivery or high-delivery states. Low delivery of meibomian gland secretions can be caused either by hyposecretion of meibum or obstruction of glandular ducts or orifices [1].

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Dry Eye Association

MGD has a strong association with dry eye disease, which may be primary aqueous deficient, secondary evaporative, or a combination of the two. MGD is thought to be the leading cause of evaporative dry eye [2, 3].

Epidemiology and Risk Factors

To date, no studies have specifically established the epidemiology of posterior blepharitis in general, but a number of population-based studies have sought to determine the prevalence of MGD in particular. The numbers vary widely and reported prevalence ranges from 3.5% in the Salisbury Eye Evaluation study to 69.3% in the Beijing Eye Study [2]. The disparity comes as least in part from lack of consensus on disease-defining characteristics between the studies. Some of the discrepancy can also be accounted for by racial differences, as studies of Asian populations appear to demonstrate higher rates of MGD [2]. Age distribution of the study groups may also play a role in reported disease prevalence because increasing age correlates well with increasing prevalence of MGD.

Hormones

Sex steroids have a major impact on meibomian gland function. Androgens appear to promote meibum secretion and reduce inflammation, while estrogens appear to increase inflammation in meibomian glands in the same manner that other sebaceous glands are affected throughout the body [4]. Androgen deficiency and complete androgen-insensitivity syndrome are each associated with both MGD and tear film instability [2]. Pathologic states that alter androgen action are particularly associated with keratinization of the posterior lid margin and a secondary obstructive MGD [4].

Sex

While it is well known that female sex is a risk factor for dry eye disease [5], the relationship between sex and MGD is less clear [2]. Better tear function in postmenopausal women is associated with higher testosterone levels; however, better tear function in premenopausal women is associated with lower testosterone levels [6]. The effect of menopause on MGD has yet to be elucidated. Meibomian glands in men have a higher expression of particular fatty acid products than age-matched women [5], but it is unclear what role this may play in the pathogenesis of MGD. Men older than 70 years have a higher incidence of lid margin abnormalities and meibomian gland dropout [5].

Age

Aging is a recognized risk factor for MGD. Multiple studies have demonstrated increased signs of MGD with aging, such as lid margin abnormalities and meibomian gland atrophy within the tarsal plate on meibography [2, 7, 8]. Whether this is directly related to normal degenerative changes associated with senescence or is secondary to decreased production of sex-steroid hormones, stem cell diminution, or growth factor deficiency with aging remains unclear. Peroxisome proliferator-activated receptor gamma (PPAR-gamma) is a nuclear receptor protein whose downregulation with increasing age is hypothesized to underlie decreased meibocyte differentiation and lipid synthesis [9, 10].

Medications

Retinoic acid derivatives such as isotretinoin (Accutane), a vitamin A analog, are used in the dermatologic treatment of facial acne and are also components of many anti-aging skin products. 13-cis retinoic acid results in blepharoconjunctivitis, abnormal meibomian secretions, atrophy of meibomian glands, and dry eye signs and symptoms [4, 11]. During treatment with isotretinoin, meibomian glands appear less dense and more atrophic by meibography with an increase in meibum thickness and elevation of tear osmolarity [11]. Additionally, multiple topical medications have been found to alter meibomian gland structure or function. Topical epinephrine causes keratinization of the duct epithelium and subsequent obstructive MGD [12]. Topical glaucoma medications such as beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogs are associated with changes in meibomian gland structure such as decreased acinar area and density and have been associated with MGD in patients on chronic therapy [13, 14].

Systemic Diseases

Rosacea is a chronic inflammatory skin disease characterized by facial erythema and telangiectasia. The disease most commonly affects Caucasians and may cause eyelid and ocular surface inflammation. Compared to age-matched controls, patients with rosacea are more likely to demonstrate lid margin abnormalities, meibomian gland dropout, and decreased density of meibomian glands along the eyelids [15]. Lid margin abnormalities include meibomian orifice retro-placement, lid margin telangiectasia, and rounding or notching of the lid margin. Other systemic disorders have also been associated with posterior blepharitis and these include atopic dermatitis, seborrheic dermatitis, psoriasis, ichthyosis, Sjogren's syndrome, discoid lupus, and ectodermal dysplasia [2]. Posterior blepharitis has also been associated with cicatricial conjunctivitis in diseases such as mucus membrane pemphigoid (MMP), trachoma, erythema multiforme (Stevens-Johnson syndrome), and graft versus host disease (GVHD) [2].

Other

Contact lens wearers have greater degrees of meibomian gland dropout on infrared meibography when compared to age-matched controls who do not wear contact lenses [16]. Young contact lens wearers have been observed to have a meibomian gland dropout rate similar to individuals in their 60's with age-related glandular degeneration [16]. Arita et al. found that the duration of contact lens wear was also positively correlated with extent of meibomian gland dropout. This suggests that dry eye associated with contact lens wear may be at least in part related to MGD. One hypothesis for the etiology of meibomian gland dropout is that chronic irritation of the meibomian gland by the contact lens through the conjunctiva causes these pathologic changes.

Smoking may be another risk factor and smokers with MGD have increased lid margin and meibum abnormalities compared to non-smokers with MGD [17].

Anatomy, Etiology, and Pathogenesis

There are 20–30 meibomian glands in the lower eyelid and 25–40 in the upper eyelid [4]. The orifices of the meibomian glands are located just anterior to the mucocutaneus junction, and the normal vertical extent of the glands corresponds roughly to the extent of the respective tarsal plates. Each meibo-

mian gland is composed of secretory acini connected via short ductules to a long central duct. The entire internal system is lined by stratified squamous epithelium with signs of emerging keratinization [4]. Full keratinization is normally only seen in the terminal part of the central duct as it approaches the meibomian gland orifice [4].

Meibum is secreted through a holocrine secretion mechanism and is normally a clear oil, but in MGD it may appear more white or yellow and the consistency may be creamy or like toothpaste. Meibum is composed most abundantly of wax, fatty acids and fatty alcohols, cholesterol, and protein [4]. The transition temperature for meibomian lipids from solid to liquid ranges from 28 to 32 degrees Celsius, and therefore eyelid temperature will affect the viscosity of meibum [4].The meibum is secreted onto the eyelid margin under both neural and hormonal control and is aided by blinking. During sleep the meibum is thought to accumulate in the glands near the orifices and with waking and recommencement of blinking, the excess is discharged from the glands [18].

Pathogenesis

The pathophysiology of posterior blepharitis and MGD is complex and likely multifactorial. Hyperkeratinization of ductal epithelium has been considered to be an important cause of obstructive MGD and is influenced by a variety of factors such as advancing age, hormonal abnormalities, medication toxicity, and contact lens wear [4]. The secretory ducts then become plugged and obstructed by desquamated epithelial cells and thickened, viscous meibum. Progressively the ducts then become dilated secondary to accumulation of meibum, and subsequently there is secondary loss of secretory meibocytes [4]. This process results in diminished delivery of meibum to the tear film and ocular surface. Meibomian gland obstruction is probably the most common form of MGD [1].

Atrophy and degeneration of the glandular acini may result in a secondary hyposecretion [4]. Meibomian gland dropout has been correlated with decreased meibum production [19]. Atrophy may be caused by increased intraglandular pressure secondary to obstruction and meibum stasis, and this may inhibit normal cell differentiation. Eventually the short ductules and subsequently the acini undergo squamous metaplasia that results in keratinization of the epithelium of the ducts and acini. The meibomian gland orifices also narrow. There is also evidence that atrophy is a primary process in some individuals and may be related to advancing age [4]. Histology of atrophic meibomian glands demonstrates decreased acini size, irregular acini shape, and basement membrane thickening [4]. Corroborative with the above notions, a recent histopathological study, based on a small sample size, suggests potentially distinct pathogenic mechanisms in MGD for patients of different ages. Hyperproliferation and aberrant differentiation of the central ductal epithelia may lead to the obstruction by overproduced cytokeratins in younger adults, whereas decreased cell proliferation in acinar basal epithelia may lead to MG glandular atrophy in older adults [20].

Inflammation

Inflammation, either infectious or noninfectious, can cause posterior blepharitis, but it is not likely an important factor in the development of obstructive MGD [4]. A number of histologic studies have demonstrated granulation tissue with inflammatory cell infiltrate within the meibomian glands of patients with MGD; however, in specimens with ductal dilation and acinar atrophy indicative of obstructive MGD, no inflammatory infiltrate was identified on histology [4]. In vivo confocal microscopy has suggested the possible presence of periglandular inflammatory cells in some individuals with obstructive MGD; however, differentiating between various cell types is difficult with confocal.

Infection

Chronic blepharitis is known to be influenced by overgrowth of commensal bacteria such as coagulase negative staphylococci, *Staphylococcus aureus*, and *Propionibacterium acnes*; however, the role of bacterial infection in MGD is somewhat controversial. Bacterial infection does not appear to play a role in the pathogenesis of obstructive MGD; however, even in the absence of active infection, it is conceivable that bacterial products such as toxins and lipase may play a role in posterior blepharitis [4]. Bacterial lipases and esterases can degrade meibomian lipids resulting in abnormal free fatty acids that may cause inflammation and hyperkeratinization of the lid margin [4]. Oral antibiotics have demonstrated efficacy in the treatment of MGD and posterior blepharitis, but this may have more to do with the anti-inflammatory effects than the antimicrobial effects of these medications [4, 21, 22]. Additionally, *Demodex brevis* mites reside in meibomian glands and may play a role in the pathogenesis of posterior blepharitis [23].

Growth Factors and Cytokines

Fibroblast growth factor receptors (FGFRs) are important for cell differentiation, survival, migration and differentiation. High levels of fibroblast growth factor receptor type 2 (FGFR2) are expressed in the acinar and ductal epithelial cells in meibomian glands of both mice and humans. Deletions of FGFR2 in mice models result in severe meibomian gland acinar atrophy [24]. This suggests that a FGFR2 plays an important role in meibomian gland hemostasis and may be a potential target for novel MGD therapy in the future.

A number of inflammatory tear film cytokines have been associated with MGD. These include IL-4, IL-6, IL-10, IL-17a, and TNF-α [25]. Choi et al. demonstrated decreased levels of these cytokines in the tear film after treatment with intense pulsed light (IPL) therapy. Measurement of inflammatory tear cytokines may serve as an indicator of treatment response in MGD.

Clinical Findings

In normal individuals, the meibomian gland orifices are located just anterior to the mucocutaneous junction and are spaced regularly along the eyelid margins. Clinical findings of posterior blepharitis include eyelid margin telangiectasias, injection, and keratinization. Rounding, notching, dimpling, or scalloping of the posterior lid margin may be observed. Additionally, an epithelial ridge between orifices may be present. Exam findings indicative of MGD also include capping, plugging, or atrophy of the meibomian gland orifices [2]. Manual expression of the glands can demonstrate either excessive or decreased meibum of various characteristics, such as thick or toothpaste-like meibum. The tear film may also be abnormal or unstable, either as a secondary or primary process. In early stages, MGD may be subclinical and asymptomatic, but later it may progress to be both symptomatic and clinically obvious on slit lamp exam.

With chronic posterior blepharitis, the location of the meibomian orifices relative to the mucocutaneous junction may change [18]. The mucocutaneous junction may move anteriorly in the process of conjunctivalization and is thought to represent an aging process. With progression, periductal fibrosis around the meibomian orifices can be visualized. Conversely, in MGD in the setting of cicatricial disease the glands are pulled posteriorly onto the conjunctiva [18]. In this setting, there is stretching and exposure of the terminal ducts that is called ductal exposure. Clinically these orifices appear slightly elevated and rib-like. When periductal fibrosis or ductal exposure is present, these clinical

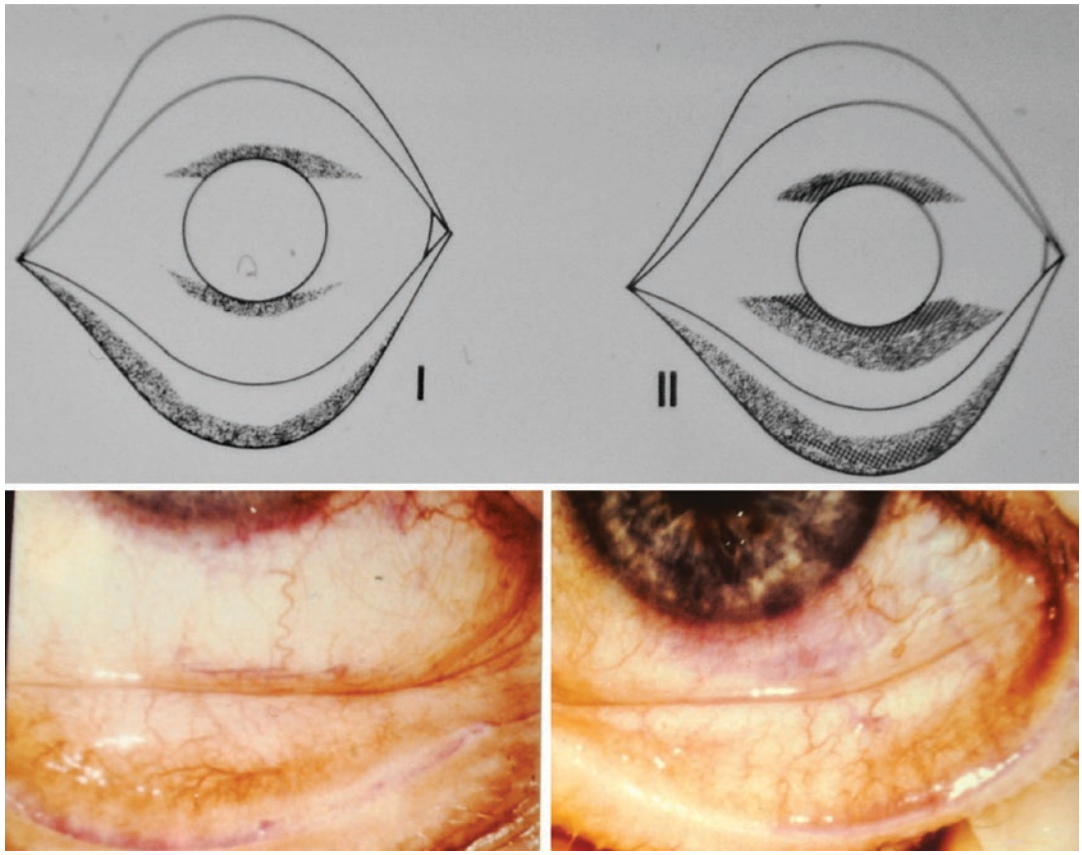

Fig. 2.1 The top images are drawings of classic lid margin and corresponding conjunctival staining patterns seen in posterior blepharitis. The bottom images are representative patient photos demonstrating these staining patterns with rose Bengal.

conditions are thought to be irreversible [18]. Abnormal staining patterns with fluorescein, rose Bengal, or lissamine green may be present. Classically there is staining of the posterior lid margin associated with corresponding staining of the inferior or superior conjunctiva and limbus that are in apposition with the eyelid margins (Fig. 2.1).

Symptoms

MGD has been associated with ocular surface symptoms such as irritation, burning, itching, subjective eye dryness, and teary eyes. It has also been associated with eyelid crusting and stickiness (especially in the morning), eyelid puffiness and heaviness, and both eye and eyelid redness [2]. Notably, these symptoms are similar to those reported in both anterior blepharitis and dry eye disease. Due to abnormal meibum production, MGD may cause evaporative dry eye. Although the pathogenesis of MGD differs from aqueous-deficient dry eye, these two conditions may also co-exist, and it can be difficult to determine whether symptoms are related to MGD, aqueous deficiency, or both [2, 4]. Vision and contrast sensitivity may also be impact by MGD due to tear film instability.

Complications

Posterior blepharitis and MGD are associated with a number of eyelid and ocular surface complications. Chalazia are chronic, granulomatous inflammatory reactions of meibomian glands in the eyelids, and they are generally considered to be noninfectious [26]. Chalazia may arise from internal hordeola, which are acute inflammatory reactions of the meibomian glands that may or may not have an infectious etiology [26]. Both chalazia and internal hordeola are thought to be at least partially related to meibomian gland obstruction and meibum stasis [26]. Blepharitis and acne rosacea are known risk factors for the development of chalazion [15, 26, 27].

Ocular surface disease has also been associated with posterior blepharitis and MGD. This includes conjunctival hyperemia, punctate keratitis, marginal infiltrates, pannus or corneal neovascularization, corneal scar or opacity, phlyctenular keratitis, and peripheral ulcerative keratitis (PUK) (Fig. 2.2) [18, 27, 28]. Proposed mechanisms for these corneal abnormalities include mechanical rubbing of the inflamed eyelid margin, release of inflammatory mediators into the tear film, or consequences of secondary dry eye [18, 27].

Diagnosis

Posterior blepharitis and MGD can be symptomatic and diagnosed on the basis of the clinical findings described previously. MGD can also be an asymptomatic, subclinical condition with subtle or no gross clinical signs. In those cases, it may only be diagnosed with gland expression or additional diagnostic testing. Manual expression of the glands can be performed to determine the color, consistency, and quantity of secretion. Use of a standardized expression device to describe the "expressibility" of the glands has been described [18].

Additional diagnostic tests may be used to further quantify or qualify the disease process, monitor for progression, or confirm the diagnosis. Interferometry can be used to quantify the thickness of the tear film lipid layer, the normal thickness of which is reported to range from 20 to 160 nm [18]. With the upstroke of a blink, the lipid layer can also be seen to spread upwards and then to stabilize. In eyes with lipid deficiency of the tears, the lipid layer is noted to take longer to stabilize [18]. Tear break-up time (TBUT) is a useful tool to evaluate the tear film stability in these patients, and describes the time interval between the last complete blink and the appearance of the first corneal dry spot [3]. A TBUT less than 10 seconds is generally considered abnormal [29].

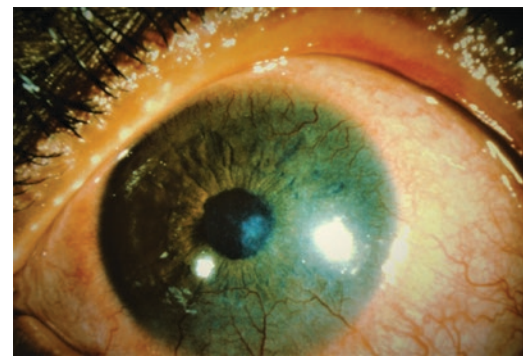

Fig. 2.2 This image demonstrates corneal neovascularization in a patient with meibomian gland dysfunction (MGD). Note the presence of meibomian gland plugging and telangiectasias of the posterior lid margin

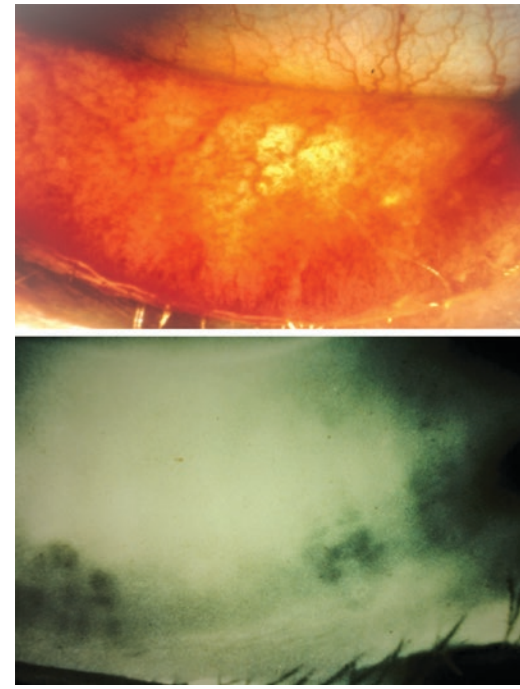

Fig. 2.3 The top color photo depicts loss of meibomian gland architecture that is normally visible through the tarsal conjunctiva. The bottom black-and-white photo was taken of the same patient and confirms the loss of normal meibomian glands, which normally appear black in this type of image

Meibography can be used to assess the architecture of the meibomian glands via transillumination of the eyelids using white light, near infrared, or infrared light (Fig. 2.3). More recently infrared photography and videography with or without transillumination have been utilized in non-contact methods and reported as faster and easier means of obtaining information related to meibomian gland architecture through meibography [2, 8]. The eyelids are everted to obtain the images in all of these techniques. In vivo confocal microscopy has also been used to measure gland diameter through the everted tarsal plate [30].

Meibometry is a technique to quantify the amount of lipid present in the lower lid reservoir and involves blotting a sample of meibum onto a loop of plastic tape [18]. Tests of tear quantity and quality such as TBUT, tear osmolarity, and Schirmer's testing can be used as an indirect measure of meibomian gland dysfunction; however, these tests are generally not specific to MGD [31].

Differential Diagnosis

Chronic allergy with severe ocular inflammation such as atopic keratoconjunctivitis and contact dermatitis due to medications or chemical exposure can often induce severe lid inflammation and mimic MGD or posterior blepharitis. Occasionally, basal cell carcinoma or squamous cell carcinoma can involve the lid margin with secondary MGD. In the presentation of a unilateral blepharoconjunctvitis, sebaceous cell carcinoma arising from meibomian glands or other pilo-sebaceous glands should always be included in the differential diagnosis of MGD. There may be pagetoid spread of the sebaceous cell carcinoma across the bulbar or tarsal conjunctiva [32].

Treatment

Treatment goals of posterior blepharitis are to reduce any present inflammation, improve the flow of meibum, stabilize the tear film, improve ocular comfort, and prevent corneal complications.

Heat and Mechanical Massage

A classic initial treatment for MGD involves application of warmth to the eyelids along with mechanical eyelid massage. Heat application to the eyelids is based on the idea that melting meibum lipids may soften the secretions and improve evacuation of the meibomian glands. The warming has been described and studied in a variety of means, ranging from simple warm compresses to devices such as infrared or hot air sources [21, 33, 34]. In patients treated with daily "eyelid hygiene" consisting of daily eyelid warming, massage, and lid margin scrubbing, one study demonstrated a 5% reversal of meibomian gland dropout [35].

Thermal Pulsation

LipiFlow (TearScience, Morrisville, NC) is an automated, vectored, thermal pulsation system that provides a combination of targeted heat therapy and mechanical massage. The device covers both the back and front of the eyelids. The posterior portion applies heat to the meibomian glands, and the anterior portion gives mechanical stimulation. A recent meta-analysis analyzed the combined outcomes of 4 randomized controlled trials on the efficacy of a single treatment with LipiFlow followed by daily warm compresses for the treatment of MGD [34]. All of the studies included were determined by the authors to be at high risk for inclusion of some type of bias. Improvement in TBUT and a standardized subjective dry-eye score was observed at 2–4 weeks; however, this effect was not sustained at 3 months. Standardized Patient Evaluation of Eye Dryness (SPEED) scores were noted to improve at 2–4 weeks in the treatment group compared to the control group, but this effect was lost at 3 months. There was no change in ocular surface staining pattern, tear osmolarity, Schirmer's test, or lipid layer thickness at any time interval. Ocular Surface Disease Index (OSDI) score was the only metric noted to be improved in the treatment group at both 2–4 weeks and 3 months [34]. This suggests that LipiFlow may not have a lasting therapeutic effect. Providers interested in offering this treatment modality could consider repeating it every 1–2 months.

Intense Pulsed Light (IPL) Therapy

IPL is an accepted, effective, and well-tolerated treatment for a range of dermatologic conditions including hypertrichosis, port wine stains, and telangiectasias [36]. IPL combined with meibomian gland expression has been shown to improve both objective signs and subjective symptoms for a broad range of patients with MGD, including those with severe, refractory MGD [37]. The mechanism of improvement in MGD is likely related to the heating of the eyelid and subsequent melting of the meibum. Hemoglobin absorption of light may also account for decreased lid margin telangiectasias [37].

Mechanical Expression of Meibum

Expression of the meibomian glands to relieve and remove ductal obstructions has been described for over 100 years [38]. Simple manual methods have been described and more recently an instrument called the "Meibomian Gland Squeezer" was found to improve both signs and symptoms of MGD at 1 month [38]. All of the patients in that study reported at least mild pain with the treatment.

Meibomian Gland Probing

In view of the obstructive nature of MGD in many patients, meibomian gland probing has been proposed as a treatment method and a means of restoring intraductal integrity. The theory behind this treatment is that the cycle of meibum stasis and subsequent glandular atrophy can be improved if orifice obstructions that prevent normal meibum expression can be mitigated. One study examined the impact of probing the glands of individuals with refractory MGD with a special cannula. At 3 months, there was an improvement in the OSDI score, an increase in the tear break-up time (TBUT), and a decrease in both conjunctival injection and eyelid margin vascularization [39].

A recent study involving gland probing with a 1 mm intraductal probe demonstrated mechanical resistance to probing in 84% of glands [40]. Of the glands that demonstrated resistance, 79.5% of them were classified as fixed, firm, focal, unyielding resistance (FFFUR) consistent with presumed findings of periglandular fibrosis by confocal microscopy. The probe findings suggest that obstruction of meibomian gland orifices in patients with MGD may be related to more chronic and permanent changes than mere plugging and keratinization.

Artificial Tears and Lipid Supplements

Artificial lubricants are often used to treat concomitant dry eye in patients with MGD [3]. Topical lipid supplements in the form of 2% castor oil drops have demonstrated improved signs and symptoms of MGD [41]. Oral supplementation with omega-3 fatty acids in patients with MGD may improve both tear film stability and contrast sensitivity [42]. Improved contrast sensitivity likely correlates to improved ocular surface and tear film stability. Omega-3 fatty acids are known to be anti-inflammatory as opposed to omega-6 fatty acids, which are proinflammatory. While the study did not specifically distinguish MGD from aqueous tear deficiency, a recent well-controlled trial known as Dry Eye Assessment and Management (DREAM) Research showed omega-3 fatty acid supplements taken orally proved no better than placebo at relieving symptoms or signs of dry eye [43].

Antibiotics

In the United States, oral azithromycin and tetracyclines such as tetracycline, doxycycline, and minocycline are commonly used off-label for treatment of MGD. The efficacy of the tetracyclines is thought to be primarily due to their anti-inflammatory action; however, their antibacterial impact on the commensal eyelid species may also play a role [44]. The tetracycline family is bacteriostatic and have been shown to decrease the production of bacterial lipases, modulate neutrophil and lymphocyte function, and inhibit inflammatory cytokines such as TNF-alpha, MMP-8, and MMP-9 [21]. There are many studies on the use of tetracyclines for MGD; however, very few of them are randomized control trials. One study of 60 patients comparing the use of oral minocycline demonstrated improvement in

all signs and symptoms of MGD that were measured in the study [45]. Typically prescribed doses of doxycycline and minocycline are 50-100 mg once or twice per day. At these doses, it is thought that the anti-inflammatory effect plays a larger role than the antibiotic effect on the ocular surface. Patients should be forewarned about the potential side effects of systemic tetracyclines such as skin photosensitivity and gastric irritation. Tetracyclines should be avoided in pediatric patients due to the risk of tooth discoloration [46].

Azithromycin, a macrolide antibiotic, reduces growth of eyelid bacteria, suppresses bacterial lipases, and improves conjunctival inflammation by decreasing the release of proinflammatory molecules [21]. Additionally and uniquely, azithromycin directly stimulates meibomian gland epithelial cells in humans and increases cellular levels of many components of meibum [44]. Multiple studies have demonstrated improvement in signs and symptoms of MGD when treated with oral azithromycin [47]. Yildiz et al. demonstrated improvement in OSDI score, lissamine green staining, and Schirmer's test results with both oral and topical azithromycin in patients with posterior blepharitis [48]. In this study, topical azithromycin also improved TBUT. Topical azithromycin has also been shown to decrease proinflammatory mediators in the tear film [49]. Typically prescribed doses of oral azithromycin for posterior blepharitis are 500 mg to 1 g per day for 1–3 days at a time [47]. Azithromycin may be prescribed in a pulsed fashion because of its long half-life. A one-time oral dose of 1 g of azithromycin maintains its minimum inhibitory concentration (MIC) of 0.25 μg/mL for *Staphylococcus aureus* for 4 days in tears and 14 days in conjunctiva [47].

Oral and topical metronidazole have been reported as treatment modalities for blepharoconjunctvitis in rosacea, both in adult and pediatric populations [27]. Topical metronidazole improves clinical signs of oculocutaneous rosacea compared to placebo [50]. Oral and topical metronidazole have also been studied for the treatment of Demodex blepharitis, but in a recent meta-analysis neither treatment was found to improve the eradication rate of mites or patient-reported symptoms [23].

Tea Tree Oil

Topical tea tree oil and terpinen-4-ol are also used to treat Demodex blepharitis. Based on results of the same recent meta-analysis, both treatments decrease mite counts, improve eradication rates, and improve symptoms [23].

Anti-Inflammatory Agents

Cyclosporine A is an immunosuppressive medication with anti-inflammatory properties that has gained popularity in a dilute topical formulation for the treatment of dry eye conditions. Interestingly, topical 0.05% cyclosporine A has also been shown to improve signs, but not symptoms, of posterior blepharitis [51].

Tacrolimus is a macrolide with immunomodulatory effects and a similar mechanism of action to that of cyclosporine; however, it is 10 to 100 times more potent. Compared to placebo, 0.03% tacrolimus ointment was effective for treatment of signs of posterior blepharitis including improvement in fluorescein staining, rose Bengal staining, eyelid margin telangiectasias, and meibomian gland secretion [52]. However, there was no statistical difference between the treatment and control groups in terms of symptoms studied.

Lifitegrast is a T-cell antagonist that prevents the release of proinflammatory cytokines. It has demonstrated efficacy in the treatment of dry eye disease, but to date there have been no studies examining its role in the treatment of patients with posterior blepharitis [21].

Topical steroids are efficacious in the management of acute inflammation associated with posterior blepharitis and associated corneal complications; however, there are currently no published studies to support the long-term and efficacious use of topical steroids for MGD [21]. In noninfectious MGD, judicious pulsed therapy of topical steroids to suppress the ocular surface inflammation may be warranted.

Future Horizons

Although the literature is ripe with studies on MGD, there is limited understanding of its pathogenesis and effective therapeutic strategies. Future work should focus on elucidating the role of inflammation in MGD more definitively as well as the underlying cellular and molecular mechanisms of MGD and glandular homeostasis. These efforts will aid in the development of targeted therapies for MGD and regenerative medicine for involutional MG atrophy.

Compliance with Ethical Requirements

Conflict of Interest
Christine Martinez, Andrew Huang, and Lixing Reneker declare that they have no conflict of interest.

Informed Consent
No human studies were carried out by the authors for this chapter.

Animal Studies
No animal studies were carried out by the authors for this chapter.

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